CONTRAST AGENTS - FULL LIST OF THE 30 IODINATED PRODUCTS FOR WHICH REPORTS HAVE BEEN SENT OVER THE FIRST 40 YEARS OF THE WHO PHARMACOVIGILANCE SYSTEM, SUBDIVIDED INTO TWO 20-YEAR PERIODS. FOURTH WHO-ITA/ITA-OMS 2010-2011 CONTRIBUTION ON THE 30 BASIC AGGREGATED WHO SYSTEM-ORGAN CLASS DISORDERS (SOCDs), AND SUSPECTED[+] ADVERSE REACTIONS AND EVENT PREFERRED NAMES (SADRs[+])

Dan Bradu and Luigi Rossini*

Servizio Nazionale collaborativo WHO-ITA/ITA-OMS, Universita' Politecnica delle Marche e Progetto di Farmacotossicovigilanza pre-, post-marketing, Azienda Ospedaliera Universitaria Ospedali Riuniti di Ancona, Regione Marche, Italia

Summary

We have examined the PR-22 2010 data set, which includes 155,164 accepted SADRs associated with 30 iodinated contrast agents in use in the Countries participating in the WHO Pharmacovigilance Programme. The SADRs encompass 40 years, from 1968 to 2010, divided into two 20 year periods (1968-1989 and 1990-2010). The data, provided by the UMC, have been analysed in the framework of the Matlab software of correlation clustering leading to an objective classification based on the 30 standard WHO-SOCDs and preferred names.

As reflected in the Title the first set of analyses regarded ATC-V08A sub-classes A (9 agents; 63,578 reports), B (12; 84,105), and C (8; 7,171). These were examined

separately, then the results of the same procedure applied to the full matrix of 30 products and "876 non empty" SADRs, including ATC-V08A sub-class D (1 agent; 310 reports) were displayed in the Appendices.

As discussed previously and confirmed here, a global epidemiological evaluation of the site and adverse events related to iodinated contrast agents depends on a better definition of both the type and time of their reporting. However these effects, either simple and/or complex reactions and events, currently appear to be non homogeneously associated either with the ATC sub-classes or to the classes related to other, previously examined CA grouping. The present classification however offers a stricter adhesion to reality at least for all acute and possibly delayed & subchronic pathotoxicology clinics, and presents merits compared to the knowledge acquired from preclinical and chemico-physical data.

Other previously introduced topics are dealt with in the discussion and reported as Appendices.

Key words: WHO-International Drug Monitoring of ATC-V08A -A, -B, -C and -D Nr 30 reference iodinated contrast agents products worldwide in use, and their reporting to UMC for firstly 40 years, and two related 20 years WHO-System-Organ Class Disorders (SOCDs) and Suspected adverse Reactions and Event preferred names (SADRs) collections. A binary clustering objective autoclassification and confirmatory plots in a Matlab operative software and a model study applied to their comparisons is given in Appendix 7.

-* Corresponding author, retired October 31, 2008. [+] According to the Directive 2010/84/EU. Reference groups in inverse temporal order: books, full papers and complete "journal papers" copies, summarized and annotated, available from the home archives. Postal and email addresses: DB, Borochow 28/14, Raanana 43433, Israel; bradu@smile-net-il; LR. Via Conero 115 A, 60129 Ancona, Italy; rossiniluigi@hotmail.it

"I write because I can partake in reality only by changing it". **Orhan Pamuk's Nobel Lecture. My father's suitcase, Stockholm 2006.**

PR22-2010 dataset, provided by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC), contains the full list of reports received by that body over its 40 years of operation on 73 medicinal products. These Reports of Adverse reactions and events (ADRs) regard ATC-V08 Class contrast agents (CAs) currently used in about 100 member Countries (105 Official, and 29 Associated Members listed by the WHO Programme web page, last updated 20 December 2010). Subtraction of the four associations mentioned below from   201,928 ADRS (50,765 spanning 1968-1989 and 151,153 spanning 1990-2010) leaves a total of   201,355 of what are now called Suspected ADRs (SADRS) as per EU Directive 84 of 31 December 2010. These regard the first 30 standard WHO aggregated System Organ Class Disorders (SOCDs) over the 40 years and 69 reference, generic, branded products (See [2], and below).

The iodinated CAs used for the same 40 years, aggregated in standard 30 SOCDs, accounted for 155,164 SADRs of the 30 medicinal products branded generic and/or reference products, including the 52 acid and/or salt potentially "biosimilar" products. Here we will apply the new correlation clustering objective autoclassifications (Cf [5]) of the ordered WHO-SOCDs and of the same preferred name total SADRs only to the total 30 products, using both the full 1968-2010 dataset and two separate 20-years periods (1968-1989 and 1990-2010). In a previous pilot study we applied Wilks's chi square statistics for their related contingency tables, and Gabriel's STP procedure to the 102,605 ADRs of the seven products associated with the largest number of reports. This allowed production of profile binary clustering and Euclidean confirmatory plots on these products and associated ADRs, respectively 40,396 for the first 20 years and 62,209 for the second 20 years (in brackets, see Tables and Figures 1 in [1] and [4]), as follows: 1 – Amidotrizoate (26,017;18,631); 2 – Iodamide (659; 277); 3 – Iotalamate (725; 7,144); 4 – Iodoxamate (452; 75); 5 – Ioxaglate (1,568; 3,399); 6 – Iohexsol (2,396; 17,476); 7 – Iopamidol (2,053; 15,637).

 Appendix 1 reports ATC-V08A sub-classes -A, -B, -C and -D of the 30 numbered iodinated products along with names, synonyms and chemical identification numbers. Appendix 2 lists the aggregated WHO-SOCD numbers and codes. Appendix 3 shows the SADR dataset for whole 40-year WHO Pharmacovigilance Programme. Appendix 4 reports for the 30 CAs and their 52 total

potential "biosimilars" currently in use, and the associated number of reports over the whole 40 years period, and it will be utilized in the VIth next short Note. Appendix 5 presents the 876 (SOCD-)SADRS codes effectively appearing for whole 40- year 1968-2010 collection. Appendix 6 presents the ATC-Substances (Iodinated CA, and RMN CA), WHOART-SOC names and WHOART-PT names of the total 4,442 Reports (382 for V08A-A, 6 products and 2 biosimilars; 3,450 for V08A-B, 10 products and 1 biosimilar; 123 for V08A-C, 7 products; 487 for V08C-A, 7 products, and 6 for V08C-B, 2 products), accepted in the official UMC PR22-2010 dataset received of the 35 products in use, for the 40 years accumulation of the related Reports *collected from Italy*, and it will be utilized in the VIth next Short Note. Appendix 7 presents the full last complete, operative Matlab software versions of the clustering and confirmatory plots. Final Appendices 8 and 9 represent the application of the clustering and confirmatory plots softwares of Appendix 7 above to the aggregated SADRs of the 30 agents of the 30 SOCDs listed above (Appendices 1, and 2), and to the aggregated total SADRs together, as well as the application of the same clustering procedure to the "Big Matrix" where the sub-classes A, B, C, and D are lumped together.

Datasets for the two 1968-1989 and 1990-2010 20-year collection periods, not included here for space,   will be sent if requested by email to the Authors.

1. Iodinated contrast agents. Clustering Analysis Results.

1.1. Data presentation, correlation clusters and confirmatory plots of SOCD-SADR frequencies of separated ATC-V08A -A, -B, -C and -D sub-class products for the whole 40-year collection period (1968-2010) and for the two 20-year collections 1968-1989, and 1990-2010. For ADR concentrated in a small numbers of 30 SOCD groups. SOCD groups, classes A, B, C analyzed separately, for agents with sizeable report numbers (disregarding "scarce" agents).

30 SOCD GROUPS

1	100	11	700	21	1230
2	200	12	800	22	1300
3	300	13	900	23	1410

4	410	14	1010	24	1420
5	420	15	1020	25	1500
6	431	16	1030	26	1600
7	432	17	1040	27	1700
8	433	18	1100	28	1810
9	500	19	1210	29	1820
10	600	20	1220	30	1830

The SOCD groups of ADRs with codes 420 and 1600 contain in all 4 reports and will be eliminated. All the report numbers matrices will have 28 rows, for the 28 SOCD groups remaining after removal of groups 420 and 1600. The SOCD groups are specified in detail in Appendix Nr. 2.

The Iodinated Agents considered, in number of 30, are belonging to four classes A, B, C, D. These Iodinated Agents are, in order, 9 representatives of class A, 12- of class B, 8- of class C and 1 representative of class D. They are specified in detail in Appendices Nr. 1 and 4.

The reports numbers are given in matrices 28x9 for class A, 28x12 for class B, 28x8 for class C, and by a one column matrices 28x1 for class D. For each class, there will be 3 matrices, for the 40 years period 1968-2010, for the 20 years period 1968-1989 and for the 20 years period 1990-2010, respectively. For each class, these 3 matrices are dependent: the cell values of the first of them are equal to the sums of the values in the corresponding cells of the last two of them.

The cluster analysis will be done for classes A, B, C separately. By examining the results for the 3 above mentioned period, one attempts to check whether there is a change in time of the pattern of the ADRs numbers.

CLASS A

Matrices

TA1(28x9) (years 1968-2010)

TA2(28x9) (years 1968-1989)

TA3(28x9) (years 1990-2010)

Nr of reports per contrast agent 1-9:

Years\Drug	1	2	3	4	5	6	7	8	9	Total

1968-2010	33	44648	9	101	936	165	14395	2223	1068	**63578**
1968-1989	29	26017	9	87	659	123	7251	671	1031	**35877**
1990-2010	4	18631	0	14	277	42	7144	1552	37	**27701**

Drugs with few reports:

Years 1968-2010: 1, 3 and to a lesser extent 4, 6

Years 1968-1989: 1, 3 and to a lesser extent 4, 6

Years 1990-2010: 1, 3, 4, 6, 9

CLASS B

Matrices

TB1(28x12)   (years 1968-2010)

TB2(28x12)   (years 1968-1989)

TB3(28x12)   (years 1990-2010)

Nr of reports per contrast agent 1-12:

Years\Drug	1	2	3	4	5	6	7	8	9	10	11	12	Total
1968-2010	1629	4815	19872	4617	17718	434	19387	773	7569	5200	82	2012	**84105**
1968-1989	0	0	2396	0	2053	0	193	8	0	1587	0	1939	**8176**
1990-2010	1629	4815	17476	4617	15665	434	19194	765	7569	3613	82	73	**75929**

Drugs with few reports:

Years 1968-2010: 11

Years 1968-1989: 1, 2, 4, 6, 8, 9, 11 and to a lesser extent 7

Years 1990-2010: 11, 12

CLASS C

Matrices

TC1(28x8)   (years 1968-2010)

TC2(28x8)   (years 1968-1989)

TC3(28x8)   (years 1990-2010)

Nr of reports per contrast agent 1-8:

Years\Drug	1	2	3	4	5	6	7	8	Total
1968-2010	2721	621	193	527	878	484	880	867	**7171**
1968-1989	2656	621	145	452	874	394	734	204	**6080**
1990-2010	65	0	48	75	4	90	146	663	**1091**

Drugs with few reports:

Years 1968-2010: none

Years 1968-1989: none

Years 1990-2010: 2, 5

===

CLASS A, 1968-2010

Groupings (Clusters and supplementary pairs of possible interest)
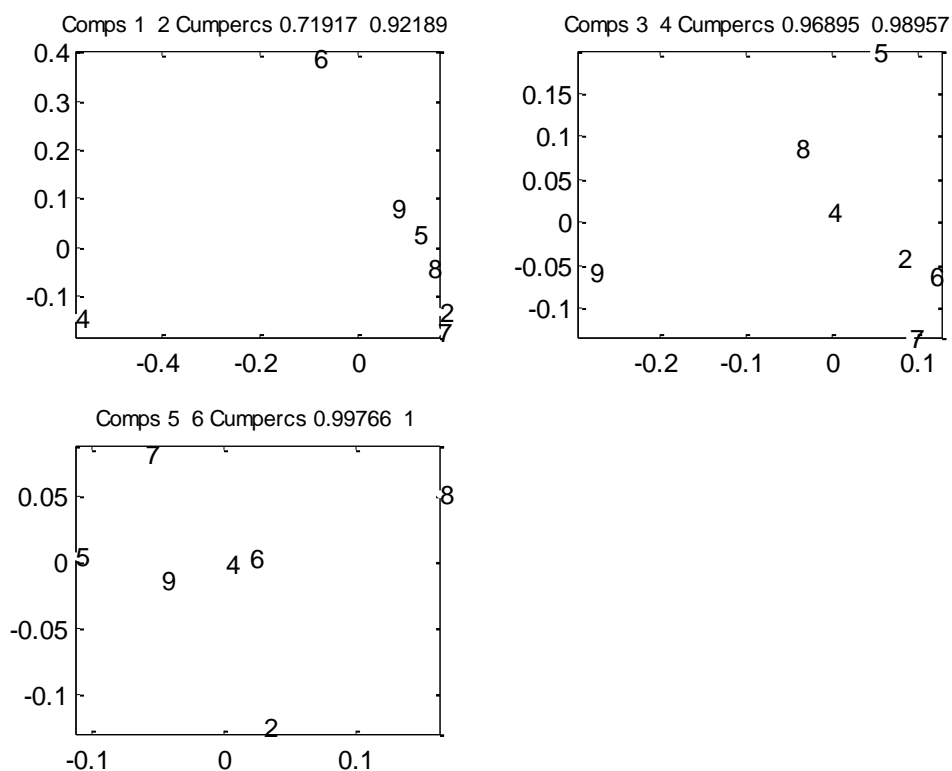
X=TA1'; scarce=[1 3]; ALLCLUSTERSFINAL(X,scarce);

Follow up to four confirmatory plots (in this case 3).

Note. Here is a fact which may be sometimes puzzling: namely the variation in the number of confirmatory plots (1, 2, 3 or 4). An explanation is required. Normally, when dealing with a matrix having many columns, one begins with an approximating matrix in the first two dimensions, dim1 and dim2. Then, if possible, one adds successively approximations in dimensions 3, 4, dimensions 5, 6 and dimensions 7, 8 where in our implementation we stop. It follows that the number of plots we can construct is as follows :

Nr of columns of the matrix	Plots which can be constructed
2 or 3	1 plot
4 or 5	2 plots
6 or 7	3 plots
8 or more	4 plots

(the limitation to 4 plots was our decision).

As an example, in the clustering of the 7 iodinate agents we were busy in the beginning, we have had always 3 confirmatory plots.

Comps 1 2 Cumpercs 0.71917 0.92189

Comps 3 4 Cumpercs 0.96895 0.98957

Comps 5 6 Cumpercs 0.99766 1

==

GAUGES(=MAX DIAMETERS) and CORRELATIONS(PAIRWISE AT LEAST=)

0.2958   0.825

0.27386   0.85

0.22361   0.9

0.19365   0.925

0.15811   0.95

0.1118   0.975

THESE GAUGES AND CORRELATIONS ARE VALID THROUGHOUT

==

CLUSTERS:

cluster 1 = 2 5 7 8 9

  pairwise correls = at least 0.89547

cluster 2 = 2 5 7 8

  pairwise correls = at least 0.94608

cluster 3 = 5 8

  pairwise correls = 0.97807

cluster 4 = 2 7

  pairwise correls = 0.99262

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

   6   9   0.8385

   5   6   0.8609

Summary of clusters

  5 8

  2 7

  2 5 7 8

  2 5 7 8 9

===

CLASS A, 1968-1989

Groupings (Clusters and supplementary pairs of possible interest)

X=TA2'; scarce=[1 3]; ALLCLUSTERSFINAL(X,scarce);

Follow up to four confirmatory plots (in this case 3)

Comps 1 2 Cumpercs 0.7038 0.91238

Comps 3 4 Cumpercs 0.95573 0.98935

Comps 5 6 Cumpercs 0.99845 1
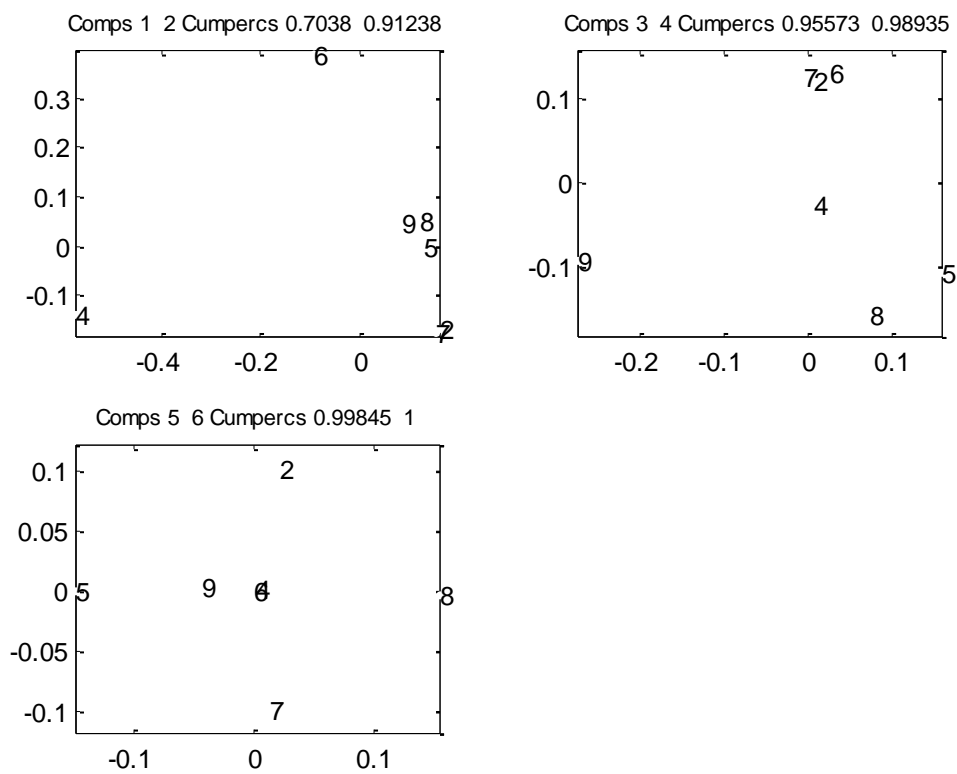
CLUSTERS:

cluster 1 = 2 5 7 8 9

 pairwise correls = at least 0.91843

cluster 2 = 2 5 7 8

 pairwise correls = at least 0.94362

cluster 3 = 5 8

 pairwise correls = 0.97823

cluster 4 = 2 7

 pairwise correls = 0.99672

==
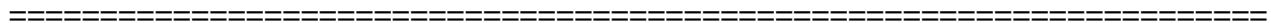
PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

    6   9   0.8311

    6   8   0.8539

Summary of clusters

  5 8

  2 7

  2 5 7 8

  2 5 7 8 9

==

CLASS A, 1990-2010

Groupings (Clusters and supplementary pairs of possible interest)

X=TA3'; scarce=[1 3 4 6 9]; ALLCLUSTERSFINAL(X,scarce);

Follow up to four confirmatory plots (in this case 2)

==
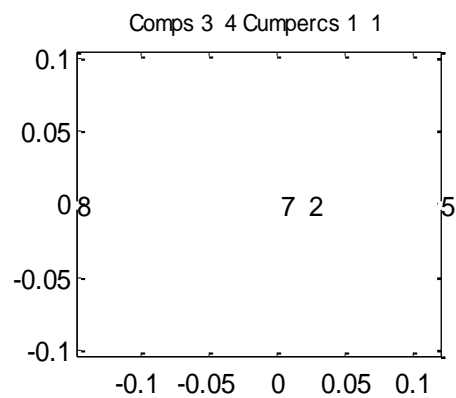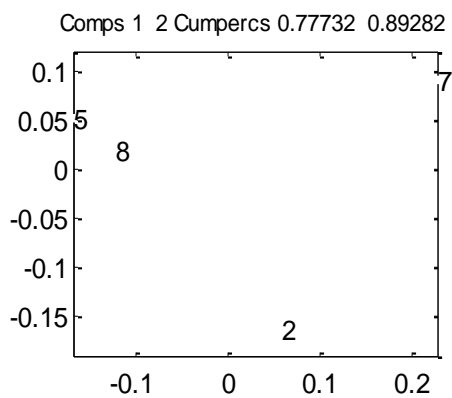
CLUSTERS:

cluster 1 = 2 7

 pairwise correls = 0.98267

cluster 2 = 5 8

 pairwise correls = 0.98905

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

5	7	0.9418
7	8	0.9552
2	5	0.9774
2	8	0.9822

Summary of clusters

 5 8

 2 7

==

Comments: Cluster [2 5 7 8 9] is suggested, with [2 5 7 8] as a more precise sub-cluster. In TA1, TA2, agent 6 forms recommended non-cluster pairs with agents 5,8,9 of the larger cluster. In TA3, clusters [2 7], [5 8], together with the four recommended pairs [5 7], [7 8], [2 5], [2 8] constitute all the pairs of cluster [2 5 7 8]. One observe in all a remarkable consistency.

For TA1, the results are consistent very much with those of ZA1, for "BIG

MATRIX", classes A, B, C analysed separately.

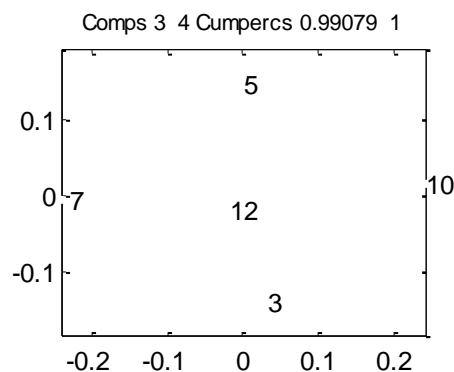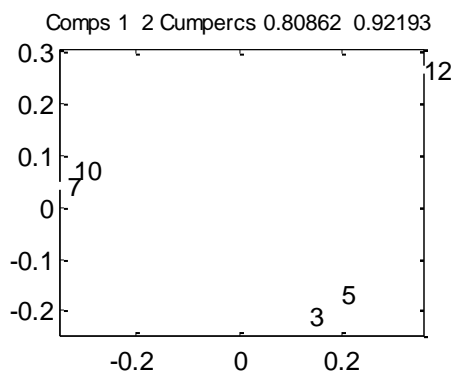==

CLASS B, 1968-2010

Groupings (Clusters and supplementary pairs of possible interest)

X=TB1'; scarce=[11]; ALLCLUSTERSFINAL(X, scarce);

Follow up to four confirmatory plots (here actually 4)

==
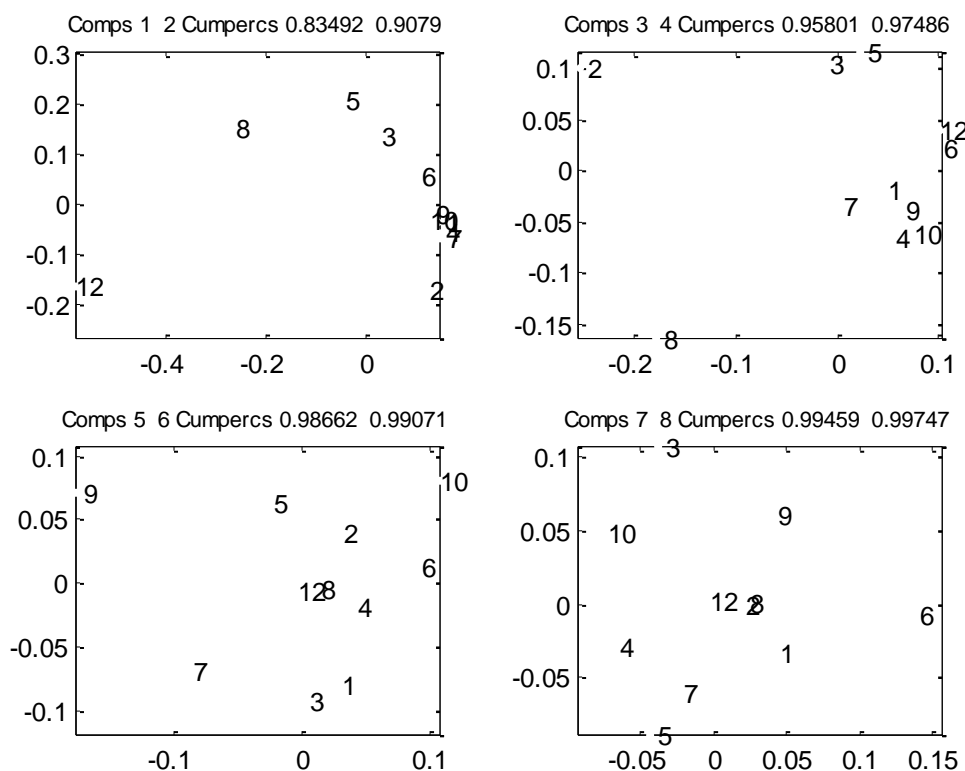
CLUSTERS:

 cluster 1 = 1 2 3 4 5 6 7 9 10

  pairwise correls = at least 0.8592

cluster 2 = 1 3 4 5 6 7 9 10

  pairwise correls = at least 0.9372

cluster 3 =   1 4 6 7 9 10

  pairwise correls = at least 0.97726

cluster 4 =   3 5

  pairwise correls = 0.98829

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

     6   8   0.8424

     3   8   0.9146

     5   8   0.9287

Summary of clusters

  3 5

  1 4 6 7 9 10

  1 3 4 5 6 7 9 10

  1 2 3 4 5 6 7 9 10

===

CLASS B, 1968-1989

Groupings (Clusters and supplementary pairs of possible interest)

X=TB2'; scarce=[1 2 4 6 8 9 11]; ALLCLUSTERSFINAL(X,scarce);

Follow up to four confirmatory plots (2 in this case)

==

CLUSTERS:

cluster 1 =   3 5

 pairwise correls = 0.98387

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

   3　　**12**　　**0.8277**

   5　　**12**　　**0.8802**

   7　　**10**　　**0.8928**

Summary of clusters

  3 5

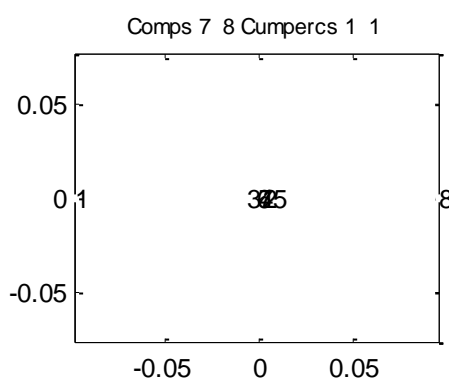==
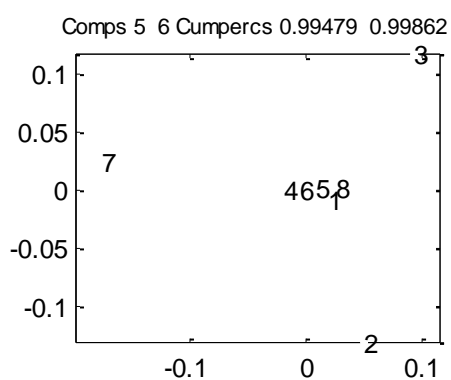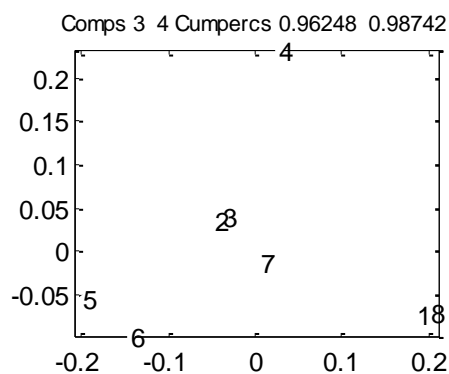
CLASS B, 1990-2010

Groupings (Clusters and supplementary pairs of possible interest)

X=TB3'; scarce=[11 12]; ALLCLUSTERSFINAL(X, scarce);

Follow up to four confirmatory plots (here actually 4)

==
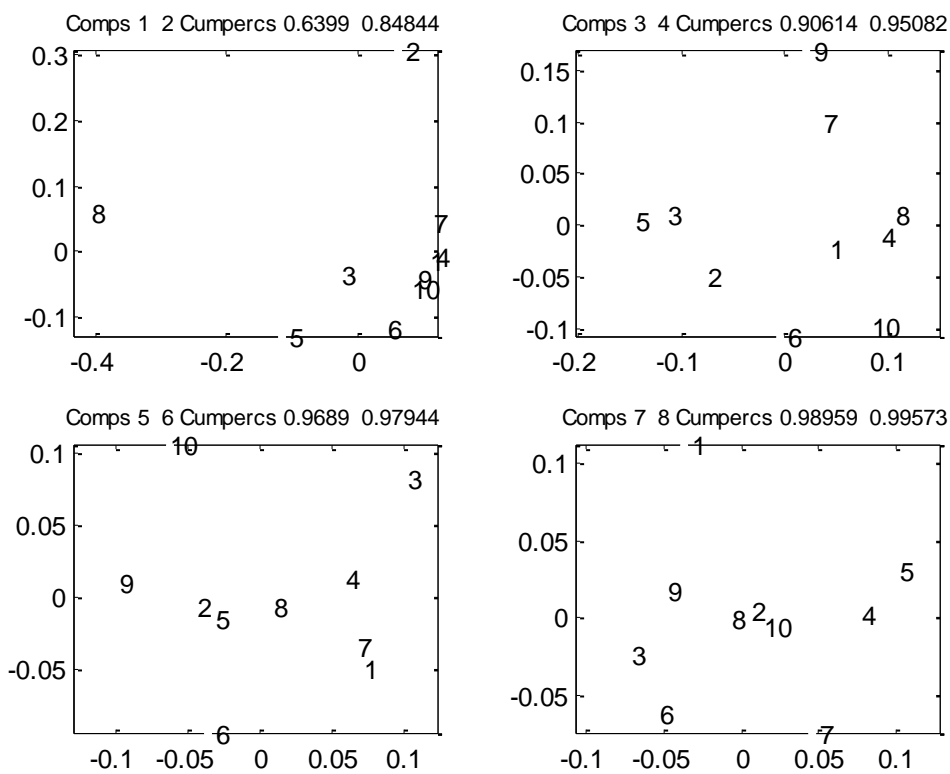
CLUSTERS:

cluster 1 =   1 2 3 4 5 6 7 9 10

  pairwise correls = at least 0.88307

cluster 2 =   1 3 4 5 6 7 9 10

  pairwise correls = at least 0.95616

cluster 3 =   1 4 6 7 9 10

  pairwise correls = at least 0.97726

cluster 4 =   3 5

  pairwise correls = 0.98812

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

   6   8   0.8459

   3   8   0.8993

   5   8   0.9157

Summary of clusters

  3 5

  1 4 6 7 9 10

  1 3 4 5 6 7 9 10

  1 2 3 4 5 6 7 9 10

==

Comments: Data set TB2 is of small weight. Analyses of TB1 and TB3 suggest cluster [1 3 4 5 6 7 9 10] of high correlation low bound, and including all other clusters, except the first. In the first cluster, the agent 2 is responsible for lowering the correlation bound, and might be eliminated.

The analysis of TB2 gives only the cluster [3 5] (of maximal correlation).

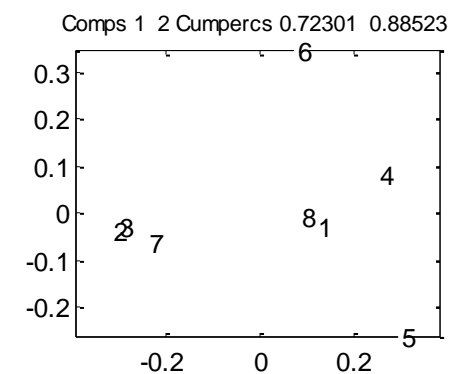**Agents 8 and 12 enter in almost all recommended non-cluster pairs.**

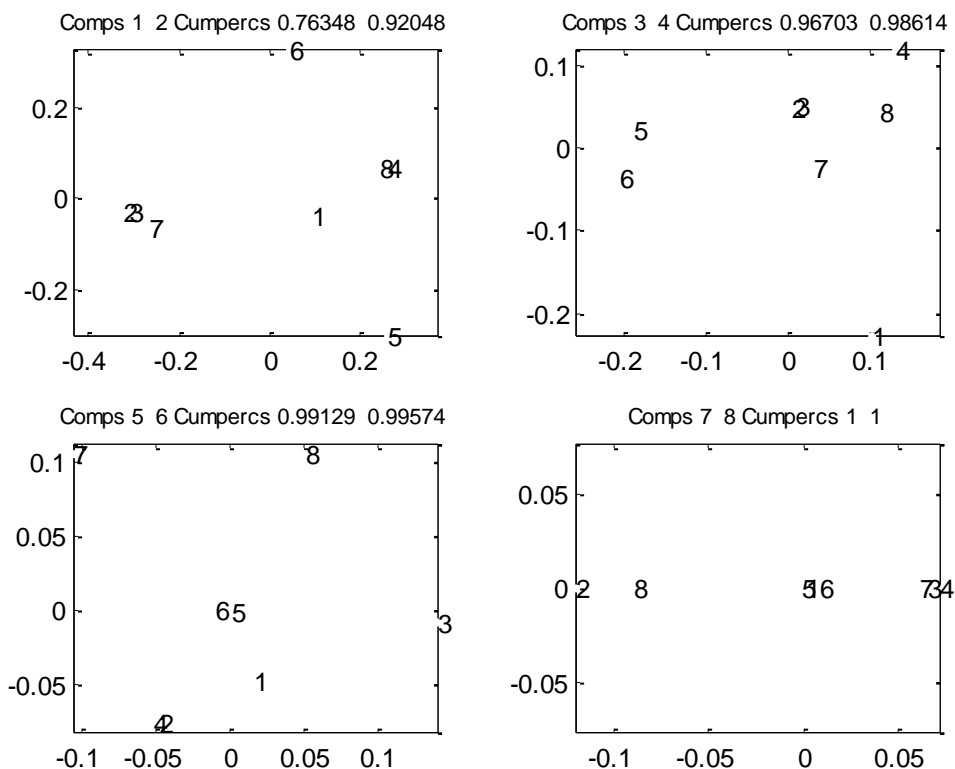==

CLASS C, 1968-2010

Groupings (Clusters and supplementary pairs of possible interest)

X=TC1'; scarce=[ ]; ALLCLUSTERSFINAL(X, scarce);

Follow up to four confirmatory plots (actually 4 here)

Comps 1 2 Cumpercs 0.72301 0.88523

Comps 3 4 Cumpercs 0.96248 0.98742

Comps 5 6 Cumpercs 0.99479 0.99862

Comps 7 8 Cumpercs 1 1

===

CLUSTERS:

cluster 1 = 1 2 3 7 8

 pairwise correls = at least 0.84255

cluster 2 = 4 6

 pairwise correls = at least 0.88545

cluster 3 = 2 3 7

 pairwise correls = 0.98373

cluster 4 = 1 8

pairwise correls = 0.99693

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

5	8	0.8439
1	6	0.8627
6	8	0.8686
4	5	0.8709
1	5	0.8780
4	8	0.9430
1	4	0.9488

Summary of clusters

4 6

2 3 7

1 8

1 2 3 7 8

==

CLASS C, 1968-1989

Groupings (Clusters and supplementary pairs of possible interest)

X=TC2'; scarce= [ ]; ALLCLUSTERSFINAL(X, scarce);

Follow up to four confirmatory plots (actually 4 here)

Comps 1 2 Cumpercs 0.76348 0.92048
Comps 3 4 Cumpercs 0.96703 0.98614
Comps 5 6 Cumpercs 0.99129 0.99574
Comps 7 8 Cumpercs 1 1

==

CLUSTERS:

cluster 1 = 1 4 5 8

  pairwise correls = at least 0.86216

cluster 2 = 2 3 7

  pairwise correls = at least 0.98614

cluster 3 = 1 4 8

  pairwise correls = at least 0.94095

cluster 4 = 4 8

  pairwise correls = 0.98829

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

   1   2   **0.8435**

   1   6   **0.8526**

   1   3   **0.8533**

   4   6   **0.8620**

   6   8   **0.8871**

   1   7   **0.9053**

Summary of clusters

  4 8

  2 3 7

  1 4 8

  1 4 5 8

===

CLASS C, 1990-2010

Groupings (Clusters and supplementary pairs of possible interest)

X=TC3'; scarce=[2 5]; ALLCLUSTERSFINAL(X,scarce);

Follow up to four confirmatory plots (actually 4 in this case)

===
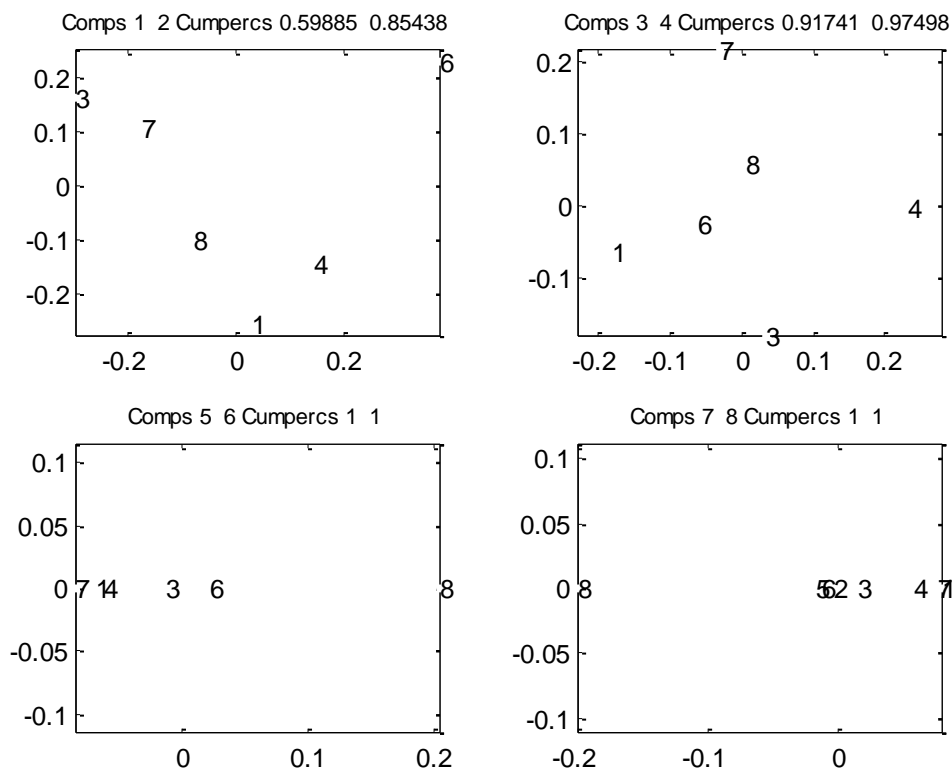
CLUSTERS:

cluster 1 = 1 4 8

  pairwise correls = at least 0.91969

cluster 2 = 3 7

  pairwise correls = 0.93075

cluster 3 = 1 8

  pairwise correls = 0.94869

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

   4   6   0.8352

   4   7   0.8396

   1   7   0.8489

   3   8   0.9030

   7   8   0.9470

Summary of clusters

  3 7

  1 8

  1 4 8

==

Comments: The analysis leads to clusters [1 4 8], [2 3 7] and [4 6].

Note that [4 6] appears as a cluster for TC1 and as recommended pair

for TC2 and TC3.

==

1.2. Data collection, correlation clusters and confirmatory plots of SADR frequencies of separated ATC-V08A -A, -B, -C and -D sub-class products for the whole 40-year collection period (1968-2010) and for the two 20-years collections 1968-1989, and 1990-2010. The "Big Matrix" sub-classes -A, -B and -C treated separately.

The "Big Matrix" is a 2364x30 matrix in which the same ADRs data as in section I are classified in more detail. The columns stand for the same representative Agents for classes A, B, C, D, but the rows stand each for the ADR whose number is that of the row (the last line, 2364 correspond to the ADR of largest number in the WHO list). As one sees reflected in the

following, only 876 of the rows are non-empty (the remaining ones corresponding to ADRs which did not occur). As a consequence, the matrices to be analyzed have numbers of rows much smaller than 2364.

CLASS A

Matrices

ZA1(577x9)   (years 1968-2010, 577 ADRs for which there are reports)

ZA2(426x9)   (years 1968-1989, 426 ADRs for which there are reports)

ZA3(460x9)   (years 1990-2010, 460 ADRs for which there are reports)

Nr of reports per contrast agent 1-9:

Years\Drug	1	2	3	4	5	6	7	8	9	Total
1968-2010	33	44648	9	101	936	165	14395	2223	1068	**63578**
1968-1989	29	26017	9	87	659	123	7251	671	1031	**35877**
1990-2010	4	18631	0	14	277	42	7144	1552	37	**27701**

Drugs with few reports:

Years 1968-2010: 1, 3 and to a lesser extent 4, 6

Years 1968-1989: 1, 3 and to a lesser extent 4, 6

Years 1990-2010: 1, 3, 4, 6, 9

CLASS B

Matrices

ZB1(801x12)   (years 1968-2010, 801ADRs for which there are reports)

ZB2(361x12)   (years 1968-1989, 361 ADRs for which there are reports)

ZB3(778x12)   (years 1990-2010, 778 ADRs for which there are reports)

Nr of reports per contrast agent 1-12:

Years\Drug	1	2	3	4	5	6	7	8	9	10	11	12	Total
1968-2010	1629	4815	19870	4617	17716	434	19387	773	7570	5200	82	2012	**84105**
1968-1989	0	0	2396	0	2053	0	193	8	0	1587	0	1939	**8176**
1990-2010	1629	4815	17474	4617	15663	434	19194	765	7570	3613	82	73	**75929**

Drugs with few reports:

Years 1968-2010: 11

Years 1968-1989: 1, 2, 4, 6, 8, 9, 11 and to a lesser extent 7

Years 1990-2010: 11, 12

CLASS C

Matrices

ZC1(257x8)   (years 1968-2010, 257ADRs for which there are reports)

ZC2(222x8)   (years 1968-1989, 222 ADRs for which there are reports)

ZC3(144x8)   (years 1990-2010, 144 ADRs for which there are reports)

Nr of reports per contrast agent 1-8:

Years\Drug	1	2	3	4	5	6	7	8	Total
1968-2010	2721	621	193	527	878	484	880	867	**7171**
1968-1989	2656	621	145	452	874	394	734	204	**6080**
1990-2010	65	0	48	75	4	90	146	663	**1091**

Drugs with few reports:

Years 1968-2010: none

Years 1968-1989: none

Years 1990-2010: 2, 5

===
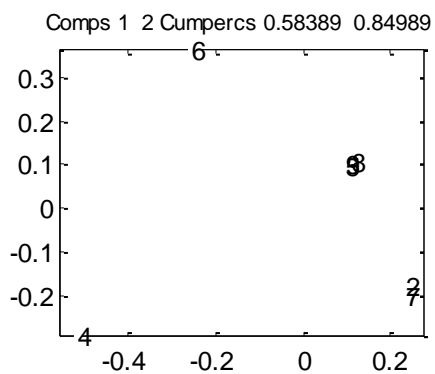
CLASS A, 1968-2010 (data set ZA1)

Groupings (Clusters and supplementary pairs of possible interest)

scarce = [1 3]; X=ZA1'; ALLCLUSTERSFINAL(X, scarce);

Follow 3 confirmatory plots
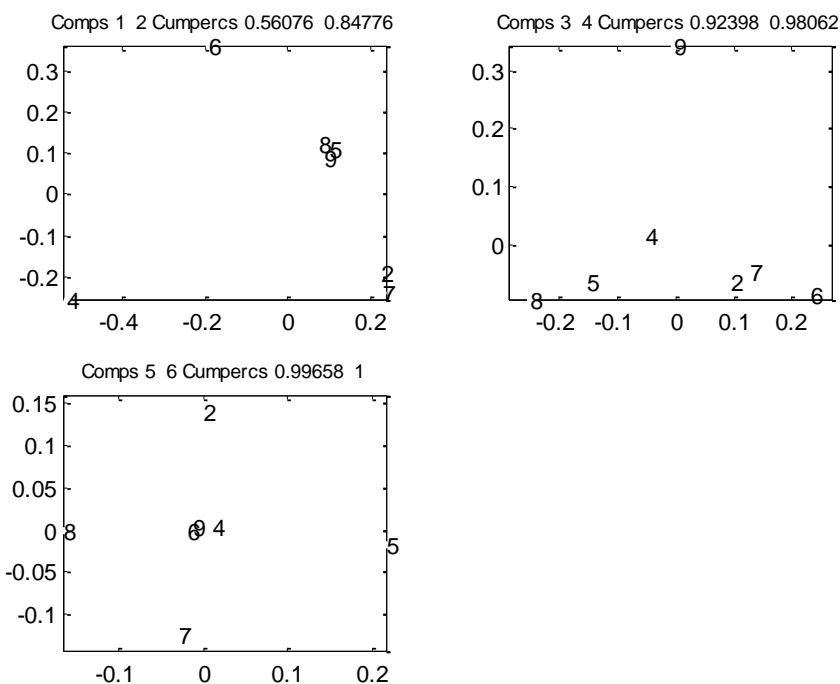
===

GAUGES(=MAX DIAMETERS) and CORRELATIONS(PAIRWISE AT LEAST=)

 0.2958   0.825

0.27386   0.85

0.22361   0.9

0.19365   0.925

0.15811   0.95

 0.1118   0.975

THESE GAUGES AND CORRELATIONS ARE VALID THROUGHOUT

===

CLUSTERS:

cluster 1 = 5 8

  pairwise correls = 0.94967

cluster 2 = 2 7

  pairwise correls = 0.98897

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

5	7	0.8332
2	9	0.8333
2	8	0.8337
8	9	0.8479
5	9	0.8827
2	5	0.8864

Summary of clusters

 5 8

 2 7

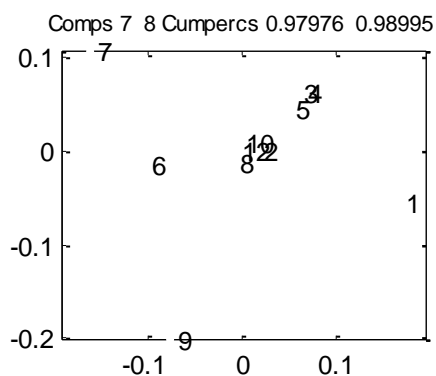==

CLASS A, 1968-1989 (data set ZA2)

Groupings (Clusters and supplementary pairs of possible interest)

X=ZA2'; scarce=[1 3]; ALLCLUSTERSFINAL(X,scarce);

Follow 4 confirmatory plots

===
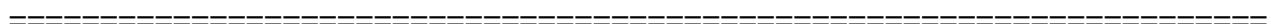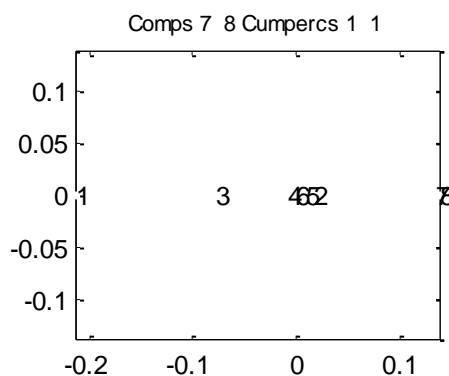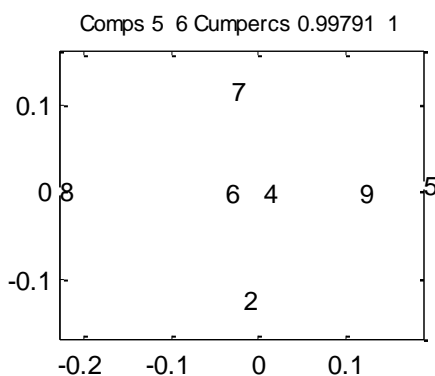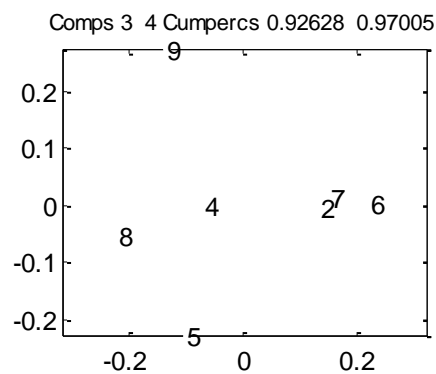
CLUSTERS:

cluster 1 =   5 8

  pairwise correls = 0.90475

cluster 2 =   2 7

  pairwise correls = 0.99337

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

  7   9   0.8277

5   7   0.8348

2   8   0.8408

2   9   0.8445

2   5   0.8657

Summary of clusters

5 8

5 8 9

2 7

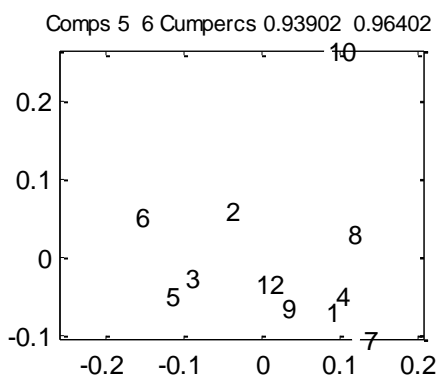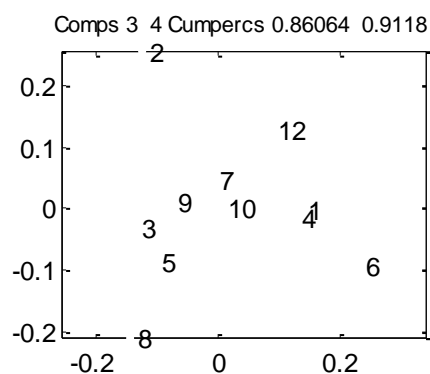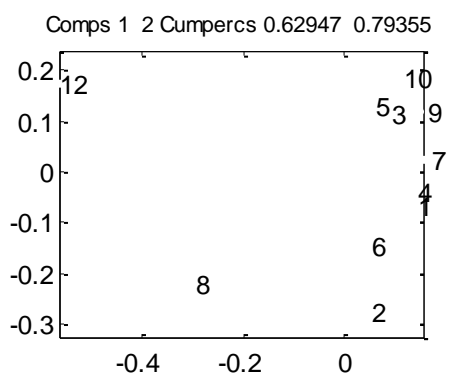==
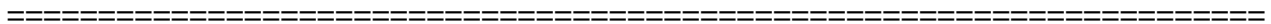
CLASS A, 1990-2010 (data set ZA3)

Groupings (Clusters and supplementary pairs of possible interest)

X=ZA3'; scarce=[1 3]; ALLCLUSTERSFINAL(X,scarce);

In fact, we could take scarce=[1 3 4 6 9]. The program took care of all the

"scarce" agents.

Follow 3 confirmatory plots

Comps 1 2 Cumpercs 0.46038 0.73841

Comps 3 4 Cumpercs 0.88471 0.97574

Comps 5 6 Cumpercs 0.99396 1

==
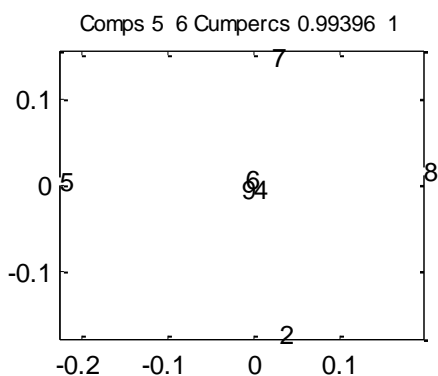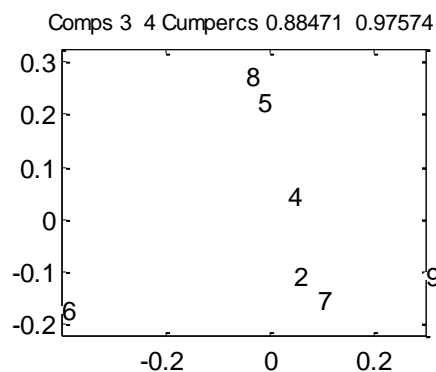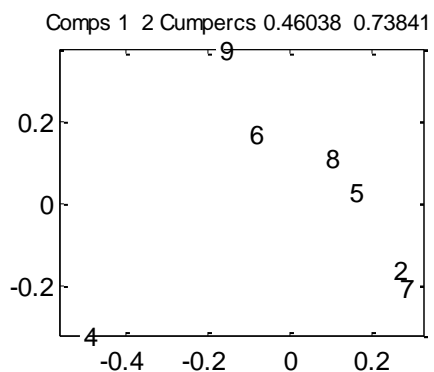
CLUSTERS:

cluster 1 =   5 8

  pairwise correls = 0.92494

cluster 2 =   2 7

  pairwise correls = 0.97555

==

PAIRS of possible interest:

Cols 1, 2= pair, Col 3= correlation

   2   **5**   **0.8632**

Summary of clusters

  5 8

  2 7

==

Comments: All three data sets ZA1, ZA2, ZA3 indicate as worth studying the clusters [5 8] and [2 7] and the non-cluster pair [2 5]. Beyond this, it is a matter of appreciation: the non-cluster pair [5 9] could be included, and possibly others.

==

**CLASS B, 1968-2010 (data set ZB1)**

Groupings (Clusters and supplementary pairs of possible interest)

X=ZB1'; scarce=[11]; ALLCLUSTERSFINAL(X,scarce);

Follow 4 confirmatory plots

Comps 1 2 Cumpercs 0.62947 0.79355
Comps 3 4 Cumpercs 0.86064 0.9118
Comps 5 6 Cumpercs 0.93902 0.96402
Comps 7 8 Cumpercs 0.97976 0.98995

==

CLUSTERS:

cluster 1 = 1 3 4 5 7 9 10

  pairwise correls = at least 0.89503

cluster 2 = 1 3 4 5 7 9

  pairwise correls = at least 0.91158

cluster 3 = 1 4 7

  pairwise correls = at least 0.93984

cluster 4 = 3 5 9

  pairwise correls = 0.95742

cluster 5 = 1 4

 pairwise correls = 0.97856

cluster 6 =   3 5

 pairwise correls = 0.98205

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

    2   6   0.8256

    2   3   0.8398

    6   9   0.8489

    2   7   0.8545

    3   6   0.8573

    2   4   0.8648

    1   2   0.8656

    5   6   0.8713

    6   7   0.8731

    1   6   0.9265

    4   6   0.9365

Summary of clusters

 3 5

 3 5 9

 1 4

 1 4 7

1 3 4 5 7 9

1 3 4 5 7 9 10

==

CLASS B, 1968-1989 (data set ZB2)

Groupings (Clusters and supplementary pairs of possible interest)

X=ZB2'; scarce= [1 2 4 6 8 9 11]; ALLCLUSTERSFINAL(X,scarce);

Follow 4 confirmatory plots

==
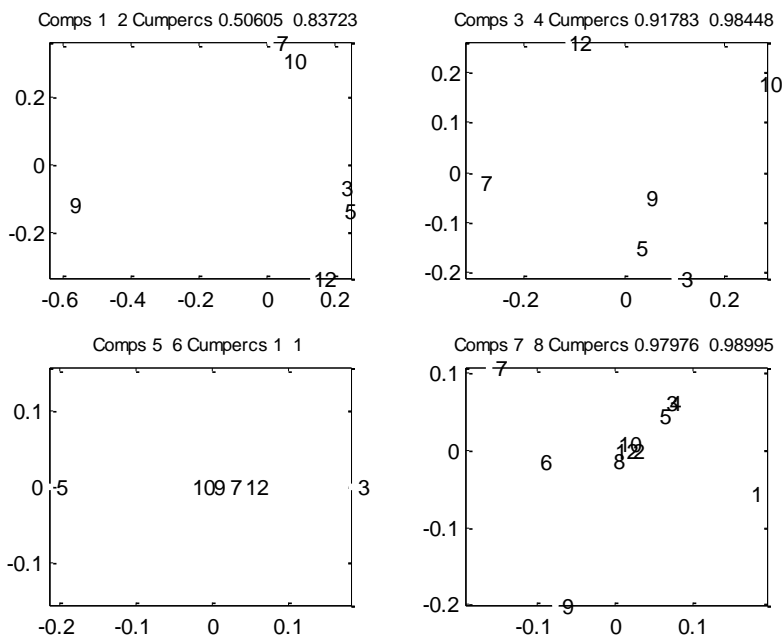
CLUSTERS:

cluster 1 =   3 5

  pairwise correls = 0.94056

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

   5   12   0.8272

Summary of clusters

  3 5

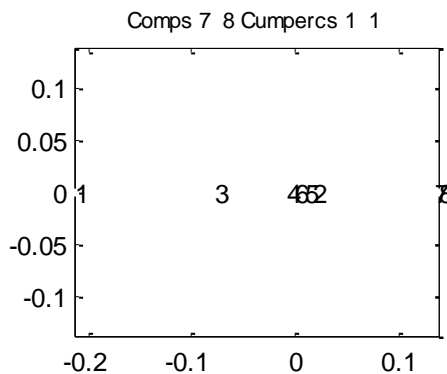===

CLASS B, 1990-2010 (data set ZB3)

Groupings (Clusters and supplementary pairs of possible interest)

X=ZB3'; scarce= [11 12]; ALLCLUSTERSFINAL(X,scarce);

Follow 4 confirmatory plots

===
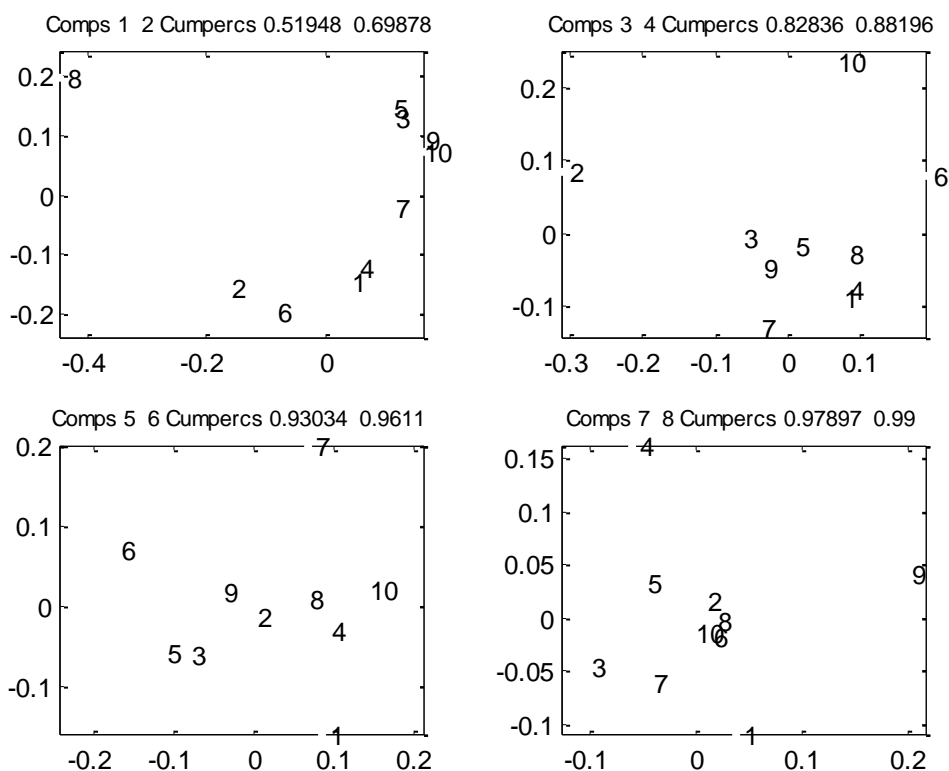
CLUSTERS:

cluster 1 = 1 3 4 5 6 7 9 10

  pairwise correls = at least 0.83942

cluster 2 = 1 3 4 5 7 9 10

  pairwise correls = at least 0.90408

cluster 3 = 3 5 7 9

  pairwise correls = at least 0.94365

cluster 4 = 1 4

  pairwise correls = at least 0.97856

cluster 5 = 3 5 9

  pairwise correls = 0.97058

 cluster 6 = 3 5

  pairwise correls = 0.98184

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

2	6	0.8256
2	3	0.8531
2	7	0.8547
2	4	0.8648
1	2	0.8656

Summary of clusters

 3 5

   3 5 9

   3 5 7 9

   1 4

   1 3 4 5 7 9 10

   1 3 4 5 6 7 9 10

==

Comments: Data set ZB2 has a relatively small weight; the main results will be determined by ZB1 and ZB3. Their analyses point to the cluster [1 3 4 5 7 9 10] as worth studying. All its pairs of agents have a high correlation (at least .8950 in ZB1, .9041 in ZB3). Agent 6 in ZB3 appears as responsible for lowering the pairwise correlation bound in cluster [1 3 4 5 6 7 9 10]. In ZB1 however, agent 6 enters in a few non-cluster pairs recommended. The pair [5 12] might be tentatively examined.

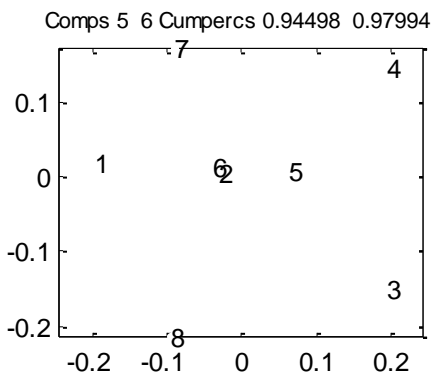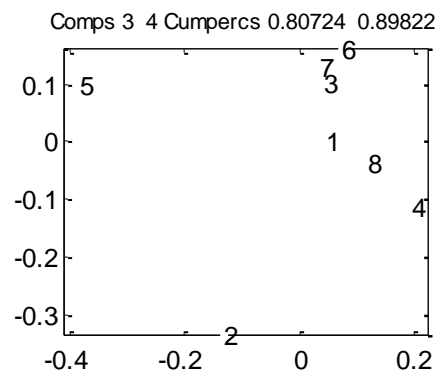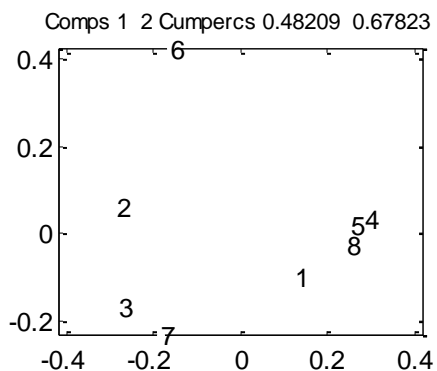==

CLASS C, 1968-2010 (data set ZC1)

Groupings (Clusters and supplementary pairs of possible interest)

X=ZC1';scarce=[ ]; ALLCLUSTERSFINAL(X,scarce);

Follow 4 confirmatory plots

==
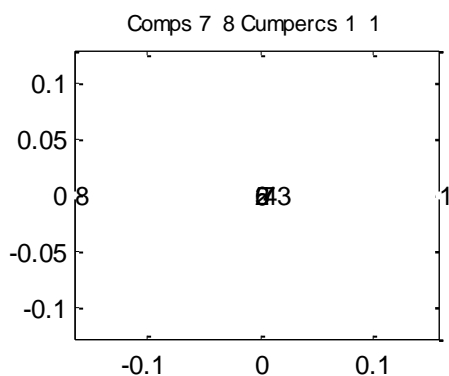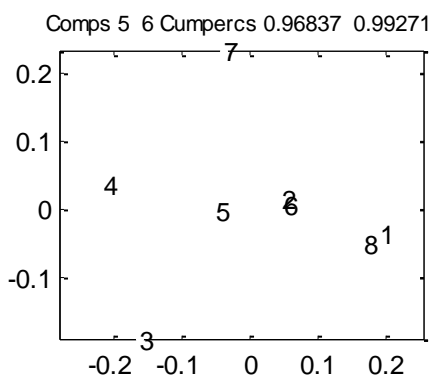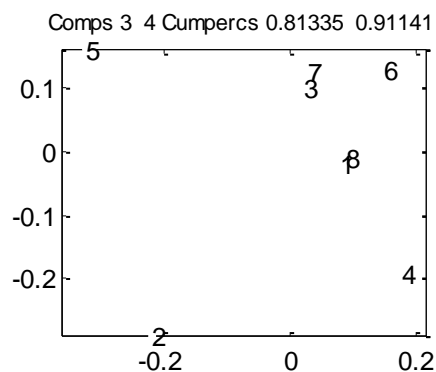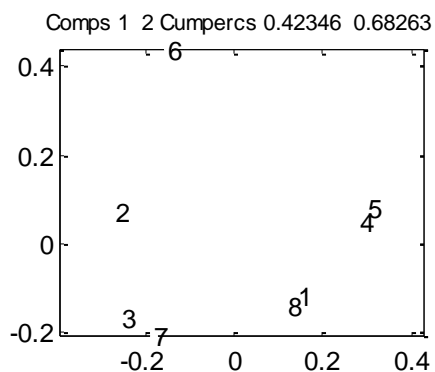
CLUSTERS:

cluster 1 = 3 7

  pairwise correls = 0.91891

cluster 2 = 1 8

  pairwise correls = 0.97753

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

   1   7   0.8366

   4   8   0.8385

1   4   0.8401

7   8   0.8568

Summary of clusters

  3 7

  1 8

===

CLASS C, 1968-1989 (data set ZC2)

Groupings (Clusters and supplementary pairs of possible interest)

X=ZC2';scarce= [ ]; ALLCLUSTERSFINAL(X, scarce);

Follow 4 confirmatory plots

==

CLUSTERS:

cluster 1 =   1 4 8

  pairwise correls = at least 0.83408

cluster 2 =   3 7

  pairwise correls = 0.88335

cluster 3 =   1 8

  pairwise correls = 0.90784

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

     1   7   0.8391

Summary of clusters

  3 7

  1 8

  1 4 8

==
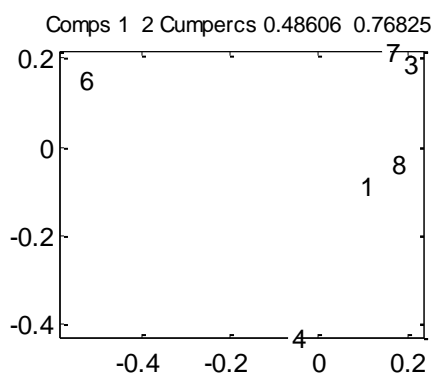
CLASS C, 1990-2010 (data set ZC3)

Groupings (Clusters and supplementary pairs of possible interest)

X=ZC3';scarce = [2 5]; ALLCLUSTERSFINAL(X, scarce);

Follow 4 confirmatory plots

===
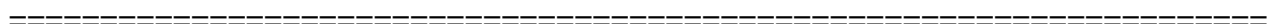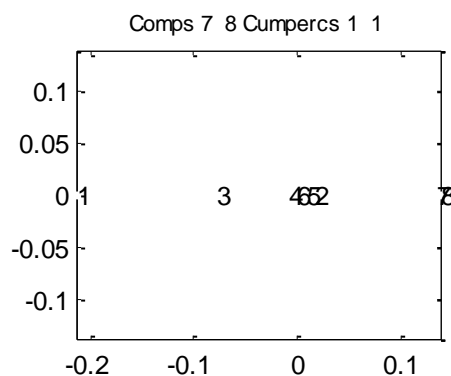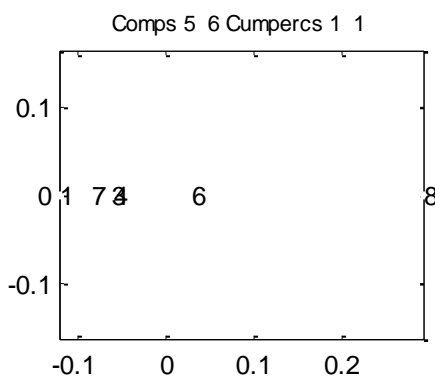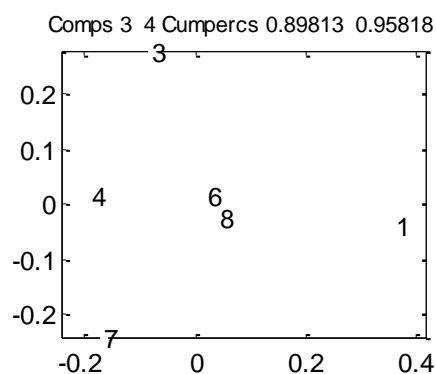
CLUSTERS:

cluster 1 =   3 7

  pairwise correls = 0.84477

cluster 2 =   1 8

  pairwise correls = 0.84539

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

   7   8   0.8258

3   8   0.8400

Summary of clusters

  3 7

  1 8

  ==

Comments: ZC1 and ZC2 cover most of the reports and will influence most the results. Are recommended for study the clusters [3   7] and [1   8]. Cluster [1   4   8] appears to be deteriorated by introduction of agent 4. Could consider non-cluster pairs formed by taking one agent from each of the two clusters, as well as non-cluster pairs involving agent 4 and one agent taken in one of the above clusters.

  ==

Discussion.

<u>**Part 1.**</u> The first paper of our recent series on iodinated CAs [1] dates back to 1990. Over these years the WHO classification and even its stances on their use have changed considerably. For example, the 5th Model List of Essential drugs, Section 14.2 [1], included amidotrizoate, whose withdrawal is now being considered in Germany (see Ref [8], in [2]), iohexol and iotroxate, the only complementary alternatives "in cases of rare diseases or in exceptional circumstances". Besides the ATC updates (Cf Appendix 1), other sources, e.g. Wikipedia, distinguish in class V08A (X rays and CT applications) water-soluble nephrotropic agents with high (sub-class A) and low osmolality (sub-class B) and hepatotropic agents (sub-class C) from water-insoluble products, here represented only by iophendylate (sub-class D) (January 12, 2011). The other classification criteria based on physico-chemical, structural and even "individual therapeutic toxicity" parameters, distinguish, especially in sub-classes B and C, between nonionic monomers with low viscosity and dimeric high-viscosity CAs (Cf: metrizamide-B, the first but unstable low osmolal ratio iodine/particle 3 nonionic monomer; see Almen (1995) [11]); ioxaglate-B, first low osmolal ratio 3 ionic dimer; iobitridol-B, first stable iso-osmolal ratio 3 nonionic monomer; ipodate-C, low

osmolal, ratio 3 ionic monomer; and iodixanol-B (first, 1980), ioxalan-B, as well iotrolan-B ratio 6 iso-osmolal, nonionic dimers with high viscosity, which have been of interest for a further evolution as dimers with smaller size *in vivo*, and lower viscosity (See Sovak (1996)[11]); etc). Already in 1994, Krause (see [11]) noted that dynamic osmolality, observed during dilution in plasma, may differ from static osmolality, possibly because of formation of "quasi-oligomers", while disaggregation occurs during dilution and at 37°C, and osmolality increases slightly). In 1991 Eloy, Corot & Belleville (see [11]) found that the new family of low osmolal, ionic and nonionic contrast molecules had reduced the incidence of minor reactions, but did not alter the frequency of severe accidents and even led to the emergence of new iatrogenic syndromes. In 2000 Dooley & Jarvis [11] considered iomeprol, of the same low osmolal nonionic monomeric sub-class B, to have a similar adverse event profile to other nonionic CAs. In 2008 Belhadjali et al reported DRESS (drug rush with eosinophilia and systemic symptoms) induced by the sodium meglumine ioxitalamate, also previously reported for iohexol, iobitridol and ioxaglate, with late adverse reactions delayed up to 7 days. In rats the high osmolal ratio ionic sub-class A ioxitalamate, but not ioxaglate, iohexol and iodixanol-B at same doses for IV use, may induce acute tubular injury and apoptosis through aggravation of renal hemodynamics, elevated plasma renin activity, and reactive oxygen species production. An Italian 2008 questionnaire study concluded that monomeric low osmolal iopromide, iomeprol and iobitridol are at higher risk of immediate nonrenal reactions, whereas the dimeric iso-osmolal nonionic agent iodixanol, same B sub-class, is at significantly higher risk for delayed 1 h to 1 week reactions (see Lapi et al, in [11]). In 2010, the study of the Deutsches Herzzentrum Muenchen compared iodixanol (320 mg iodine/ml) to iomeprol (350 mg/ml) and concluded that the first is associated with a significantly lower incidence of contrast-induced nephropathy (CIN) in patients with impaired renal function after coronary intervention [11], while contrast-induced acute kidney injury (CIAKI) was reviewed in 2008 (see Welsbord, in [11]). CIN had already been examined in 2006, and the iso-osmolal nonionic dimer iodixanol was seen to exhibit a less frequent association than the nonionic low osmolal ratio monomers iopamidol and iohexol and the low osmolal ratio ionic dimer ioxaglate, although randomized controlled studies were needed to confirm these differences (see Tepel et al, 2006, and Katzberg & Haller, 2006 in [11]). Indeed, Tepel, Aspelin et al, in the NEPHRIC trial (2006; in [11]), suggested that CIN arose less frequently with the iso-osmolar nonionic dimer iodixanol than with nonionic low osmolal monomers in patients with moderate diabetic nephropathy; however Thomsen, Morcos, Erley et al (2008), Solomon, Natarayan et al

(2007), and Barrett, Katzberg et al (2006) (see all in [11]) have not confirmed the NEPHRIC trial results. Controversy may exist about differences in nephrotoxicity between iso-osmolar and low-osmolar agents following intra-arterial administration (Thomsem, Morcos & Barrett, 2008, in [11]), and there is no clear advantage in using iodixanol for IV injection (see Thomsen, Morcos & Barrett (2008), again Thomsen, Morcos, Erley et al (2008), and Nguyen et al (2008), Barrett & Parfrey (2006), and even Carraro et al (1998) in [11]). The prospects presented by Katzberg & Haller are also particularly worrying, since they involve not only CA evolution and classification, but also the tremendously increased exposure to these highly used CAs, which cannot but result in an increased number of at risk patients. The authors reach the unavoidable conclusion that the prevalence of risk factors for CIN will continue to increase with exposure. Some of the problems of the common acute reactions to iodinated CAs and delayed reactions to Gd-chelate based (GBCA) media and the spreading epidemic of chronic nephrogenic systemic fibrosis (NSF)[5] are updated in [12].

Part 2. Whereas the associated physico-chemical parameters and those of "individual therapeutic toxicity", as per the "specific WHO-SOCDs and basic single SADRs clustered based classifications, at least for the 30 presently reported reference products are under study (see [1, 4-5], and the collateral contribution for the individual "biosimilar" products), the cost-effectiveness analysis of iodinated (Cf [13]) and NMR agents cannot yet be associated with any Defined Daily Doses established for substances classified in ATC group V08 (as Hanne Strøm, the new Director of the WHO Collaborating Centre for Drug Statistics Methodology pointed out in her EPLI/HAST letter of 14/02/2011). Nevertheless, it can be made, for an example, at least for those ATC-V08A and V08C classes, using their normalized price in Euros for the year 2010 based on the official cost per ml of the proprietary products available in Italy. Table 1 reports these averaged data. For the iodinated CM, taking for the coronary TA the minimum 300 mg iodine / ml of the reference choice iopamidol-B sub-class products mostly distributed at around 100 ml units, and for a maximum rate 2 g iodine / sec for their ev administration, the averaged index cost calculated is 0.28 € /ml/sec/kg body weight, and the same for the listed V08A-B products results 0.39 €/ml/sec/kg bw. While for the ATC V08C-A RMN contrast enhancement agents, the values of 12 physico-chemical and kinetics parameters can be found at p 753 in [5], and if one example of the administration cost of the 9 available C-A paramagnetic sub-class Gd-chelates, dimeglumine gadobenate (MultiHance R, 100 ml vials) molecular weigth 1058.1, containing 6.72% Gd^{3+}

(standard atomic weight 157.25 g / mol^{-1}), being the product according to the London Pharmaceutical Press' Martyndale Pharmacopoeia online edition (2010) administered ev at 0.1 ml / kg of the 0.5 mmol/ml marketed solution, the calculated cost is of 0.595 € for the standard dose, containing 7.86 mg Gd^{3+} / kg bw - that is for an average 70 kg adult human, 550.2 mg Gd^{3+}, contained in 7 ml of the administered product, being the cost of € 41.66 -, and, if these products potentially injected ev at equal ml/sec/kg bw, their averaged cost results € 8.51, that is 21.8 times that of the averaged iodinated –B cost of above.

Table 1. Physico-chemical parameters of ATC-V08A, and prices of V08A and V08C iodinated and RMN contrast agents available in Italy (data from the Compendio Farmaceutico Ospedaliero, Farmadati Italia, 69th Aggiornamento, and Informatore Farmaceutico, Elsevier Italia, 70th ed, 2010).

Group	Generic & Trade Name	Osmolality (mOsm/kg H$_2$0)		Nonionic Ionic	Monomeric Dimer	Ratio: Iodine/ Particle	Administration cost (€/ml/sec/kg bw)
		Low	Iso				
A-A	1-Amidotrizoate (Gastrographin os/rett R)					1,5	0.080
	2-Iodamide (Opacist R)					1,5	0.029
A-B	1-Iobitridol (Xenetix R)	695		nonionic	monomer	3.0	0.572
	2-Iodixanol (Visipaque R)		290	nonionic	dimer	6.0	0.461
	3-Iohexsol (Omnipaque R)	640		nonionic	monomer	3.0	0.441
	" (generic branded)	"		"	"	"	0.271
	4-Iomeprol (Iomeron R)	565		nonionic	monomer	3.0	0.566
	5-Iopamidol (Iopamiro R)	648		nonionic	monomer	3.0	0.372
	" (generic branded)	"		"	"	"	0.216
	7-Iopromide (Ultravist R)	615		nonionic	monomer	3.0	0.416
	9-Ioversol (Optiray R)	630		nonionic	monomer	3.0	0.340
	10-Ioxaglate (Hexabrix R)	590		ionic	dimer	3.0	0.247
							€
C-A	1-Dimeglumine Gadobenate (Multihance R; 0.5 mmol/ml; 5.95 €/ml): at 0.1 ml/kg,						0.595
	2-Gadobutrol (Gadovist R; 1 mmol/ml; 12.49 €/ml): at 0.1 ml/kg,						1.249
	3- Gadodiamide (Omniscan R; 0.5 mmol/ml; 4.99 €/ml): at 0.1 ml/kg						0.449
	4-Trisodium Gadofosveset (Vasovist R; 0.25 mmol/ml; 14.89 €/ml); at 0,02 ml/kg,						0.298
	5-Meglumine Gadopentetate (Magnevist R; 0.5 mmol/ml; 4.34 €/ml); at 0.1 ml/kg,						0.434
	6-Meglumine Gadoterate (Dotarem R; 0.5 mmol/ml; 5.36 €/ml); at 0.1ml/kg,						0.536
	7-Gadoteridol (Prohance R; 0.5 mmol/ml; 4.99 €/ml); at 0.1 ml/kg,						0.499
	8-Gadoversetamide (OptiMARK; 0.5 mmol/ml; 3.50 €/ml); at 0.1 ml/kg,						0.350
	9-Disodium Gadoxetate (Primovist R; 0.25 mmol/ml; 26.60 €/ml); at 0.025 ml/kg,						0.665
	10-Trisodium Mangafodipir (Teslascan; 5 mmoles/ml; 3.21 €/ml); at 0.1 ml/kg,						0.321
C-B	1-Ferumoxsil (Lumirem R; 0.175 mg/ml Fe); ml sosp os/ret/kg,						0.780
	2-Ferucarbotran (Endorem R; 11.2 mg/ml Fe; 0.075 ml/kg); ml ev						42.610

The rough selection presented above may seem to be justified by the large differences between these widely prescribed sub-classes existing at the national level, but there are quite good and

permanent reasons that should not be forgotten, including international evaluations that have also been illustrated and discussed on pages 498-503 of the 1st note [1] of this series. The price adjustments that have intervened may have reduced the largest differences in cost-effectiveness between subclasses –A and –B of iodinated products, and of course those between some V08A-A agents and the V08C-A sub-class products listed above. However, a further and wider epidemiological and **ethical-professional** evaluation is urgently needed, including information on reactions and adverse syndromes connected to the various groups (as well as the reasons warranting the more frequent prescription and use of each product, maybe including their "biosimilars" – see the collateral 5th note), their onset (which can undeniably arise even long after administration), severity and evolution (chronic, degenerative). All such data are of local, regional, national and global **direct and indirect econometric interest,** and relate to the exclusive role and responsibility of the WHO. In addition, comparison of the products of the various sub-classes of the 30 iodinated contrast agents subjected to the WHO Pharmacovigilance Programme to, for instance, those available in Italy in 1998, shows that of the 12 items of subgroup V08A-A, only 2-amidotrizoate, 5-iodamide and 7-iotalamate were available at the time, and were further whittled down to 2-amidotrizoate and 2-iodamide in 2010 (the latter was scheduled for gradual elimination beginning in 12/2006). The average cost of the remaining amidotrizoate products was from 9.55 to 10.33 times less than that of the averaged –B subclass estimated above, which of cource is a matter of a pharmacoeconomic general relevant topic, while underlining a strong pressure to public and private, direct and indirect, family and personal heavy balances (See, for a local national recent overview [15]). Moreover, and certainly not irrelevantly (thus deserving examination of the historical reasons that led to it) –B subclass products 11-ioxilan and 12-metrizamide were already unavailable in Italy in 1998, and –B products 6-iopentol and 8-iotrolan were no longer on the market in 2010. As regards the eight –C monitored products, only 6-iopanoate was available in 1998 (but no longer in 2010), and one –D subclass product, iophendylate, has never been sold in Italy.

Indeed, when beginning a new research avenue, the originator is not perhaps chosen to represent it at the national, regional and/or the international level. This maybe applies to the contributions to WHO-ITA/ITA-OMS by persons and institutions: all national Representatives no doubt remember that Italy had the qualifications (and the votes, including that of the same fabulous Dr WHW Inman, the founder of the most prestigious *UK monitored release* throughout the Sir Derrick

Dunlop' (1964) "yellow pad"!) to be selected as the international collaborative Headquarters, whereas the alternative, Uppsala, was chosen thanks to the financing offered by the Swedish Crown and government. This was never offered by Italy, and the work performed there never really received any support, being a kind of volunteer work structured by the Ministries of Health and of Teaching and Research. Subsequently, when the national voluntary programme was framed into a more formal, extended agreement, WHO-ITA/ITA-OMS—though of course envisaged by the World Health Assembly, it was ignored by the national authorities. The political/administrative representatives were clearly unprepared, inattentive and incoherent — either those at the regional hospital level and those at the national and local university level, who were appointed by rotation regardless of the ongoing programmes, both those under way and those being developed, following undeniably and horridly cynical scandals involving decadent central and peripheral bureaucrats, which were later the origin of striking economic privileges bestowed in the teeth of a vaunted permanent meritocratic democracy; in this kind of democracy, often sunk to the worst type of corrupt partisanship, conflicts of interest were ignored in favour of unjustified personal sympathies, which have already been discussed, and documented, also in this series ([1], pp 498-504; [2], pp 481-485; [4], pp 748-749; [5], pp 730-731, and [15], p 778). Therefore, undoubtedly and undeniably, to confine ourselves only to the reports on iodinated contrast agents sent from Italy, received as WHO Programme Reports, their total number over the first four decades has never been sufficient for any objective assessment of any autoclassification model despite our continuing efforts. See Appendix 6 which, as reported in the introduction, lists all the 4,442 Reports of the UPM 40 year collection of the 35 products, 3,955 for the 26 effective Iodinated ATC-V08A-A (as indicated in the Introduction above: 8 contrast agents: metrizoate, ioxitalamate, ioglicicate, iotalamate, amidotrizoate, and iodamide, including the 2 "biosimilars" ioxitalamate meglumine/ioxitalamate sodium, total n 382 SADRs), -B (11 agents: ioxaglicate, iotrolan, iopentol, ioversol, iohexsol, iobitridol, iodixanol, iopamidol, iopromide, and iometrol, including the "biosimilar" ioxaglate meglumine/ioxaglate sodium; total n 3,450 SADRs), and –C (7 agents: benzamate, glycamate, iodoxamate, iocetamate, adipiodone meglumine, iopanoate and iotroxate; total n 123 SADRs; no "biosimilar", and no -D subclass agents); 487 for the 9 V08C-A (gadoxetate, gadofosveset, gadodiamide, gadobutrol, gadoteridol, gadopentetate and gadobenate) & -B (ferumoxil and ferrixan) MRI contrast agents, sent by the WHO-ITA /ITA-OMS Italian Centre and then by the Health Ministry. The Centre, which operated by ministerial delegation, initially collected ADR data by its own voluntary initiative, but the   national Ministry

of Heath was subsequently formally charged with the task of obligatory monitoring drug reactions. It is therefore clear that also in this context our knowledge is still inadequate, raising a widely felt need by the experts involved not only of continuing the WHO Programme but also of further developing and financing it. This is our most cherished hope at the end of this new endeavour.

Part 3. Therefore, in our next, VIth & short contribution based on the data from the Uppsala PR22 2010 file, we will focus on the Reports of ATC-Iodinated -V08A and RMN -VO8C Contrast Agents sent from Italy, which we will subject to our new algorithm (Cf: [14], at work). Of course, Italy is becoming increasingly multiethnic too [16], and here, too, ever different mixes of the available reference agents and "biosimilar" generic products (the two major variables included) have been used in different time periods. This, we hope, will be another application of our method to highlight the trends emerging from our post-hoc epidemiological analytical and objective study, *which might then be iteratively adopted by other national Autorities participating in the WHO programme* and/or by the Organization itself (For recent reviews on "Dealing with Data", See [17]). Indeed, following basic Venulet's studies and the development of new algorhitms (some of which have been adopted) to ameliorate scientific acceptance and to provide for the broadest evaluation of adverse reactions ever since the inception of reporting activities to the Uppsala Centre (a topic that we shall not address here), all efforts have, to our knowledge, been directed to enhancing the collection process through ADR reports, providing to those sending the report, and not only to the contributing governmental and political Organizations, the results of the trends emerging from report analyses. It is a basic and fundamental requirement for the optimization of any drug monitoring project, including ours, that feedback activities follow these guidelines.

Part 4. In this new series we have recalled the unanimous decision made on the occasion of the 5th Meeting of National Representatives (Portonovo di Ancona, Italy, 1982; Cf Pharmacologyonline Newsletter 2:497-517(2010), p 506 [1]: *The number of reports will be corrected, for the Countries for which data are available, with the product use indices*), the results achieved and the critical recommendations developed. We have addressed these topics both in the paper itself (pp 503-504) and in a previous overview (Pharmacologyonline Newsletter 2:475-596(2010)[2]. These notions have been confirmed in the current press as well as in one of the most authoritative scientific journals (Cf [3]), and again on pp 747-748 of Pharmacologyonline, the

online journal of the Italian National Pharmacological Society 2:727-753(2010), pp 753-754 [4], and finally in its subsequent issue [5] 3:728-781(2010). Here, we repeat our support for them.

After our latest contribution had been accepted for publication we were disappointed (issue 1101, 27/1/2011 of the European Medicines Agency Monthly Reports HMA - Cf: EMA/CHMP/PhVWP/51040/2011) by the new EU pharmacovigilance legislation, published on 31 December 2010 (35 pp: Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, Text with EEA relevance). This new piece of legislation (subparagraphs 5, 17-21, and 35) extends reporting obligations to cover overdosing, the misuse and abuse of medical products, and medication errors; however, reports are now to be renamed as "SADRs" even when they regard events associated with occupational exposure of healthcare professionals and patients, etc. No mention is made of the simultaneous transfer of information not only to the "Eudravigilance database", but also to the International WHO Data Bank "VigiBase" –UMC Thesaurus itself, despite previous official agreements, etc. A global discussion to modify the Directive (which is to be "adopted by the Member states by 21 July 2012 at the latest" and will "enter into force on the 20th day following its publication") is therefore urgently needed. Although the Directive does present many interesting elements, it is unfortunate that many of the issues extensively addressed, conceived and first implemented by the WHO-ITA, such as the requirement to *correct the number of reports with the product use indices* mentioned above, have been omitted (see arts 106a, sub 1, and 107b, sub (c)). Another point, officially ignored at the time (Title IX, Chapter 1, General provisions, art. 102, sub (c)), must be also stressed here: although *The Member states shall take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports*, the WHO-ITA/ITA-OMS ever since its foundation and the ministerial delegation for many years of voluntary work (Cf: [2], p. 481, reference [56], and pp. 484-485), effectively organized, implemented and processed any alert suspicion and event reported in Italy by consulting in each case all appropriate experts (pathologists, law enforcement professionals, etc, besides of course a pharmacologist and a toxicologist), inviting the manufacturer representatives as well as the reporting healthcare professional (after obtaining the valid consent of the first patient involved), *finally draw up, as soon possible the first basic document, to be later integrated as needed by a prompt scientific and technical analytical pharmacotoxicological evaluation. Only in this way, by*

way of constant published procedures, and following an internationally acclarated quality control scheme, was WHO-ITA/ITA-OMS able to assess any report sent to the cofounded Uppsala Collaborating Centre (See [7]). Then, for the international pharmacovigilance Programme, we at the WHO-ITA/ITA-OMS rigorously did what was needed, in line with the suggestions of the great JW Black (See [8]). Indeed, an SADR on which an agreement can be reached based only on paperwork is a wrong conclusion of such an evaluation (see at least [9], too); in fact, there is an absolute, essential interest in performing evaluation procedures that substantiate any event as a real Adverse Reaction prior to its inclusion in any (international) Thesaurus: this cannot be done through a chain of events based on paperwork, which is then communicated and translated into a Report.

In this context, and because statistical analysis cannot be applied to any single event or suspected adverse reaction, appropriate statistical tools must continue to be improved to analyse the large number of reports using the best experimental-clinical epidemiological models, to enable the progress of a pharmaco-toxicological exploratory science. At the same time, our efforts must be directed to a greater development of the regulatory field, which is not clearly defined even in the new EU Directory mentioned above. Our new present series of contributions aims at identifying the most urgent outstanding priorities (see [10]).

Part 5. Without any doubt our programme can provide a contribution to the 5-year European PREDECT programme, whose goal is to overcome the "forced transverse simplification" gap between preclinical and clinical experimentation, and to be germane to those started by NIH Director Francis Collins (Cf [17]) as a complementary, parallel if not alternative option, to the increasingly egregious problems that remain unsolved, especially the "band wagon" of clinical pharmacotoxicological trials (Cf [2, 18]). Innovation needs novel thinking, and unexamined bodies of evidence; computational approaches and algorithms could speed and simplify the quest for new therapies (Cf [19, 20]).

Finally, a further consideration is in order with regard to the continuing lack of an impact factor of the single Journal of the Italian Pharmacological Society, Pharmacologyonline & Newsletter, which has published our series of contributions [1, 2, 4, 5, 14, 22, 23]. Financing of these contributions, which we have often referred to (Cf [2, 4, 24, 25]), has been blocked since 13 January 1989 (Cf [4], p. 749) by inconsiderate measures of the Medical School and due to

unexplained and unnotified provisions by local and ministerial authorities. The Editor of the new Journal, associated to the board of Referees that also includes international reviewers (Cf PharmacologyOnline.it; Editorial Board; ISSN-1827-8620), is still awaiting the attribution of the Impact Factor. Notably, Science's Editor in Chief, as previously mentioned in [26], has clearly commented on this fact ("Articles should be judged on their own merit, not the impact factor of the journal in which they are published"; Cf [27]). In addition, more recently Science, in discussing the assessment of individual research performances (Cf [28]), wrote: "Bibliometrics could potentially improve objective evaluation of individual researchers if qualitative measurements are included". Here we are again then, proposing our work to our competent Readers, confident in their attention and approval. We hope that this series of contributions may represent a single, national effort of the Polytechnic University of Marche and United General Hospitals along the lines of demythification and demystification, as again stated on 19th May 2008 at Accademia Marchigiana Scienze, Lettere ed Arti, Ancona [29].

Appendix Nr 1.

 Iodinated generic, reference contrast agents, their ATC V08A -A, -B, -C, -D ordered sub-classes and synonyms, in alphabetic and numeric partial and total order, and if the products are used as "biosimilar"/equivalents, with their acids, salts and associations indicated. Their monography numbers are according to The Merck Index, twelph edition 1996 (1997), Merck & Co, Inc, Publishers, or with their Chemical Abstracts Service CAS Registry Numbers reported in brackets.

Sub-class A (9 Agents): 1.1. Acetrizoate (Acetrizoic acid; Sodium acetrizoate/Meglumine acetrizoate)(79), 2.1. Amidotrizoate (Amidotrizoic acid, Diatrizoate; Meglumine amidotrizoate/Sodium amidotrizoate; Meglumine amidotrizoate/Sodium amidotrizoate/Calcium amidotrizoate; Meglumine amidotrizoate/Sodium amidotrizoate/Iodine; Sodium amidotrizoate/Lysine amidotrizoate; Sodium amidotrizoate/Meglumine)(3040), 3.1. Diodone (Iodopyracet; Diodone/Dextran; Diodone/Dextran pv)(5061), 4.1 Iocarmate (Iocarmic acid)(5029), 5.1 Iodamide (Iodamide/Iodamide meglumine; Iodine/Iodamide meglumine; Meglumine/Iodamide sodium)(5031), 6.1. Ioglicicate (Ioglicic acid)(CAS 49755-67-1), 7.1. Iotalamate (Iotalamic acid, Iothalamate; Iotalamate meglumine/Iotalamate sodium)(5080), 8.1 Ioxitalamate (Ioxitalamic acid; Ioxitalamate meglumine/Ioxitalamate monoethanolamine; Meglumine/Sodium chloride/Ioxitalamic acid)(CAS 28179-44-4), 9.1. Metrizoate (Metrizoic acid; Meglumine metrizoate/Calcium metrizoate; Meglumine metrizoate/Calcium metrizoate/Magnesium metrizoate; Sodium calcium edetate(Sodium metrizoate/Meglumine metrizoate/Calcium metrizoate/Magnesium metrizoate; Sodium metrizoate/Calcium metrizoate/Magnesium metrizoate; Sodium metrizoate/Meglumine metrizoate/Calcium metrizoate; Sodium metrizoate/Meglumine metrizoate/Calcium metrizoate/Magnesium metrizoate)(6241);

Sub-class B (12 Agents): 10.1 Iobitridol (CAS 136949-58-1), 11.2. Iodixanol (5044), 12.3. Iohexol (5068), 13.4. Iomeprol (CAS 78649-41-9), 14.5. Iopamidol (Iopamidol; Iodine/Iopamidol) (5071), 15.6. Iopentol (5073), 16.7. Iopromide (5076), 17.8. Iotrolan (5082), 18.9. Ioversol (5083), 19.10. Ioxaglate (Ioxaglicate; Ioxaglic acid; Ioxaglate meglumine/Ioxaglate sodium)(5084), 20.11. Ioxalan (Ioxilan)(5085), 21.12. Metrizamide (6240);

Sub-class C (8 Agents): 22.1. Adipiodone (Iodipamide)(5943), 23.2. Iobenzamate (Iobenzamic acid)(5028), 24.3. Iocetamate (Iocetamic acid)(5030), 25.4. Iodoxamate (Iodoxamic acid)(CAS 51764-33-1), 26.5. Ioglycamate (Ioglycamic acid)(5067), 27.6. Iopanoate (Iopanoic acid)(5072), 28.7. Iopodate (Iopodic acid, ipodate)(CAS 1221-56-3; 1151-11-7), 29.8. Iotroxate (Iotroxic acid)(CAS 51022-74-3);

Sub-class D (1 Agent): 30.1. Iofendylate (Iophendylate)(5074).

In the study, the associations of Adipiodone meglumine and Iodamide Sodium (total 5 Reports collected in the years 1968-2010), of Iopydol and Iopydone (27 Reports, as above), of Iotalamate sodium and Ioxitalamate meglumine (289 Reports, as above), of Meglumine acetrizoate and Polyvidone (1 Report, as above), and of Meglumine amidotrizoate and Adipiodone meglumine (252 Reports, as above) had been excluded. The differences between the Reported SADRs Numbers of the Tables & Legends indicated in the previous Pharmacologyonline Newsletter 2:497-517 (2010) and 2:727-753(2019) notes are only due to the exclusion in the collection of the 1968-2010 40 years (and/or in the two 1968-1989 and 1990-2010 ventennials) of the possible combinations of the products with iodine added to the media.

Appendix Nr 2.

Aggregated WHO System Organ Class Disorders (SOCDs), numbers and codes: 1- 0100, Skin and   appendages; 2 - 0200, Musculo-skeletal; 3 – 0300, Collagen; 4 – 0410, Central & peripheral nervous system; 5 – 0420, Autonomic nervous system; 6 – 0431, Vision; 7 – 0432, Hearing and vestibular; 8 – 0433, Special senses; 9 – 0500, Psychiatric; 10 – 0600, Gastrointestinal; 11 – 0700, Liver and biliary; 12 – 0800, Metabolic and nutritional; 13 – 0900, Endocrine; 14 – 1010, Cardiovascular, general; 15 – 1020, Myo-, endo- pericardial & valve; 16 – 1030, Heart rate and rhytm; 17 – 1040, Vascular (extracardiac); 18 – 1100, Respiratory; 19 – 1210, Red blood cell; 20 – 1220, White cell and RES; 21 – 1230, Platelet, bleeding & clotting; 22 – 1300, Urinary; 23 – 1410, Reproductive, male; 24 – 1420, Reproductive, female; 25 – 1500, Foetal; 26 – 1600, Neonatal and infancy; 27 – 1700, Neoplasms; 28 - 1810, Body as a whole, general; 29 – 1820, Application site; 30 – 1830, Resistance mechanism.

New SOCDs 31 **-** 2000, Secondary term, and 32 – Poison specific terms had not been used.

Appendix Nr 3

V08A- A, -B, -C and -D iodinated diagnostic agents. SADRs data of PR22-2010 file of the n 30 generic/reference products monitored in the total first 40 years 1968-2010 collection.

For each product the total number of SADRs (in bold, in brackets) are listed, then the frequencies in rising order as aggregated in the WHO-standardized maximum 30 SOCDs, numbered in increasing order, their codes and total numbers per class (in bold, in brackets). The total number of the SADRs reported in the first 40 years is 155,164. For reason of space, same list for the two ventennium collection periods (1st: 1968-1989; 2nd: 1990-2010) not presented, but available at request.

Sub-class A (n 9 Agents): n 1, Acetrizoate (33): 100 (n 6): (Pruritus (0024): 1; Rash (0027): 1; Rash maculo-papular (0030): 1; Sweating increased (0043): 1; Urticaria (0044): 2); **200 (n 1)**: (Arthralgia (0063): 1); **410 (n 2)**: (Convulsions (0093): 1; Spasm generalized (0149): 1); **431 (n 2)**: (Conjunctivitis (0238): 1; Mydriasis (0219): 1); **600 (n 8)**: (Abdominal pain (0268): 2; Diarrhoea (0205): 1; Duodenal ulcer (0274): 1; Haematemesis (0297): 1; Nausea (0308): 1; Peptic ulcer (0315): 1; Vomiting (0228): 1); **1010 (n 3)**: (Circulatory failure (0499): 1; Hypotension (0212): 2); **1030 (n 1)**: (Cardiac arrest (0437): 1); **1040 (n 1)**: (Flushing (0207): 1); **1100 (n 2)**: (Dyspnoea (0514): 1; Respiratory depression (0144): 1); **1300 (n 2)**: (Face oedema (0602): 1; Micturition disorder (0605): 1); **1810 (n 5)**: (Death (0722): 1; Pain (0730): 1; Pallor (0220): 1; Syncope (0223): 1; Therapeutic response decreased (0878): 1); **n 2, Amidotrizoate (44,648)**: **100 (n 15,915)**: (Pruritus genital (0026): 1; Acne (0001): 1; Melanosis (0019): 1; Skin reaction localised (1650): 1; Otitis externa (0059): 1; Erythema nodosum (0015): 1; Piloerection (1071): 1; Livedo reticularis (1410): 1; Pruritus ani (0025): 1; Hair texture abnormal (0855): 1; Rash psoriaform (0031): 1; Chloasma (0006): 1; Skin atrophy (0034): 1; Alopecia (0002): 2; Eczema (0012): 2; Stevens Johnson syndrome (0042): 2; Skin ulceration (0041): 2; Skin nodule (0061): 2; Rash pustular (0032): 3; Fixed eruption (1249): 3; Skin exfoliation (1199): 3; Rash purpuric (0462): 4; Nail disorder (0020): 4; Skin necrosis (0060): 4; Epidermal necrolysis (0013): 4; Erythema multiforme (0014): 5; Skin disorder (0037): 10; Dermatitis exfoliative (0008): 11; Rash follicular (0029): 17; Skin cold clammy (0932): 18; Urticaria acute (0045): 20; Skin discolouration (0036): 26; Dermatitis (0007): 26; Bullous eruption (0871): 40; Angioedema (0003): 231; Sweating increased (0043): 267; Rash maculo-papular (0030): 273; Rash erythematous (0028): 607; Rash (0027): 1,565; Pruritus (0024): 2,865; Urticaria (0044): 9,886); **200 (n 76)**: (Muscle atrophy (0072): 1; Avascular necrosis bone (2222): 1; Fracture pathological (0069): 1; Skeletal pain (1347): 1; Myositis (0748): 1; Arthritis (0064): 2; Arthrosis (0066): 2; Fracture (2190): 2; Arthropathy (0065): 2; Rhabdomyolysis (1210): 3; Myopathy (0074): 4; Muscle weakness (1128): 6; Synovitis (0864): 8; Myalgia (0073): 13; Arthralgia (0063): 29); **300 (n 2)**: (LE rash (0080): 2); **410 (n 2,570)**: (Hyporeflexia (0850): 1; Meningism (0120): 1; Arachnoiditis (1031): 1; Meningitis (0955): 1; Cerebellar syndrome (0089): 1; Migraine (0121): 1; CSF abnormal (0098): 1; Myasthenia gravis-like syndrome (1063): 1; Hypertension intracranial (0115): 1; Myelitis (0123): 1; Torticollis (0077): 1; Neuritis (0125): 1; Choreoathetosis (0090): 1; Neuritis sensory (0129): 1; Abscences (1208): 1; Neuropathy peripheral (1313): 1; Dyskinesia tardive (1065): 1; Ptosis (0142): 1; Blindness cortical (1890): 1; Tongue paralysis (0153): 1; Hypokinesia (0118): 2; Hyperkinesia (0114): 2; Cerebral disorder (1960): 2; Monoplegia (0122): 2; Extrapyramidal disorder (0106): 2; Ataxia (0088): 3; Hyperaesthesia (0113): 3; Dyskinesia (0102): 3; Convulsions aggravated (0094): 3; Nystagmus (0131): 3; Anaesthesia mouth (1473):

4; Neurologic disorder NOS (2133): 4; Gait abnormal (0108): 4; Cramps legs (0939): 5; Convulsions local (0096): 5; Neuralgia (0124): 5; EEG abnormal (0104): 5; Visual field defect (0159): 6; Paraplegia (0140): 6; Sensory disturbance (0148): 6; Quadriplegia (0143): 6; Spasm generalized (0149): 7; Paresis (0141): 7; Hypotonia (0119): 8; Dysaesthesia (1491): 8; Hemiparesis (0111): 9; Oculogyric crisis (0132): 9; Neuropathy (0130): 9; Tetany (0152): 9; Encephalopathy (0105): 12; Dystonia (0068): 12; Oedema cerebral (0891): 13; Paralysis (0138): 15; Aphasia (0087): 16; Faecal incontinence (0107): 16; Hemiplegia (0112): 30; Speech disorder (0150): 45; Muscle contractions involuntary (0155): 48; Hypertonia (0116): 48; Vertigo (0158): 57; Hypoaesthesia (0117): 66; Convulsions grand mal (0095): 71; Stupor (0151): 94; Dysphonia (0103): 119; Coma (0091): 161; Headache (0109): 239; Paraesthesia (0137): 306; Convulsions (0093): 331; Tremor (0154): 336; Dizziness (0101): 368); **431 (n 602)**: (Corneal ulceration (0240): 1; Photophobia (0250): 1; Blindness temporary (1280): 1; Myopia (0248): 1; Miosis (0217): 1; Retinal disorder (0251): 2; Scleritis (0255): 3; Blepharitis (1007): 4; Papilloedema (0249): 6; Mydriasis (0219): 7; Eye abnormality (0243): 8; Diplopia (0241): 8; Lacrimal gland disorder (0216): 16; Eye pain (0244): 19; Blindness (0232): 25; Vision abnormal (0257): 65; Lacrimation abnormal (1049): 86; Conjunctivitis (0238): 348); **432 (n 37)**: (Vestibular disorder (1126): 1; Ear disorder NOS (1.255): 3; Deafness (0258): 6; Ear ache (0260): 13; Tinnitus (0264): 14); **433 (n 23)**: (Parosmia (0265): 1; Taste perversion (0267): 22); **500 (n 484)**: (Impotence (0182): 1; Sleep disorder (0195): 1; Insomnia (0183): 1; Suicide attempt (2362): 1; Personality disorder (0192): 1; Apathy (0167): 1; Psychosis (0193): 1; Drug abuse (0175): 2; Depression (0172): 2; Delirium (0099): 2; Catatonic reaction (0169): 2; Neurosis (0189): 2; Anorexia (0165): 3; Emotional lability (0177): 4; Hysteria (0180): 5; Hallucination (0179): 6; Depersonalization (0171): 9; Amnesia (0164): 14; Aggressive reaction (0162): 14; Thinking abnormal (0199): 15; Nervousness (0188): 52; Somnolence (0197): 63; Anxiety (0166): 66; Agitation (0163): 94; Confusion (0092): 122); **600 (n 5,044)**: (Increased stool urgency (1843): 1; Tongue discolouration (0329): 1; Malabsorption (1025): 1; Enteritis (0282): 1; Melaena (0306): 1; Eructation (0283): 1; Mucositis NOS (1351): 1; Constipation (0204): 1; Oesophageal ulceration haemorrhagic (0312): 1; Gastroenteritis (0293): 1; Oesophagitis (0309): 1; Enterocolitis (1324): 1; Teeth-grinding (1086): 1; Intestinal obstruction (0302): 2; Colitis (0271): 2; Enanthema (0281): 2; Intestinal perforation (0754): 2; Tooth disorder (0336): 2; Haemorrhage rectum (1014): 2; Oesophagospasm (0310): 2; Gastritis (0291): 2; Saliva altered (0758): 2; Ileus (0214): 2; Flatulence (0285): 2; Gastro-intestinal disorder NOS (1262): 3; Salivary gland pain (0326): 3; GI haemorrhage (0294): 4; Amylase increased (1101): 5; Stomatitis ulcerative (0328): 5; Hiccup (0300): 5; Haematemesis (0297): 6; Tenesmus (0231): 6; Salivary gland enlargement (0325): 7; Tongue disorder (0330): 7; Cheilitis (0270): 7; Stomatitis (0327): 8; Peritonitis (0320): 10; Glossitis (0295): 11; Dyspepsia (0279): 17; Pancreatitis (0314): 17; Saliva increased (0222): 19; Mouth dry (0218): 39; Tongue oedema (0331): 89; Diarrhoea (0205): 132; Dysphagia (0280): 164; Abdominal pain (0268): 269; Nausea (0308): 1,638; Vomiting (0228): 2,538); **700 (n 28)**: (Cholecystitis (0342): 1; Hepatorenal syndrome (1103): 1; Coma hepatic (0344): 1; Bilirubinaemia (0339): 1; Biliary pain (0338): 1; Gallbladder disorder (0345): 2; Hepatitis (0350): 2; Hepatic failure (0933): 2; Cholangitis (1576): 3; Hepatic function abnormal (0348): 5; Jaundice (0356): 9); **800 (n 61)**: (Hypocalcaemia (0387): 1; Electrolyte abnormality (0374): 1; Glucose tolerance abnormal (0376): 1; Alkalosis respiratory (0366): 1; Hypoglycaemic reaction (0390): 1; Weight decrease (0407): 1; Hyponatraemia (0392): 1; Anion gap abnormal (1589): 1; LDH increased (0394): 1; Acidosis respiratory (1465): 2; Dehydration (0370): 2; Xerophthalmia (0943): 2; Weight increase (0408): 2; Oedema pharynx (1395): 2; Hyperglycaemia (0382): 3; Thirst

(0405): 4; Hypoglycaemia (0389): 4; Hypokalaemia (0391): 4; Creatine phosphokinase increased (0791): 7; Hyperkalaemia (0383): 9; Acidosis (0363): 11); **900 (n 17)**: (Diabetes insipidus (0411): 1; Endocrine disorder NOS (1252): 2; Hypothyroidism (0417): 2; Hyperthyroidism aggravated (0416): 2; Hyperthyroidism (0415): 10); **1010 (n 2,472)**: (Cor pulmonale (1295): 1; Aneurysm (0915): 1; Cardiac failure left (0497): 1; Cardiomegaly (1320): 1; Hypotension postural (0213): 4; Cardiac failure right (0498): 6; Pulse weak (1401): 7; ECG abnormal specific (0503): 7; Heart disorder (0504): 12; ECG abnormal (0502): 21; Cardiac failure (0496): 25; Hypertension (0210): 217; Cyanosis (0501): 298; Circulatory failure (0499): 422; Hypotension (0212): 1,449); **1020 (n 128)**: (Aortic stenosis (0424): 1; Angina pectoris aggravated (0423): 1; Pericardial effusion (0910): 1; Thrombosis coronary (0488): 1; Pericarditis (0430): 2; Coronary artery disorder (0426): 8; Myocardial ischaemia (0429): 8; Angina pectoris (0422): 44; Myocardial infarction (0428): 62); **1030 (n 1,658)**: (Fibrillation cardiac (0442): 1; Arrhythmia atrial (0434): 4; Tachycardia supraventricular (0229): 4; Bundle branch block (0436): 5; Adams Stokes syndrome (0432): 6; AV block complete (1378): 6; Arrhythmia ventricular (0435): 7; Heart block (0441): 8; Extrasystoles (0438): 10; AV block (0431): 16; Fibrillation atrial (0439): 19; Tachycardia ventricular (0230): 48; Arrhythmia (0433): 67; Palpitation (0221): 89; Fibrillation ventricular (0440): 123; Bradycardia (0208): 223; Tachycardia (0224): 433; Cardiac arrest (0437): 589); **1040 (n 1,431)**: (Peripheral gangrene (0453): 1; Transient ischaemic attack (1694): 1; Capillary fragility increased (0443): 1; Ocular haemorrhage (1004): 1; Pulmonary infarction (0458): 1; Thrombophlebitis leg superficial (0473): 1; Subarachnoid haemorrhage (0463): 1; Arteriosclerosis (0771): 2; Thrombophlebitis leg deep (0472): 2; Haemorrhage intracranial (1068): 2; Phlebitis superficial (0457): 3; Thrombophlebitis arm superficial (0468): 3; Thrombophlebitis superficial (0479): 3; Cerebral infarction (1986): 3; Thrombophlebitis deep (0470): 4; Gangrene (0911): 4; Vascular disorder (0491): 5; Cerebral ischaemia (1987): 6; Cerebral haemorrhage (0444): 7; Vasculitis (0085): 9; Vasospasm (0226): 14; Peripheral ischaemia (0454): 24; Thrombophlebitis (0466): 34; Cerebrovascular disorder (0445): 49; Phlebitis (0455): 100; Flushing (0207): 390; Vasodilatation (0225): 760); **1100 (n 6,368)**: (Larynx pain (1648): 1; Pleural fibrosis (0525): 1; Yawning (0201): 1; Pulmonary disorders (2032): 1; Sputum disorder (1976): 1; Respiratory tract haemorrhage (0538): 1; Cheyne-Stokes respiration (1016): 1; Sinusitis (0540): 1; Pleural effusion (0524): 2; Hemothorax (1153): 2; Hypopnoea (1712): 2; Pulmonary haemorrhage (0534): 2; Upper respiratory tract infection (0543): 2; Pneumonitis (1141): 3; Atelectasis (1197): 3; Pneumothorax (0531): 3; Airways obstruction (1749): 4; Respiratory distress syndrome (2252): 4; Bronchitis (0805): 4; Bradypnoea (0510): 4; Haemoptysis (0516): 4; Epistaxis (0515): 4; Sputum increased (0541): 5; Asthma (1367): 6; Aspiration (1030): 7; Pneumonia (0528): 11; Throat tightness (1489): 16; Hypoxia (0519): 20; Laryngitis (0521): 20; Respiratory insufficiency (0537): 21; Hypoventilation (0518): 22; Stridor (0542): 33; Hyperventilation (0517): 58; Respiratory depression (0144): 61; Respiratory disorder (0536): 94; Pulmonary oedema (0535): 139; Pharyngitis (0523): 301; Apnoea (0507): 303; Laryngismus (0520): 320; Larynx oedema (0522): 325; Coughing (0513): 411; Bronchospasm (0511): 768; Rhinitis (0539): 1,159; Dyspnoea (0514): 2,217); **1210 (n 15)**: (Anaemia hypochromic (0553): 1; Erythrocytes agglutination (0559): 1; Anaemia haemolytic (0548): 3; Haemolysis (0560): 4; Anaemia (0544): 6); **1220 (n 31)**: Monocytosis (0793): 1; Lymphopenia (0845): 1; Agranulocytosis (0570): 1; Granulocytopenia (0572): 1; Lymphangitis (0580): 1; Leucopenia (0908): 5; Leukocytosis (0576): 7; Lymphadenopathy (0577): 7; Eosinophilia (0571): 7; **1230 (n 110)**: (Haemorrhage retroperitoneal (1214): 1; Haematoma (1353): 1; Thrombosis retinal artery (0794): 1; Haemoperitoneum (0588): 1; Embolism limb (0449): 1; Purpura allergic (0460): 1; Platelets abnormal

(0589): 2; Embolism arterial (0447): 2; Gingival bleeding (0930): 2; Coagulation factor decreased (1122): 2; Disseminated intravascular coagulation (1175): 3; Purpura thrombocytopenic (1348): 3; Embolism - blood clot (0446): 3; Thrombosis arterial (0482): 3; Prothrombin decreased (0590): 3; Thrombosis carotid (0485): 3; Thrombosis mesenteric vessel (0489): 3; Thrombosis cerebral (0486): 4; Thrombosis (0481): 6; Embolism pulmonary (0451): 9; Haemorrhage NOS (0452): 9; Thrombocytopenia (0594): 11; Coagulation disorder (0586): 11; Purpura (0459): 25; **1300 (n 1,650)**:   (Nephrosclerosis (1177): 1; Bacteriuria (1956): 1; Micturition urgency (1497): 1; Cystitis haemorrhagic (0600): 1; Urethral disorder (0626): 1; Renal calculus (0617): 1; Urinary retention (0157): 2; Renal failure chronic aggravated (2330): 2; Polyuria (0613): 2; Renal tubular disorder (0623): 2; Urine abnormal (0629): 2; Nephritis (0607): 2; Nephrosis (0610): 3; Renal pain (0621): 3; Creatinine clearance decreased (0598): 3; Urinary tract infection (0628): 3; Micturition frequency (0606): 3; Dysuria (0601): 3; Nephropathy toxic (0609): 9; Haematuria (0604): 10; Renal failure chronic (2329): 10; Anuria (0596): 16; Oliguria (0612): 21; Urinary incontinence (0156): 23; Renal tubular necrosis (0624): 23; Renal function abnormal (0619): 31; Azotaemia (2328): 89; Renal failure acute (0618): 98; Face oedema (0602): 1,284); **1410 (n 2)**:   (Priapism (0890): 1; Prostatic disorder (0632): 1); **1420 (n 11)**:   (Breast pain (1839): 1; Mastitis (0655): 1; Breast enlargement (0639): 1; Menopausal symptoms (1496): 1; Breast discomfort (2129): 1; Perineal pain female (0631): 1; Breast necrosis (1738): 1; Vaginitis (0669): 4; **1500 (n 4)**: (Chondrodystrophy (1120): 1; Artery malformation (0676): 3); **1700 (n 7)**:   (Lymphoma-like disorder (0582): 1; Thrombocythaemia (0593): 1; Skin hypertrophy (0038): 1; Neoplasm NOS (1259): 2; Carcinoma (0746): 2); **1810 (n 5,373)**:   (Leg pain (1439): 1; Halitosis (0990): 1; Tolerance decreased (0761): 1; ESR increased (0723): 1; Anaesthetic complication (2160): 1; Scar (1522): 1; Posture abnormal (2012): 1; Medicine ineffective (1948): 2; Oedema dependent (0399):2; Therapeutic response increased (0874):2; Hypovolaemia (0929):3; Multiple organ failure (1819): 3; Hyperpyrexia malignant (0893): 4; Hyperpyrexia (0894): 4; Chest pain substernal (0720): 6; Allergy (1058): 9; Influenza-like symptoms (1222): 9; Abdomen enlarged (0711): 9; Hypothermia (0727): 10; Anaphylactic reaction (2237): 11; Chest pain precordial (0719): 12; Oedema mouth (1485): 17; Oedema generalised (0400): 17; Therapeutic response decreased (0878): 20; Condition aggravated (0965): 28; Back pain (0717): 37; Fatigue (0724): 44; Oedema peripheral (0401): 60; Asthenia (0716): 61; Temperature changed sensation (1705): 75; Malaise (0728): 100; Pallor (0220): 114; Pain (0730): 182; Oedema (0398): 271; Syncope (0223): 278; Oedema periorbital (1009): 290; Fever (0725): 305; Anaphylactic shock (0713): 349; Allergic reaction (0712): 440; Death (0722): 500; Rigors (0731): 568; Anaphylactoid reaction (0714): 727; Chest pain (0718): 797); **1820 (n 496)**: (Infusion site reaction (2137): 1; Implantation complication (1035): 1; Injection site infection (1910): 2; Anaesthesia local (0062): 2; Application site oedema (0048): 2; Cellulitis (1372): 4; Application site reaction (0047): 7; Injection site mass (0055): 7; Injection site necrosis (0056): 19; Injection site inflammation (0054): 45; Injection site pain (0057): 158; Injection site reaction (0058): 248; **1830 (n 33)**: (Immune system disorder (1903): 1; Abscess (0887): 1; Moniliasis (0741): 1; Herpes zoster (0862): 2; Infection (0736): 10; Sepsis (0744): 18; **n 3, Diodone (9): 100 (n 3)**: (Pruritus (0024): 1; Urticaria (0044): 2); **600 (n 1)**: (Nausea (0308): 1); **1100 (n 1)**: (Bronchospasm (0511): 1); **1810 (n 4)**: (Anaphylactoid reaction (0714): 1; Death (0722): 1; Anaphylactic shock (0713): 2); **n 4, Iocarmate (101): 100 (n 5)**: (Urticaria (0044): 1; Rash (0027): 2; Pruritus (0024): 2; **200 (n 6)**: (Muscle atrophy (0072): 1; Myalgia (0073): 5; **410 (n 54)**:   (Arachnoiditis (1031): 1; Tremor (0154): 1; Coma (0091): 1; Myelitis (0123): 1; Extrapyramidal disorder (0106): 1; Neuropathy (0130): 1; Hypertension intracranial (0115): 1; Oedema cerebral

(0891): 1; Torticollis (0077): 1; Paralysis (0138): 1; Hyperaesthesia (0113): 1; Paralysis flaccid (0139): 1; Cramps legs (0939): 1; Paresis (0141): 1; Hypoaesthesia (0117): 1; Spasm generalized (0149): 1; Meningitis (0955): 2; Hypertonia (0116): 2; Muscle contractions involuntary (0155): 2; Meningism (0120): 3; Paraesthesia (0137): 3; Convulsions grand mal (0095): 4; Headache (0109): 9; Convulsions (0093): 13; **500 (n 3)**: (Confusion (0092): 1; Amnesia (0164): 1; Somnolence (0197): 1); **600 (n 7)**: (Diarrhoea (0205): 1; Nausea (0308): 2; Vomiting (0228): 4); **1010 (n 3)**: (Circulatory failure (0499): 1; Cyanosis (0501): 2); **1040 (n 1)**: (Cerebrovascular disorder (0445): 1); **1220 (n 1)**: (Leukocytosis (0576): 1); **1300 (n 2)**: (Renal function abnormal (0619): 1; Urinary retention (0157): 1); **1810 (n 19)**: (Fatigue (0724): 1; Anaphylactic shock (0713): 1; Syncope (0223): 1; Temperature changed sensation (1705): 1; Pain (0730): 2; Rigors (0731): 2; Death (0722): 2; Fever (0725): 3; Back pain (0717): 3; Anaphylactoid reaction (0714): 3); **n 5, Iodamide (936): 100 (n 266)**: (Dermatitis exfoliative (0008): 1; Skin nodule (0061): 1; Skin cold clammy (0932): 1; Bullous eruption (0871): 1; Skin discolouration (0036): 1; Angioedema (0003): 6; Rash maculo-papular (0030): 9; Sweating increased (0043): 13; Rash erythematous (0028): 30; Pruritus (0024): 35; Rash (0027): 51; Urticaria (0044): 117); **200 (n 1)**: (Muscle weakness (1128): 1); **410 (n 59)**: (Hemiplegia (0112): 1; Hyperkinesia (0114): 1; Convulsions grand mal (0095): 1; Hypotonia (0119): 1; Dysphonia (0103): 1; Oculogyric crisis (0132): 1; Tetany (0152): 1; Oedema cerebral (0891): 1; Hemiparesis (0111): 1; Spasm generalized (0149): 1; Dementia (0100): 1; Stupor (0151): 1; Hypertonia (0116): 2; Dizziness (0101): 2; Vertigo (0158): 2; Paraesthesia (0137): 4; Hypoaesthesia (0117): 4; Coma (0091): 5; Headache (0109): 6; Convulsions (0093): 6; Tremor (0154): 16); **431 (n 9)**: (Blindness (0232): 1; Mydriasis (0219): 1; Vision abnormal (0257): 2; Conjunctivitis (0238): 5); **433 (n 2)**: (Taste perversion (0267): 2); **500 (n 9)**: (Anxiety (0166): 1; Confusion (0092): 1; Amnesia (0164): 1; Depersonalization (0171): 1; Agitation (0163): 1; Somnolence (0197): 4); **600 (n 142)**: (Dysphagia (0280): 1; Constipation (0204): 1; Tongue oedema (0331): 1; Diarrhoea (0205): 3; Abdominal pain (0268): 11; Nausea (0308): 59; Vomiting (0228): 66); **1010** (n 79): (Cardiac failure left (0497): 1; Cardiac failure (0496): 2; Hypertension (0210): 4; Cyanosis (0501): 14; Circulatory failure (0499): 16; Hypotension (0212): 42); **1020 (n 2)**: (Myocardial infarction (0428): 2); **1030 (n 32)**: (Extrasystoles (0438): 1; Fibrillation ventricular (0440): 1; Bradycardia (0208): 4; Tachycardia (0224): 11; Cardiac arrest (0437): 15); **1040 (n 11)**: (Thrombophlebitis arm (0467): 1; Thrombophlebitis (0466): 2; Vasodilatation (0225): 2; Flushing (0207): 6); **1100 (n 167)**: (Hypoxia (0519): 1; Respiratory insufficiency (0537): 1; Stridor (0542): 1; Asthma (1367): 2; Pharyngitis (0523): 2; Apnoea (0507): 4; Respiratory depression (0144): 4; Laryngismus (0520): 4; Pulmonary oedema (0535): 4; Respiratory disorder (0536): 5; Larynx oedema (0522): 7; Coughing (0513): 15; Bronchospasm (0511): 19; Rhinitis (0539): 23; Dyspnoea (0514): 75); **1300 (n 11)**: (Face oedema (0602): 11); **1810 (n 142)**: (Hypovolaemia (0929): 1; Hyperpyrexia (0894): 1; Pain (0730): 1; Oedema mouth (1485): 1; Anaphylactic reaction (2237): 1; Oedema peripheral (0401): 1; Allergy (1058): 2; Pallor (0220): 2; Malaise (0728): 3; Oedema periorbital (1009): 3; Oedema (0398): 3; Chest pain (0718): 6; Temperature changed sensation (1705): 7; Fever (0725): 9; Syncope (0223): 9; Rigors (0731): 9; Allergic reaction (0712): 12; Death (0722): 14; Anaphylactic shock (0713): 28; Anaphylactoid reaction (0714): 29); **1820 (n 4)**: (Injection site pain (0057): 1; Injection site reaction (0058): 3); **n 6, Ioglicicate (165): 100 (n 17)**: (Rash maculo-papular (0030): 1; Pruritus ani (0025): 1; Urticaria acute (0045): 1; Rash pustular (0032): 1; Skin disorder (0037): 1; Rash erythematous (0028): 2; Pruritus (0024): 3; Urticaria (0044): 3; Rash (0027): 4); **200 (n 1)**: (Arthralgia (0063): 1); **410 (n 7)**: (Faecal incontinence (0107): 1; Coma (0091): 1; Vertigo (0158): 1; Convulsions (0093): 1; Headache (0109): 3); **431 (n 6)**:

(Eye pain (0244): 1; Vision abnormal (0257): 1; Conjunctivitis (0238): 4; **500 (n 1)**: (Confusion (0092): 1); **600 (n 31)**: (Dyspepsia (0279): 1; Diarrhoea (0205): 1; Abdominal pain (0268): 4; Vomiting (0228): 12; Nausea (0308): 13); **1010 (n 20)**: (Cardiac failure (0496): 1; Hypertension (0210): 1; Heart disorder (0504): 1; Cyanosis (0501): 3; Circulatory failure (0499): 6; Hypotension (0212): 8); **1020 (n 1)**: (Angina pectoris (0422): 1); **1030 (n 8)**: (Bradycardia (0208): 1; Palpitation (0221): 1; Tachycardia (0224): 2; Cardiac arrest (0437): 4); **1040 (n 8)**: (Phlebitis (0455): 1; Flushing (0207): 3; Vascular disorder (0491): 4); **1100 (n 23)**: (Laryngismus (0520): 1; Coughing (0513): 1; Bronchospasm (0511): 2; Larynx oedema (0522): 2; Pulmonary oedema (0535): 2; Respiratory depression (0144): 2; Dyspnoea (0514): 13); **1300 (n 5)**: (Renal failure acute (0618): 1; Urinary incontinence (0156): 1; Face oedema (0602): 3); **1810 (n 36)**: (Allergy (1058): 1; Syncope (0223): 1; Rigors (0731): 3; Death (0722): 5; Allergic reaction (0712): 6; Anaphylactoid reaction (0714): 9; Anaphylactic shock (0713): 11); **1820 (n 1)**: (Injection site inflammation (0054): 1); **n 7, Iotalamate (14,395): 100 (n 5,763)**: (Pruritus genital (0026): 1; Photosensitivity reaction (0022): 1; Pemphigoid reaction (0938): 1; Skin dry (1123): 1; Skin necrosis (0060): 2; Dermatitis exfoliative (0008): 2; Skin cold clammy (0932): 3; Bullous eruption (0871): 4; Dermatitis (0007): 7; Skin disorder (0037): 7; Skin discolouration (0036): 10; Erythema induratum (0912): 10; Rash maculo-papular (0030): 20; Angioedema (0003): 49; Sweating increased (0043): 76; Rash erythematous (0028): 86; Rash (0027): 665; Pruritus (0024): 961; Urticaria (0044): 3,857); **200 (n 55)**: (Ligament disorder (2086): 1; Arthrosis (0066): 1; Myopathy (0074): 1; Arthropathy (0065): 2; Fracture (2190): 2; Arthritis (0064): 3; Synovitis (0864): 3; Muscle weakness (1128): 5; Rhabdomyolysis (1210): 6; Myalgia (0073): 12; Arthralgia (0063): 19); **410 (n 833)**: (Hyperkinesia (0114): 1; Tongue paralysis (0153): 1; Upper motor neurone lesion (0892): 1; Convulsions aggravated (0094): 1; Meningism (0120): 1; Cramps legs (0939): 1; Myelitis (0123): 1; Gait abnormal (0108): 1; Neuralgia (0124): 1; Brain stem disorder (0810): 1; Neuritis (0125): 1; CSF abnormal (0098): 1; Nystagmus (0131): 1; Convulsions local (0096): 1; Oculogyric crisis (0132): 1; Hemianopia (0110): 1; Ptosis (0142): 1; Vocal cord paralysis (0942): 2; Paraplegia (0140): 2; Paresis (0141): 2; Faecal incontinence (0107): 2; Hyperreflexia (0774): 2; Paralysis flaccid (0139): 2; Quadriplegia (0143): 2; Oedema cerebral (0891): 2; Tetany (0152): 2; Dystonia (0068): 2; Coordination abnormal (0097): 2; Hypotonia (0119): 3; EEG abnormal (0104): 3; Neuropathy (0130): 3; Hemiparesis (0111): 3; Ataxia (0088): 3; Visual field defect (0159): 3; Dysaesthesia (1491): 3; Encephalopathy (0105): 5; Dyskinesia (0102): 5; Paralysis (0138): 7; Vertigo (0158): 8; Hypertonia (0116): 9; Aphasia (0087): 11; Muscle contractions involuntary (0155): 14; Speech disorder (0150): 16; Hemiplegia (0112): 17; Hypoaesthesia (0117): 21; Stupor (0151): 26; Convulsions grand mal (0095): 30; Dysphonia (0103): 30; Coma (0091): 42; Headache (0109): 62; Dizziness (0101): 98; Convulsions (0093): 102; Paraesthesia (0137): 129; Tremor (0154): 141); **431 (n 227)**: (Blepharitis (1007): 1; Papilloedema (0249): 1; Glaucoma (0227): 1; Conjunctival discolouration (1303): 1; Eye abnormality (0243): 1; Keratoconjunctivitis (0247): 1; Keratitis (0246): 1; Diplopia (0241): 2; Lacrimal gland disorder (0216): 6; Eye pain (0244): 7; Blindness (0232): 11; Vision abnormal (0257): 17; Lacrimation abnormal (1049): 32; Conjunctivitis (0238): 145); **432 (n 11)**: (Hearing decreased (1368): 1; Ear ache (0260): 1; Ear disorder NOS (1255): 4; Tinnitus (0264): 5; **433 (n 4)**: (Taste perversion (0267): 4; **500 (n 170)**: (Dreaming abnormal (1243): 1; Hysteria (0180): 1; Anorexia (0165): 1; Personality disorder (0192): 1; Mental deficiency (0187): 1; Psychosis (0193): 4; Depersonalization (0171): 4; Thinking abnormal (0199): 5; Hallucination (0179): 7; Aggressive reaction (0162): 8; Nervousness (0188): 9; Amnesia (0164): 11; Anxiety (0166): 22; Agitation (0163): 23; Somnolence (0197): 27; Confusion (0092): 45; **600 (n 1,199):** (Haematemesis (0297): 1; Melaena (0306):

1; Gastritis (0291): 1; GI haemorrhage (0294): 1; Constipation (0204): 1; Dyspepsia (0279): 1; Cheilitis (0270): 2; Salivary gland enlargement (0325): 2; Tongue disorder (0330): 2; Stomatitis (0327): 4; Amylase increased (1101): 6; Saliva increased (0222): 6; Pancreatitis (0314): 6; Mouth dry (0218): 7; Diarrhoea (0205): 10; Tongue oedema (0331): 31; Dysphagia (0280): 56; Abdominal pain (0268): 60; Nausea (0308): 346; Vomiting (0228): 655); **700 (n 11)**: (Bilirubinaemia (0339): 1; SGPT increased (0360): 1; SGOT increased (0359): 2; Jaundice (0356): 3; Hepatic function abnormal (0348): 4); **800 (n 14)**: (Hypervolaemia (1178): 1; Hyperglycaemia (0382): 1; Lipase increased (1621): 1; Thirst (0405): 1; Oedema pharynx (1395): 1; Acidosis (0363): 2; Hypokalaemia (0391): 2; Enzyme abnormality (0993): 2; Creatine phosphokinase increased (0791): 3); **900 (n 1)**: (Sialoadenitis (0986): 1; **1010 (n 565)**: (Cardiomegaly (1320): 1; ECG abnormal specific (0503): 1; Hypotension postural (0213): 2; Cardiac failure (0496): 2; Cardiac failure right (0498): 2; ECG abnormal (0502): 3; Pulse weak (1401): 3; Heart disorder (0504): 5; Hypertension (0210): 66; Circulatory failure (0499): 66; Cyanosis (0501): 83; Hypotension (0212): 331); **1020 (n 23)**: (Coronary artery disorder (0426): 1; Myocarditis (1352): 1; Myocardial ischaemia (0429): 3; Angina pectoris (0422): 6; Myocardial infarction (0428): 12); **1030 (n 328)**: (Arrhythmia atrial (0434): 1; Tachycardia supraventricular (0229): 1; Arrhythmia ventricular (0435): 2; AV block (0431): 2; Extrasystoles (0438): 3; Fibrillation atrial (0439): 3; Tachycardia ventricular (0230): 7; Palpitation (0221): 10; Arrhythmia (0433): 12; Fibrillation ventricular (0440): 16; Bradycardia (0208): 47; Cardiac arrest (0437): 111; Tachycardia (0224): 113); **1040 (n 431)**: (Vein pain (0494): 1; Cerebral haemorrhage (0444): 1; Thrombophlebitis superficial (0479): 1; Thrombophlebitis arm superficial (0468): 1; Phlebitis superficial (0457): 1; Thrombophlebitis leg deep (0472): 1; Vasculitis (0085): 2; Gangrene (0911): 2; Thrombophlebitis deep (0470): 2; Thrombophlebitis arm (0467): 3; Vascular disorder (0491): 3; Cerebral infarction (1986): 5; Vasospasm (0226): 7; Peripheral ischaemia (0454): 10; Cerebral ischaemia (1987): 11; Thrombophlebitis (0466): 14; Cerebrovascular disorder (0445): 31; Flushing (0207): 56; Phlebitis (0455): 68; Vasodilatation (0225): 211); **1100 (n 2,411)**: (Yawning (0201): 1; Haemoptysis (0516): 1; Bradypnoea (0510): 1; Pneumothorax (0531): 1; Aspiration (1030): 1; Respiratory insufficiency (0537): 2; Asthma (1367): 2; Sputum increased (0541): 2; Hypoventilation (0518): 3; Sinusitis (0540): 3; Pneumonia (0528): 4; Hypoxia (0519): 8; Respiratory depression (0144): 13; Throat tightness (1489): 14; Hyperventilation (0517): 15; Stridor (0542): 16; Laryngitis (0521): 16; Pulmonary oedema (0535): 29; Respiratory disorder (0536): 35; Apnoea (0507): 82; Laryngismus (0520): 128; Larynx oedema (0522): 133; Coughing (0513): 178; Pharyngitis (0523): 205; Bronchospasm (0511): 246; Rhinitis (0539): 575; Dyspnoea (0514): 697); **1210 (n 2)**: (Haemolysis (0560): 2); **1220 (n 11)**: (Eosinophilia (0571): 2; Leucopenia (0908): 4; Leukocytosis (0576): 5; **1230 (n 45)**: (Haematoma (1353): 1; Fibrinogen plasma decreased (0877): 1; Purpura thrombocytopenic (1348): 1; Prothrombin decreased (0590): 1; Thrombosis carotid (0485): 2; Embolism cerebral (0448): 2; Thrombosis (0481): 2; Haemorrhage NOS (0452): 4; Thrombocytopenia (0594): 5; Embolism pulmonary (0451): 6; Purpura (0459): 8; Coagulation disorder (0586): 12; **1300 (n 460)**: (Oliguria (0612): 1; Renal cortical necrosis (0808): 1; Nephropathy toxic (0609): 1; Urinary tract infection (0628): 1; Hydronephrosis (0779): 1; Urinary retention (0157): 1; Haematuria (0604): 2; Renal tubular necrosis (0624): 2; Anuria (0596): 5; Azotaemia (2328): 9; Urinary incontinence (0156): 12; Renal function abnormal (0619): 12; Renal failure acute (0618): 16; Face oedema (0602): 396); **1420 (n 1)**: (Salpingitis (0963): 1); **1810 (n 1,578)**: (Granulomatous lesion (0876): 1; Abdomen enlarged (0711): 1; ESR increased (0723): 1; Therapeutic response decreased (0878): 1; Chest pain substernal (0720): 1; Choking (1460): 1; Oedema dependent (0399): 1; Influenza-like symptoms (1222): 1;

Anaphylactic reaction (2237): 3; Hypothermia (0727): 4; Asthenia (0716): 7; Condition aggravated (0965): 11; Oedema generalised (0400): 14; Temperature changed sensation (1705): 17; Oedema peripheral (0401): 22; Malaise (0728): 23; Back pain (0717): 23; Oedema mouth (1485): 24; Fatigue (0724): 27; Pallor (0220): 29; Anaphylactic shock (0713): 62; Oedema (0398): 68; Fever (0725): 70; Pain (0730): 71; Oedema periorbital (1009): 73; Syncope (0223): 82; Death (0722): 115; Allergic reaction (0712): 173; Anaphylactoid reaction (0714): 175; Rigors (0731): 206; Chest pain (0718): 271); **1820 (n 239)**: (Injection site mass (0055): 1; Injection site infection (1910): 3; Application site reaction (0047): 4; Injection site necrosis (0056): 4; Injection site inflammation (0054): 19; Injection site pain (0057): 94; Injection site reaction (0058): 114); **1830 (n 13)**: (Otitis media (0750): 1; Abscess (0887): 1; Infection (0736): 3; Sepsis (0744): 8); **n 8, Ioxitalamate (2,223): 100 (n 763)**: (Urticaria acute (0045): 1; Rash purpuric (0462): 1; Skin exfoliation (1199): 1; Rash vesicular (1443): 1; Heat rash (1469): 1; Skin cold clammy (0932): 1; Bullous eruption (0871): 2; Fixed eruption (1249): 2; Skin necrosis (0060): 3; Erythema multiforme (0014): 5; Skin discolouration (0036): 10; Eczema (0012): 11; Sweating increased (0043): 23; Angioedema (0003): 34; Rash maculo-papular (0030): 52; Rash erythematous (0028): 106; Pruritus (0024): 119; Rash (0027): 153; Urticaria (0044): 237); **200 (n 6)**: (Muscle weakness (1128): 1; Arthralgia (0063): 1; Myopathy (0074): 1; Avascular necrosis bone (2222): 1; Myalgia (0073): 2); **410 (n 118)**: (Meningism (0120): 1; Myasthenia gravis-like syndrome (1063): 1; Convulsions grand mal (0095): 1; Neuralgia (0124): 1; Hemiparesis (0111): 1; Neurologic disorder NOS (2133): 1; Hyperaesthesia (0113): 1; Oedema cerebral (0891): 1; Hypertonia (0116): 1; Paralysis (0138): 1; Visual field defect (0159): 1; Paraplegia (0140): 1; Hemiplegia (0112): 1; Speech disorder (0150): 1; Hypotonia (0119): 1; Tetany (0152): 1; Hypertension intracranial (0115): 1; Vertigo (0158): 1; Dysphonia (0103): 1; Tongue paralysis (0153): 2; Muscle contractions involuntary (0155): 4; Spasm generalized (0149): 5; Hypoaesthesia (0117): 7; Coma (0091): 7; Dizziness (0101): 10; Paraesthesia (0137): 12; Headache (0109): 14; Convulsions (0093): 14; Tremor (0154): 24); **431 (n 13)**: (Eye pain (0244): 1; Photopsia (1172): 1; Vision abnormal (0257): 2; Lacrimal gland disorder (0216): 4; Conjunctivitis (0238): 5); **432 (n 3)**: (Hearing decreased (1368): 1; Deafness (0258): 1; Tinnitus (0264): 1); **433 (n 1)**: (Taste perversion (0267): 1); **500 (n 27)**: (Breath holding (0752): 1; Apathy (0167): 1; Amnesia (0164): 2; Confusion (0092): 2; Nervousness (0188): 3; Somnolence (0197): 8; Anxiety (0166): 10); **600 (n 334)**: (Haematemesis (0297): 1; Flatulence (0285): 1; Enterocolitis (1324): 1; Stomatitis (0327): 1; Diarrhoea bloody (1382): 1; Tongue oedema (0331): 2; Dysphagia (0280): 2; Saliva increased (0222): 2; Mouth dry (0218): 6; Diarrhoea (0205): 7; Abdominal pain (0268): 12; Vomiting (0228): 111; Nausea (0308): 187); **700 (n 4)**: (SGPT increased (0360): 1; Hepatocellular damage (0353): 1; SGOT increased (0359): 2); **800 (n 4)**: (LDH increased (0394): 1; Creatine phosphokinase increased (0791): 1; Hyponatraemia (0392): 2); **1010 (n 129)**: (Hypotension postural (0213): 1; Heart disorder (0504): 2; Cardiac failure (0496): 2; Hypertension (0210): 16; Cyanosis (0501): 16; Circulatory failure (0499): 27; Hypotension (0212): 65); **1020 (n 2)**: (Angina pectoris (0422): 2); **1030 (n 61)**: (Tachycardia supraventricular (0229): 1; Fibrillation ventricular (0440): 1; Fibrillation cardiac (0442): 3; Arrhythmia (0433): 3; Palpitation (0221): 6; Bradycardia (0208): 7; Cardiac arrest (0437): 14; Tachycardia (0224): 26); **1040 (n 40)**: (Thrombophlebitis (0466): 1; Peripheral ischaemia (0454): 1; Cerebral ischaemia (1987): 1; Vasculitis (0085): 1; Vascular disorder (0491): 2; Thrombophlebitis superficial (0479): 3; Vasodilatation (0225): 4; Flushing (0207): 27); **1100 (n 263)**: (Hemothorax (1153): 1; Bronchospasm paradoxical (1490): 1; Hyperventilation (0517): 1; Laryngitis (0521): 1; Aspiration (1030): 2; Hypoxia (0519): 2; Throat tightness (1489): 3; Laryngismus (0520): 4; Pulmonary oedema (0535): 4; Apnoea

(0507): 4; Respiratory insufficiency (0537): 4; Pharyngitis (0523): 5; Larynx oedema (0522): 6; Respiratory disorder (0536): 8; Respiratory depression (0144): 11; Rhinitis (0539): 17; Bronchospasm (0511): 25; Coughing (0513): 37; Dyspnoea (0514): 127); **1210 (n 2)**: (Anaemia haemolytic, angiopathic (1740): 1; Haemolysis (0560): 1); **1230 (n 8)**: (Fibrinolysis increased (0756): 1; Haemorrhage NOS (0452): 1; Disseminated intravascular coagulation (1175): 1; Purpura (0459): 1; Bleeding time increased (0584): 1; Purpura thrombocytopenic (1348): 1; Embolism cerebral (0448): 1; Thrombocytopenia (0594): 1); **1300 (n 41)**: (Anuria (0596): 1; Renal function abnormal (0619): 2; Azotaemia (2328): 4; Renal failure acute (0618): 13; Face oedema (0602): 21); **1500 (n 1)**: (Abortion (0634): 1); **1810 (n 387)**: (Drug level increased (1281): 1; Oedema generalised (0400): 1; Unexpected therapeutic effect (0735): 1; Pain (0730): 2; Oedema mouth (1485): 2; Asthenia (0716): 4; Back pain (0717): 5; Allergy (1058): 6; Fatigue (0724): 7; Oedema periorbital (1009): 9; Oedema (0398): 10; Pallor (0220): 11; Death (0722): 12; Anaphylactic reaction (2237): 13; Malaise (0728): 16; Fever (0725): 18; Chest pain (0718): 19; Syncope (0223): 22; Temperature changed sensation (1705): 33; Allergic reaction (0712): 38; Rigors (0731): 47; Anaphylactoid reaction (0714): 48; Anaphylactic shock (0713): 62); **1820 (n 15)**: (Injection site mass (0055): 1; Injection site inflammation (0054): 1; Application site oedema (0048): 2; Injection site pain (0057): 2; Injection site reaction (0058): 3; Injection site necrosis (0056): 6); **1830 (n 1)**: (Sepsis (0744): 1); **n 9, Metrizoate (1,068): 100 (n 314)**: (Erythema multiforme (0014): 1; Epidermal necrolysis (0013): 1; Bullous eruption (0871): 1; Dermatitis exfoliative (0008): 1; Rash psoriaform (0031): 1; Urticaria acute (0045): 3; Skin necrosis (0060): 3; Sweating increased (0043): 7; Angioedema (0003): 15; Pruritus (0024): 22; Skin discolouration (0036): 23; Rash erythematous (0028): 24; Rash (0027): 43; Urticaria (0044): 169); **200 (n 4)**: (Arthralgia (0063): 1; Arthritis (0064): 3); **410 (n 43)**: (Muscle contractions involuntary (0155): 1; Visual field defect (0159): 1; Neuropathy (0130): 1; Convulsions grand mal (0095): 1; Nystagmus (0131): 1; Faecal incontinence (0107): 1; Paralysis (0138): 1; EEG abnormal (0104): 1; Paresis (0141): 1; Convulsions (0093): 1; Tremor (0154): 2; Hemiparesis (0111): 3; Dizziness (0101): 5; Headache (0109): 6; Paraesthesia (0137): 7; Coma (0091): 10); **431 (n 19)**: (Blindness (0232): 2; Vision abnormal (0257): 7; Conjunctivitis (0238): 10); **432 (n 3)**: (Tinnitus (0264): 3); **500 (n 19)**: (Psychosis (0193): 1; Personality disorder (0192): 1; Hallucination (0179): 1; Amnesia (0164): 2; Confusion (0092): 4; Anxiety (0166): 10); **600 (n 108)**: (Dysphagia (0280): 1; Saliva increased (0222): 1; Dyspepsia (0279): 1; Diarrhoea (0205): 2; Vomiting (0228): 34; Nausea (0308): 69); **700 (n 2)**: (Hepatic function abnormal (0348): 1; Jaundice (0356): 1); **900 (n 2)**: (Goitre (0414): 1; Sialoadenitis (0986): 1); **1010 (n 35)**: (Cardiac failure (0496): 1; Cyanosis (0501): 5; Circulatory failure (0499): 8; Hypotension (0212): 21); **1020 (n 3)**: (Myocardial infarction (0428): 3); **1030 (n 31)**: (Fibrillation atrial (0439): 1; Arrhythmia ventricular (0435): 2; Fibrillation ventricular (0440): 2; Palpitation (0221): 5; Bradycardia (0208): 5; Cardiac arrest (0437): 7; Tachycardia (0224): 9); **1040 (n 23)**: (Thrombophlebitis arm (0467): 1; Phlebitis (0455): 1; Cerebral infarction (1986): 1; Vasospasm (0226): 1; Thrombophlebitis deep (0470): 1; Thrombophlebitis arm deep (0505): 2; Cerebrovascular disorder (0445): 2; Thrombophlebitis superficial (0479): 2; Thrombophlebitis leg deep (0472): 3; Flushing (0207): 9); **1100 (n 129)**: (Hypoventilation (0518): 1; Apnoea (0507): 2; Pharyngitis (0523): 2; Pulmonary oedema (0535): 2; Respiratory depression (0144): 2; Stridor (0542): 3; Larynx oedema (0522): 4; Bronchospasm (0511): 11; Coughing (0513): 15; Rhinitis (0539): 17; Dyspnoea (0514): 70); **1210 (n 1)**: (Haemolysis (0560): 1); **1230 (n 4)**: (Purpura allergic (0460): 1; Thrombocytopenia (0594): 3); **1300 (n 19)**: (Anuria (0596): 1; Renal function abnormal (0619): 1; Oliguria (0612): 1; Nephrosis (0610): 1; Albuminuria (0595): 2; Face oedema (0602): 13); **1420 (n 2)**: (Salpingitis

(0963): 2); **1810 (n 298)**: (Malaise (0728): 1; Back pain (0717): 1; Oedema peripheral (0401): 1; Pain (0730): 1; Chest pain (0718): 2; Oedema periorbital (1009): 2; Sudden death (1134): 2; Fatigue (0724): 3; Oedema (0398): 4; Temperature changed sensation (1705): 6; Syncope (0223): 8; Fever (0725): 8; Rigors (0731): 11; Death (0722): 27; Allergic reaction (0712): 48; Anaphylactic shock (0713): 81; Anaphylactoid reaction (0714): 92); **1820 (n 9)**: (Injection site necrosis (0056): 2; Injection site reaction (0058): 7).

Sub-class B (n 12 Agents; n 1/10-12/21): n 1/10, Iobitridol (1,629): 100 (n 501): (Rash pustular (0032): 1; Rash vesicular (1443): 1; Pigmentation abnormal (0973): 1; Skin reaction localised (1650): 1; Cold urticaria (1207): 1; Epidermal necrolysis (0013): 1; Skin necrosis (0060): 1; Bullous eruption (0871): 2; Skin exfoliation (1199): 2; Eczema (0012): 2; Urticaria acute (0045): 3; Skin cold clammy (0932): 3; Skin disorder (0037): 6; Sweating increased (0043): 7; Rash maculo-papular (0030): 18; Angioedema (0003): 34; Rash (0027): 67; Pruritus (0024): 71; Rash erythematous (0028): 91; Urticaria (0044): 188); **200 (n 2)**: (Arthralgia (0063): 1; Myalgia (0073): 1); **410 (n 105)**: (Brain stem disorder (0810): 1; Tetany (0152): 1; Neuropathy (0130): 1; Cramps legs (0939): 1; Muscle contractions involuntary (0155): 2; Nystagmus (0131): 2; Hyperkinesia (0114): 2; Dysaesthesia (1491): 2; Speech disorder (0150): 3; Stupor (0151): 3; Hypoaesthesia (0117): 4; Convulsions (0093): 5; Vertigo (0158): 7; Dysphonia (0103): 10; Coma (0091): 11; Tremor (0154): 11; Headache (0109): 12; Dizziness (0101): 13; Paraesthesia (0137): 14); **431 (n 13)**: (Diplopia (0241): 1; Blindness temporary (1280): 1; Vision abnormal (0257): 1; Papilloedema (0249): 1; Lacrimation abnormal (1049): 2; Conjunctivitis (0238): 7); **432 (n 2)**: (Deafness (0258): 1; Hearing decreased (1368): 1); **433 (n 4)**: (Parosmia (0265): 1; Taste perversion (0267): 3); **500 (n 37)**: (Amnesia (0164): 1; Appetite increased (0168): 1; Mental disorder (1944): 2; Psychosis (0193): 3; Anxiety (0166): 4; Confusion (0092): 6; Nervousness (0188): 6; Agitation (0163): 7; Somnolence (0197): 7); **600 (n 174)**: (Gastro-intestinal disorder NOS (1262): 1; Dyspepsia (0279): 1; Cheilitis (0270): 1; Constipation (0204): 1; Pancreatitis (0314): 1; Stomatitis ulcerative (0328): 1; Saliva increased (0222): 2; Mucositis NOS (1351): 3; Tongue oedema (0331): 4; Abdominal pain (0268): 5; Diarrhoea (0205): 5; Dysphagia (0280): 7; Vomiting (0228): 67; Nausea (0308): 75); **700 (n 2)**: (Hepatitis (0350): 2); **800 (n 6)**: (Hyponatraemia (0392): 1; Xerophthalmia (0943): 1; Dehydration (0370): 1; Oedema pharynx (1395): 3); **900 (n 1)**: (Hyperthyroidism (0415): 1); **1010 (n 91)**: (Cardio-respiratory failure (1899): 1; Pulse weak (1401): 1; Blood pressure fluctuation (1762): 1; Cardiac failure (0496): 2; Cardiovascular disorders (2031): 4; Cyanosis (0501): 6; Circulatory failure (0499): 16; Hypertension (0210): 16; Hypotension (0212): 44); **1020 (n 8)**: (Angina pectoris (0422): 2; Myocardial infarction (0428): 3; Myocardial ischaemia (0429): 3); **1030 (n 58):** (Palpitation (0221): 1; Fibrillation atrial (0439): 1; Extrasystoles (0438): 2; Arrhythmia (0433): 3; Fibrillation ventricular (0440): 4; Bradycardia (0208): 4; Cardiac arrest (0437): 19; Tachycardia (0224): 24); **1040 (n 26):** (Compartment syndrome (2220): 1; Vasculitis (0085): 1; Vasospasm (0226): 1; Cerebral infarction (1986): 2; Cerebrovascular disorder (0445): 2; Flushing (0207): 19); **1100 (n 238)**: (Bronchospasm paradoxical (1490): 1; Pneumonia (0528): 1; Haemoptysis (0516): 1; Asphyxia (0508): 1; Larynx pain (1648): 1; Laryngismus (0520): 2; Pharyngitis (0523): 2; Asthma (1367): 2; Apnoea (0507): 2; Respiratory distress syndrome (2252): 2; Hyperventilation (0517): 2; Respiratory insufficiency (0537): 3; Respiratory depression (0144): 3; Laryngitis (0521): 4; Respiratory disorder (0536): 4; Pulmonary oedema (0535): 8; Throat tightness (1489): 10; Bronchospasm (0511): 12; Rhinitis (0539): 13; Larynx oedema (0522): 19; Coughing (0513): 34; Dyspnoea (0514): 111); **1220 (n 3)**: (Lymphangitis (0580): 1; Eosinophilia (0571): 2); **1230 (n 6)**: (Haematoma

(1353): 1; Purpura (0459): 1; Disseminated intravascular coagulation (1175): 1; Thrombosis arterial (0482): 1; Coagulation disorder (0586): 1; Thrombosis venous arm (1370): 1); **1300 (n 57)**: (Oliguria (0612): 1; Renal tubular necrosis (0624): 1; Renal failure chronic aggravated (2330): 1; Nephropathy toxic (0609): 2; Renal failure chronic (2329): 2; Azotaemia (2328): 4; Renal failure acute (0618): 14; Face oedema (0602): 32; **1810 (n 283)**: (Fatigue (0724): 1; Chest pain substernal (0720): 1; Pain (0730): 1; Choking (1460): 1; Back pain (0717): 1; Oedema peripheral (0401): 1; Condition aggravated (0965): 2; Hypovolaemia (0929): 2; Oedema generalised (0400): 2; Pallor (0220): 2; Allergy (1058): 3; Asthenia (0716): 3; Death (0722): 3; Fever (0725): 6; Syncope (0223): 8; Oedema (0398): 10; Chest pain (0718): 10; Temperature changed sensation (1705): 15; Oedema mouth (1485): 17; Allergic reaction (0712): 18; Anaphylactic reaction (2237): 18; Malaise (0728): 24; Oedema periorbital (1009): 29; Rigors (0731): 29; Anaphylactoid reaction (0714): 31; Anaphylactic shock (0713): 45; **1820 (n 11)**: (Injection site mass (0055): 1; Injection site necrosis (0056): 1; Injection site dermatitis (1768): 1; Injection site pain (0057): 1; Application site reaction (0047): 1; Injection site urticaria (1968): 1; Injection site inflammation (0054): 2; Injection site reaction (0058): 3); **1830 (n 1)**: (Sepsis (0744): 1); **n 2/11, Iodixanol (4,815):   100 (n 2,052)**: (Erythema multiforme (0014): 1; Eyelid skin disorder (2253): 1; Dermatitis lichenoid (0010): 1; Fixed eruption (1249): 1; Erythema induratum (0912): 1; Photosensitivity reaction (0022): 1; Epidermal necrolysis (0013): 1; Urticaria acute (0045): 1; Skin necrosis (0060): 1; Rash psoriaform (0031): 1; Acne (0001): 2; Acute generalized exanthematous pustulosis (1846): 2; Stevens Johnson syndrome (0042): 3; Skin reaction localised (1650): 3; Skin cold clammy (0932): 3; Skin dry (1123): 3; Skin disorder (0037): 3; Rash vesicular (1443): 4; Rash purpuric (0462): 4; Dermatitis exfoliative (0008): 5; Heat rash (1469): 5; Skin discolouration (0036): 6; Eczema (0012): 7; Rash pustular (0032): 8; Bullous eruption (0871): 14; Dermatitis (0007): 15; Sweating increased (0043): 21; Skin exfoliation (1199): 40; Angioedema (0003): 72; Rash maculo-papular (0030): 118; Rash erythematous (0028): 371; Pruritus (0024): 402; Urticaria (0044): 444; Rash (0027): 487); **200 (n 18)**: (Muscle weakness (1128): 1; Arthritis (0064): 1; Skeletal pain (1347): 1; Osteomyelitis (1184): 1; Fasciitis plantar (1558): 1; Rhabdomyolysis (1210): 1; Periarthritis (2353): 2; Arthropathy (0065): 2; Myalgia (0073): 4; Arthralgia (0063): 4); **410 (n 252)**: (Muscle contractions involuntary (0155): 1; Neuralgia (0124): 1; Faecal incontinence (0107): 1; Tetany (0152): 1; Oculogyric crisis (0132): 1; Migraine (0121): 1; Oedema cerebral (0891): 1; Anaesthesia mouth (1473): 1; Paresis (0141): 1; Visual field defect (0159): 1; Scotoma (0147): 1; Cognitive disorders (1877): 2; Hemiplegia (0112): 2; Tongue paralysis (0153): 2; Hypokinesia (0118): 3; Cholinergic syndrome (0203): 3; Ataxia (0088): 3; Paralysis (0138): 3; Vertigo (0158): 4; Convulsions (0093): 4; Dyskinesia (0102): 4; Sensory disturbance (0148): 4; Neurologic disorder NOS (2133): 5; Encephalopathy (0105): 5; Hemiparesis (0111): 7; Aphasia (0087): 8; Stupor (0151): 8; Convulsions grand mal (0095): 8; Hypoaesthesia (0117): 9; Dysphonia (0103): 10; Tremor (0154): 12; Dysaesthesia (1491): 15; Speech disorder (0150): 15; Coma (0091): 20; Dizziness (0101): 21; Paraesthesia (0137): 31; Headache (0109): 33); **431 (n 51)**: (Conjunctival discolouration (1303): 1; Blindness (0232): 1; Eye pain (0244): 1; Blindness temporary (1280): 2; Lacrimation abnormal (1049): 4; Vision abnormal (0257): 15; Conjunctivitis (0238): 27; **432 (n 3)**: (Tinnitus (0264): 1; Ear ache (0260): 2); **433 (n 3)**: (Parosmia (0265): 1; Taste perversion (0267): 2); **500 (n 46)**: (Hallucination (0179): 1; Insomnia (0183): 1; Suicide ideation (2363): 1; Somnolence (0197): 1; Mental disorder (1944): 1; Depression (0172): 1; Nervousness (0188): 1; Catatonic reaction (0169): 1; Personality disorder (0192): 1; Sleep disorder (0195): 1; Psychosis (0193): 1; Depersonalization (0171): 3; Aggressive reaction (0162): 3; Anxiety (0166): 7; Confusion

(0092): 10; Agitation (0163): 12); **600 (n 329)**: (Increased stool urgency (1843): 1; Ileus paralytic (0215): 1; Haemorrhoids (0298): 1; Stomatitis ulcerative (0328): 1; Intestinal obstruction (0302): 1; Dyspepsia (0279): 1; Lip disorder (1852): 1; Gastroenteritis (0293): 1; Melaena (0306): 1; Glossitis (0295): 1; Mucositis NOS (1351): 1; Colitis (0271): 1; Oesophageal stricture (1028): 1; Gastro-intestinal disorder NOS (1262): 1; Rectal prolapse (1652): 1; Enanthema (0281): 1; Salivary gland enlargement (0325): 1; Haemorrhage rectum (1014): 1; Stomatitis aphthous (0751): 1; Amylase increased (1101): 2; Saliva increased (0222): 2; Flatulence (0285): 3; Constipation (0204): 3; Stomatitis (0327): 3; Cheilitis (0270): 3; Mouth dry (0218): 3; Tongue oedema (0331): 10; Abdominal pain (0268): 11; Diarrhoea (0205): 11; Pancreatitis (0314): 11; Dysphagia (0280): 16; Vomiting (0228): 101; Nausea (0308): 131); **700 (n 4)**: (Hepatic function abnormal (0348): 1; Hepatic enzymes increased (1346): 1; Hepatic failure (0933): 2); **800 (n 26)**: (Glucose tolerance abnormal (0376): 1; Hypercholesterolaemia (0381): 1; Acidosis lactic (0364): 1; Weight increase (0408): 1; Acidosis (0363): 2; Lipase increased (1621): 2; Fluid overload (1018): 2; Weight decrease (0407): 2; Hyperglycaemia (0382): 3; Hypoglycaemia (0389): 3; Oedema pharynx (1395): 4; Hyperkalaemia (0383): 4); **900 (n 2)**: (Breast pain male (0837): 1; Sialoadenitis (0986): 1); **1010 (n 189)**: (ECG abnormal (0502): 1; Hypotension postural (0213): 1; Blood pressure fluctuation (1762): 1; Cardiac failure left (0497): 2; Heart disorder (0504): 2; ECG abnormal specific (0503): 4; Hypertension pulmonary (0211): 4; Cardiac failure (0496): 4; Pulse weak (1401): 4; Cyanosis (0501): 7; Circulatory failure (0499): 22; Hypertension (0210): 27; Hypotension (0212): 110); **1020 (n 30)**: (Aortic stenosis (0424): 1; Angina pectoris (0422): 1; Myocardial ischaemia (0429): 1; Thrombosis coronary (0488): 12; Myocardial infarction (0428): 15); **1030 (n 132)**: (Extrasystoles (0438): 1; Arrhythmia atrial (0434): 1; Sick sinus syndrome (1514): 1; T wave inversion (1688): 1; Sinoatrial block (1400): 1; Arrhythmia (0433): 2; Tachycardia ventricular (0230): 3; AV block complete (1378): 4; Fibrillation atrial (0439): 5; Fibrillation ventricular (0440): 5; Palpitation (0221): 12; Bradycardia (0208): 30; Cardiac arrest (0437): 31; Tachycardia (0224): 35); **1040 (n 153)**: (Arteriosclerosis (0771): 1; Cerebellar infarction (1492): 1; Vasculitis allergic (0086): 1; Vasculitis (0085): 1; Vascular disorder (0491): 1; Cerebral ischaemia (1987): 1; Compartment syndrome (2220): 1; Thrombophlebitis deep (0470): 2; Cerebral infarction (1986): 3; Transient ischaemic attack (1694): 3; Peripheral ischaemia (0454): 7; Vasodilatation (0225): 11; Cerebrovascular disorder (0445): 20; Flushing (0207): 100); **1100 (n 381)**: (Hyperpnoea (1711): 1; Sputum disorder (1976): 1; Aspiration (1030): 1; Yawning (0201): 1; Bronchial obstruction (1820): 1; Atelectasis (1197): 1; Pneumonia lobar (0530): 1; Pneumonia (0528): 1; Pleural effusion (0524): 2; Respiratory distress syndrome (2252): 2; Hyperventilation (0517): 3; Asthma (1367): 3; Haemoptysis (0516): 3; Laryngismus (0520): 4; Respiratory disorder (0536): 4; Hypoxia (0519): 5; Laryngitis (0521): 6; Apnoea (0507): 6; Stridor (0542): 7; Pharyngitis (0523): 7; Respiratory depression (0144): 9; Larynx oedema (0522): 13; Respiratory insufficiency (0537): 13; Throat tightness (1489): 19; Pulmonary oedema (0535): 20; Bronchospasm (0511): 21; Coughing (0513): 30; Rhinitis (0539): 33; Dyspnoea (0514): 163); **1210 (n 3)**: (Anaemia (0544): 1; Anaemia hypochromic (0553): 2); **1220 (n 15)**: (Lymphadenopathy mediastinal (2138): 1; Leukocytosis (0576): 2; Lymphadenopathy (0577): 2; Leucopenia (0908): 2; Eosinophilia (0571): 8); **1230 (n 20)**: (Haemorrhage retroperitoneal (1214): 1; Embolism arterial (0447): 1; Embolism cerebral (0448): 1; Haematoma (1353): 1; Haemorrhage NOS (0452): 1; Thrombosis cerebral arterial (0487): 2; Thrombosis arterial (0482): 2; Thrombosis (0481): 2; Thrombocytopenia (0594): 4; Purpura (0459): 5); **1300 (n 312)**: (Renal calculus (0617): 1; Renal tubular disorder (0623): 1; Renal pain (0621): 1; Urinary incontinence (0156): 1; Urethritis (1827): 2; Creatinine clearance decreased (0598): 2; Micturition frequency

(0606): 2; Renal failure chronic aggravated (2330): 2; Oliguria (0612): 4; Nephritis interstitial (0608): 4; Anuria (0596): 5; Renal tubular necrosis (0624): 7; Renal function abnormal (0619): 8; Nephropathy toxic (0609): 10; Renal failure chronic (2329): 18; Azotaemia (2328): 21; Renal failure acute (0618): 56; Face oedema (0602): 167); **1420 (n 1)**: (Breast pain (1839): 1); **1700 (n 3)**: (Pancreas cyst (1388): 1; Gastric carcinoma (0788): 1; Pharynx neoplasm malignant (1288): 1); **1810 (n 755)**: (Drug interaction (2356): 1; Drug level increased (1281): 1; Scar (1522): 1; Abdomen enlarged (0711): 1; Chest pain precordial (0719): 1; Allergy (1058): 2; C-reactive protein increased (2351): 2; Condition aggravated (0965): 2; Choking (1460): 3; Hypothermia (0727): 3; Medicine ineffective (1948): 3; Influenza-like symptoms (1222): 3; Hyperpyrexia (0894): 4; Multiple organ failure (1819): 4; Fatigue (0724): 5; Leg pain (1439): 6; Pallor (0220): 7; Drug hypersensitivity syndrome (2309): 7; Pain (0730): 7; Asthenia (0716): 8; Oedema generalised (0400): 9; Death (0722): 11; Syncope (0223): 13; Oedema peripheral (0401): 17; Malaise (0728): 21; Anaphylactic reaction (2237): 25; Oedema mouth (1485): 25; Back pain (0717): 27; Fever (0725): 32; Temperature changed sensation (1705): 36; Rigors (0731): 36; Oedema (0398): 44; Chest pain (0718): 49; Oedema periorbital (1009): 56; Anaphylactic shock (0713): 81; Anaphylactoid reaction (0714): 84; Allergic reaction (0712): 118); **1820 (n 24)**: (Injection site mass (0055): 1; Injection site necrosis (0056): 1; Cellulitis (1372): 1; Injection site inflammation (0054): 1; Application site reaction (0047): 1; Injection site urticaria (1968): 1; Injection site rash (1881): 1; Injection site pain (0057): 2; Injection site bleeding (1752): 2; Infusion site reaction (2137): 3; Medical device complication (2139): 3; Injection site reaction (0058): 7); **1830 (n 11)**: (Herpes zoster (0862): 1; Infection bacterial (0738): 1; Periodontal infection (2164): 1; Abscess (0887): 1; Infection staphylococcal (1867): 2; Infection viral (0740): 2; Sepsis (0744): 3); **3/12, Iohexol (19,872): 100 (n 5,219)**: (Psoriasis aggravated (0782): 1; Acne (0001): 1; Acute generalized exanthematous pustulosis (1846): 1; Vitiligo (0046): 1; Photosensitivity reaction (0022): 1; Pruritus ani (0025): 1; Dermatitis contact (0049): 1; Pruritus genital (0026): 1; Heat rash (1469): 1; Skin ulceration (0041): 1; Rash vesicular (1443): 1; Livedo reticularis (1410): 1; Scleroderma (0971): 1; Induration (1891): 1; Skin nodule (0061): 1; Sweat discolouration (1244): 1; Skin odor abnormal (0039): 1; Fixed eruption (1249): 2; Skin dry (1123): 2; Erythema nodosum (0015): 2; Sweating decreased (1298): 3; Erythema multiforme (0014): 3; Psoriasis (1398): 3; Skin necrosis (0060): 3; Skin reaction localised (1650): 3; Rash purpuric (0462): 4; Hypotrichosis (0828): 4; Epidermal necrolysis (0013): 5; Eyelid skin disorder (2253): 6; Rash pustular (0032): 6; Stevens Johnson syndrome (0042): 7; Urticaria acute (0045): 9; Skin disorder (0037): 10; Eczema (0012): 10; Dermatitis exfoliative (0008): 10; Skin exfoliation (1199): 12; Skin cold clammy (0932): 14; Skin discolouration (0036): 23; Dermatitis (0007): 23; Bullous eruption (0871): 50; Angioedema (0003): 99; Sweating increased (0043): 112; Rash maculo-papular (0030): 155; Rash erythematous (0028): 381; Rash (0027): 940; Pruritus (0024): 990; Urticaria (0044): 2,311); **200 (n 105)**: (Fracture pathological (0069): 1; Ligament disorder (2086): 1; Fibromyalgia (1838): 1; Arthritis aggravated (1015): 1; Fasciitis plantar (1558): 1; Osteomyelitis (1184): 1; Muscle haemorrhage (1193): 1; Fasciitis (1707): 1; Musculoskeletal pain (1889): 1; Arthritis infective (2024): 2; Myopathy (0074): 2; Tendinitis (1001): 2; Arthropathy (0065): 3; Rhabdomyolysis (1210): 3; Arthritis (0064): 5; Skeletal pain (1347): 5; Arthrosis (0066): 6; Muscle weakness (1128): 22; Arthralgia (0063): 23; Myalgia (0073): 23); **300 (n 1)**: (Auto-antibody response (1096): 1); **410 (n 2,679)**: (Hypertension intracranial (0115): 1; Hyperreflexia (0774): 1; Ataxia cerebellar (1459): 1; Spasm generalized (0149): 1; Vocal cord paralysis (0942): 1; Demyelination (1547): 1; MS-like syndrome (1039): 1; Cognitive disorders (1877): 1; Opisthotonos (0134): 1; Hyperaesthesia (0113): 1; Optic neuritis (0136): 1; Torticollis

(0077): 2; Hyporeflexia (0850): 2; Encephalomyelitis (0974): 2; Hemianopia (0110): 2; Dementia (0100): 2; Cranial nerve lesion (0983): 2; Neuropathy peripheral (1313): 2; Coordination abnormal (0097): 2; Dyskinesia tardive (1065): 2; Reflex plantar extensor (1607): 2; Quadriplegia (0143): 2; Hypotonia (0119): 3; Paraplegia (0140): 3; Hydrocephalus (0692): 3; Faecal incontinence (0107): 3; Paralysis flaccid (0139): 3; Convulsions aggravated (0094): 3; Myelitis (0123): 4; Oculomotor nerve paralysis (0133): 4; Neuralgia (0124): 4; Cerebral disorder (1960): 4; Hypokinesia (0118): 5; Blindness cortical (1890): 5; Hyperkinesia (0114): 5; Brain stem disorder (0810): 5; Pleocytosis (1318): 5; Paresis (0141): 5; Gait abnormal (0108): 6; Tongue paralysis (0153): 6; EEG abnormal (0104): 6; Tetany (0152): 6; Sensory disturbance (0148): 6; Nystagmus (0131): 7; Migraine (0121): 7; Neurologic disorder NOS (2133): 7; Dystonia (0068): 8; Ataxia (0088): 8; Oculogyric crisis (0132): 8; Dyskinesia (0102): 9; Vertigo (0158): 9; Visual field defect (0159): 9; Neuropathy (0130): 14; Oedema cerebral (0891): 15; Dysaesthesia (1491): 15; Hemiparesis (0111): 19; Arachnoiditis (1031): 19; Hemiplegia (0112): 20; Encephalopathy (0105): 26; Speech disorder (0150): 30; Paralysis (0138): 30; Muscle contractions involuntary (0155): 30; Aphasia (0087): 36; Dysphonia (0103): 40; CSF abnormal (0098): 49; Meningism (0120): 65; Hypoaesthesia (0117): 66; Cramps legs (0939): 68; Convulsions grand mal (0095): 70; Stupor (0151): 72; Coma (0091): 92; Convulsions (0093): 135; Hypertonia (0116): 146; Paraesthesia (0137): 169; Dizziness (0101): 174; Tremor (0154): 176; Meningitis (0955): 185; Headache (0109): 719); **420 (n 1)**: (Complex regional pain syndrome (2323): 1); **431 (n 295)**: (Corneal ulceration (0240): 1; Papilloedema (0249): 1; Anisocoria (1174): 1; Conjunctival discolouration (1303): 1; Eye infection (1555): 1; Blindness colour (0233): 1; Keratitis (0246): 1; Conjunctival ulceration (1381): 1; Lacrimal gland disorder (0216): 1; Exophthalmos (0242): 2; Blepharitis (1007): 2; Photopsia (1172): 3; Mydriasis (0219): 4; Eye abnormality (0243): 5; Eye muscle paralysis (1429): 5; Blindness temporary (1280): 7; Diplopia (0241): 9; Eye pain (0244): 14; Lacrimation abnormal (1049): 22; Blindness (0232): 27; Photophobia (0250): 38; Vision abnormal (0257): 61; Conjunctivitis (0238): 87); **432 (n 52)**: (Ear disorder NOS (1255): 1; Application site pain (2035): 1; Hyperacusis (0261): 2; Ear ache (0260): 3; Hearing decreased (1368): 5; Deafness (0258): 19; Tinnitus (0264): 21); **433 (n 46)**: (Taste loss (0266): 3; Parosmia (0265): 5; Taste perversion (0267): 38; **500 (n 440)**: (Euphoria (0178): 1; Emotional lability (0177): 1; Dreaming abnormal (1243): 1; Neurosis (0189): 1; Sleep disorder (0195): 1; Depression psychotic (0173): 1; Apathy (0167): 1; Delusion (0170): 1; Mental deficiency (0187): 1; Suicide ideation (2363): 2; Mental disorder (1944): 2; Hysteria (0180): 3; Impotence (0182): 3; Hallucination (0179): 5; Personality disorder (0192): 5; Insomnia (0183): 5; Depression (0172): 7; Anorexia (0165): 7; Psychosis (0193): 8; Aggressive reaction (0162): 12; Delirium (0099): 12; Thinking abnormal (0199): 17; Depersonalization (0171): 22; Amnesia (0164): 32; Nervousness (0188): 36; Agitation (0163): 41; Anxiety (0166): 43; Somnolence (0197): 48; Confusion (0092): 121); **600 (n 1,867)**: (Intestinal gangrene (0301): 1; Ileus paralytic (0215): 1; Haemorrhage rectum (1014): 1; Anus disorder (0269): 1; Diarrhoea, clostridium difficile (1201): 1; Intestinal ischaemia (1308): 1; Eructation (0283): 1; Lip ulceration (1854): 1; Gastric ulcer perforated (0290): 1; Melaena (0306): 1; Tenesmus (0231): 1; Mouth cyst (1659): 1; Duodenal ulcer perforated (0277): 1; Pancreatic disorder (1994): 1; Gingivitis (1083): 1; Saliva altered (0758): 1; Flatulence (0285): 1; Salivary gland pain (0326): 1; Stomatitis ulcerative (0328): 1; Stomatitis aphthous (0751): 1; Haematemesis (0297): 2; Colitis (0271): 2; Intestinal necrosis (1215): 2; Lip disorder (1852): 2; Gastroenteritis (0293): 2; Glossitis (0295): 2; Tooth disorder (0336): 2; Dyspepsia (0279): 2; Gastric ulcer (0287): 2; Peritonitis (0320): 3; Constipation (0204): 3; Enanthema (0281): 3; Amylase increased (1101): 4; GI haemorrhage (0294): 4; Salivary gland enlargement (0325): 4;

Tongue disorder (0330): 5; Mucositis NOS (1351): 5; Stomatitis (0327): 6; Saliva increased (0222): 6; Gastro-intestinal disorder NOS (1262): 7; Cheilitis (0270): 8; Pancreatitis (0314): 11; Diarrhoea (0205): 15; Mouth dry (0218): 25; Tongue oedema (0331): 34; Abdominal pain (0268): 72; Dysphagia (0280): 80; Nausea (0308): 654; Vomiting (0228): 880); **700 (n 45)**: (Hepatitis cholestatic (0351): 1; Hepatitis (0350): 1; Hepatocellular damage (0353): 2; Hepatorenal syndrome (1103): 2; Hepatic failure (0933): 2; SGPT increased (0360): 3; Hepatosplenomegaly (0355): 3; Hepatic enzymes increased (1346): 3; SGOT increased (0359): 4; Jaundice (0356): 5; Bilirubinaemia (0339): 5; Hepatic function abnormal (0348): 14); **800 (n 93)**: (Hypoglycaemia (0389): 1; Weight increase (0408): 1; Hypoproteinaemia (0827): 1; Anion gap abnormal (1589): 1; Myoglobinuria (1002): 1; Acidosis lactic (0364): 1; Phosphatase alkaline increased (0404): 1; Electrolyte abnormality (0374): 1; Thirst (0405): 2; Hypokalaemia (0391): 3; LDH increased (0394): 3; Diabetes mellitus (0371): 3; Hyponatraemia (0392): 3; Weight decrease (0407): 3; Xerophthalmia (0943): 3; Acidosis respiratory (1465): 4; Oedema pharynx (1395): 7; Acidosis (0363): 9; Creatine phosphokinase increased (0791): 11; Dehydration (0370): 12; Hyperkalaemia (0383): 22); **900 (n 30)**: (T3 decreased (1830): 1; Diabetes insipidus (0411): 1; TSH decreased (1690): 1; T3 increased (1445): 1; Hyperthyroidism aggravated (0416): 1; T4 increased (1446): 1; Hyperprolactinaemia (1072): 1; Thyroid disorder (0419): 1; Pituitary neoplasm NOS (1394): 1; Thyroxine decreased (1349): 1; TSH increased (1831): 2; SIADH (1225): 3; Hypothyroidism (0417): 3; Antidiuretic hormone disorder (0883): 3; Sialoadenitis (0986): 3; Hyperthyroidism (0415): 6); **1010 (n 925)**: (Vascular graft occlusion (2109): 1; Cardiovascular disorders (2031): 2; Aneurysm (0915): 2; Hypotension postural (0213): 2; Cardio-respiratory failure (1899): 2; Hypertension aggravated (0762): 2; Cardiac failure left (0497): 2; Hypertension pulmonary (0211): 3; Heart disorder (0504): 3; Cardiomegaly (1320): 3; Blood pressure fluctuation (1762): 5; Cardiac failure right (0498): 7; Cardiac failure (0496): 17; Pulse weak (1401): 19; ECG abnormal specific (0503): 21; ECG abnormal (0502): 22; Cyanosis (0501): 58; Circulatory failure (0499): 127; Hypertension (0210): 155; Hypotension (0212): 472); **1020 (n 101)**: (Cardiac tamponade (1573): 1; Aortic stenosis (0424): 1; Myocarditis (1352): 2; Pericardial effusion (0910): 2; Myocardial ischaemia (0429): 5; Thrombosis coronary (0488): 14; Angina pectoris (0422): 18; Coronary artery disorder (0426): 28; Myocardial infarction (0428): 30); **1030 (n 671)**: (Arrhythmia atrial (0434): 1; QT prolonged (1361): 1; Tachycardia supraventricular (0229): 1; Arrhythmia nodal (0809): 2; Extrasystoles (0438): 2; Bundle branch block (0436): 3; Arrhythmia ventricular (0435): 4; AV block (0431): 4; AV block complete (1378): 5; Fibrillation atrial (0439): 9; Arrhythmia (0433): 25; Tachycardia ventricular (0230): 33; Palpitation (0221): 37; Fibrillation ventricular (0440): 72; Bradycardia (0208): 96; Tachycardia (0224): 174; Cardiac arrest (0437): 202; **1040 (n 548)**: (Haemorrhage stroke (1989): 1; Arteritis (0078): 1; Cerebellar infarction (1492): 1; Renal artery occlusion (1546): 1; Vein pain (0494): 1; Telangiectasis (0464): 1; Gangrene (0911): 1; Thrombophlebitis deep (0470): 1; Phlebitis (0455): 2; Retinal haemorrhage (0252): 2; Vasculitis allergic (0086): 2; Thrombophlebitis (0466): 2; Subarachnoid haemorrhage (0463): 4; Haemorrhage intracranial (1068): 4; Cerebral infarction (1986): 5; Vasculitis (0085): 5; Cerebral ischaemia (1987): 6; Vascular disorder (0491): 7; Cerebral haemorrhage (0444): 8; Compartment syndrome (2220): 9; Vasospasm (0226): 10; Peripheral ischaemia (0454): 20; Cerebrovascular disorder (0445): 48; Vasodilatation (0225): 123; Flushing (0207): 283); **1100 (n 2,450)**: (Haemoptysis (0516): 1; Hyperpnoea (1711): 1; Aspiration (1030): 1; Hypocapnia (1591): 1; Atelectasis (1197): 1; Pulmonary infiltration (1038): 1; Pneumonitis (1141): 1; Breath sounds decreased (1716): 1; Cheyne-Stokes respiration (1016): 1; Bronchitis (0805): 1; Bronchospasm aggravated (1066): 1;

Airways obstruction (1749): 1; Yawning (0201): 2; Pneumothorax (0531): 2; Pleural fibrosis (0525): 2; Pulmonary disorders (2032): 2; Asphyxia (0508): 3; Bradypnoea (0510): 3; Hypopnoea (1712): 3; Chronic obstructive airways disease (1493): 3; Respiratory distress syndrome (2252): 4; Epistaxis (0515): 4; Sputum increased (0541): 6; Pleural effusion (0524): 6; Upper respiratory tract infection (0543): 7; Pulmonary congestion (1721): 8; Sinusitis (0540): 9; Hyperventilation (0517): 15; Asthma (1367): 15; Hypoventilation (0518): 16; Hypoxia (0519): 17; Pneumonia (0528): 17; Respiratory insufficiency (0537): 28; Respiratory depression (0144): 39; Stridor (0542): 45; Respiratory disorder (0536): 49; Pharyngitis (0523): 58; Laryngitis (0521): 64; Apnoea (0507): 64; Laryngismus (0520): 76; Pulmonary oedema (0535): 81; Throat tightness (1489): 94; Larynx oedema (0522): 116; Coughing (0513): 232; Bronchospasm (0511): 240; Rhinitis (0539): 327; Dyspnoea (0514): 781); **1210 (n 7)**: (Anaemia hypochromic (0553): 1; Haemolytic-uraemic syndrome (1479): 1; Anaemia haemolytic (0548): 1; Haemolysis (0560): 2; Spinal cord infarction (2290): 2); **1220 (n 43)**: (Lymphadenopathy mediastinal (2138): 1; Agranulocytosis (0570): 2; Lymphadenopathy (0577): 2; Leucopenia (0908): 4; Granulocytopenia (0572): 5; Eosinophilia (0571): 10; Leukocytosis (0576): 19; **1230 (n 89)**: (Bleeding time increased (0584): 1; Thrombosis venous arm (1370): 1; Prothrombin increased (0591): 1; Embolism limb (0449): 1; Purpura allergic (0460): 1; Haemorrhage retroperitoneal (1214): 1; Thromboembolism (0465): 1; Haematoma (1353): 1; Thrombocytopenia (0594): 2; Coagulation factor decreased (1122): 2; Thrombosis cerebral arterial (0487): 2; Prothrombin decreased (0590): 3; Haemorrhage NOS (0452): 3; Disseminated intravascular coagulation (1175): 3; Thrombosis cerebral (0486): 3; Embolism cerebral (0448): 4; Thrombosis arterial leg (0484): 4; Coagulation disorder (0586): 5; Thrombosis arterial (0482): 6; Embolism pulmonary (0451): 7; Thrombosis (0481): 11; Embolism - blood clot (0446): 12; Purpura (0459): 14; **1300 (n 779)**: (Renal calculus (0617): 1; Urinary tract disorder (1999): 1; Urinary crystals (1461): 1; Renal interstitial fibrosis (1328): 1; Nephrosis (0610): 1; Renal pain (0621): 1; Polyuria (0613): 2; Urine abnormal (0629): 2; Cystitis (0599): 2; Dysuria (0601): 2; Micturition disorder (0605): 2; Renal tubular disorder (0623): 2; Urinary retention (0157): 3; Creatinine clearance decreased (0598): 3; Urinary tract infection (0628): 3; Nephritis (0607): 3; Renal failure chronic aggravated (2330): 6; Haematuria (0604): 7; Urinary incontinence (0156): 11; Nephropathy toxic (0609): 19; Anuria (0596): 23; Renal failure chronic (2329): 24; Renal tubular necrosis (0624): 26; Oliguria (0612): 33; Renal function abnormal (0619): 58; Azotaemia (2328): 133; Renal failure acute (0618): 192; Face oedema (0602): 217); **1420 (n 4)**: (Placental disorder (0660): 1; Vaginal disorder (1995): 1; Mastitis (0655): 2); **1500 (n 1)**: (Drug exposure in pregnancy (2221): 1); **1600 (n 1)**: (Birth premature (0637): 1); **1700 (n 6)**: (Hepatic neoplasm (1023): 1; Skin hypertrophy (0038): 1; Pulmonary carcinoma (0906): 1; Neoplasm NOS (1259): 3); **1810 (n 3,035)**: (Abdomen enlarged (0711): 1; Body odour (1392): 1; Tenderness NOS (1911): 1; Hypothermia (0727): 1; Drug level below therapeutic (2172): 1; Oedema genital (1092): 1; Night sweats (1898): 1; Granulomatous lesion (0876): 1; Oedema dependent (0399): 1; Drug interaction (2356): 2; Drug level increased (1281): 2; Influenza-like symptoms (1222): 2; Chest pain precordial (0719): 2; Posture abnormal (2012): 2; Therapeutic response increased (0874): 3; Hyperpyrexia malignant (0893): 3; ESR increased (0723): 3; Hernia NOS (1832): 3; Serum sickness (0733): 3; Crying abnormal (1162): 3; Medicine ineffective (1948): 4; Chest pain substernal (0720): 4; Sudden death (1134): 5; Hyperpyrexia (0894): 6; Multiple organ failure (1819): 6; Choking (1460): 10; Allergy (1058): 11; Oedema generalised (0400): 11; Leg pain (1439): 12; Drug hypersensitivity syndrome (2309): 14; Pallor (0220): 27; Asthenia (0716): 31; Condition aggravated (0965): 40; Oedema peripheral (0401): 43; Fatigue (0724): 49; Anaphylactic reaction (2237):54; Oedema mouth (1485):61; Malaise (0728):69; Oedema

(0398):80; Temperature changed sensation (1705): 92; Syncope (0223): 99; Back pain (0717): 105; Oedema periorbital (1009): 113; Fever (0725): 196; Rigors (0731): 218; Pain (0730): 232; Death (0722): 234; Anaphylactic shock (0713): 241; Allergic reaction (0712): 241; Chest pain (0718): 334; Anaphylactoid reaction (0714): 356); **1820 (n 270)**: (Infusion site mass (2135): 1; Injection site pruritus (1880): 1; Infusion site rash (2136): 1; Infusion site bruising (2140): 1; Injection site anaesthesia (1917): 1; Injection site bleeding (1752): 2; Injection site mass (0055): 2; Cellulitis (1372): 2; Injection site infection (1910): 3; Injection site rash (1881): 3; Application site reaction (0047): 9; Infusion site reaction (2137): 15; Injection site inflammation (0054): 19; Injection site pain (0057): 56; Injection site reaction (0058): 154); **1830 (n 69)**: (Herpes zoster (0862): 1; Moniliasis (0741): 1; Skin tightness (2098): 1; Periodontal infection (2164): 1; Infection fungal (0739): 2; Abscess (0887): 7; Infection (0736): 8; Infection bacterial (0738): 9; Sepsis (0744): 17; Infection staphylococcal (1867): 22);   **n 4/13, Iomeprol (4,617): 100 (n 1,422)**: (Photosensitivity reaction (0022): 1; Psoriasis (1398): 1; Erythema multiforme (0014): 1; Heat rash (1469): 1; Epidermal necrolysis (0013): 1; Photosensitivity allergic reaction (0021): 1; Dermatitis contact (0049): 1; Stevens Johnson syndrome (0042): 1; Dermatitis (0007): 2; Skin cold clammy (0932): 2; Rash vesicular (1443): 2; Eyelid skin disorder (2253): 2; Rash purpuric (0462): 2; Skin dry (1123): 2; Skin discolouration (0036): 3; Skin exfoliation (1199): 3; Eczema (0012): 5; Skin reaction localised (1650): 5; Rash pustular (0032): 7; Skin disorder (0037): 8; Urticaria acute (0045): 9; Bullous eruption (0871): 14; Sweating increased (0043): 32; Rash maculo-papular (0030): 41; Angioedema (0003): 59; Rash (0027): 193; Pruritus (0024): 223; Rash erythematous (0028): 248; Urticaria (0044): 552; **200 (n 7)**: (Arthralgia (0063): 1; Skeletal pain (1347): 1; Rhabdomyolysis (1210): 2; Myalgia (0073) :3); **410 (n 273)**: (Faecal incontinence (0107): 1; Hemianopia (0110): 1; Blindness cortical (1890): 1; Hypertonia (0116): 1; Dystonia (0068): 1; Migraine aggravated (1021): 1; Paresis (0141): 1; Neuropathy (0130): 1; Extrapyramidal disorder (0106): 1; Brain stem disorder (0810): 1; Oedema cerebral (0891): 2; Paralysis (0138): 2; Hyperkinesia (0114): 3; Meningism (0120): 3; Vertigo (0158): 3; Ataxia (0088): 3; Neurologic disorder NOS (2133): 3; Hemiplegia (0112): 4; Muscle contractions involuntary (0155): 7; Hemiparesis (0111): 7; Speech disorder (0150): 7; Hypoaesthesia (0117): 7; Dysaesthesia (1491): 7; Stupor (0151): 9; Aphasia (0087): 9; Convulsions grand mal (0095): 12; Dysphonia (0103): 13; Convulsions (0093): 16; Tremor (0154): 17; Dizziness (0101): 28; Paraesthesia (0137): 28; Coma (0091): 34; Headache (0109): 39); **431 (n 51)**: (Conjunctival disorder (2008): 1; Blepharitis (1007): 1; Thrombosis retinal vein (1157): 1; Blindness temporary (1280): 3; Diplopia (0241): 3; Lacrimation abnormal (1049): 4; Blindness (0232): 6; Vision abnormal (0257): 7; Conjunctivitis (0238): 25); **432 (n 9)**: (Hearing decreased (1368): 1; Ear disorder NOS (1255): 2; Deafness (0258): 2; Tinnitus (0264): 4); **433 (n 6)**: (Parosmia (0265): 1; Taste perversion (0267): 5); **500 (n 78)**: (Personality disorder (0192): 1; Catatonic reaction (0169): 2; Mental disorder (1944): 2; Suicide attempt (2362): 2; Amnesia (0164): 5; Anxiety (0166): 7; Somnolence (0197):7; Depersonalization (0171): 8; Confusion (0092): 9; Nervousness (0188): 12; Agitation (0163): 23; **600 (n 604)**: (Gastroenteritis (0293): 1; Tooth discolouration (0335): 1; Ileus (0214): 1; Cheilitis (0270): 1; Oesophagospasm (0310): 1; Gastric ulcer (0287): 1; Pancreatitis (0314): 1; Diarrhoea bloody (1382): 1; Salivary gland enlargement (0325): 1; Achalasia cardiae (1152): 1; Tongue disorder (0330): 1; Mouth dry (0218): 2; Stomatitis (0327): 2; Glossitis (0295): 2; Diarrhoea (0205): 5; Dysphagia (0280): 12; Abdominal pain (0268): 13; Tongue oedema (0331): 13; Mucositis NOS (1351): 14; Vomiting (0228): 256; Nausea (0308): 274); **700 (n 8)**: (Hepatic failure (0933): 1; Bilirubinaemia (0339): 1; Gamma-GT increased (1334): 1; Hepatic enzymes increased (1346): 1; SGPT increased (0360): 1; Liver fatty (0358): 1;

Jaundice (0356): 2); **800 (n 14)**: (Hypoglycaemia (0389): 1; Thirst (0405): 1; Phosphatase alkaline increased (0404): 1; Hypokalaemia (0391): 2; Creatine phosphokinase increased (0791): 2; Oedema pharynx (1395): 7); **900 (n 7)**: (Hyperthyroidism (0415): 1; TSH decreased (1690): 1; Goitre (0414): 1; Hyperthyroidism aggravated (0416): 2; Sialoadenitis (0986): 2); **1010 (n 323)**: (Cardio-respiratory failure (1899): 1; ECG abnormal (0502): 1; Cardiac failure left (0497): 2; Pulse weak (1401): 2; Cardiovascular disorders (2031): 3; Blood pressure fluctuation (1762): 5; ECG abnormal specific (0503): 6; Cardiac failure (0496): 9; Cyanosis (0501): 23; Hypertension (0210): 37; Circulatory failure (0499): 79; Hypotension (0212): 155); **1020 (n 31)**: (Mitral insufficiency (0899): 1; Coronary artery disorder (0426): 2; Myocardial ischaemia (0429): 2; Thrombosis coronary (0488): 6; Myocardial infarction (0428): 7; Angina pectoris (0422): 13; **1030 (n 148)**: (Torsade de pointes (1431): 1; Tachycardia supraventricular (0229): 1; Fibrillation atrial (0439): 2; Fibrillation cardiac (0442): 2; Arrhythmia ventricular (0435): 2; Extrasystoles (0438): 3; AV block (0431): 3; Palpitation (0221): 5; Arrhythmia (0433): 7; Fibrillation ventricular (0440): 9; Bradycardia (0208): 27; Cardiac arrest (0437): 38; Tachycardia (0224): 48); **1040 (n 135)**: (Conjunctival haemorrhage (1211): 1; Cerebral haemorrhage (0444): 1; Cerebral infarction (1986): 1; Vasospasm (0226): 1; Cerebral ischaemia (1987): 1; Compartment syndrome (2220): 1; Thrombophlebitis (0466): 1; Vasculitis allergic (0086): 1; Vasculitis (0085): 1; Peripheral ischaemia (0454): 3; Cerebrovascular disorder (0445): 3; Vasodilatation (0225): 3; Flushing (0207): 117); **1100 (n 625)**: (Airways obstruction (1749): 1; Larynx pain (1648): 1; Tracheitis (1468): 1; Pneumonitis (1141): 1; Bradypnoea (0510): 1; Pulmonary congestion (1721): 1; Aspiration (1030): 1; Pulmonary infiltration (1038): 1; Bronchospasm paradoxical (1490): 1; Sputum increased (0541): 1; Upper respiratory tract infection (0543): 2; Asphyxia (0508): 2; Hyperventilation (0517): 2; Hypoxia (0519): 2; Bronchial obstruction (1820): 2; Apnoea (0507): 3; Pharyngitis (0523): 6; Laryngismus (0520): 6; Asthma (1367): 7; Respiratory disorder (0536): 7; Stridor (0542): 9; Respiratory insufficiency (0537): 11; Laryngitis (0521): 17; Respiratory depression (0144): 20; Throat tightness (1489): 20; Pulmonary oedema (0535): 23; Bronchospasm (0511): 33; Larynx oedema (0522): 43; Rhinitis (0539): 72; Coughing (0513): 75; Dyspnoea (0514): 253; **1210 (n 1)**: (Haemolysis (0560): 1); **1220 (n 2)**: (Eosinophilia (0571): 1; Lymphoedema (0581): 1); **1230 (n 15)**: (Haematoma (1353): 1; Disseminated intravascular coagulation (1175): 1; Embolism arterial (0447): 1; Purpura thrombopenic thrombotic (0592): 1; Thrombosis (0481): 2; Purpura (0459): 3; Thrombocytopenia (0594): 3; Embolism pulmonary (0451): 3); **1300 (n 122)**: (Oliguria (0612): 1; Nephropathy toxic (0609): 1; Renal failure chronic aggravated (2330): 1; Creatinine clearance decreased (0598): 1; Renal function abnormal (0619): 2; Renal failure chronic (2329): 2; Urinary tract infection (0628): 2; Azotaemia (2328): 3; Urinary incontinence (0156): 6; Renal failure acute (0618): 15; Face oedema (0602): 88; **1420 (n 2)**: (Breast pain (1839): 1; Mastitis (0655): 1); **1810 (n 714)**: (Chest pain precordial (0719): 1; Influenza-like symptoms (1222): 1; Sudden death (1134): 1; Drug hypersensitivity syndrome (2309): 2; Asthenia (0716): 2; Medicine ineffective (1948): 2; Drug interaction (2356): 2; Death (0722): 3; Multiple organ failure (1819): 3; Chest pain substernal (0720): 4; Back pain (0717): 5; Oedema generalised (0400): 6; Choking (1460): 6; Condition aggravated (0965): 6; Pallor (0220): 6; Pain (0730): 6; Oedema peripheral (0401): 11; Fever (0725): 15; Allergy (1058): 17; Chest pain (0718): 23; Malaise (0728): 30; Oedema (0398): 33; Syncope (0223): 33; Rigors (0731): 38; Anaphylactic reaction (2237): 39; Oedema mouth (1485): 46; Oedema periorbital (1009): 47; Temperature changed sensation (1705): 47; Allergic reaction (0712): 71; Anaphylactoid reaction (0714): 88; Anaphylactic shock (0713): 120); **1820 (n 17)**: (Injection site pain (0057): 1; Injection site rash (1881): 1; Application site oedema (0048): 1; Injection site inflammation (0054): 3;

Injection site reaction (0058): 4; Injection site urticaria (1968): 7); **1830 (n 3)**: (Sepsis (0744): 1; Immune system disorder (1903): 1; Skin tightness (2098): 1**); n 5/14, Iopamidol (17,718): 100 (n 3,813)**: (Heat rash (1469): 1; Livedo reticularis (1410): 1; Dermatitis contact (0049): 1; Alopecia (0002): 1; Sweating decreased (1298): 1; Rash vesicular (1443): 1; Dermatitis lichenoid (0010): 1; Skin ulceration (0041): 1; Psoriasis aggravated (0782): 2; Rash pustular (0032): 2; Eczema (0012): 2; Hypotrichosis (0828): 2; Epidermal necrolysis (0013): 3; Skin dry (1123): 3; Skin necrosis (0060): 3; Urticaria acute (0045): 3; Skin reaction localised (1650): 3; Skin exfoliation (1199): 4; Dermatitis exfoliative (0008): 4; Eyelid skin disorder (2253): 5; Stevens Johnson syndrome (0042): 5; Erythema multiforme (0014): 6; Photosensitivity reaction (0022): 8; Skin disorder (0037): 10; Skin discolouration (0036): 13; Skin cold clammy (0932): 16; Dermatitis (0007): 25; Bullous eruption (0871): 31; Angioedema (0003): 49; Rash maculo-papular (0030): 69; Sweating increased (0043): 117; Rash erythematous (0028): 287; Rash (0027): 545; Pruritus (0024): 824; Urticaria (0044): 1,764); **200 (n 123)**: (Back disorders (1901): 1; Bone disorder (0067): 1; Arthritis aggravated (1015): 1; Tendon disorder (1074): 1; Synovitis (0864): 1; Tenosynovitis (1374): 1; Avascular necrosis bone (2222): 1; Osteomyelitis (1184): 1; Fracture pathological (0069): 2; Myopathy (0074): 2; Tendinitis (1001): 2; Musculoskeletal pain (1889): 4; Arthropathy (0065): 4; Arthrosis (0066): 5; Arthritis (0064): 7; Rhabdomyolysis (1210): 8; Skeletal pain (1347): 10; Arthralgia (0063): 20; Myalgia (0073): 21; Muscle weakness (1128): 30); **410 (n 2,739)**: (Abscences (1208): 1; Migraine aggravated (1021): 1; Automatism (1434): 1; Myasthenia gravis-like syndrome (1063): 1; Dementia (0100): 1; Optic neuritis (0136): 1; Tongue paralysis (0153): 1; Paralysis spastic (0775): 1; Encephalomyelitis (0974): 1; Ptosis (0142): 1; Cerebral disorder (1960): 1; Spasm generalized (0149): 1; Monoplegia (0122): 2; Neuropathy peripheral (1313): 2; Hypertension intracranial (0115): 2; Sensory disturbance (0148): 2; Hyperreflexia (0774): 2; Myelitis (0123): 2; Oculomotor nerve paralysis (0133): 2; Neuroleptic malignant syndrome (1202): 2; Opisthotonos (0134): 2; Neuralgia (0124): 2; Guillain-Barré syndrome (2354): 2; Migraine (0121): 2; Scotoma (0147): 2; Torticollis (0077): 3; Hemianopia (0110): 3; Cranial nerve lesion (0983): 3; Visual field defect (0159): 3; Cognitive disorders (1877): 3; Nystagmus (0131): 4; Hydrocephalus (0692): 4; Tetany (0152): 4; Coordination abnormal (0097): 4; Hyperaesthesia (0113): 4; Paralysis flaccid (0139): 4; Brain stem disorder (0810): 4; Hyporeflexia (0850): 5; Quadriplegia (0143): 5; Blindness cortical (1890): 5; Hyperkinesia (0114): 6; Arachnoiditis (1031): 7; EEG abnormal (0104): 7; Paraplegia (0140): 7; Dystonia (0068): 7; Neurologic disorder NOS (2133): 8; Faecal incontinence (0107): 8; Paresis (0141): 9; Dyskinesia (0102): 9; Hypokinesia (0118): 9; Neuritis (0125): 9; Gait abnormal (0108): 10; Neuropathy (0130): 11; Hypotonia (0119): 11; Vertigo (0158): 12; Oculogyric crisis (0132): 12; Ataxia (0088): 12; Dysaesthesia (1491): 14; Hemiparesis (0111): 19; Encephalopathy (0105): 24; Oedema cerebral (0891): 25; Paralysis (0138): 26; CSF abnormal (0098): 30; Hemiplegia (0112): 32; Muscle contractions involuntary (0155): 34; Aphasia (0087): 38; Cramps legs (0939): 42; Dysphonia (0103): 43; Meningism (0120): 57; Hypoaesthesia (0117): 59; Speech disorder (0150): 62; Stupor (0151): 86; Hypertonia (0116): 113; Coma (0091): 128; Tremor (0154): 135; Dizziness (0101): 138; Convulsions grand mal (0095): 142; Paraesthesia (0137): 158; Meningitis (0955): 183; Convulsions (0093): 277; Headache (0109): 624; **431 (n 298)**: (Accommodation abnormal (0202): 1; Miosis (0217): 1; Corneal oedema (1284): 1; Eye muscle paralysis (1429): 1; Photopsia (1172): 1; Vitreous detachment (1136): 1; Pupillary reflex impaired (0852): 1; Uveitis (0860): 1; Scleritis (0255): 1; Epiphora (1462): 1; Strabismus (0256): 1; Papilloedema (0249): 2; Fixed pupils (1605): 2; Eye pain (0244): 3; Lacrimal gland disorder (0216): 5; Eye abnormality (0243): 6; Mydriasis (0219): 7; Blindness temporary (1280): 9; Diplopia (0241): 14;

Blindness (0232): 20; Photophobia (0250): 26; Lacrimation abnormal (1049): 40; Vision abnormal (0257): 46; Conjunctivitis (0238): 107; **432 (n 50)**: (Deafness nerve (0259): 1; Vestibular disorder (1126): 1; Hyperacusis (0261): 3; Hearing decreased (1368): 5; Ear disorder NOS (1255): 6; Tinnitus (0264): 15; Deafness (0258): 19; **433 (n 21)**: (Parosmia (0265): 2; Taste loss (0266): 4; Taste perversion (0267): 15); **500 (n 542)**: (Concentration impaired (1127): 1; Delusion (0170): 1; Appetite increased (0168): 1; Suicide ideation (2363): 1; Sleep disorder (0195): 1; Euphoria (0178): 1; Communication disorder (1970): 1; Psychosomatic disorder (2115): 1; Depression (0172): 2; Hysteria (0180): 2; Paroniria (0191): 2; Emotional lability (0177): 3; Apathy (0167): 3; Insomnia (0183): 3; Anorexia (0165): 3; Neurosis (0189): 3; Mental deficiency (0187): 4; Delirium (0099): 4; Personality disorder (0192): 6; Hallucination (0179): 8; Thinking abnormal (0199): 13; Psychosis (0193): 17; Nervousness (0188): 26; Aggressive reaction (0162): 29; Depersonalization (0171): 32; Amnesia (0164): 37; Somnolence (0197): 44; Anxiety (0166): 50; Agitation (0163): 67; Confusion (0092): 176); **600 (n 1,725)**: (Ileus (0214): 1; Lip disorder (1852): 1; Amylase increased (1101): 1; Haemorrhage rectum (1014): 1; Gastritis (0291): 1; Haematemesis (0297): 1; Duodenal ulcer (0274): 1; Oesophagitis (0309): 1; Stomatitis ulcerative (0328): 1; Peritonitis (0320): 1; Enanthema (0281): 1; Saliva altered (0758): 1; Constipation (0204): 2; Diarrhoea bloody (1382): 2; Salivary gland enlargement (0325): 2; Tenesmus (0231): 2; Saliva increased (0222): 3; Stomatitis (0327): 3; GI haemorrhage (0294): 3; Cheilitis (0270): 4; Dyspepsia (0279): 4; Mucositis NOS (1351): 4; Glossitis (0295): 5; Pancreatitis (0314): 7; Tongue disorder (0330): 9; Diarrhoea (0205): 24; Tongue oedema (0331): 32; Mouth dry (0218): 41; Abdominal pain (0268): 53; Dysphagia (0280): 74; Nausea (0308): 649; Vomiting (0228): 790); **700 (n 21)**: (Hepatitis cholestatic (0351): 1; Liver fatty (0358): 1; Hepatocellular damage (0353): 1; Hepatic necrosis (0349): 1; Jaundice (0356): 1; Hepatitis (0350): 2; Gamma-GT increased (1334): 2; Bilirubinaemia (0339): 2; Hepatic function abnormal (0348): 2; SGOT increased (0359): 2; Hepatic enzymes increased (1346): 3; SGPT increased (0360): 3); **800 (n 83)**: (Glucose tolerance abnormal (0376): 1; Gout (0378): 1; Fluid overload (1018): 1; Globulins increased (0375): 1; Diabetes mellitus (0371): 1; Acidosis respiratory (1465): 1; Enzyme abnormality (0993): 1; Hypernatraemia (0384): 1; Weight increase (0408): 1; Hypocalcaemia (0387): 1; Fluid intake reduced (2340): 1; Phosphatase alkaline increased (0404): 1; Eating disorder (2336): 1; Thirst (0405): 1; Acidosis lactic (0364): 2; LDH increased (0394): 2; Hypokalaemia (0391): 2; Hypoglycaemia (0389): 2; Electrolyte abnormality (0374): 3; Creatine phosphokinase increased (0791): 4; Weight decrease (0407): 4; Dehydration (0370): 5; Hyponatraemia (0392): 6; Hyperkalaemia (0383): 9; Acidosis (0363): 12; Oedema pharynx (1395): 18); **900 (n 9)**: (Diabetes insipidus (0411): 1; Sialoadenitis (0986): 3; Hyperthyroidism (0415): 5); **1010 (n 1,029)**: (Cardio-respiratory failure (1899): 1; Heart murmur (1471): 1; Aneurysm (0915): 2; Hypertension aggravated (0762): 2; Hypotension postural (0213): 3; Cardiac failure right (0498): 4; Blood pressure fluctuation (1762): 6; Heart disorder (0504): 7; ECG abnormal (0502): 18; Cardiac failure (0496): 19; Pulse weak (1401): 23; ECG abnormal specific (0503): 40; Cyanosis (0501): 86; Circulatory failure (0499): 172; Hypertension (0210): 189; Hypotension (0212): 456); **1020 (n 104)**: (Myocardial ischaemia (0429): 3; Thrombosis coronary (0488): 12; Coronary artery disorder (0426): 18; Angina pectoris (0422): 30; Myocardial infarction (0428): 41); **1030 (n 660)**: (Fibrillation cardiac (0442): 1; T wave inversion (1688): 2; Torsade de pointes (1431): 2; Arrhythmia ventricular (0435): 3; AV block complete (1378): 5; Tachycardia supraventricular (0229): 5; Extrasystoles (0438): 7; AV block (0431): 9; Tachycardia ventricular (0230): 11; Palpitation (0221): 14; Fibrillation atrial (0439): 16; Arrhythmia (0433): 25; Fibrillation ventricular (0440): 43; Bradycardia (0208): 115; Cardiac arrest (0437): 191; Tachycardia (0224): 211); **1040 (n 500)**:

(Telangiectasis (0464): 1; Cerebral haemorrhage (0444): 1; Thrombophlebitis cerebral vein (0469): 1; Ocular haemorrhage (1004): 1; Vasculitis allergic (0086): 1; Vein disorder (0492): 1; Thrombophlebitis deep (0470): 2; Thrombophlebitis leg deep (0472): 2; Subarachnoid haemorrhage (0463): 2; Cerebellar infarction (1492): 3; Haemorrhage intracranial (1068): 3; Phlebitis (0455): 3; Vasculitis (0085): 3; Transient ischaemic attack (1694): 4; Cerebral infarction (1986): 7; Thrombophlebitis (0466): 8; Vasospasm (0226): 9; Vascular disorder (0491): 9; Peripheral ischaemia (0454): 11; Compartment syndrome (2220): 11; Cerebrovascular disorder (0445): 53; Flushing (0207): 175; Vasodilatation (0225): 189); **1100 (n 2,538)**: (Emphysema (1093): 1; Epiglottitis (1624): 1; Bronchostenosis (2000): 1; Pulmonary disorders (2032): 1; Aspiration (1030): 1; Bronchospasm aggravated (1066): 1; Hypopnoea (1712): 1; Atelectasis (1197): 1; Pulmonary collapse (0979): 1; Asphyxia (0508): 2; Pulmonary congestion (1721): 2; Bradypnoea (0510): 2; Hypoventilation (0518): 3; Yawning (0201): 3; Pulmonary infiltration (1038): 3; Epistaxis (0515): 3; Haemoptysis (0516): 4; Respiratory distress syndrome (2252): 4; Airways obstruction (1749): 4; Breath sounds decreased (1716): 5; Sinusitis (0540): 5; Pneumonia (0528): 8; Sputum increased (0541): 9; Hypoxia (0519): 10; Upper respiratory tract infection (0543): 12; Hyperventilation (0517): 19; Asthma (1367): 20; Respiratory disorder (0536): 35; Respiratory insufficiency (0537): 39; Stridor (0542): 40; Laryngitis (0521): 44; Pharyngitis (0523): 61; Respiratory depression (0144): 65; Pulmonary oedema (0535): 79; Apnoea (0507): 84; Larynx oedema (0522): 94; Throat tightness (1489): 106; Laryngismus (0520): 147; Bronchospasm (0511): 207; Coughing (0513): 223; Rhinitis (0539): 350; Dyspnoea (0514): 837); **1210 (n 15)**: (Anaemia hypochromic (0553): 1; Anaemia haemolytic (0548): 1; Spleen disorder (0568): 1; Haemolysis (0560): 3; Anaemia (0544): 9); **1220 (n 32)**: (Eosinophilia (0571): 1; Granulocytopenia (0572): 1; Lymphopenia (0845): 1; Lymphadenopathy cervical (0578): 1; Leucopenia (0908): 2; Agranulocytosis (0570): 2; Lymphadenopathy (0577): 2; Leukocytosis (0576): 22); **1230 (n 95)**: (Haematoma (1353): 1; Thrombosis pulmonary (0490): 1; Haemoperitoneum (0588): 1; Embolism arterial (0447): 1; Thrombosis cerebral (0486): 1; Purpura thrombocytopenic (1348): 1; Coagulation factor decreased (1122): 1; Purpura thrombopenic thrombotic (0592): 1; Gingival bleeding (0930): 1; Thrombosis arterial leg (0484): 1; Embolism - blood clot (0446): 2; Embolism cerebral (0448): 2; Thrombosis cerebral arterial (0487): 2; Haemorrhage NOS (0452): 3; Embolism pulmonary (0451): 5; Disseminated intravascular coagulation (1175): 6; Thrombosis arterial (0482): 7; Purpura (0459): 11; Thrombocytopenia (0594): 12; Thrombosis (0481): 15; Coagulation disorder (0586): 20); **1300 (n 551)**: (Micturition urgency (1497): 1; Nephritis interstitial (0608): 1; Glomerulonephritis (0603): 1; Bladder discomfort (1718): 1; Renal tubular disorder (0623): 1; Albuminuria (0595): 1; Creatinine clearance decreased (0598): 1; Renal calculus (0617): 1; Micturition disorder (0605): 2; Dysuria (0601): 2; Cystitis (0599): 2; Renal pain (0621): 2; Urinary tract infection (0628): 3; Micturition frequency (0606): 3; Anuria (0596): 5; Urinary retention (0157): 5; Nephropathy toxic (0609): 6; Haematuria (0604): 6; Renal tubular necrosis (0624): 7; Oliguria (0612): 10; Renal failure chronic (2329): 10; Urinary incontinence (0156): 26; Renal function abnormal (0619): 41; Azotaemia (2328): 52; Renal failure acute (0618): 74; Face oedema (0602): 287); **1420 (n 2)**: (Breast pain (1839): 1; Vaginitis (0669): 1; **1500 (n 1)**: (Vascular malformation peripheral (0764): 1); **1600 (n 2)**: (Death neonatal (0710): 1; Developmental delay (1577): 1); **1700 (n 2)**: (Ovarian cyst (0796): 2); **1810 (n 2,546)**: (Drug interaction (2356): 1; Tenderness NOS (1911): 1; Drug level below therapeutic (2172): 1; Ascites (0715): 1; Abdomen enlarged (0711): 1; Anaesthetic complication (2160): 1; Night sweats (1898): 1; Chest pain substernal (0720): 1; Oedema genital (1092): 1; ESR increased (0723): 2; Drug level increased (1281): 2; Scar (1522): 2; Sudden death (1134): 3; Tolerance

decreased (0761): 4; Medicine ineffective (1948): 4; Multiple organ failure (1819): 4; Choking (1460): 5; Therapeutic response decreased (0878): 5; Hyperpyrexia (0894): 6; Influenza-like symptoms (1222): 6; Drug hypersensitivity syndrome (2309): 6; Oedema generalised (0400): 6; Leg pain (1439): 10; Hypothermia (0727): 10; Allergy (1058): 15; Fatigue (0724): 22; Asthenia (0716): 28; Condition aggravated (0965): 29; Oedema peripheral (0401): 33; Pallor (0220): 36; Oedema mouth (1485): 58; Oedema (0398): 67; Anaphylactic reaction (2237): 74; Malaise (0728): 79; Temperature changed sensation (1705): 80; Oedema periorbital (1009): 93; Syncope (0223): 94; Back pain (0717): 108; Death (0722): 161; Anaphylactic shock (0713): 172; Allergic reaction (0712): 173; Rigors (0731): 185; Fever (0725): 212; Anaphylactoid reaction (0714): 214; Pain (0730): 219; Chest pain (0718): 310); **1820 (n 185)**: (Injection site bruising (1753): 1; Cellulitis (1372): 1; Injection site necrosis (0056): 1; Injection site anaesthesia (1917): 1; Application site reaction (0047): 1; Injection site infection (1910): 1; Anaesthesia local (0062): 2; Injection site bleeding (1752): 3; Injection site rash (1881): 3; Infusion site reaction (2137): 5; Application site oedema (0048): 6; Medical device complication (2139): 6; Injection site inflammation (0054): 16; Injection site pain (0057): 38; Injection site reaction (0058): 100); **1830 (n 32)**: (Abscess (0887): 1; Vaccination complication (1034): 1; Healing impaired (0896): 1; Infection viral (0740): 1; Herpes zoster (0862): 2; Infection bacterial (0738): 7; Sepsis (0744): 8; Infection (0736): 11); **n 6/15, Iopentol (434): 100 (n 112)**: (Rash maculo-papular (0030): 1; Rash purpuric (0462): 1; Epidermal necrolysis (0013): 1; Skin cold clammy (0932): 1; Stevens Johnson syndrome (0042): 1; Urticaria acute (0045): 1; Angioedema (0003): 3; Sweating increased (0043): 6; Rash (0027): 13; Pruritus (0024): 19; Rash erythematous (0028): 30; Urticaria (0044): 35); **200 (n 1)**: (Arthralgia (0063): 1); **410 (n 37)**: (Faecal incontinence (0107): 1; Dystonia (0068): 1; Convulsions (0093): 1; Tetany (0152): 1; Paresis (0141): 1; Hypertonia (0116): 1; Dizziness (0101): 2; Tremor (0154): 3; Speech disorder (0150): 3; Dysphonia (0103): 3; Paraesthesia (0137): 4; Headache (0109): 8; Coma (0091): 8); **431 (n 5)**: (Conjunctivitis (0238): 2; Vision abnormal (0257): 3); **433 (n 2)**: (Parosmia (0265): 1; Taste perversion (0267): 1); **500 (n 9)**: (Anxiety (0166): 1; Agitation (0163): 1; Nervousness (0188): 1; Depression (0172): 2; Confusion (0092): 4); **600 (n 47)**: (Mouth dry (0218): 1; Hiccup (0300): 1; GI haemorrhage (0294): 1; Tongue discolouration (0329): 1; Pancreatitis (0314): 1; Abdominal pain (0268): 3; Vomiting (0228): 14; Nausea (0308): 25); **800 (n 2)**: (Hypokalaemia (0391): 1; Oedema pharynx (1395): 1); **900 (n 1)**: (Sialoadenitis (0986): 1); **1010 (n 36)**: (Cardiac failure right (0498): 1; Cardiac failure (0496): 1; Hypertension (0210): 4; Cyanosis (0501): 4; Circulatory failure (0499): 9; Hypotension (0212): 17); **1020 (n 1)**: (Myocardial infarction (0428): 1); **1030 (n 14)**: (Tachycardia supraventricular (0229): 1; Fibrillation ventricular (0440): 2; Cardiac arrest (0437): 2; Bradycardia (0208): 2; Tachycardia (0224): 7); **1040 (n 7)**: (Vasospasm (0226): 1; Flushing (0207): 6); **1100 (n 64)**: (Apnoea (0507): 1; Stridor (0542): 1; Asphyxia (0508): 1; Respiratory insufficiency (0537): 2; Coughing (0513): 4; Pulmonary oedema (0535): 6; Larynx oedema (0522): 7; Bronchospasm (0511): 8; Rhinitis (0539): 8; Dyspnoea (0514): 26); **1220 (n 1)**: (Lymphadenopathy (0577): 1); **1230 (n 1)**: (Embolism pulmonary (0451): 1); **1300 (n 13)**: (Anuria (0596): 1; Urinary incontinence (0156): 1; Renal failure acute (0618): 1; Azotaemia (2328): 1; Renal function abnormal (0619): 2; Face oedema (0602): 7); **1500 (n 1)**: (Drug exposure in pregnancy (2221): 1); **1810 (n 76)**: (Condition aggravated (0965): 1; Chest pain precordial (0719): 1; Malaise (0728): 1; Asthenia (0716): 1; Oedema generalised (0400): 1; Oedema peripheral (0401): 1; Oedema mouth (1485): 1; Temperature changed sensation (1705): 2; Anaphylactic reaction (2237):2; Fever (0725):3; Death (0722):3; Syncope (0223):3; Pallor (0220):3; Pain (0730): 4; Rigors (0731): 4; Chest pain (0718): 4; Oedema (0398): 5; Allergic reaction (0712):

9; Anaphylactoid reaction (0714): 11; Anaphylactic shock (0713): 16); **1820 (n 3)**: (Application site oedema (0048): 1; Application site reaction (0047): 2); **1830 (n 1)**: (Sepsis (0744): 1); **n 7/16, Iopromide (19,387): 100 (n 6,323)**: (Psoriasis (1398): 1; Pruritus ani (0025): 1; Pruritus genital (0026): 1; Nail disorder (0020): 1; Photosensitivity allergic reaction (0021): 1; Dermographia (0011): 1; Alopecia (0002): 1; Furunculosis (0016): 1; Acne (0001): 1; Skin necrosis (0060): 1; Rash vesicular (1443): 1; Livedo reticularis (1410): 1; Rosacea (1020): 1; Erythema exudativum (0925): 1; Scleroderma (0971): 1; Dermatitis exfoliative (0008): 2; Skin ulceration (0041): 2; Epidermal necrolysis (0013): 2; Rash purpuric (0462): 2; Skin dry (1123): 2; Rash follicular (0029): 2; Skin exfoliation (1199): 2; Piloerection (1071): 2; Erythema multiforme (0014): 2; Sweating decreased (1298): 3; Eyelid skin disorder (2253): 3; Stevens Johnson syndrome (0042): 5; Skin reaction localised (1650): 5; Eczema (0012): 8; Dermatitis (0007): 9; Skin discolouration (0036): 12; Urticaria acute (0045): 22; Rash pustular (0032): 22; Skin disorder (0037): 23; Skin cold clammy (0932): 25; Bullous eruption (0871): 30; Sweating increased (0043): 135; Rash maculo-papular (0030): 138; Angioedema (0003): 209; Rash (0027): 730; Rash erythematous (0028): 781; Pruritus (0024): 1,330; Urticaria (0044): 2,800); **200 (n 23)**: (Arthrosis (0066): 1; Arthropathy (0065): 1; Musculoskeletal pain (1889): 1; Fibromyalgia (1838): 1; Tendon disorder (1074): 2; Muscle weakness (1128): 3; Skeletal pain (1347): 4; Myalgia (0073): 4; Arthralgia (0063): 6); **300 (n 1)**: (Graft versus host disease (1770): 1); **410 (n 1,197)**: (Hyperaesthesia (0113): 1; Upper motor neurone lesion (0892): 1; Anaesthesia mouth (1473): 1; Cholinergic syndrome (0203): 1; Neuralgia (0124): 1; EEG abnormal (0104): 1; Neuritis (0125): 1; Brain stem disorder (0810): 1; Neuropathy peripheral (1313): 1; Hemiplegia (0112): 1; Paralysis flaccid (0139): 1; Convulsions aggravated (0094): 1; Paraplegia (0140): 1; Hyperkinesia (0114): 2; Cognitive disorders (1877): 2; Visual field defect (0159): 2; Coordination abnormal (0097): 2; Neurologic disorder NOS (2133): 2; Apraxia (1285): 2; Tongue paralysis (0153): 2; Cerebellar syndrome (0089): 2; Blindness cortical (1890): 2; Oedema cerebral (0891): 2; Nystagmus (0131): 2; Dyskinesia (0102): 3; Gait abnormal (0108): 3; Paresis (0141): 3; Dystonia (0068): 4; Neuropathy (0130): 5; Hypokinesia (0118): 5; Hypotonia (0119): 5; Sensory disturbance (0148): 5; Oculogyric crisis (0132): 5; Tetany (0152): 6; Encephalopathy (0105): 6; Ataxia (0088): 6; Hypertonia (0116): 7; Paralysis (0138): 8; Migraine (0121): 9; Faecal incontinence (0107): 9; Muscle contractions involuntary (0155): 11; Vertigo (0158): 12; Aphasia (0087): 14; Hemiparesis (0111): 16; Dysaesthesia (1491): 33; Speech disorder (0150): 38; Convulsions grand mal (0095): 40; Stupor (0151): 47; Convulsions (0093): 50; Dysphonia (0103): 75; Hypoaesthesia (0117): 79; Tremor (0154): 87; Coma (0091): 103; Headache (0109): 121; Paraesthesia (0137): 142; Dizziness (0101): 205); **431 (n 254)**: (Thrombosis retinal vein (1157): 1; Myopia (0248): 1; Exophthalmos (0242): 1; Strabismus (0256): 1; Eye muscle paralysis (1429): 1; Glaucoma (0227): 1; Photopsia (1172): 1; Scleritis (0255): 1; Retinitis (0254): 1; Papilloedema (0249): 2; Photophobia (0250): 3; Eye abnormality (0243): 3; Mydriasis (0219): 5; Blindness temporary (1280): 5; Blindness (0232): 6; Diplopia (0241): 6; Eye pain (0244): 10; Vision abnormal (0257): 40; Lacrimation abnormal (1049): 51; Conjunctivitis (0238): 114); **432 (n 16)**: (Deafness (0258): 1; Hearing decreased (1368): 1; Ear ache (0260): 2; Ear disorder NOS (1255): 6; Tinnitus (0264): 6); **433 (n 51)**: (Taste loss (0266): 1; Taste perversion (0267): 50); **500 (n 297)**: (Delirium (0099): 1; Sleep disorder (0195): 1; Thinking abnormal (0199): 1; Apathy (0167): 1; Manic reaction (0186): 1; Anorexia (0165): 1; Mental deficiency (0187): 1; Concentration impaired (1127): 1; Mental disorder (1944): 1; Hallucination (0179): 2; Personality disorder (0192): 2; Euphoria (0178): 2; Hysteria (0180): 2; Emotional lability (0177): 3; Depression (0172): 3; Aggressive reaction (0162): 4; Psychosis (0193): 12; Depersonalization (0171): 13; Amnesia (0164): 21;

Nervousness (0188): 24; Agitation (0163): 41; Anxiety (0166): 42; Somnolence (0197): 47; Confusion (0092): 70); **600 (n 1,985)**: (Ileus (0214): 1; Gingivitis (1083): 1; Colitis (0271): 1; Flatulence (0285): 1; Oesophagitis (0309): 1; Stomatitis ulcerative (0328): 1; Peritonitis (0320): 1; Saliva increased (0222): 1; GI haemorrhage (0294): 2; Tenesmus (0231): 3; Salivary gland enlargement (0325): 3; Glossitis (0295): 4; Dyspepsia (0279): 4; Gastro-intestinal disorder NOS (1262): 5; Stomatitis (0327): 5; Tongue disorder (0330): 8; Pancreatitis (0314): 8; Diarrhoea (0205): 18; Mouth dry (0218): 26; Mucositis NOS (1351): 28; Abdominal pain (0268): 46; Cheilitis (0270): 60; Tongue oedema (0331): 70; Dysphagia (0280): 85; Vomiting (0228): 714; Nausea (0308): 888); **700 (n 19)**: (Cholelithiasis (0343): 1; Liver fatty (0358): 1; Gallbladder disorder (0345): 1; Hepatic enzymes increased (1346): 2; Hepatic failure (0933): 2; Bilirubinaemia (0339): 2; Gamma-GT increased (1334): 2; Jaundice (0356): 2; Hepatic function abnormal (0348): 3; Hepatitis (0350): 3); **800 (n 77)**: (Hyperkalaemia (0383): 1; Hypocalcaemia (0387): 1; Acidosis respiratory (1465): 1; Xerophthalmia (0943): 1; Hypoglycaemia (0389): 1; Fluid overload (1018): 1; Hypokalaemia (0391): 1; Hypercalcaemia (0380): 1; Hyponatraemia (0392): 1; Glucose tolerance abnormal (0376): 1; Troponin t increased (2090): 1; Dehydration (0370): 1; Weight increase (0408): 1; Acidosis lactic (0364): 2; Phosphatase alkaline increased (0404): 2; Hyperammonaemia (1113): 2; Hypoproteinaemia (0827): 2; Weight decrease (0407): 2; Acidosis (0363): 3; Diabetes mellitus (0371): 3; Hyperglycaemia (0382): 6; Oedema pharynx (1395): 42); **900 (n 9)**: (Sialoadenitis (0986): 1; Myxoedema (0418): 1; Hypothyroidism (0417): 1; Thyroiditis (0420): 1; Thyroid disorder (0419): 1; Hyperthyroidism (0415): 2; TSH increased (1831): 2); **1010 (n 1,176)**: (Heart murmur (1471): 1; Hypertension pulmonary (0211): 1; Hypertension aggravated (0762): 1; Aneurysm (0915): 2; Hypotension postural (0213): 3; Cardiac failure left (0497): 3; Cardio-respiratory failure (1899): 3; Cardiomegaly (1320): 4; Heart disorder (0504): 5; ECG abnormal specific (0503): 7; Cardiovascular disorders (2031): 8; ECG abnormal (0502): 9; Blood pressure fluctuation (1762): 10; Cardiac failure (0496): 17; Pulse weak (1401): 18; Cyanosis (0501): 76; Hypertension (0210): 139; Circulatory failure (0499): 177; Hypotension (0212): 692); **1020 (n 76)**: (Cardiomyopathy (0425): 1; Cardiac enzymes increased (1888): 1; Mitral insufficiency (0899): 1; Myocardial ischaemia (0429): 4; Thrombosis coronary (0488): 5; Coronary artery disorder (0426): 6; Myocardial infarction (0428): 15; Angina pectoris (0422): 43); **1030 (n 675)**: (Tachycardia supraventricular (0229): 1; Arrhythmia atrial (0434): 2; AV block (0431): 2; Bundle branch block (0436): 3; QT prolonged (1361): 3; Heart block (0441): 3; AV block complete (1378): 4; Tachycardia ventricular (0230): 5; Fibrillation atrial (0439): 9; Palpitation (0221): 19; Arrhythmia (0433): 37; Fibrillation ventricular (0440): 45; Extrasystoles (0438): 66; Bradycardia (0208): 113; Cardiac arrest (0437): 165; Tachycardia (0224): 198); **1040 (n 812)**: (Atherosclerosis (0772): 1; Haemorrhage intracranial (1068): 1; Cerebral haemorrhage (0444): 1; Vasculitis allergic (0086): 1; Vasculitis (0085): 1; Thrombophlebitis (0466): 1; Erythromelalgia (1413): 1; Thrombophlebitis deep (0470): 1; Conjunctival haemorrhage (1211): 1; Thrombophlebitis superficial (0479): 1; Cerebral infarction (1986): 2; Transient ischaemic attack (1694): 2; Compartment syndrome (2220): 2; Vasospasm (0226): 3; Cerebral ischaemia (1987): 3; Phlebitis (0455): 3; Vascular disorder (0491): 4; Peripheral ischaemia (0454): 10; Cerebrovascular disorder (0445): 17; Vasodilatation (0225): 54; Flushing (0207): 702; **1100 (n 2,928)**: (Pharyngeal disorder (2211): 1; Yawning (0201): 1; Tracheitis (1468): 1; Bronchial obstruction (1820): 1; Cheyne-Stokes respiration (1016): 1; Pneumonitis (1141): 1; Haemoptysis (0516): 1; Pulmonary fibrosis (0532): 1; Epistaxis (0515): 1; Pulmonary infiltration (1038): 1; Bronchospasm paradoxical (1490): 1; Respiratory paralysis (1466):1; Upper respiratory tract infection (0543):3; Pleural effusion (0524):3; Respiratory distress syndrome (2252): 3; Airways

obstruction (1749): 4; Pneumonia (0528): 4; Aspiration (1030): 4; Bronchospasm aggravated (1066): 4; Chronic obstructive airways disease (1493): 4; Hypoventilation (0518): 4; Atelectasis (1197): 5; Asphyxia (0508): 5; Sputum increased (0541): 5; Pulmonary congestion (1721): 8; Hyperventilation (0517): 8; Sinusitis (0540): 11; Hypoxia (0519): 18; Asthma (1367): 20; Apnoea (0507): 24; Respiratory disorder (0536): 29; Pulmonary oedema (0535): 29; Laryngismus (0520): 43; Respiratory insufficiency (0537): 49; Pharyngitis (0523): 53; Respiratory depression (0144): 85; Stridor (0542): 86; Laryngitis (0521): 114; Larynx oedema (0522): 143; Throat tightness (1489): 159; Bronchospasm (0511): 181; Coughing (0513): 259; Rhinitis (0539): 621; Dyspnoea (0514): 928); **1210 (n 11)**: (Haemosiderosis (1427): 1; Serum iron increased (1294): 1; Myoglobinaemia (2223): 1; Anaemia (0544): 4; Haemolysis (0560): 4); **1220 (n 13)**: (Agranulocytosis (0570): 1; Eosinophilia (0571): 1; Leucopenia (0908): 2; Lymphadenopathy (0577): 4; Leukocytosis (0576): 5); **1230 (n 16)**: (Embolism arterial (0447): 1; Thrombosis (0481): 1; Prothrombin decreased (0590): 1; Disseminated intravascular coagulation (1175): 1; Thrombocytopenia (0594): 1; Haemorrhage NOS (0452): 2; Coagulation disorder (0586): 2; Embolism pulmonary (0451): 3; Purpura (0459): 4); **1300 (n 627)**: (Oliguria (0612): 1; Pyelonephritis (0614): 1; Anuria (0596): 1; Urine abnormal (0629): 1; Micturition disorder (0605): 1; Urinary tract infection (0628): 1; Renal tubular disorder (0623): 1; Cystitis (0599): 2; Micturition frequency (0606): 2; Nephritis (0607): 2; Renal tubular necrosis (0624): 3; Micturition urgency (1497): 4; Haematuria (0604): 4; Renal pain (0621): 5; Renal failure chronic (2329): 5; Nephropathy toxic (0609): 7; Strangury (0625): 10; Azotaemia (2328): 11; Renal function abnormal (0619): 13; Urinary incontinence (0156): 21; Renal failure acute (0618): 36; Face oedema (0602): 495); **1420 (n 4)**: (Breast pain female (0643): 1; Mastitis (0655): 1; Breast pain (1839): 2); **1500 (n 2)**: (Congenital anomaly NOS (1256): 1; Drug exposure in pregnancy (2221): 1); **1810 (n 2,684)**: (Hypovolaemia (0929): 1; Influenza-like symptoms (1222): 1; C-reactive protein increased (2351): 1; Scar (1522): 1; Tolerance decreased (0761): 1; Sudden death (1134): 1; Drug level decreased (1282): 1; Tenderness NOS (1911): 1; Hyperpyrexia (0894): 2; ESR increased (0723): 2; Ascites (0715): 2; Medicine ineffective (1948): 2; Hypothermia (0727): 4; Leg pain (1439): 4; Multiple organ failure (1819): 5; Chest pain substernal (0720): 6; Chest pain precordial (0719): 10; Condition aggravated (0965): 10; Drug hypersensitivity syndrome (2309): 12; Fatigue (0724): 16; Choking (1460): 16; Asthenia (0716): 17; Back pain (0717): 18; Allergy (1058): 21; Death (0722): 31; Pallor (0220): 35; Oedema generalised (0400): 35; Oedema peripheral (0401): 39; Pain (0730): 45; Fever (0725): 47; Malaise (0728): 80; Oedema (0398): 99; Oedema mouth (1485): 103; Syncope (0223): 124; Anaphylactic reaction (2237): 135; Rigors (0731): 160; Oedema periorbital (1009): 189; Allergic reaction (0712): 194; Anaphylactoid reaction (0714): 200; Chest pain (0718): 244; Anaphylactic shock (0713): 256; Temperature changed sensation (1705): 513); **1820 (n 99)**: (Injection site necrosis (0056): 1; Application site reaction (0047): 2; Infusion site rash (2136): 2; Application site oedema (0048): 3; Injection site mass (0055): 4; Infusion site reaction (2137): 4; Injection site rash (1881): 6; Injection site inflammation (0054): 7; Injection site urticaria (1968): 7; Injection site pain (0057): 11; Injection site reaction (0058): 52); **1830 (n 12)**: (Infection bacterial (0738): 1; Abscess (0887): 1; Herpes NOS (2055): 1; Infection staphylococcal (1867): 2; Sepsis (0744): 2; Infection (0736): 2; Skin tightness (2098): 3; **n 8/17, Iotrolan (773): 100 (n 175)**: (Urticaria acute (0045): 1; Bullous eruption (0871): 2; Dermatitis (0007): 3; Sweating increased (0043): 3; Eczema (0012): 4; Rash maculo-papular (0030): 6; Angioedema (0003): 12; Urticaria (0044): 24; Pruritus (0024): 35; Rash erythematous (0028): 41; Rash (0027): 44); **200 (n 2)**: (Arthrosis (0066): 1; Rhabdomyolysis (1210): 1); **300 (n 1)**: (LE syndrome (0081): 1); **410 (n 199)**: (Hyperkinesia (0114): 1; Hemiplegia (0112): 1; Hemianopia

(0110): 1; Brain stem disorder (0810): 1; Choreoathetosis (0090): 1; Meningoencephalitis (1885): 1; Dysphonia (0103): 1; Muscle contractions involuntary (0155): 1; Faecal incontinence (0107): 1; Neuralgia (0124): 1; Dyskinesia (0102): 1; Neuropathy (0130): 1; Sensory disturbance (0148): 1; Oculogyric crisis (0132): 1; Dystonia (0068): 1; Paresis (0141): 1; Tremor (0154): 2; Hydrocephalus (0692): 2; Nystagmus (0131): 2; Quadriplegia (0143): 2; Cranial nerve lesion (0983): 2; Cognitive disorders (1877): 2; Aphasia (0087): 3; Speech disorder (0150): 3; Paraplegia (0140): 3; Hypoaesthesia (0117): 3; Ataxia (0088): 3; Encephalopathy (0105): 4; Convulsions grand mal (0095): 4; Coma (0091): 4; Paraesthesia (0137): 6; Vertigo (0158): 6; Stupor (0151): 7; Oedema cerebral (0891): 8; Convulsions (0093): 11; Meningism (0120): 12; Dizziness (0101): 14; Meningitis (0955): 19; Headache (0109): 61); **431 (n 11)**: (Conjunctivitis (0238): 1; Pupillary reflex impaired (0852): 1; Photopsia (1172): 1; Photophobia (0250): 2; Diplopia (0241): 2; Vision abnormal (0257): 4); **432 (n 7)**: (Tinnitus (0264): 1; Hearing decreased (1368): 2; Deafness (0258): 4); **433 (n 1)**: (Taste perversion (0267): 1); **500 (n 52)**: (Anxiety (0166): 1; Delusion (0170): 1; Euphoria (0178): 1; Amnesia (0164): 2; Nervousness (0188): 2; Mental disorder (1944): 2; Aggressive reaction (0162): 3; Concentration impaired (1127): 3; Psychosis (0193): 4; Delirium (0099): 5; Agitation (0163): 5; Hallucination (0179): 5; Confusion (0092): 8; Somnolence (0197): 10; **600 (n 77)**: (Flatulence (0285): 1; Tongue oedema (0331): 1; Stomatitis ulcerative (0328): 1; Pancreatitis (0314): 2; Dyspepsia (0279): 2; Vomiting (0228): 32; Nausea (0308): 38; **700 (n 2)**: (Hepatic failure (0933): 1; Hepatic function abnormal (0348): 1); **800 (n 3)**: (Acidosis lactic (0364): 1; Oedema pharynx (1395): 2); **1010 (n 37)**: (Hypertension (0210): 2; Hypotension (0212): 9; Circulatory failure (0499): 26); **1030 (n 8)**: (QT prolonged (1361): 1; Bradycardia (0208): 1; Tachycardia ventricular (0230): 1; Extrasystoles (0438): 1; Tachycardia (0224): 4); **1040 (n 19)**: (Vasculitis (0085): 1; Thrombophlebitis superficial (0479): 1; Cerebral haemorrhage (0444): 1; Cerebral infarction (1986): 2; Cerebrovascular disorder (0445): 3; Flushing (0207): 11); **1100 (n 54)**: (Asthma (1367): 1; Throat tightness (1489): 1; Respiratory insufficiency (0537): 1; Respiratory distress syndrome (2252): 1; Pneumonia (0528): 2; Coughing (0513): 2; Bronchospasm (0511): 2; Rhinitis (0539): 2; Laryngismus (0520): 2; Stridor (0542): 3; Larynx oedema (0522): 9; Dyspnoea (0514): 28; **1210 (n 1)**: (Spinal cord infarction (2290): 1); **1220 (n 2)**: (Leukocytosis (0576): 2); **1230 (n 5)**: (Haematoma (1353): 1; Disseminated intravascular coagulation (1175): 1; Haemorrhage NOS (0452): 1; Embolism arterial (0447): 1; Spinal haematoma (1858): 1); **1300 (n 36)**: (Renal failure acute (0618): 1; Urinary incontinence (0156): 1; Urinary retention (0157): 2; Face oedema (0602): 32); **1810 (n 75)**: (Hyperpyrexia (0894): 1; Oedema mouth (1485): 1; Multiple organ failure (1819): 1; Allergy (1058): 1; Oedema dependent (0399): 1; Asthenia (0716): 2; Anaphylactic shock (0713): 2; Anaphylactoid reaction (0714): 2; Allergic reaction (0712): 2; Anaphylactic reaction (2237): 2; Oedema generalised (0400): 3; Oedema peripheral (0401): 3; Malaise (0728): 4; Fatigue (0724): 4; Temperature changed sensation (1705): 5; Rigors (0731): 5; Oedema (0398): 6; Back pain (0717): 6; Pain (0730): 7; Syncope (0223): 8; Fever (0725): 9); **1820 (n 2)**: (Application site reaction (0047): 1; Injection site pain (0057): 1; **1830 (n 4)**: (Infection bacterial (0738): 1; Moniliasis (0741): 1; Infection (0736): 1; Sepsis (0744): 1); **n 9/18, Ioversol (7,570): 100 (n 2,147)**: (Pruritus genital (0026): 1; Acute generalized exanthematous pustulosis (1846): 1; Erythema induratum (0912): 1; Skin ulceration (0041): 1; Erythema multiforme (0014): 1; Dermatitis lichenoid (0010): 1; Fixed eruption (1249): 1; Dermatitis exfoliative (0008): 1; Skin necrosis (0060): 1; Urticaria acute (0045): 2; Skin disorder (0037): 2; Eyelid skin disorder (2253): 2; Skin reaction localised (1650): 2; Skin cold clammy (0932): 3; Eczema (0012): 3; Skin discolouration (0036): 3; Rash pustular (0032): 4; Skin exfoliation (1199): 8; Bullous eruption (0871): 13; Dermatitis

(0007): 15; Rash maculo-papular (0030): 40; Sweating increased (0043): 43; Angioedema (0003): 44; Rash erythematous (0028): 147; Rash (0027): 293; Pruritus (0024): 492; Urticaria (0044): 1022); **200 (n 14)**: (Arthrosis (0066): 1; Crepitations (1922): 1; Arthritis (0064): 1; Rhabdomyolysis (1210): 1; Myalgia (0073): 5; Arthralgia (0063): 5); **410 (n 478)**: (Hyperaesthesia (0113): 1; Hyperreflexia (0774): 1; Arachnoiditis (1031): 1; Hemiplegia (0112): 1; Cerebral disorder (1960): 1; Convulsions aggravated (0094): 1; Sensory disturbance (0148): 1; Coordination abnormal (0097): 1; CSF abnormal (0098): 1; Cramps legs (0939): 1; EEG abnormal (0104): 1; Meningism (0120): 1; Optic ischaemic neuropathy (1978): 1; Neuropathy (0130): 1; Faecal incontinence (0107): 1; Neuropathy peripheral (1313): 1; Dyskinesia tardive (1065): 1; Oculogyric crisis (0132): 1; Vertigo (0158): 2; Encephalopathy (0105): 2; Dystonia (0068): 2; Neurologic disorder NOS (2133): 2; Gait abnormal (0108): 2; Paresis (0141): 2; Hypokinesia (0118): 3; Paralysis (0138): 4; Neuritis (0125): 4; Dyskinesia (0102): 4; Oedema cerebral (0891): 4; Hypertonia (0116): 5; Migraine (0121): 5; Visual field defect (0159): 5; Dysaesthesia (1491): 8; Muscle contractions involuntary (0155): 8; Aphasia (0087): 8; Stupor (0151): 11; Convulsions grand mal (0095): 14; Speech disorder (0150): 16; Dysphonia (0103): 17; Hypoaesthesia (0117): 19; Convulsions (0093): 24; Paraesthesia (0137): 48; Coma (0091): 53; Headache (0109): 57; Tremor (0154): 64; Dizziness (0101): 67); **431 (n 134)**: (Exophthalmos (0242): 1; Chromatopsia (0237): 1; Miosis (0217): 1; Blepharitis (1007): 2; Diplopia (0241): 2; Lacrimal gland disorder (0216): 2; Mydriasis (0219): 3; Eye abnormality (0243): 4; Eye pain (0244): 4; Blindness (0232): 5; Lacrimation abnormal (1049): 18; Vision abnormal (0257): 44; Conjunctivitis (0238): 47); **432 (n 7)**: (Deafness (0258): 1; Tinnitus (0264): 1; Hearing decreased (1368): 1; Ear disorder NOS (1255): 2; Ear ache (0260): 2); **433 (n 23)**: (Parosmia (0265): 2; Taste perversion (0267): 21); **500 (n 141)**: (Delirium (0099): 1; Psychosis (0193): 1; Personality disorder (0192): 1; Communication disorder (1970): 1; Thinking abnormal (0199): 2; Aggressive reaction (0162): 3; Depression (0172): 3; Hallucination (0179): 3; Depersonalization (0171): 7; Nervousness (0188): 8; Somnolence (0197): 12; Amnesia (0164): 13; Anxiety (0166): 23; Agitation (0163): 26; Confusion (0092): 37); **600 (n 840)**: (Increased stool urgency (1843): 1; Lip disorder (1852): 1; Amylase increased (1101): 1; Haemorrhage rectum (1014): 1; Eructation (0283): 1; Gastritis (0291): 1; Oral haemorrhage (0313): 1; Oesophagitis (0309): 1; Dyspepsia (0279): 2; Salivary gland enlargement (0325): 2; Pancreatitis (0314): 2; Haematemesis (0297): 2; Saliva increased (0222): 2; Tongue disorder (0330): 4; Stomatitis (0327): 4; Gastro-intestinal disorder NOS (1262): 5; Diarrhoea (0205): 10; Cheilitis (0270): 12; Mouth dry (0218): 16; Tongue oedema (0331): 20; Abdominal pain (0268): 23; Dysphagia (0280): 51; Nausea (0308): 284; Vomiting (0228): 393); **700 (n 7)**: (Hepatocellular damage (0353): 1; SGOT increased (0359): 1; SGPT increased (0360): 1; Hepatic function abnormal (0348): 4); **800 (n 45)**: (Hypercholesterolaemia (0381): 1; Glucose tolerance abnormal (0376): 1; Acidosis lactic (0364): 1; Dehydration (0370): 1; LDH increased (0394): 1; Hypoglycaemia (0389): 1; Hypernatraemia (0384): 1; Creatine phosphokinase increased (0791): 3; Fluid overload (1018): 3; Hyperglycaemia (0382): 4; Hyperkalaemia (0383): 6; Oedema pharynx (1395): 22); **900 (n 3)**: (Hyperthyroidism (0415): 1; Sialoadenitis (0986): 2); **1010 (n 386)**: (Cardiac failure right (0498): 1; Cardio-respiratory failure (1899): 2; Blood pressure fluctuation (1762): 2; Heart disorder (0504): 2; ECG abnormal specific (0503): 5; Pulse weak (1401): 6; ECG abnormal (0502): 8; Cardiac failure (0496): 8; Cyanosis (0501): 36; Circulatory failure (0499): 48; Hypertension (0210): 83; Hypotension (0212): 185); **1020 (n 31)**: (Echocardiogram abnormal (1912): 1; Pericardial effusion (0910): 1; Myocardial rupture (post infarct) (1366): 1; Angina pectoris aggravated (0423): 1; Thrombosis coronary (0488): 3; Angina pectoris (0422): 7; Coronary artery

disorder (0426): 8; Myocardial infarction (0428): 9); **1030 (n 418)**: (AV block complete (1378): 1; T wave inversion (1688): 1; Arrhythmia atrial (0434): 1; Extrasystoles (0438): 1; Fibrillation cardiac (0442): 2; Adams Stokes syndrome (0432): 2; AV block (0431): 4; Arrhythmia ventricular (0435): 5; Arrhythmia (0433): 6; Fibrillation atrial (0439): 8; Palpitation (0221): 14; Tachycardia ventricular (0230): 19; Bradycardia (0208): 61; Tachycardia (0224): 69; Cardiac arrest (0437): 101; Fibrillation ventricular (0440): 123); **1040 (n 210)**: (Phlebitis (0455): 1; Atherosclerosis (0772): 1; Renal artery occlusion (1546): 1; Transient ischaemic attack (1694): 1; Thrombophlebitis deep (0470): 1; Cerebral ischaemia (1987): 2; Cerebral infarction (1986): 2; Vascular disorder (0491): 2; Vasculitis (0085): 3; Compartment syndrome (2220): 4; Peripheral ischaemia (0454): 4; Vasospasm (0226): 5; Cerebrovascular disorder (0445): 13; Vasodilatation (0225): 78; Flushing (0207): 92); **1100 (n 1,307)**: (Sleep apnoea (1515): 1; Pulmonary infiltration (1038): 1; Pharyngeal disorder (2211): 1; Aspiration (1030): 1; Sputum increased (0541): 1; Breath sounds decreased (1716): 1; Pleural pain (0526): 1; Atelectasis (1197): 1; Pulmonary disorders (2032): 1; Asphyxia (0508): 1; Pulmonary fibrosis (0532): 1; Hypoventilation (0518): 2; Chronic obstructive airways disease (1493): 2; Epistaxis (0515): 2; Respiratory distress syndrome (2252): 2; Upper respiratory tract infection (0543): 3; Pulmonary congestion (1721): 3; Bradypnoea (0510): 3; Pneumonia (0528): 3; Pleural effusion (0524): 3; Pneumonitis (1141): 7; Hyperventilation (0517): 8; Asthma (1367): 10; Hypoxia (0519): 10; Respiratory disorder (0536): 12; Respiratory insufficiency (0537): 17; Respiratory depression (0144): 19; Apnoea (0507): 26; Pharyngitis (0523): 30; Stridor (0542): 33; Pulmonary oedema (0535): 33; Laryngitis (0521): 49; Larynx oedema (0522): 49; Laryngismus (0520): 50; Throat tightness (1489): 68; Bronchospasm (0511): 94; Coughing (0513): 117; Rhinitis (0539): 173; Dyspnoea (0514): 468); **1210 (n 5)**: (Anaemia hypochromic (0553): 1; Haemolysis (0560): 1; Anaemia (0544): 3); **1220 (n 7)**: (Leukocytosis (0576): 3; Eosinophilia (0571): 4); **1230 (n 28)**: (Coagulation disorder (0586): 1; Haemorrhage retroperitoneal (1214): 1; Coagulation factor decreased (1122): 1; Prothrombin decreased (0590): 1; Thrombosis venous arm (1370): 1; Thrombocytopenia (0594): 1; Haematoma (1353): 2; Purpura thrombopenic thrombotic (0592): 2; Embolism - blood clot (0446): 2; Embolism arterial (0447): 2; Disseminated intravascular coagulation (1175): 2; Thrombosis (0481): 2; Embolism pulmonary (0451): 3; Purpura (0459): 7); **1300 (n 306)**: (Urine abnormal (0629): 1; Creatinine clearance decreased (0598): 1; Renal tubular disorder (0623): 1; Renal failure chronic aggravated (2330): 1; Renal pain (0621): 1; Haematuria (0604): 2; Urinary incontinence (0156): 3; Anuria (0596): 5; Micturition urgency (1497): 6; Renal tubular necrosis (0624): 6; Oliguria (0612): 10; Renal failure chronic (2329): 11; Renal function abnormal (0619): 12; Nephropathy toxic (0609): 16; Azotaemia (2328): 44; Renal failure acute (0618): 69; Face oedema (0602): 117); **1420 (n 1)**: (Mastitis (0655): 1); **1500 (n 3)**: (Death foetal (0647): 1; Abortion (0634): 1; Drug exposure in pregnancy (2221): 1); **1810 (n 907)**: (Hyperpyrexia (0894): 1; Hernia NOS (1832): 1; Sudden death (1134): 1; Chest pain substernal (0720): 1; Hyperpyrexia malignant (0893): 1; Crying abnormal (1162): 1; Hypothermia (0727): 1; Ascites (0715): 1; Hypovolaemia (0929): 1; Drug level increased (1281): 1; Leg pain (1439): 1; Scar (1522): 1; Medicine ineffective (1948): 1; Therapeutic response decreased (0878): 3; Halitosis (0990): 3; Drug hypersensitivity syndrome (2309): 4; Therapeutic response increased (0874): 5; Oedema generalised (0400): 5; Allergy (1058): 6; Condition aggravated (0965): 6; Choking (1460): 6; Back pain (0717): 6; Asthenia (0716): 7; Oedema peripheral (0401): 12; Oedema mouth (1485): 15; Fatigue (0724): 15; Pallor (0220): 16; Pain (0730): 18; Anaphylactic reaction (2237): 25; Temperature changed sensation (1705): 28; Oedema (0398): 32; Fever (0725): 32; Malaise (0728): 33; Syncope (0223): 45; Oedema periorbital (1009): 48; Death (0722): 52; Rigors

(0731): 58; Anaphylactic shock (0713): 62; Anaphylactoid reaction (0714): 64; Allergic reaction (0712): 94; Chest pain (0718): 194); **1820 (n 118)**: (Infusion site rash (2136): 1; Implantation complication (1035): 1; Injection site infection (1910): 1; Injection site anaesthesia (1917): 1; Injection site necrosis (0056): 2; Application site reaction (0047): 2; Cellulitis (1372): 2; Injection site bleeding (1752): 3; Infusion site reaction (2137): 3; Medical device complication (2139): 5; Injection site rash (1881): 9; Injection site inflammation (0054): 11; Injection site pain (0057): 12; Injection site reaction (0058): 65); **1830 (n 4)**: (Infection secondary (2097): 1; Sepsis (0744): 1; Infection (0736): 1; Skin tightness (2098): 1); **n 10/19, Ioxaglate (5,200): 100 (n 1,439)**: (Psoriasis (1398): 1; Erythema nodosum (0015): 1; Fixed eruption (1249): 1; Dermatitis (0007): 1; Heat rash (1469): 1; Dermatitis exfoliative (0008): 1; Skin disorder (0037): 1; Rash pustular (0032): 1; Eczema (0012): 2; Rash vesicular (1443): 2; Erythema multiforme (0014): 2; Stevens Johnson syndrome (0042): 2; Skin exfoliation (1199): 2; Urticaria acute (0045): 5; Skin discolouration (0036): 5; Bullous eruption (0871): 6; Sweating increased (0043): 22; Rash maculo-papular (0030): 31; Angioedema (0003): 46; Rash erythematous (0028): 95; Rash (0027): 141; Pruritus (0024): 199; Urticaria (0044): 871); **200 (n 17)**: (Synovitis (0864): 1; Muscle weakness (1128): 2; Myalgia (0073): 2; Myopathy (0074): 4; Arthralgia (0063): 4; Arthritis (0064): 4); **410 (n 299)**: (Hyperkinesia (0114): 1; Vocal cord paralysis (0942): 1; Brain stem disorder (0810): 1; Oculogyric crisis (0132): 1; Encephalomyelitis (0974): 1; Paralysis (0138): 1; Tongue paralysis (0153): 1; Paraplegia (0140): 1; Hemianopia (0110): 1; Quadriplegia (0143): 1; Hypoaesthesia (0117): 2; Encephalopathy (0105): 2; EEG abnormal (0104): 2; Ataxia (0088): 2; Oedema cerebral (0891): 2; Hypertonia (0116): 3; Dysaesthesia (1491): 3; Nystagmus (0131): 3; Vertigo (0158): 3; Paresis (0141): 4; Hemiplegia (0112): 5; Aphasia (0087): 5; Stupor (0151): 5; Neuropathy (0130): 5; Dysphonia (0103): 6; Muscle contractions involuntary (0155): 6; Speech disorder (0150): 8; Hemiparesis (0111): 9; Dizziness (0101): 12; Convulsions grand mal (0095): 17; Coma (0091): 25; Convulsions (0093): 28; Paraesthesia (0137): 35; Headache (0109): 38; Tremor (0154): 59); **431 (n 56)**: (Blindness temporary (1280): 1; Miosis (0217): 1; Lacrimal gland disorder (0216): 2; Eye pain (0244): 3; Diplopia (0241): 3; Blindness (0232): 8; Lacrimation abnormal (1049): 10; Vision abnormal (0257): 13; Conjunctivitis (0238): 15); **432 (n 4)**: (Ear ache (0260): 1; Tinnitus (0264): 3); **433 (n 1)**: (Parosmia (0265): 1); **500 (n 97)**: (Delirium (0099): 1; Insomnia (0183): 1; Thinking abnormal (0199): 1; Paranoid reaction (0190): 1; Euphoria (0178): 2; Aggressive reaction (0162): 2; Psychosis (0193): 2; Amnesia (0164): 3; Nervousness (0188): 5; Hallucination (0179): 6; Anxiety (0166): 6; Somnolence (0197): 11; Agitation (0163): 18; Confusion (0092): 38); **600 (n 721)**: (Mucositis NOS (1351): 1; Amylase increased (1101): 1; Oesophagospasm (0310): 1; Haematemesis (0297): 1; Peritonitis (0320): 1; Saliva increased (0222): 1; Pancreatitis (0314): 2; Stomatitis (0327): 3; Diarrhoea (0205): 3; Mouth dry (0218): 3; Salivary gland enlargement (0325): 4; Tongue oedema (0331): 10; Dysphagia (0280): 12; Abdominal pain (0268): 23; Nausea (0308): 254; Vomiting (0228): 401); **700 (n 12)**: (Hepatitis cholestatic (0351): 1; Bilirubinaemia (0339): 1; Hepatorenal syndrome (1103): 1; Hepatic enzymes increased (1346): 1; Hepatitis (0350): 2; SGOT increased (0359): 3; SGPT increased (0360): 3); **800 (n 16)**: (Hypervolaemia (1178): 1; Hypoproteinaemia (0827): 1; Hyperglycaemia (0382): 1; Xerophthalmia (0943): 1; Ketosis (0393): 1; Acidosis (0363): 2; Lipase increased (1621): 2; Hyperkalaemia (0383): 2; Oedema pharynx (1395): 2; Creatine phosphokinase increased (0791): 3); **900 (n 6)**: (Hypothyroidism (0417): 1; Hyperthyroidism aggravated (0416): 1; TSH increased (1831):1; T4 decreased (1447):1; Hyperthyroidism (0415):2); **1010 (n 400)**: (Hypertension pulmonary (0211): 1; ECG abnormal specific (0503): 2; ECG abnormal (0502): 3; Cardiac failure right (0498): 3; Cardiac failure (0496): 4; Cyanosis (0501): 25; Circulatory

failure (0499): 43; Hypertension (0210): 45; Hypotension (0212): 274); **1020 (n 32)**: (Pericardial effusion (0910): 1; Coronary artery disorder (0426): 4; Thrombosis coronary (0488): 4; Myocardial ischaemia (0429): 4; Angina pectoris (0422): 6; Myocardial infarction (0428): 13); **1030 (n 219)**: (Bundle branch block (0436): 1; Torsade de pointes (1431): 1; Palpitation (0221): 1; AV block (0431): 1; Tachycardia supraventricular (0229): 1; Fibrillation atrial (0439): 4; Arrhythmia ventricular (0435): 4; Arrhythmia (0433): 9; Fibrillation ventricular (0440): 13; Tachycardia ventricular (0230): 15; Bradycardia (0208): 44; Cardiac arrest (0437): 51; Tachycardia (0224): 74); **1040 (n 122)**: (Haemorrhage intracranial (1068): 1; Peripheral ischaemia (0454): 1; Vasospasm (0226): 1; Vasculitis (0085): 1; Cerebral ischaemia (1987): 1; Vasculitis allergic (0086): 1; Arteritis (0078): 2; Cerebral haemorrhage (0444): 2; Transient ischaemic attack (1694): 3; Cerebral infarction (1986): 5; Flushing (0207): 19; Cerebrovascular disorder (0445): 21; Vasodilatation (0225): 64); **1100 (n 634)**: (Cheyne-Stokes respiration (1016): 1; Pulmonary infiltration (1038): 1; Haemoptysis (0516): 1; Bronchospasm paradoxical (1490): 1; Hypoventilation (0518): 1; Bronchitis (0805): 1; Pneumonia (0528): 1; Laryngitis (0521): 2; Pulmonary congestion (1721): 2; Asthma (1367): 2; Respiratory distress syndrome (2252): 2; Sputum increased (0541): 2; Respiratory insufficiency (0537): 4; Stridor (0542): 5; Throat tightness (1489): 5; Hyperventilation (0517): 8; Respiratory disorder (0536): 11; Larynx oedema (0522): 11; Respiratory depression (0144): 12; Pharyngitis (0523): 12; Hypoxia (0519): 17; Laryngismus (0520): 27; Apnoea (0507): 29; Pulmonary oedema (0535): 45; Coughing (0513): 48; Bronchospasm (0511): 89; Rhinitis (0539): 103; Dyspnoea (0514): 191); **1210 (n 7)**: (Haemolysis (0560): 2; Anaemia (0544): 5); **1220 (n 8)**: (Lymphoedema (0581): 1; Leukocytosis (0576): 7); **1230 (n 31)**: (Embolism arterial (0447): 1; Thrombosis cerebral arterial (0487): 1; Embolism - blood clot (0446): 1; Haemorrhage NOS (0452): 1; Purpura thrombopenic thrombotic (0592): 1; Purpura allergic (0460): 1; Haematoma (1353): 2; Thrombosis (0481): 2; Disseminated intravascular coagulation (1175): 2; Thromboembolism (0465): 3; Purpura (0459): 5; Thrombocytopenia (0594): 5; Coagulation disorder (0586): 6); **1300 (n 233)**: (Dysuria (0601): 1; Renal failure chronic (2329): 1; Micturition disorder (0605): 1; Creatinine clearance decreased (0598): 1; Oliguria (0612): 1; Nephritis (0607): 2; Renal failure chronic aggravated (2330): 4; Anuria (0596): 5; Renal tubular necrosis (0624): 6; Renal function abnormal (0619): 13; Azotaemia (2328): 28; Nephropathy toxic (0609): 40; Renal failure acute (0618): 51; Face oedema (0602): 79); **1420 (n 2)**: (Uterine spasm (0667): 2); **1810 (n 828)**: (Drug interaction (2356): 1; Serum sickness (0733): 1; Hyperpyrexia malignant (0893): 1; Oedema generalised (0400): 1; Allergy aggravated (1027): 1; Chest pain precordial (0719): 2; Hypothermia (0727): 2; Hyperpyrexia (0894): 3; Oedema mouth (1485): 3; Fatigue (0724): 3; Asthenia (0716): 4; Allergy (1058): 5; Oedema peripheral (0401): 5; Anaphylactic reaction (2237): 7; Condition aggravated (0965): 8; Pallor (0220): 10; Temperature changed sensation (1705): 11; Back pain (0717): 11; Oedema (0398): 13; Pain (0730): 15; Malaise (0728): 19; Oedema periorbital (1009): 22; Syncope (0223): 23; Chest pain (0718): 54; Allergic reaction (0712): 66; Death (0722): 68; Rigors (0731): 96; Fever (0725): 102; Anaphylactic shock (0713): 123; Anaphylactoid reaction (0714): 148); **1820 (n 8)**: (Anaesthesia local (0062): 1; Injection site inflammation (0054): 2; Injection site pain (0057): 2; Injection site reaction (0058): 3; **1830 (n 8)**: (Healing impaired (0896): 2; Sepsis (0744): 6); **n 11/20, Ioxalan (82): 100 (n 29)**: (Dermographia (0011): 1; Skin discolouration (0036): 1; Rash erythematous (0028): 3; Rash (0027): 4; Pruritus (0024): 8; Urticaria (0044): 12); **410 (n 8)**: (Hemiparesis (0111): 1; Headache (0109): 1; Speech disorder (0150): 1; Tremor (0154): 2; Dizziness (0101): 3); **431 (n 1)**: (Vision abnormal (0257): 1); **500 (n 2)**: (Hysteria (0180): 1; Psychosomatic disorder (2115): 1); **600 (n 9)**: (Dyspepsia (0279): 1; Nausea (0308): 4; Vomiting (0228):

4); **800 (n 1)**: (Oedema pharynx (1395): 1); **1010 (n 7)**: (Cyanosis (0501): 1; Hypertension (0210): 2; Circulatory failure (0499): 2; Hypotension (0212): 2); **1020 (n 1)**: (Myocardial infarction (0428): 1); **1030 (n 2)**: (Fibrillation atrial (0439): 1; Tachycardia (0224): 1); **1100 (n 13)**: (Respiratory disorder (0536): 1; Respiratory depression (0144): 1; Stridor (0542): 1; Upper respiratory tract infection (0543): 1; Throat tightness (1489): 1; Rhinitis (0539): 2; Dyspnoea (0514): 3; Coughing (0513): 3); **1810 (n 9)**: (Anaphylactic shock (0713): 1; Allergic reaction (0712): 1; Anaphylactic reaction (2237): 1; Temperature changed sensation (1705): 1; Rigors (0731): 1; Fever (0725): 4); **n 12/21, Metrizamide (2,012): 100 (n 47)**: (Eczema (0012): 1; Photosensitivity reaction (0022): 1; Bullous eruption (0871): 1; Skin cold clammy (0932): 1; Angioedema (0003): 2; Rash maculo-papular (0030): 2; Pruritus (0024): 4; Rash erythematous (0028): 4; Sweating increased (0043): 6; Urticaria (0044): 12; Rash (0027): 13); **200 (n 13)**: (Fracture pathological (0069): 1; Skeletal pain (1347): 1; Muscle weakness (1128): 2; Myopathy (0074): 2; Myalgia (0073): 7); **300 (n 1)**: (LE syndrome (0081): 1); **410 (n 938)**: (Hyperaesthesia (0113): 1; Tetany (0152): 1; Neuritis sensory (0129): 1; Hydrocephalus (0692): 1; Cramps legs (0939): 1; Hyperreflexia (0774): 1; Coordination abnormal (0097): 1; Migraine (0121): 1; Encephalopathy hypertensive (0209): 1; Neuritis cranial (0127): 1; Gait abnormal (0108): 2; Myelitis (0123): 2; Hemiparesis (0111): 2; Dystonia (0068): 2; Dementia (0100): 2; Extrapyramidal disorder (0106): 2; Oculomotor nerve paralysis (0133): 2; Choreoathetosis (0090): 3; Dysphonia (0103): 3; Paralysis flaccid (0139): 3; Convulsions local (0096): 3; Quadriplegia (0143): 3; Neuralgia (0124): 3; Spasm generalized (0149): 3; Visual field defect (0159): 3; Torticollis (0077): 3; Vertigo (0158): 4; Faecal incontinence (0107): 4; Opisthotonos (0134): 4; Nystagmus (0131): 4; Dyskinesia (0102): 4; Hypoaesthesia (0117): 5; Paraplegia (0140): 5; Hyperkinesia (0114): 5; CSF abnormal (0098): 5; Neuritis (0125): 5; Neuropathy (0130): 5; Hemiplegia (0112): 6; Ataxia (0088): 6; Arachnoiditis (1031): 8; Paresis (0141): 9; Tremor (0154): 10; Aphasia (0087): 10; Oedema cerebral (0891): 11; EEG abnormal (0104): 11; Muscle contractions involuntary (0155): 15; Speech disorder (0150): 16; Paralysis (0138): 16; Paraesthesia (0137): 16; Stupor (0151): 18; Encephalopathy (0105): 19; Hypertonia (0116): 24; Coma (0091): 30; Meningism (0120): 35; Dizziness (0101): 43; Convulsions grand mal (0095): 72; Meningitis (0955): 95; Convulsions (0093): 117; Headache (0109): 250); **431 (n 50)**: (Accommodation abnormal (0202): 1; Retinal deposits (1283): 1; Papilloedema (0249): 1; Anisocoria (1174): 1; Pupillary reflex impaired (0852): 1; Eye abnormality (0243): 2; Conjunctivitis (0238): 2; Blindness (0232): 3; Diplopia (0241): 8; Photophobia (0250): 15; Vision abnormal (0257): 15); **432 (n 21)**: (Hyperacusis (0261): 2; Vestibular disorder (1126): 2; Tinnitus (0264): 6; Deafness (0258): 11); **500 (n 260)**: (Emotional lability (0177): 1; Depression psychotic (0173): 1; Schizophrenic reaction (0194): 1; Euphoria (0178): 1; Paroniria (0191): 1; Insomnia (0183): 1; Catatonic reaction (0169): 2; Apathy (0167): 2; Impotence (0182): 2; Delirium (0099): 2; Aggressive reaction (0162): 3; Delusion (0170): 3; Depersonalization (0171): 3; Paranoid reaction (0190): 4; Nervousness (0188): 5; Psychosis (0193): 5; Depression (0172): 5; Anxiety (0166): 6; Personality disorder (0192): 6; Thinking abnormal (0199): 9; Somnolence (0197): 13; Agitation (0163): 15; Amnesia (0164): 20; Hallucination (0179): 23; Confusion (0092): 126); **600 (n 292)**: (Pancreatitis (0314): 1; Dyspepsia (0279): 1; Haematemesis (0297): 2; Hiccup (0300): 2; Amylase increased (1101): 2; Oesophageal ulceration (0311): 2; Abdominal pain (0268): 2; Dysphagia (0280): 4; Nausea (0308): 105; Vomiting (0228): 171); **700 (n 5)**: (Hepatocellular damage (0353): 1; SGPT increased (0360): 1; Hepatitis (0350): 1; Jaundice (0356): 2); **800 (n 9)**: (Hypoglycaemia (0389): 1; Weight decrease (0407): 1; Thirst (0405): 1; Hypernatraemia (0384): 1; Electrolyte abnormality (0374): 2; Hyponatraemia (0392): 3); **900 (n 2)**: (Antidiuretic hormone disorder

(0883): 1; Diabetes insipidus (0411): 1); **1010 (n 33)**: (ECG abnormal specific (0503): 1; Heart disorder (0504): 1; Cyanosis (0501): 4; Circulatory failure (0499): 8; Hypertension (0210): 9; Hypotension (0212): 10); **1020 (n 1)**: (Myocardial infarction (0428): 1); **1030 (n 22)**: (Fibrillation atrial (0439): 1; Palpitation (0221): 1; Arrhythmia (0433): 2; Cardiac arrest (0437): 5; Tachycardia (0224): 6; Bradycardia (0208): 7); **1040 (n 42)**: (Flushing (0207): 1; Haemorrhage intracranial (1068): 1; Cerebral infarction (1986): 1; Polyarteritis nodosa (0083): 1; Cerebral ischaemia (1987): 1; Subarachnoid haemorrhage (0463): 1; Vasculitis (0085): 2; Vasodilatation (0225): 3; Cerebral haemorrhage (0444): 6; Cerebrovascular disorder (0445): 25); **1100 (n 45)**: (Hyperventilation (0517): 1; Bronchitis (0805): 1; Respiratory disorder (0536): 1; Larynx oedema (0522): 1; Bronchospasm (0511): 2; Hypoventilation (0518): 3; Coughing (0513): 3; Pulmonary oedema (0535): 4; Respiratory depression (0144): 4; Apnoea (0507): 10; Dyspnoea (0514): 15); **1210 (n 3)**: (Anaemia haemolytic (0548): 1; Anaemia (0544): 1; Marrow depression (0561): 1); **1220 (n 6)**: (Monocytosis (0793): 1; Leukocytosis (0576): 5); **1230 (n 10)**: (Embolism pulmonary (0451): 1; Purpura (0459): 1; Disseminated intravascular coagulation (1175): 1; Haemorrhage NOS (0452): 3; Thrombosis cerebral (0486): 4); **1300 (n 37)**: (Renal tubular necrosis (0624): 1; Renal failure chronic (2329): 1; Oliguria (0612): 1; Dysuria (0601): 1; Polyuria (0613): 1; Creatinine clearance decreased (0598): 1; Renal failure acute (0618): 1; Haematuria (0604): 2; Azotaemia (2328): 2; Anuria (0596): 2; Micturition disorder (0605): 4; Urinary retention (0157): 5; Face oedema (0602): 6; Urinary incontinence (0156): 9); **1410 (n 1)**: (Epididymitis (1076): 1); **1810 (n 162)**: (Hyperpyrexia (0894): 1; Hypothermia (0727): 1; ESR increased (0723): 1; Oedema periorbital (1009): 1; Pallor (0220): 1; Therapeutic response decreased (0878): 2; Oedema generalised (0400): 2; Oedema (0398): 3; Chest pain (0718): 4; Allergic reaction (0712): 5; Rigors (0731): 5; Fatigue (0724): 6; Syncope (0223): 7; Anaphylactoid reaction (0714): 9; Back pain (0717): 9; Asthenia (0716): 10; Pain (0730): 22; Death (0722): 22; Fever (0725): 51); **1820 (n 6)**: (Injection site reaction (0058): 1; Injection site inflammation (0054): 1; Injection site pain (0057): 4); **1830 (n 6)**: (Herpes simplex (0867): 1; Sjogren's syndrome (1541): 1; Abscess (0887): 1; Infection (0736): 3).

Sub-class C (n 8 Agents; n 1/22-8/29): n 1/22, Adipiodone meglumine (2,721): 100 (n 787): (Pruritus genital (0026): 1; Skin cold clammy (0932): 1; Rash pustular (0032): 1; Rash purpuric (0462): 1; Eczema (0012): 1; Dermatitis (0007): 2; Skin discolouration (0036): 4; Urticaria acute (0045): 5; Angioedema (0003): 11; Rash maculo-papular (0030): 46; Sweating increased (0043): 48; Rash (0027): 78; Rash erythematous (0028): 87; Pruritus (0024): 168; Urticaria (0044): 333); **200 (n 7)**: (Arthrosis (0066): 2; Arthralgia (0063): 2; Myalgia (0073): 3); **410 (n 190)**: (Gait abnormal (0108): 1; Hemiparesis (0111): 1; Extrapyramidal disorder (0106): 1; Hypotonia (0119): 1; Speech disorder (0150): 1; Paralysis (0138): 1; Hyperkinesia (0114): 2; Hypoaesthesia (0117): 2; Faecal incontinence (0107): 2; Hypertonia (0116): 2; Dysphonia (0103): 3; Tongue paralysis (0153): 3; Spasm generalized (0149): 4; Convulsions (0093): 15; Dizziness (0101): 18; Vertigo (0158): 23; Coma (0091): 25; Paraesthesia (0137): 27; Tremor (0154): 27; Headache (0109): 31); **431 (n 29)**: (Lacrimation abnormal (1049): 1; Lacrimal gland disorder (0216): 1; Strabismus (0256): 1; Vision abnormal (0257): 4; Conjunctivitis (0238): 22); **432 (n 3)**: (Deafness (0258): 1; Tinnitus (0264): 2); **433 (n 1)**: (Taste perversion (0267): 1); **500 (n 44)**: (Aggressive reaction (0162): 1; Anorexia (0165): 1; Nervousness (0188): 1; Delusion (0170): 1; Amnesia (0164): 1; Depression (0172): 1; Somnolence (0197): 5; Confusion (0092): 5; Agitation (0163): 12; Anxiety (0166): 16); **600 (n 431)**: (Mouth dry (0218): 1; Ileus paralytic (0215): 1; Colitis (0271): 1; Dyspepsia (0279): 1; Tongue disorder (0330): 1; Enteritis (0282): 1; Tenesmus (0231): 1; Salivary gland

enlargement (0325): 1; Stomatitis (0327): 1; Tongue oedema (0331): 2; Saliva increased (0222): 5; Dysphagia (0280): 8; Diarrhoea (0205): 18; Abdominal pain (0268): 35; Vomiting (0228): 166; Nausea (0308): 188); **700 (n 7)**: (Hepatomegaly (0354): 1; Biliary pain (0338): 1; SGPT increased (0360): 1; Jaundice (0356): 2; Hepatic function abnormal (0348): 2); **1010 (n 264)**: (ECG abnormal (0502): 1; Cardiac failure (0496): 1; Heart disorder (0504): 1; Hypertension (0210): 5; Cyanosis (0501): 33; Circulatory failure (0499): 88; Hypotension (0212): 135); **1020 (n 8)**: (Myocardial ischaemia (0429): 2; Angina pectoris (0422): 6); **1030 (n 83)**: (Extrasystoles (0438): 1; Fibrillation cardiac (0442): 1; Heart block (0441): 2; Arrhythmia (0433): 3; Palpitation (0221): 9; Bradycardia (0208): 11; Cardiac arrest (0437): 16; Tachycardia (0224): 40); **1040 (n 59)**: (Phlebitis (0455): 1; Thrombophlebitis vena cava (0480): 1; Vasodilatation (0225): 2; Flushing (0207): 55); **1100 (n 314)**: (Laryngitis (0521): 1; Asphyxia (0508): 1; Respiratory insufficiency (0537): 1; Respiratory disorder (0536): 1; Haemoptysis (0516): 1; Hyperventilation (0517): 1; Pulmonary oedema (0535): 2; Stridor (0542): 4; Pharyngitis (0523): 6; Larynx oedema (0522): 7; Laryngismus (0520): 7; Respiratory depression (0144): 7; Apnoea (0507): 17; Coughing (0513): 23; Bronchospasm (0511): 37; Rhinitis (0539): 52; Dyspnoea (0514): 146); **1230 (n 4)**: (Thrombocytopenia (0594): 1; Purpura (0459): 3; **1300 (n 56)**: (Polyuria (0613): 1; Renal cortical necrosis (0808): 1; Oliguria (0612): 1; Renal function abnormal (0619): 1; Urinary incontinence (0156): 2; Azotaemia (2328): 2; Renal failure acute (0618): 7; Face oedema (0602): 41); **1420 (n 1)**: (Breast pain female (0643): 1); **1810 (n 424)**: (Condition aggravated (0965): 1; Chest pain precordial (0719): 1; Oedema generalised (0400): 1; Fatigue (0724): 1; Oedema peripheral (0401): 2; Back pain (0717): 3; Pain (0730): 4; Temperature changed sensation (1705): 6; Oedema periorbital (1009): 6; Oedema (0398): 7; Asthenia (0716): 11; Death (0722): 13; Chest pain (0718): 18; Fever (0725): 26; Malaise (0728): 29; Pallor (0220): 34; Allergic reaction (0712): 34; Syncope (0223): 41; Anaphylactoid reaction (0714): 52; Rigors (0731): 63; Anaphylactic shock (0713): 71); **1820 (n 9)**: (Application site reaction (0047): 1; Injection site pain (0057): 2; Injection site reaction (0058): 6; **n 2/23, Iobenzamate (621)**: **100 (n 373)**: (Eczema (0012): 1; Dermatitis exfoliative (0008): 1; Urticaria acute (0045): 1; Rash purpuric (0462): 1; Dermatitis (0007): 1; Angioedema (0003): 4; Sweating increased (0043): 5; Urticaria (0044): 50; Rash (0027): 53; Rash erythematous (0028): 57; Rash maculo-papular (0030): 67; Pruritus (0024): 132); **200 (n 1)**: (Arthralgia (0063): 1); **410 (n 29)**: (Oedema cerebral (0891): 1; Coma (0091): 2; Dizziness (0101): 2; Paraesthesia (0137): 2; Vertigo (0158): 9; Headache (0109): 13); **432 (n 1)**: (Deafness (0258): 1); **500 (n 4)**: (Agitation (0163): 2; Anxiety (0166): 2); **600 (n 49)**: (Melaena (0306): 1; Tongue oedema (0331): 1; Abdominal pain (0268): 5; Diarrhoea (0205): 6; Vomiting (0228): 15; Nausea (0308): 21); **700 (n 1)**: (Bilirubinaemia aggravated (0936): 1); **1010 (n 25)**: (Cyanosis (0501): 3; Hypotension (0212): 10; Circulatory failure (0499): 12); **1030 (n 4)**: (Cardiac arrest (0437): 1; Tachycardia (0224): 3); **1040 (n 13)**: (Flushing (0207): 13); **1100 (n 19)**: (Pulmonary oedema (0535): 1; Bronchospasm (0511): 2; Rhinitis (0539): 2; Larynx oedema (0522): 3; Dyspnoea (0514): 11); **1230 (n 2)**: (Gingival bleeding (0930): 1; Purpura (0459): 1); **1300 (n 53)**: (Dysuria (0601): 1; Anuria (0596): 1; Renal pain (0621): 1; Polyuria (0613): 1; Face oedema (0602): 49); **1810 (n 46)**: (Anaphylactoid reaction (0714): 1; Asthenia (0716): 1; Oedema generalised (0400): 1; Chest pain precordial (0719): 1; Malaise (0728): 2; Death (0722): 2; Anaphylactic shock (0713): 3; Oedema periorbital (1009): 4; Temperature changed sensation (1705): 4; Oedema (0398): 4; Rigors (0731): 5; Fever (0725): 8; Syncope (0223): 10); **1820 (n 1)**: (Anaesthesia local (0062): 1); **n 3/24, Iocetamate (193): 100 (n 117)**: (Rash maculo-papular (0030): 2; Angioedema (0003): 12; Pruritus (0024): 20; Rash (0027): 22; Rash erythematous (0028): 23; Urticaria (0044): 38); **410 (n 5)**: (Paraesthesia (0137): 1; Headache (0109):

4); **431 (n 3)**: (Conjunctivitis (0238): 3); **600 (n 19)**: (Duodenal ulcer (0274): 1; Diarrhoea (0205): 1; Tongue oedema (0331): 1; Tenesmus (0231): 1; Salivary gland enlargement (0325): 3; Nausea (0308): 4; Vomiting (0228): 8); **800 (n 1)**: (Hyperglycaemia (0382): 1); **1010 (n 2)**: (Hypertension (0210): 2); **1040 (n 2)**: (Flushing (0207): 1; Vasodilatation (0225): 1); **1100 (n 8)**: (Coughing (0513): 1; Rhinitis (0539): 1; Laryngismus (0520): 1; Dyspnoea (0514): 5); **1220 (n 1)**: (Lymphadenopathy (0577): 1); **1230 (n 6)**: (Prothrombin decreased (0590): 1; Purpura (0459): 1; Coagulation time increased (0587): 4); **1300 (n 8)**: (Face oedema (0602): 8); **1810 (n 21)**: (Malaise (0728): 1; Pain (0730): 1; Therapeutic response increased (0874): 1; Serum sickness (0733): 1; Oedema (0398): 2; Anaphylactoid reaction (0714): 2; Oedema periorbital (1009): 2; Rigors (0731): 3; Allergic reaction (0712): 3; Fever (0725): 5); **n 4/25, Iodoxamate (527): 100 (n 108)**: (Angioedema (0003): 1; Bullous eruption (0871): 2; Rash (0027): 9; Sweating increased (0043): 12; Skin discolouration (0036):13; Rash erythematos (0028): 14; Pruritus (0024): 15; Urticaria (0044): 42); **410 (n 22)**: (Hypertonia (0116): 1; Coma (0091): 1; Faecal incontinence (0107): 1; Sensory disturbance (0148): 1; Hyperkinesia (0114): 1; Speech disorder (0150): 1; Vertigo (0158): 1; Tremor (0154): 1; Paraesthesia (0137): 3; Dizziness (0101): 5; Headache (0109): 6); **431 (n 4)**: (Conjunctivitis (0238): 4); **432 (n 2)**: (Tinnitus (0264): 2); **500 (n 11)**: (Somnolence (0197): 1; Agitation (0163): 2; Confusion (0092): 2; Anxiety (0166): 6); **600 (n 124)**: (Diarrhoea (0205): 1; Abdominal pain (0268): 7; Vomiting (0228): 35; Nausea (0308): 81); **1010 (n 38)**: (Cardiac failure (0496): 1; Cyanosis (0501): 3; Hypertension (0210): 6; Circulatory failure (0499): 9; Hypotension (0212): 19); **1020 (n 2)**: (Angina pectoris (0422): 2); **1030 (n 22)**: (Fibrillation ventricular (0440): 1; Cardiac arrest (0437): 2; Bradycardia (0208): 2; Arrhythmia (0433): 4; Tachycardia (0224): 13); **1040 (n 15)**: (Peripheral ischaemia (0454): 1; Vasodilatation (0225): 2; Flushing (0207): 12); **1100 (n 83)**: (Apnoea (0507): 1; Respiratory disorder (0536): 1; Pharyngitis (0523): 1; Bradypnoea (0510): 1; Pulmonary oedema (0535): 1; Laryngismus (0520): 2; Bronchospasm (0511): 2; Respiratory depression (0144): 3; Rhinitis (0539): 8; Coughing (0513): 12; Dyspnoea (0514): 51); **1300 (n 11)**: (Renal function abnormal (0619): 1; Urinary incontinence (0156): 1; Face oedema (0602): 9); **1700 (n 1)**: (Skin hypertrophy (0038): 1); **1810 (n 82)**: (Fever (0725): 1; Back pain (0717): 1; Pain (0730): 1; Malaise (0728): 1; Allergic reaction (0712): 2; Chest pain (0718): 3; Death (0722): 3; Oedema (0398): 4; Pallor (0220): 5; Anaphylactoid reaction (0714): 5; Fatigue (0724): 6; Syncope (0223): 6; Anaphylactic shock (0713): 8; Temperature changed sensation (1705): 17; Rigors (0731): 19); **1820 (n 2)**: (Application site reaction (0047): 1; Injection site reaction (0058): 1); **n 5/26, Ioglycamate (878): 100 (n 121)**: (Pruritus ani (0025): 1; Bullous eruption (0871): 3; Urticaria acute (0045): 4; Rash maculo-papular (0030): 5; Angioedema (0003): 7; Sweating increased (0043): 11; Rash erythematous (0028): 14; Rash (0027): 15; Pruritus (0024): 20; Urticaria (0044): 41); **200 (n 3)**: (Myalgia (0073): 1; Arthralgia (0063): 2); **410 (n 63)**: (Encephalopathy (0105): 1; Tetany (0152): 1; Visual field defect (0159): 1; Convulsions local (0096): 1; Hypotonia (0119): 1; Convulsions grand mal (0095): 1; Speech disorder (0150): 1; Hemiparesis (0111): 2; Dizziness (0101): 2; Vertigo (0158): 2; Dysphonia (0103): 2; Paraesthesia (0137): 5; Tremor (0154): 7; Headache (0109): 8; Convulsions (0093): 8; Coma (0091): 20); **431 (n 9)**: (Mydriasis (0219): 1; Vision abnormal (0257): 1; Conjunctivitis (0238): 7); **433 (n 1)**: (Taste perversion (0267): 1); **500 (n 12)**: (Nervousness (0188): 1; Confusion (0092): 2; Anxiety (0166): 3; Agitation (0163): 3; Somnolence (0197): 3); **600 (n 98)**: (Dysphagia (0280): 1; Saliva increased (0222): 1; Tongue oedema (0331): 2; Tongue disorder (0330): 2; Diarrhoea (0205): 4; Abdominal pain (0268): 11; Vomiting (0228): 34; Nausea (0308): 43); **700 (n 18)**: (Hepatic function abnormal (0348): 1; Jaundice (0356): 2; SGOT increased (0359): 3; SGPT increased (0360): 12); **800 (n 2)**:

(Phosphatase alkaline increased (0404): 2); **900 (n 1)**: (Breast pain male (0837): 1); **1010 (n 143)**: (ECG abnormal (0502): 1; Cardiac failure (0496): 1; Heart disorder (0504): 2; Hypertension (0210): 5; Cyanosis (0501): 10; Hypotension (0212): 41; Circulatory failure (0499): 83); **1020 (n 5)**: (Myocardial ischaemia (0429): 1; Myocardial infarction (0428): 2; Angina pectoris (0422): 2); **1030 (n 55)**: (Extrasystoles (0438): 1; Fibrillation atrial (0439): 1; Arrhythmia (0433): 1; Palpitation (0221): 1; Fibrillation ventricular (0440): 3; Bradycardia (0208): 4; Cardiac arrest (0437): 21; Tachycardia (0224): 23); **1040 (n 15)**: (Peripheral ischaemia (0454): 1; Vascular disorder (0491): 1; Vasodilatation (0225): 1; Flushing (0207): 12); **1100 (n 101)**: (Hyperventilation (0517): 1; Yawning (0201): 1; Asphyxia (0508): 1; Respiratory insufficiency (0537): 1; Upper respiratory tract infection (0543): 1; Stridor (0542): 2; Laryngismus (0520): 3; Coughing (0513): 3; Respiratory depression (0144): 4; Larynx oedema (0522): 5; Pulmonary oedema (0535): 8; Rhinitis (0539): 9; Bronchospasm (0511): 10; Apnoea (0507): 17; Dyspnoea (0514): 35); **1230 (n 1)**: (Purpura (0459): 1); **1300 (n 17)**: (Creatinine clearance decreased (0598): 1; Anuria (0596): 1; Azotaemia (2328): 1; Urinary incontinence (0156): 1; Renal failure acute (0618): 1; Face oedema (0602): 12); **1810 (n 209)**: (Fatigue (0724): 1; Oedema (0398): 1; Chest pain precordial (0719): 2; Pain (0730): 2; Chest pain substernal (0720): 3; Asthenia (0716): 3; Malaise (0728): 4; Pallor (0220): 7; Temperature changed sensation (1705): 8; Syncope (0223): 8; Fever (0725): 9; Allergic reaction (0712): 13; Anaphylactoid reaction (0714): 18; Rigors (0731): 33; Death (0722): 38; Anaphylactic shock (0713): 59); **1820 (n 4)**: (Injection site inflammation (0054): 2; Injection site pain (0057): 2); **n 6/27, Iopanoate (484): 100 (n 152)**: (Nail disorder (0020): 1; Dermatitis exfoliative (0008): 1; Urticaria acute (0045): 1; Eczema (0012): 1; Dermatitis contact (0049): 1; Erythema multiforme (0014): 1; Angioedema (0003): 2; Dermatitis (0007): 2; Rash purpuric (0462): 2; Sweating increased (0043): 4; Rash maculo-papular (0030): 10; Urticaria (0044): 27; Rash (0027): 29; Rash erythematous (0028): 30; Pruritus (0024): 40); **200 (n 1)**: (Myalgia (0073): 1); **410 (n 24)**: (Hypertonia (0116): 1; Convulsions (0093): 1; Gait abnormal (0108): 1; Stupor (0151): 1; Headache (0109): 2; Vertigo (0158): 3; Tremor (0154): 3; Paraesthesia (0137): 4; Dizziness (0101): 8); **431 (n 3)**: (Conjunctivitis (0238): 1; Vision abnormal (0257): 2); **432 (n 1)**: (Tinnitus (0264): 1); **500 (n 6)**: (Confusion (0092): 1; Hallucination (0179): 1; Anxiety (0166): 1; Nervousness (0188): 1; Amnesia (0164): 1; Somnolence (0197): 1); **600 (n 177)**: (Mouth dry (0218): 1; Flatulence (0285): 1; Dyspepsia (0279): 1; Tongue oedema (0331): 1; Salivary gland enlargement (0325): 3; Vomiting (0228): 23; Abdominal pain (0268): 29; Nausea (0308): 31; Diarrhoea (0205): 87); **700 (n 8)**: (Hepatic failure (0933): 1; Hepatic function abnormal (0348): 1; Gamma-GT increased (1334): 1; Bilirubinaemia (0339): 1; SGOT increased (0359): 2; SGPT increased (0360): 2); **800 (n 4)**: (Phosphatase alkaline increased (0404): 1; Dehydration (0370): 3); **1010 (n 7)**: (ECG abnormal (0502): 1; Hypotension postural (0213): 2; Hypotension (0212): 4); **1030 (n 4)**: (Cardiac arrest (0437): 1; Tachycardia (0224): 1; Arrhythmia (0433): 2); **1040 (n 5)**: (Flushing (0207): 5); **1100 (n 14)**: (Apnoea (0507): 1; Rhinitis (0539): 1; Hypoxia (0519): 1; Bronchospasm (0511): 1; Pharyngitis (0523): 2; Dyspnoea (0514): 8); **1220 (n 1)**: (Eosinophilia (0571): 1); **1230 (n 2)**: (Purpura (0459): 2); **1300 (n 29)**: (Anuria (0596): 2; Oliguria (0612): 3; Azotaemia (2328): 3; Renal function abnormal (0619): 3; Renal tubular necrosis (0624): 4; Renal failure acute (0618): 6; Face oedema (0602): 8); **1810 (n 46)**: (Drug level increased (1281): 1; Allergic reaction (0712): 1; Anaphylactic reaction (2237): 1; Therapeutic response decreased (0878): 1; Malaise (0728): 1; Ascites (0715): 1; Oedema peripheral (0401): 1; Fatigue (0724): 2; Anaphylactic shock (0713): 2; Pain (0730): 2; Fever (0725): 2; Anaphylactoid reaction (0714): 2; Chest pain (0718): 2; Oedema (0398): 3; Asthenia (0716): 3; Death (0722): 3; Syncope (0223): 4; Rigors (0731): 5; Drug level decreased (1282): 9); **n 7/28,**

Iopodate (880): 100 (n 423): (Pemphigoid reaction (0938): 1; Erythema nodosum (0015): 1; Skin exfoliation (1199): 1; Eczema (0012): 1; Rash vesicular (1443): 1; Skin discolouration (0036): 1; Dermatitis (0007): 4; Sweating increased (0043): 9; Rash maculo-papular (0030): 11; Urticaria acute (0045): 13; Angioedema (0003): 17; Rash erythematous (0028): 36; Pruritus (0024): 73; Rash (0027): 76; Urticaria (0044): 178); **200 (n 2)**: (Arthralgia (0063): 2); **410 (n 52)**: (Hypertension intracranial (0115): 1; Convulsions (0093): 1; Hypoaesthesia (0117): 1; Convulsions grand mal (0095): 1; Migraine (0121): 1; Faecal incontinence (0107): 1; Neuritis (0125): 1; Vertigo (0158): 1; Speech disorder (0150): 1; Hyperkinesia (0114): 1; Stupor (0151): 1; Dysphonia (0103): 2; Tremor (0154): 2; Coma (0091): 4; Paraesthesia (0137): 9; Dizziness (0101): 11; Headache (0109): 13); **431 (n 6)**: (Vision abnormal (0257): 1; Eye pain (0244): 2; Conjunctivitis (0238): 3); **500 (n 6)**: (Insomnia (0183): 1; Nervousness (0188): 1; Somnolence (0197): 1; Anxiety (0166): 3); **600 (n 75)**: (Mouth dry (0218): 1; Cheilitis (0270): 1; Tenesmus (0231): 1; Pancreatitis (0314): 1; Dysphagia (0280): 1; Saliva increased (0222): 1; Dyspepsia (0279): 1; Stomatitis ulcerative (0328): 1; Salivary gland enlargement (0325): 1; Salivary gland pain (0326): 1; Glossitis (0295): 2; Tongue oedema (0331): 4; Abdominal pain (0268): 6; Diarrhoea (0205): 6; Nausea (0308): 17; Vomiting (0228): 30); **700 (n 3)**: (Jaundice (0356): 1; Hepatic function abnormal (0348): 2); **900 (n 2)**: (Hypothyroidism (0417): 1; Sialoadenitis (0986): 1); **1010 (n 45)**: (Cardiac failure left (0497): 1; Cyanosis (0501): 2; Hypertension (0210): 3; Circulatory failure (0499): 16; Hypotension (0212): 23); **1030 (n 14)**: (Bradycardia (0208): 1; Tachycardia supraventricular (0229): 1; Arrhythmia (0433): 2; Palpitation (0221): 2; Cardiac arrest (0437): 3; Tachycardia (0224): 5); **1040 (n 19)**: (Vasodilatation (0225): 1; Vasospasm (0226): 1; Flushing (0207): 17); **1100 (n 44)**: (Hyperventilation (0517): 1; Respiratory distress syndrome (2252): 1; Pneumonitis (1141): 1; Apnoea (0507): 2; Rhinitis (0539): 2; Larynx oedema (0522): 4; Pharyngitis (0523): 5; Bronchospasm (0511): 6; Dyspnoea (0514): 22); **1220 (n 1)**: (Granulocytopenia (0572): 1); **1230 (n 1)**: (Purpura thrombocytopenic (1348): 1); **1300 (n 64)**: (Renal pain (0621): 1; Renal failure acute (0618): 1; Urine abnormal (0629): 1; Urinary incontinence (0156): 1; Renal function abnormal (0619): 1; Urinary retention (0157): 1; Face oedema (0602): 58); **1420 (n 2)**: (Uterine haemorrhage (0666): 1; Vaginitis (0669): 1); **1810 (n 121)**: (Hypothermia (0727): 1; Back pain (0717): 1; Pallor (0220): 1; Pain (0730): 1; Allergy (1058): 1; Fatigue (0724): 2; Oedema generalised (0400): 2; Chest pain (0718): 3; Temperature changed sensation (1705): 4; Rigors (0731): 4; Asthenia (0716): 4; Oedema peripheral (0401): 5; Death (0722): 5; Anaphylactic shock (0713): 7; Syncope (0223): 7; Malaise (0728): 8; Fever (0725): 9; Allergic reaction (0712): 11; Anaphylactoid reaction (0714): 11; Oedema periorbital (1009): 13; Oedema (0398): 21); **n 8/29, Iotroxate (867): 100 (n 273)**: (Erythema multiforme (0014): 1; Rash purpuric (0462): 1; Eczema (0012): 1; Angioedema (0003): 2; Rash maculo-papular (0030): 2; Dermatitis (0007): 2; Bullous eruption (0871): 2; Skin disorder (0037): 2; Skin cold clammy (0932): 3; Sweating increased (0043): 13; Rash (0027): 34; Rash erythematous (0028): 38; Pruritus (0024): 57; Urticaria (0044): 115); **200 (n 2)**: (Arthralgia (0063): 2); **410 (n 60)**: (Brain stem disorder (0810): 1; Vertigo (0158): 1; Cholinergic syndrome (0203): 1; Convulsions grand mal (0095): 1; Speech disorder (0150): 1; Hypoaesthesia (0117): 1; Dysaesthesia (1491): 1; Paralysis (0138): 1; Hyperkinesia (0114): 2; Stupor (0151): 2; Hemiplegia (0112): 3; Dysphonia (0103): 3; Tremor (0154): 5; Convulsions (0093): 5; Dizziness (0101): 6; Paraesthesia (0137): 8; Coma (0091): 8; Headache (0109): 10); **431 (n 10)**: (Conjunctival discolouration (1303): 1; Lacrimation abnormal (1049): 1; Vision abnormal (0257): 3; Conjunctivitis (0238): 5); **432 (n 2)**: (Ear ache (0260): 1; Tinnitus (0264): 1); **500 (n 7)**: (Confusion (0092): 1; Nervousness (0188): 1; Amnesia (0164): 1; Agitation (0163): 2; Somnolence (0197): 2); **600 (n 142)**: (Gastritis

(0291): 1; Mouth dry (0218): 1; Dyspepsia (0279): 1; Salivary gland enlargement (0325): 1; Tongue oedema (0331): 1; Tenesmus (0231): 1; Mucositis NOS (1351): 4; Dysphagia (0280): 4; Abdominal pain (0268): 7; Vomiting (0228): 52; Nausea (0308): 69; **900 (n 1)**: (Sialoadenitis (0986): 1); **1010 (n 74)**: (Cardiac failure (0496): 1; Hypertension (0210): 3; Cyanosis (0501): 4; Hypotension (0212): 32; Circulatory failure (0499): 34; **1020 (n 1)**: (Angina pectoris (0422): 1); **1030 (n 22)**: (Arrhythmia (0433): 1; Bradycardia (0208): 4; Cardiac arrest (0437): 8; Tachycardia (0224): 9); **1040 (n 16)**: (Cerebrovascular disorder (0445): 1; Capillary fragility increased (0443): 1; Peripheral ischaemia (0454): 2; Flushing (0207): 12; **1100 (n 113)**: (Laryngitis (0521): 1; Laryngismus (0520): 1; Asthma (1367): 1; Bronchitis (0805): 1; Stridor (0542): 1; Bronchospasm aggravated (1066): 1; Pharyngitis (0523): 2; Pulmonary oedema (0535): 3; Respiratory depression (0144): 3; Apnoea (0507): 4; Respiratory insufficiency (0537): 4; Throat tightness (1489): 4; Larynx oedema (0522): 9; Bronchospasm (0511): 10; Coughing (0513): 10; Rhinitis (0539): 15; Dyspnoea (0514): 43); **1230 (n 2)**: (Haemorrhage NOS (0452): 1; Purpura (0459): 1); **1300 (n 15)**: (Face oedema (0602): 15; **1810 (n 124)**: (Hypothermia (0727): 1; Leg pain (1439): 1; Allergy (1058): 1; Hyperpyrexia (0894): 1; Fatigue (0724): 2; Oedema peripheral (0401): 2; Oedema periorbital (1009): 2; Pain (0730): 3; Fever (0725): 3; Oedema (0398): 3; Malaise (0728): 4; Death (0722): 4; Oedema mouth (1485): 4; Chest pain (0718): 6; Allergic reaction (0712): 10; Syncope (0223): 10; Temperature changed sensation (1705): 12; Rigors (0731): 14; Anaphylactoid reaction (0714): 16; Anaphylactic shock (0713): 25); **1820 (n 3)**: (Injection site reaction (0058): 3).

Sub-class D (n 1 Agent, n 30): Iofendylate (310): 100 (n 11): (Rash maculo-papular (0030): 1; Urticaria (0044): 1; Skin discolouration (0036): 1; Bullous eruption (0871): 1; Sweating increased (0043): 1; Rash (0027): 2; Pruritus (0024): 2; Photosensitivity reaction (0022): 2); **200 (n 5)**: (Arthritis (0064): 1; Myalgia (0073): 4); **410 (n 160)**: (Hypoaesthesia (0117): 1; Tremor (0154): 1; Sensory disturbance (0148): 1; Hemiplegia (0112): 1; Quadriplegia (0143): 1; Hyporeflexia (0850): 1; Dysaesthesia (1491): 1; Neuropathy (0130): 1; Hypokinesia (0118): 2; CSF abnormal (0098): 2; Neuritis (0125): 2; Convulsions grand mal (0095): 2; Coma (0091): 3; Paralysis (0138): 3; Encephalopathy (0105): 3; Convulsions (0093): 4; Meningitis (0955): 4; Hypertonia (0116): 4; Paraesthesia (0137): 6; Dizziness (0101): 16; Arachnoiditis (1031): 18; Meningism (0120): 21; Headache (0109): 62); **431 (n 11)**: (Papilloedema (0249): 1; Vision abnormal (0257): 1; Accommodation abnormal (0202): 1; Photophobia (0250): 8); **500 (n 5)**: (Confusion (0092): 1; Aggressive reaction (0162): 1; Depression (0172): 1; Anorexia (0165): 1; Somnolence (0197): 1); **600 (n 42)**: (Intestinal perforation (0754): 1; Diarrhoea (0205): 1; Vomiting (0228): 16; Nausea (0308): 24); **800 (n 2)**: (Acidosis lactic (0364): 2); **1010 (n 3)**: (Hypotension (0212): 1; Hypertension (0210): 2); **1030 (n 3)**: (Cardiac arrest (0437): 1; Bradycardia (0208): 1; Tachycardia (0224): 1); **1040 (n 3)**: (Vasculitis (0085): 1; Cerebral infarction (1986): 2); **1100 (n 2)**: (Laryngismus (0520): 1; Respiratory disorder (0536): 1); **1230 (n 3)**: (Thrombocytopenia (0594): 1; Coagulation disorder (0586): 1; Thrombosis cerebral (0486): 1); **1300 (n 2)**: (Hydronephrosis (0779): 1; Urinary incontinence (0156): 1); **1810 (n 54)**: (Fatigue (0724): 1; Allergic reaction (0712): 1; Anaphylactoid reaction (0714): 1; Condition aggravated (0965): 1; Syncope (0223): 1; Oedema periorbital (1009): 1; Oedema (0398): 1; Asthenia (0716): 2; Malaise (0728): 2; Chest pain (0718): 2; Rigors (0731): 3; Fever (0725): 8; Pain (0730): 11; Back pain (0717): 19); **1820 (n 4)**: (Injection site inflammation (0054): 1; Injection site pain (0057): 1; Injection site infection (1910): 1; Injection site reaction(0058): 1.

Appendix Nr 4.

Nr of total SADRs (for the 30 SOCDs Classes and the 40 years total collection) of the 52 used and reported "biosimilars" of the V08-A, B, C, and D subclasses. Of the 30 iodinated contrast agents of generic reference for the study, only those presenting "biosimilars" in use are listed, together with their total frequencies for the same first 40 years collection period.

V08A-A (9 Agents)**:**

1- Acetrizoate (33): 1-Acetrizoic acid (30); 2-Sodium acetrizoate/Meglumine acetrizoate (3).

2-Amidotrizoate (44,648): 1-Amidotrizoic acid (25,998); 2-Meglumine amidotrizoate/Sodium amidotrizoate (18,590); 3-Meglumine amidotrizoate/Sodium amidotrizoate/Calcium amidotrizoate (25); 4-Meglumine amidotrizoate/Sodium amidotrizoate/Iodine (7); 5-Sodium amidotrizoate/Lysine amidotrizoate (23); 6-sodium amidotrizoate/meglumine (5).

3-Diodone (9): 1-Diodone (7); 2-Diodone/Dextran (1); 3-Diodone/Dextran pv(1);

5-Iodamide (936): 1-Iodamide (748); 2-Iodamide/Iodamide meglumine (6); 3-Iodine/Iodamide meglumine (50); 4-Meglumine/Iodamide sodium (11).

7-Iotalamate (14,395); 1-Iotalamic acid (14,053); 2-Iotalamate meglumine/Iotalamate sodium (342).

8-Ioxitalamate (2,223): 1-Ioxitalamic acid (418); 2-Ioxitalamate meglumine/Ioxitalamate monoethanolamine (2): 3-Ioxitalamate meglumine/Ioxitalamate sodium (1,798); 4-Meglumine/Sodium chloride/Ioxitalamic acid (5).

9-Metrizoate (1,068): 1-Meglumine metrizoate/Calcium metrizoate (144); 2-Meglumine metrizoate/Calcium metrizoate/Magnesium metrizoate (5); 3-Metrizoic acid (689); 4-Sodium calcium edetate/Sodium metrizoate/Meglumine metrizoate/Calcium metrizoate/Magnesium metrizoate (37); 5-Sodium metrizoate/Calcium metrizoate/Magnesium metrizoate (6); 6-Sodium metrizoate/Meglumine metrizoate/Calcium metrizoate (99); 7-Sodium metrizoate/Meglumine metrizoate/Calcium metrizoate/Magnesium metrizoate (88).

V08A-B (12 Agents)**:**

Ioxaglate (5,200): 1-Ioxaglic acid (233); 2-Ioxaglate meglumine/Ioxaglate sodium (4,967).

V08A-C (8 Agents) and **V08A-D** (1 Agent): No "Biosimilars".

Appendix Nr 5.

Iodinate contrast agents: The 876 ADRs involved, given by their codes.

1	2	3	6	7	8	10	11	12	13	14	15
16	19	20	21	22	24	25	26	27	28	29	30
31	32	34	36	37	38	39	41	42	43	44	45
46	47	48	49	54	55	56	57	58	59	60	61
62	63	64	65	66	67	68	69	72	73	74	77
78	80	81	83	85	86	87	88	89	90	91	92

93	94	95	96	97	98	99	100	101	102	103	104
105	106	107	108	109	110	111	112	113	114	115	116
117	118	119	120	121	122	123	124	125	127	129	130
131	132	133	134	136	137	138	139	140	141	142	143
144	147	148	149	150	151	152	153	154	155	156	157
158	159	162	163	164	165	166	167	168	169	170	171
172	173	175	177	178	179	180	182	183	186	187	188
189	190	191	192	193	194	195	197	199	201	202	203
204	205	207	208	209	210	211	212	213	214	215	216
217	218	219	220	221	222	223	224	225	226	227	228
229	230	231	232	233	237	238	240	241	242	243	244
246	247	248	249	250	251	252	254	255	256	257	258
259	260	261	264	265	266	267	268	269	270	271	274
277	279	280	281	282	283	285	287	290	291	293	294
295	297	298	300	301	302	306	308	309	310	311	312
313	314	315	320	325	326	327	328	329	330	331	335
336	338	339	342	343	344	345	348	349	350	351	353
354	355	356	358	359	360	363	364	366	370	371	374
375	376	378	380	381	382	383	384	387	389	390	391
392	393	394	398	399	400	401	404	405	407	408	411
414	415	416	417	418	419	420	422	423	424	425	426
428	429	430	431	432	433	434	435	436	437	438	439
440	441	442	443	444	445	446	447	448	449	451	452
453	454	455	457	458	459	460	462	463	464	465	466
467	468	469	470	472	473	479	480	481	482	484	485
486	487	488	489	490	491	492	494	496	497	498	499
501	502	503	504	505	507	508	510	511	513	514	515
516	517	518	519	520	521	522	523	524	525	526	528
530	531	532	534	535	536	537	538	539	540	541	542
543	544	548	553	559	560	561	568	570	571	572	576
577	578	580	581	582	584	586	587	588	589	590	591
592	593	594	595	596	598	599	600	601	602	603	604
605	606	607	608	609	610	612	613	614	617	618	619
621	623	624	625	626	628	629	631	632	634	637	639
643	647	655	660	666	667	669	676	692	710	711	712
713	714	715	716	717	718	719	720	722	723	724	725
727	728	730	731	733	735	736	738	739	740	741	744
746	748	750	751	752	754	756	758	761	762	764	771
772	774	775	779	782	788	791	793	794	796	805	808
809	810	827	828	837	845	850	852	855	860	862	864
867	871	874	876	877	878	883	887	890	891	892	893
894	896	899	906	908	910	911	912	915	925	929	930
932	933	936	938	939	942	943	955	963	965	971	973
974	979	983	986	990	993	1001	1002	1004	1007	1009	1014
1015	1016	1018	1020	1021	1023	1025	1027	1028	1030	1031	1034

1035	1038	1039	1049	1058	1063	1065	1066	1068	1071	1072	1074
1076	1083	1086	1092	1093	1096	1101	1103	1113	1120	1122	1123
1126	1127	1128	1134	1136	1141	1152	1153	1157	1162	1172	1174
1175	1177	1178	1184	1193	1197	1199	1201	1202	1207	1208	1210
1211	1214	1215	1222	1225	1243	1244	1249	1252	1255	1256	1259
1262	1280	1281	1282	1283	1284	1285	1288	1294	1295	1298	1303
1308	1313	1318	1320	1324	1328	1334	1346	1347	1348	1349	1351
1352	1353	1361	1367	1368	1370	1372	1374	1378	1381	1382	1388
1392	1394	1395	1398	1400	1401	1410	1413	1427	1429	1431	1434
1439	1443	1445	1446	1447	1459	1460	1461	1462	1465	1466	1468
1469	1471	1473	1479	1485	1489	1490	1491	1492	1493	1496	1497
1514	1515	1522	1541	1546	1547	1555	1558	1573	1576	1577	1589
1591	1605	1607	1621	1624	1648	1650	1652	1659	1688	1690	1694
1705	1707	1711	1712	1716	1718	1721	1738	1740	1749	1752	1753
1762	1768	1770	1819	1820	1827	1830	1831	1832	1838	1839	1843
1846	1852	1854	1858	1867	1877	1880	1881	1885	1888	1889	1890
1891	1898	1899	1901	1903	1910	1911	1912	1917	1922	1944	1948
1956	1960	1968	1970	1976	1978	1986	1987	1989	1994	1995	1999
2000	2008	2012	2024	2031	2032	2035	2055	2086	2090	2097	2098
2109	2115	2129	2133	2135	2136	2137	2138	2139	2140	2160	2164
2172	2190	2211	2220	2221	2222	2223	2237	2252	2253	2290	2309
2323	2328	2329	2330	2336	2340	2351	2353	2354	2356	2362	2363

Appendix Nr 6.

V08A –A, -B, and -C iodinated, and V08C –A and -B diagnostic contrast agents. Total of 4,442 SADRs reported dataset of PR22-2010 file for the 35 reference & biosimilar products monitored in the total first 40 years 1958-2010 collection from Italy voluntary WHO-ITA/ITA-OMS, and subsequently from national regulatory obligatory by law drug monitoring system.

For each product the total number of SADRs (in bold, in brackets) are listed, then the frequencies in rising order as aggregated in the WHO-standardized maximum 30 SOCDs, numbered in increasing order, their codes and total numbers per class (in bold, in brackets). If, instead of the current 30 SOCDs - adopted to permit the confrontation & analysis of different periods and topics. The more recently voted 32 SOCDs aggregation followed, including the n 31 (Code 2000, title "Secondary terms"), and the n 32 (Code 2100, title "Poison specific term"), the total n would be 4,483, that is 41 SADRs more only of the class 31, and their ADRs reported so distributed: Gadobenic acid, n 2; Gadobutrol, n 1; Gadoteridol, n 2; Iobitridol, n 4; nIodamide, n 1; Iodixanol, 2; Iomeprol, n 15; Iopamidol, n 2; Iopromide, n 10; Ioversol, n 2. In the following list the products monitored in Italy are presented in alphabetic order but not any more subdivided in classes & (sub)groups, that is the ATC V08A and V08C CA, iodinated or not, have been uniformly mixed.

Adipiodone meglumine (n 5): 100 (n 2): (Rash (0027): 1; Urticaria acute (0045): 1); **600 (n 1):** (Vomiting (0228): 1); **1100 (n 2):** (Dyspnoea (0514): 2); **Amidotrizoic acid (n 42): 100 (n 18):** (Piloerection (1071): 1; Urticaria (0044): 3; Rash erythematous (0028): 3; Pruritus (0024): 4; Rash (0027): 7); **410 (n 1):** (Tremor (0154): 1); **500 (n 1):** (Anxiety (0166): 1); **600 (n 6):** (Nausea (0308): 2; Vomiting (0228): 4); **1010 (n 3):** (Circulatory failure (0499): 3); **1040 (n 1):** (Flushing (0207): 1); **1100 (n 6):** (Larynx oedema (0522): 1; Coughing (0513): 1; Dyspnoea (0514): 4); **1810 (n 6):** (Allergy (1058): 1; Anaphylactic shock (0713): 1; Allergic reaction (0712): 2; Rigors (0731): 2); **Ferrixan (n 3): 600 (n 1):** (Tenesmus (0231): 1); **1100 (n 1):** (Dyspnoea (0514): 1); **1810 (n 1):** (Allergic reaction (0712): 1); **Ferumoxsil (n 3): 100 (n 1):** (Urticaria (0044): 1); **1100 (n 1):** (Dyspnoea (0514): 1); **1810 (n 1):** (Oedema periorbital (1009): 1); **Gadobenic acid (n 253): 100 (n 78):** (Rash maculo-papular (0030): 1; Skin reaction localised (1650): 1; Angioedema (0003): 2; Skin disorder (0037): 2; Rash (0027): 8; Pruritus (0024): 9; Sweating increased (0043): 9; Rash erythematous (0028): 17; Urticaria (0044): 29); **200 (n 1):** (Myalgia (0073): 1); **410 (n 16):** (Migraine (0121): 1; Dizziness (0101): 1; Dysphonia (0103): 2; Tremor (0154): 2; Paraesthesia (0137): 2; Headache (0109): 4; Coma (0091): 4); **431 (n 4):** (Lacrimation abnormal (1049): 1; Conjunctivitis (0238): 1; Vision abnormal (0257): 2); **500 (n 1):** (Agitation (0163): 1); **600 (n 61):** (Diarrhoea (0205): 1; Dyspepsia (0279): 2; Abdominal pain (0268): 2; Vomiting (0228): 21; Nausea (0308): 35); 700 (n 2): (Bilirubinaemia (0339): 1; Hepatic function abnormal (0348): 1); 1010 (n 17): (Cardio-respiratory failure (1899): 1; Cyanosis (0501): 2; Hypertension (0210): 5; Hypotension (0212): 9); **1030 (n 7):** (Cardiac arrest (0437): 3; Tachycardia (0224): 4**); 1040 (n 5):** (Flushing (0207): 5); **1100 (n 32):** (Laryngismus (0520): 1; Hypoventilation (0518): 1; Hypoxia (0519): 1; Pharyngitis (0523): 1; Larynx oedema (0522): 1; Coughing (0513): 2; Throat tightness (1489): 2; Respiratory insufficiency (0537): 2; Bronchospasm (0511): 3; Rhinitis (0539): 3; Dyspnoea (0514): 15); **1300 (n 4):** (Face oedema (0602): 4); **1810 (n 23):** (Malaise (0728): 1; Temperature changed sensation (1705): 1; Oedema peripheral (0401): 1; Allergy (1058): 1; Rigors (0731): 2; Choking (1460): 2; Allergic reaction (0712): 3; Anaphylactic shock (0713): 3; Oedema mouth (1485): 4; Oedema periorbital (1009): 5); **1820 (n 2):** (Infusion site reaction (2137): 2); **Gadobutrol (n 42): 100 (n 12):** (Rash (0027): 1; Skin disorder (0037): 1; Pruritus (0024): 2; Rash erythematous (0028): 4; Urticaria (0044): 4); **410 (n 3):** (Tetany (0152): 1; Coma (0091): 1; Vertigo (0158): 1); **431 (n 1):** (Conjunctivitis (0238): 1); **600 (n 8):** (Mouth dry (0218): 1; Abdominal pain (0268): 1; Nausea (0308): 2; Vomiting (0228): 4); **1010 (n 1):** (Hypotension (0212): 1); **1040 (n 2):** (Flushing (0207): 2); **1100 (n 9):** (Coughing (0513): 1; Laryngitis (0521): 1; Bronchospasm (0511): 2; Larynx oedema (0522): 2; Dyspnoea (0514): 3); **1300 (n 1):** (Face oedema (0602): 1); **1810 (n 5):** (Choking (1460): 1; Allergic reaction (0712): 1; Oedema (0398): 1; Asthenia (0716): 1; Oedema periorbital (1009): 1); **Gadodiamide (n 15): 100 (n 8):** (Rash (0027): 2; Pruritus (0024): 2; Urticaria (0044): 4); **410 (n 1):** (Vertigo (0158): 1); **431 (n 1):** (Vision abnormal (0257): 1); **1100 (n 3):** (Laryngitis (0521): 1; Coughing (0513): 1; Larynx oedema (0522): 1); **1810 (n 2):** (Anaphylactic reaction (2237): 1; Choking (1460): 1**; Gadofosveset (n 5): 100 (n 2):** (Pruritus (0024): 1; Rash erythematous (0028): 1); **600 (n 2):** (Nausea (0308): 1; Vomiting (0228): 1); **1100 (n 1):** (Dyspnoea (0514): 1); **Gadopentetic acid (n 113): 100 (n 36):** (Skin disorder (0037): 1; Skin reaction localised (1650): 1; Sweating increased (0043): 2; Pruritus (0024): 6; Rash (0027): 6; Rash erythematous (0028): 10; Urticaria (0044): 10); **410 (n 6):** (Dysphonia (0103): 1; Dizziness (0101): 1; Paraesthesia (0137): 1; Hypertonia (0116): 1; Headache (0109): 2); **431 (n 2):** (Conjunctivitis (0238): 1; Lacrimation abnormal (1049): 1); **433 (n 2):** (Taste perversion (0267): 2); **500 (n 1):** (Agitation (0163): 1); **600 (n 17):** (Mouth dry (0218): 1; Abdominal pain (0268): 1;

Vomiting (0228): 6; Nausea (0308): 9); **1010 (n 7):** (Hypertension (0210): 1; Cardiac failure (0496): 1; Circulatory failure (0499): 2; Hypotension (0212): 3); **1030 (n 4):** (Cardiac arrest (0437): 1; Bradycardia (0208): 1; Tachycardia (0224): 2); **1040 (n 3):** (Flushing (0207): 3); **1100 (n 18):** (Coughing (0513): 1; Rhinitis (0539): 1; Respiratory depression (0144): 2; Bronchospasm (0511): 3; Larynx oedema (0522): 4; Dyspnoea (0514): 7); **1300 (n 1):** (Face oedema (0602): 1; **1810 (n 14):** (Oedema mouth (1485): 1; Temperature changed sensation (1705): 1; Allergic reaction (0712): 1; Chest pain (0718): 1; Oedema peripheral (0401): 1; Allergy (1058): 1; Pain (0730): 1; Fever (0725): 1; Syncope (0223): 1; Oedema periorbital (1009): 2; Rigors (0731): 3); **1820 (n 2):** (Injection site pain (0057): 1; Injection site urticaria (1968): 1); **Gadoteridol (n 52): 100 (n 16):** (Skin reaction localised (1650): 1; Sweating increased (0043): 1; Rash erythematous (0028): 4; Pruritus (0024): 5; Urticaria (0044): 5); 410 (n 5): (Dysphonia (0103): 1; Headache (0109): 1; Coma (0091): 1; Paraesthesia (0137): 2); **431 (n 4):** (Lacrimation abnormal (1049): 1; Conjunctivitis (0238): 3); **600 (n 6):** (Nausea (0308): 1; Abdominal pain (0268): 1; Vomiting (0228): 4; **1010 (n 2):** (Hypotension (0212): 2); **1040 (n 1):** (Flushing (0207): 1); **1100 (n 13):** (Laryngismus (0520): 1; Throat tightness (1489): 1; Rhinitis (0539): 1; Larynx oedema (0522): 2; Coughing (0513): 2; Dyspnoea (0514): 6); **1300 (n 2):** (Face oedema (0602): 1; Urinary incontinence (0156): 1); **1810 (n 3):** (Allergic reaction (0712): 1; Oedema periorbital (1009): 2); **Gadoxetic acid (n 1): 100 (n 1):** (Pruritus (0024): 1); **Iobenzamic acid (n 1): 600 (n 1):** (Abdominal pain (0268): 1); **Iobitridol (n 201): 100 (n 71):** (Skin reaction localised (1650): 1; Skin disorder (0037): 3; Rash (0027): 4; Pruritus (0024): 13; Rash erythematous (0028): 22; Urticaria (0044): 28); 200 (n 1): (Arthralgia (0063): 1); 410 (n 16): (Hypoaesthesia (0117): 1; Vertigo (0158): 1; Stupor (0151): 1; Dysphonia (0103): 1; Coma (0091): 2; Paraesthesia (0137): 3; Headache (0109): 3; Tremor (0154): 4); **431 (n 1):** (Conjunctivitis (0238): 1); **500 (n 1):** (Agitation (0163): 1); **600 (n 18):** (Tongue oedema (0331): 2; Dysphagia (0280): 2; Nausea (0308): 6; Vomiting (0228): 8); 1010 (n 10): (Cyanosis (0501): 1; Pulse weak (1401): 1; Circulatory failure (0499): 1; Hypertension (0210): 3; Hypotension (0212): 4); **1020 (n 2):** (Angina pectoris (0422): 1; Myocardial ischaemia (0429): 1); **1030 (n 7):** (Fibrillation ventricular (0440): 1; Tachycardia (0224): 2; Cardiac arrest (0437): 4; **1040 (n 4):** (Flushing (0207): 4); **1100 (n 30):** (Rhinitis (0539): 1; Respiratory insufficiency (0537): 1; Pulmonary oedema (0535): 1; Laryngitis (0521): 1; Respiratory depression (0144): 1; Laryngismus (0520): 1; Respiratory disorder (0536): 1; Bronchospasm (0511): 2; Larynx oedema (0522): 4; Coughing (0513): 5; Dyspnoea (0514): 12); **1300 (n 2):** (Face oedema (0602): 1; Renal failure acute (0618): 1); **1810 (n 37):** (Chest pain substernal (0720): 1; Syncope (0223): 1; Hypovolaemia (0929): 1; Chest pain (0718): 1; Pallor (0220): 1; Oedema (0398): 2; Malaise (0728): 2; Temperature changed sensation (1705): 2; Allergic reaction (0712): 4; Rigors (0731): 4; Oedema mouth (1485): 4; Anaphylactic shock (0713): 6; Oedema periorbital (1009): 8); **1820 (n 1):** (Injection site urticaria (1968): 1); **Iocetamic acid (n 5): 100 (n 2):** (Pruritus (0024): 2); **431 (n 1):** (Conjunctivitis (0238): 1); **1040 (n 1):** (Flushing (0207): 1); **1300 (n 1):** (Face oedema (0602): 1); **Iodamide (n 194): 100 (n 39):** (Bullous eruption (0871): 1; Sweating increased (0043): 2; Pruritus (0024): 4; Urticaria (0044): 9; Rash erythematous (0028): 10; Rash (0027): 13); **410 (n 4):** (Headache (0109): 1; Convulsions (0093): 1; Tremor (0154): 2); **500 (n 1):** (Somnolence (0197): 1); **600 (n 59):** (Diarrhoea (0205): 1; Constipation (0204): 1; Tongue oedema (0331): 1; Abdominal pain (0268): 4; Nausea (0308): 22; Vomiting (0228): 30); **1010 (n 23):** (Cardiac failure (0496): 1; Circulatory failure (0499): 6; Hypotension (0212): 16); **1030 (n 7):** (Bradycardia (0208): 1; Cardiac arrest (0437): 2; Tachycardia (0224): 4); **1040 (n 1):** (Thrombophlebitis arm (0467): 1); **1100 (n 41):** (Asthma (1367): 1; Respiratory disorder (0536): 1; Laryngismus (0520): 1; Pulmonary oedema

(0535): 1; Larynx oedema (0522): 1; Coughing (0513): 3; Bronchospasm (0511): 3; Dyspnoea (0514): 30); **1810 (n 17):** (Hyperpyrexia (0894): 1; Allergic reaction (0712): 1; Hypovolaemia (0929): 1; Death (0722): 1; Temperature changed sensation (1705): 1; Malaise (0728): 1; Allergy (1058): 1; Rigors (0731): 1; Oedema (0398): 2; Fever (0725): 2; Anaphylactoid reaction (0714): 5); **1820 (n 2):** (Injection site pain (0057): 1; Injection site reaction (0058): 1); **Iodixanol (n 317): 100 (n 142):** (Skin disorder (0037): 1; Skin exfoliation (1199): 1; Sweating increased (0043): 2; Skin reaction localised (1650): 2; Rash maculo-papular (0030): 3; Angioedema (0003): 7; Rash (0027): 18; Pruritus (0024): 18; Rash erythematous (0028): 43; Urticaria (0044): 47); **410 (n 12):** (Headache (0109): 1; Faecal incontinence (0107): 1; Dysaesthesia (1491): 1; Tremor (0154): 1; Stupor (0151): 1; Coma (0091): 3; Paraesthesia (0137): 4); **431 (n 4):** (Lacrimation abnormal (1049): 1; Conjunctivitis (0238): 3; **432 (n 1):** (Tinnitus (0264): 1; **433 (n 1):** (Taste perversion (0267): 1); **600 (n 27):** (Mucositis NOS (1351): 1; Mouth dry (0218): 1; Tongue oedema (0331): 1; Salivary gland enlargement (0325): 1; Lip disorder (1852): 1; Dysphagia (0280): 2; Nausea (0308): 10; Vomiting (0228): 10); **700 (n 1):** (Hepatic function abnormal (0348): 1); **1010 (n 16):** (Cyanosis (0501): 1; Hypertension (0210): 1; Circulatory failure (0499): 2; Hypotension (0212): 12); **1020 (n 2):** (Myocardial infarction (0428): 2); **1030 (n 7):** (Arrhythmia (0433): 1; Bradycardia (0208): 2; Cardiac arrest (0437): 4); **1040 (n 14):** (Vasodilatation (0225): 1; Cerebral ischaemia (1987): 1; Flushing (0207): 12); **1100 (n 39):** (Pulmonary oedema (0535): 1; Coughing (0513): 2; Bronchospasm (0511): 2; Laryngismus (0520): 3; Larynx oedema (0522): 3; Rhinitis (0539): 3; Throat tightness (1489): 4; Dyspnoea (0514): 21); **1300 (n 10):** (Urinary incontinence (0156): 1; Renal pain (0621): 1; Renal failure acute (0618): 2; Face oedema (0602): 6); **1810 (n 39):** (Choking (1460): 1; Fever (0725): 1; Allergy (1058): 1; Chest pain (0718): 1; Hypothermia (0727): 1; Syncope (0223): 1; Allergic reaction (0712): 2; Malaise (0728): 2; Hyperpyrexia (0894): 3; Rigors (0731): 3; Temperature changed sensation (1705): 3; Oedema mouth (1485): 4; Oedema periorbital (1009): 6; Anaphylactic shock (0713): 10); **1820 (n 2):** (Cellulitis (1372): 1; Injection site urticaria (1968): 1); **Iodoxamic acid (n 5): 100 (n 1):** (Sweating increased (0043): 1); **1010 (n 2):** (Circulatory failure (0499): 1; Hypotension (0212): 1); **1100 (n 2):** (Dyspnoea (0514): 1; Pulmonary oedema (0535): 1); **Ioglicic acid (n 19): 100 (n 3):** (Rash (0027): 1; Pruritus (0024): 1; Rash maculo-papular (0030): 1); **600 (n 7):** (Nausea (0308): 2; Abdominal pain (0268): 2; Vomiting (0228): 3); **1010 (n 3):** (Cyanosis (0501): 1; Hypotension (0212): 2); **1030 (n 1):** (Cardiac arrest (0437): 1); **1100 (n 2):** (Bronchospasm (0511): 1; Dyspnoea (0514): 1); **1300 (n 1):** (Face oedema (0602): 1); **1810 (n 2):** (Allergic reaction (0712): 1; Allergy (1058): 1); **Ioglycamic acid (n 4): 600 (n 1):** (Vomiting (0228): 1); **1100 (n 1):** (Dyspnoea (0514): 1); **1810 (n 2):** (Anaphylactoid reaction (0714): 1; Fever (0725): 1); **Iohexol (n 202): 100 (n 71):** (Angioedema (0003): 1; Sweating increased (0043): 1; Rash maculo-papular (0030): 1; Bullous eruption (0871): 1; Skin reaction localised (1650): 1; Skin disorder (0037): 2; Rash (0027): 9; Rash erythematous (0028): 14; Pruritus (0024): 15; Urticaria (0044): 26); **410 (n 8):** (Dysphonia (0103): 1; Spasm generalized (0149): 1; Convulsions (0093): 1; Coma (0091): 2; Tremor (0154): 3); **431 (n 4):** (Blindness temporary (1280): 1; Conjunctivitis (0238): 1; Blindness (0232): 2); **500 (n 3):** (Amnesia (0164): 1; Agitation (0163): 1; Somnolence (0197): 1); **600 (n 23):** (Lip disorder (1852): 1; Abdominal pain (0268): 1; Tongue oedema (0331): 1; Dysphagia (0280): 3; Nausea (0308): 8; Vomiting (0228): 9); **1010 (n 7):** (Circulatory failure (0499): 1; Cardiac failure (0496): 1; Hypotension (0212): 5); **1030 (n 9):** (Palpitation (0221): 1; Bradycardia (0208): 1; Cardiac arrest (0437): 3; Tachycardia (0224): 4); **1040 (n 4):** (Flushing (0207): 4); **1100 (n 45):** (Respiratory depression (0144): 1; Stridor (0542): 1; Asthma (1367): 2; Pulmonary oedema (0535): 2; Laryngismus (0520): 3; Laryngitis (0521): 4;

Bronchospasm (0511): 4; Rhinitis (0539): 4; Larynx oedema (0522): 5; Coughing (0513): 5; Dyspnoea (0514): 14); **1230 (n 1):** (Purpura (0459): 1); **1300 (n 2):** (Face oedema (0602): 1; Renal failure acute (0618): 1); **1810 (n 24):** (Death (0722): 1; Allergy (1058): 1; Chest pain substernal (0720): 1; Choking (1460): 1; Chest pain (0718): 1; Oedema periorbital (1009): 1; Syncope (0223): 1; Rigors (0731): 1; Temperature changed sensation (1705): 2; Anaphylactic shock (0713): 2; Oedema mouth (1485): 3; Oedema (0398): 4; Allergic reaction (0712): 5); **1820 (n 1):** (Infusion site reaction (2137): 1); **Iomeprol (n 1020): 100 (n 437):** (Photosensitivity reaction (0022): 1; Rash pustular (0032): 1; Skin exfoliation (1199): 1; Dermatitis (0007): 1; Urticaria acute (0045): 2; Skin reaction localised (1650): 3; Bullous eruption (0871): 4; Skin disorder (0037): 5; Rash maculo-papular (0030): 6; Angioedema (0003): 6; Sweating increased (0043): 11; Rash (0027): 47; Pruritus (0024): 68; Rash erythematous (0028): 90; Urticaria (0044): 191); 200 (n 3): (Rhabdomyolysis (1210): 1; Arthralgia (0063): 1; Skeletal pain (1347): 1); 410 (n 49): (Aphasia (0087): 1; Extrapyramidal disorder (0106): 1; Speech disorder (0150): 1; Convulsions (0093): 1; Dysaesthesia (1491): 1; Migraine aggravated (1021): 1; Vertigo (0158): 2; Neurologic disorder NOS (2133): 2; Convulsions grand mal (0095): 2; Muscle contractions involuntary (0155): 2; Stupor (0151): 2; Headache (0109): 5; Dizziness (0101): 5; Dysphonia (0103): 5; Coma (0091): 5; Tremor (0154): 5; Paraesthesia (0137): 8); **431 (n 6):** (Conjunctival disorder (2008): 1; Blepharitis (1007): 1; Conjunctivitis (0238): 1; Blindness temporary (1280): 1; Vision abnormal (0257): 2); **432 (n 2):** (Hearing decreased (1368): 1; Tinnitus (0264): 1); **500 (n 7):** (Confusion (0092): 1; Nervousness (0188): 1; Agitation (0163): 5); **600 (n 106):** (Tongue disorder (0330): 1; Stomatitis (0327): 1; Abdominal pain (0268): 1; Mouth dry (0218): 1; Salivary gland enlargement (0325): 1; Tongue oedema (0331): 2; Mucositis NOS (1351): 3; Diarrhoea (0205): 3; Dysphagia (0280): 3; Nausea (0308): 38; Vomiting (0228): 52); **700 (n 1):** (Hepatic failure (0933): 1); **1010 (n 48):** (Circulatory failure (0499): 5; Cyanosis (0501): 8; Hypertension (0210): 8; Hypotension (0212): 27); 1020 (n 3): (Myocardial infarction (0428): 1; Myocardial ischaemia (0429): 2); 1030 (n 18): (Fibrillation atrial (0439): 1; Arrhythmia (0433): 1; Fibrillation cardiac (0442): 1; Palpitation (0221): 1; Cardiac arrest (0437): 4; Bradycardia (0208): 4; Tachycardia (0224): 6); **1040 (n 27):** (Conjunctival haemorrhage (1211): 1; Flushing (0207): 26); **1100 (n 153):** (Pharyngitis (0523): 1; Asthma (1367): 1; Stridor (0542): 1; Laryngismus (0520): 2; Respiratory disorder (0536): 2; Respiratory depression (0144): 3; Respiratory insufficiency (0537): 3; Pulmonary oedema (0535): 4; Laryngitis (0521): 10; Rhinitis (0539): 11; Throat tightness (1489): 11; Bronchospasm (0511): 12; Larynx oedema (0522): 18; Coughing (0513): 21; Dyspnoea (0514): 53); **1220 (n 1):** (Lymphoedema (0581): 1); **1230 (n 1):** (Thrombosis (0481): 1); **1300 (n 15):** (Renal failure acute (0618): 1; Urinary incontinence (0156): 1; Face oedema (0602): 13); **1810 (n 132):** (Drug hypersensitivity syndrome (2309): 1; Asthenia (0716): 1; Oedema generalised (0400): 1; Back pain (0717): 1; Fever (0725): 2; Anaphylactoid reaction (0714): 2; Syncope (0223): 2; Condition aggravated (0965): 3; Oedema peripheral (0401): 3; Malaise (0728): 4; Choking (1460): 4; Rigors (0731): 6; Allergy (1058): 8; Chest pain (0718): 8; Temperature changed sensation (1705): 9; Allergic reaction (0712): 9; Oedema (0398): 14; Oedema periorbital (1009): 17; Oedema mouth (1485): 18; Anaphylactic shock (0713): 19); **1820 (n 10):** (Injection site rash (1881): 1; Injection site reaction (0058): 1; Injection site inflammation (0054): 1; Injection site urticaria (1968): 7); **1830 (n 1):** (Immune system disorder (1903): **1); Iopamidol (n 600)**: 100 (n 136): (Skin reaction localised (1650): 1; Bullous eruption (0871): 1; Dermatitis exfoliative (0008): 1; Skin disorder (0037): 2; Angioedema (0003): 2; Rash maculo-papular (0030): 2; Sweating increased (0043): 11; Pruritus (0024): 13; Rash (0027): 23; Rash erythematous (0028): 35; Urticaria (0044): 45); **200 (n 2):** (Arthralgia (0063): 1; Myalgia (0073): 1); **410 (n 91):**

(Hypokinesia (0118): 1; Hypertonia (0116): 1; Speech disorder (0150): 1; Neurologic disorder NOS (2133): 1; Faecal incontinence (0107): 1; Paresis (0141): 1; Dizziness (0101): 1; Quadriplegia (0143): 1; Aphasia (0087): 2; Hemiparesis (0111): 2; Stupor (0151): 2; Oedema cerebral (0891): 2; Hyperkinesia (0114): 2; Convulsions grand mal (0095): 2; Dysphonia (0103): 3; Dystonia (0068): 3; Coma (0091): 3; Meningitis (0955): 3; Neuritis (0125): 3; Meningism (0120): 4; Vertigo (0158): 4; Paraesthesia (0137): 6; Convulsions (0093): 9; Headache (0109): 15; Tremor (0154): 18; **431 (n 5):** (Blindness temporary (1280): 1; Vision abnormal (0257): 1; Photopsia (1172): 1; Diplopia (0241): 2); **432 (n 1):** (Vestibular disorder (1126): 1); **500 (n 9):** (Appetite increased (0168): 1; Agitation (0163): 1; Amnesia (0164): 1; Thinking abnormal (0199): 1; Nervousness (0188): 1; Confusion (0092): 4); **600 (n 95):** (Dyspepsia (0279): 1; Tongue oedema (0331): 1; Dysphagia (0280): 1; Diarrhoea (0205): 1; Saliva increased (0222): 1; Mouth dry (0218): 3; Abdominal pain (0268): 6; Nausea (0308): 38; Vomiting (0228): 43; **800 (n 1):** (Oedema pharynx (1395): 1); **1010 (n 37):** (Hypertension aggravated (0762): 1; Cardiac failure (0496): 2; Cyanosis (0501): 4; Circulatory failure (0499): 6; Hypertension (0210): 9; Hypotension (0212): 15); **1020 (n 1):** (Myocardial ischaemia (0429): 1); **1030 (n 19):** (Fibrillation atrial (0439): 1; Fibrillation ventricular (0440): 2; Cardiac arrest (0437): 6; Tachycardia (0224): 10); 1040 (n 21): (Vasospasm (0226): 3; Cerebrovascular disorder (0445): 4; Flushing (0207): 14); **1100 (n 91):** (Asthma (1367): 1; Yawning (0201): 1; Hypoxia (0519): 1; Laryngismus (0520): 1; Respiratory disorder (0536): 1; Bronchostenosis (2000): 1; Throat tightness (1489): 2; Respiratory insufficiency (0537): 2; Rhinitis (0539): 4; Respiratory depression (0144): 4; Bronchospasm (0511): 6; Coughing (0513): 7; Pulmonary oedema (0535): 8; Larynx oedema (0522): 14; Dyspnoea (0514): 38; **1230 (n 4):** (Haemorrhage NOS (0452): 1; Haematoma (1353): 1; Purpura (0459): 2); **1300 (n 3):** (Face oedema (0602): 3); **1810 (n 81):** (Asthenia (0716): 1; Oedema mouth (1485): 1; Death (0722): 1; Anaphylactic reaction (2237): 1; Drug hypersensitivity syndrome (2309): 1; Hyperpyrexia (0894): 2; Anaphylactoid reaction (0714): 2; Oedema periorbital (1009): 2; Tolerance decreased (0761): 2; Fever (0725): 3; Pain (0730): 3; Allergic reaction (0712): 4; Oedema (0398): 5; Allergy (1058): 6; Syncope (0223): 7; Anaphylactic shock (0713): 7; Malaise (0728): 7; Rigors (0731): 12; Temperature changed sensation (1705): 14; **1820 (n 3):** (Application site oedema (0048): 1; Anaesthesia local (0062): 1; Injection site necrosis (0056): 1); **Iopanoic acid (n 6): 100 (n 1):** (Rash erythematous (0028): 1); **410 (n 1):** (Dizziness (0101): 1); **600 (n 3):** (Salivary gland enlargement (0325): 1; Diarrhoea (0205): 1; Vomiting (0228): 1); **1810 (n 1):** (Asthenia (0716): 1); **Iopentol (n 24): 100 (n 3)**: (Urticaria (0044): 3); **410 (n 3):** (Coma (0091): 1; Headache (0109): 2); **500 (n 1):** (Confusion (0092): 1); **600 (n 8):** (Nausea (0308): 4; Vomiting (0228): 4); **1010 (n 2):** (Hypertension (0210): 1; Hypotension (0212): 1); **1030 (n 1):** (Tachycardia (0224): 1); **1100 (n 1):** (Dyspnoea (0514): 1); **1300 (n 1):** (Anuria (0596): 1); **1810 (n 4):** (Anaphylactoid reaction (0714): 1; Fever (0725): 1; Anaphylactic shock (0713): 1; Rigors (0731): 1); **Iopromide (n 952): 100 (n 407):** (Erythema multiforme (0014): 1; Stevens Johnson syndrome (0042): 1; Dermatitis (0007): 1; Sweating decreased (1298): 3; Bullous eruption (0871): 3; Skin reaction localised (1650): 3; Rash pustular (0032): 4; Skin disorder (0037): 7; Rash maculo-papular (0030): 9; Sweating increased (0043): 11; Angioedema (0003): 20; Rash (0027): 34; Pruritus (0024): 49; Rash erythematous (0028): 90; Urticaria (0044): 171); **410 (n 37):** (Blindness cortical (1890): 1; Tetany (0152): 1; Hyperkinesia (0114): 1; Dysaesthesia (1491): 1; Migraine (0121): 1; Convulsions grand mal (0095): 1; Muscle contractions involuntary (0155): 1; Dyskinesia (0102): 1; Stupor (0151): 1; Dysphonia (0103): 3; Tremor (0154): 3; Coma (0091): 4; Paraesthesia (0137): 5; Dizziness (0101): 6; Headache (0109): 7); **431 (n 9):** (Exophthalmos (0242): 1; Mydriasis (0219): 1; Blindness temporary (1280): 1;

Photophobia (0250): 1; Vision abnormal (0257): 2; Conjunctivitis (0238): 3); **500 (n 6):** (Amnesia (0164): 1; Somnolence (0197): 1; Confusion (0092): 2; Agitation (0163): 2); **600 (n 82):** (Mucositis NOS (1351): 1; Colitis (0271): 1; Stomatitis ulcerative (0328): 1; Salivary gland enlargement (0325): 1; Abdominal pain (0268): 3; Mouth dry (0218): 3; Dysphagia (0280): 4; Tongue oedema (0331): 4; Nausea (0308): 23; Vomiting (0228): 41); **700 (n 3):** (Hepatic enzymes increased (1346): 1; Bilirubinaemia (0339): 1; Hepatitis (0350): 1); **800 (n 1):** (Hyperglycaemia (0382): 1); **900 (n 1):** (TSH increased (1831): 1); **1010 (n 72):** (Hypertension aggravated (0762): 1; Cardio-respiratory failure (1899): 1; Cyanosis (0501): 9; Circulatory failure (0499): 9; Hypertension (0210): 13; Hypotension (0212): 39); **1030 (n 31):** (Arrhythmia (0433): 1; Bradycardia (0208): 5; Tachycardia (0224): 7; Fibrillation ventricular (0440): 8; Cardiac arrest (0437): 10); **1040 (n 26):** (Vasodilatation (0225): 2; Flushing (0207): 24); **1100 (n 132):** (Asthma (1367): 1; Pharyngeal disorder (2211): 1; Respiratory insufficiency (0537): 3; Pulmonary oedema (0535): 3; Throat tightness (1489): 4; Respiratory depression (0144): 5; Laryngismus (0520): 6; Laryngitis (0521): 6; Rhinitis (0539): 8; Bronchospasm (0511): 11; Coughing (0513): 20; Larynx oedema (0522): 23; Dyspnoea (0514): 41); **1220 (n 1):** (Leukocytosis (0576): 1); **1230 (n 1):** (Coagulation disorder (0586): 1); **1300 (n 30):** (Renal function abnormal (0619): 1; Renal failure acute (0618): 4; Face oedema (0602): 25); **1810 (n 102):** (Drug hypersensitivity syndrome (2309): 1; Hyperpyrexia (0894): 1; Anaphylactic reaction (2237): 1; Tenderness NOS (1911): 1; Malaise (0728): 1; Choking (1460): 1; Pain (0730): 1; Asthenia (0716): 1; Temperature changed sensation (1705): 1; Allergy (1058): 2; Chest pain substernal (0720): 2; Anaphylactoid reaction (0714): 2; Oedema peripheral (0401): 2; Condition aggravated (0965): 3; Rigors (0731): 3; Chest pain (0718): 4; Syncope (0223): 6; Oedema periorbital (1009): 10; Oedema (0398): 11; Oedema mouth (1485): 12; Allergic reaction (0712): 16; Anaphylactic shock (0713): 20); **1820 (n 11):** (Injection site reaction (0058): 1; Infusion site rash (2136): 2; Application site reaction (0047): 2; Injection site urticaria (1968): 6); **Iotalamic acid (n 27):** 100 (n 4): (Sweating increased (0043): 1; Urticaria (0044): 1; Rash (0027): 2); **410 (n 2):** (Coma (0091): 1; Headache (0109): 1); **600 (n 2):** (Nausea (0308): 1; Vomiting (0228): 1); **1010 (n 4):** (Circulatory failure (0499): 1; Hypotension (0212): 3); **1030 (n 2):** (Tachycardia (0224): 2); **1040 (n 2):** (Cerebrovascular disorder (0445): 1; Flushing (0207): 1); **1100 (n 6):** (Dyspnoea (0514): 1; Bronchospasm (0511): 1; Pulmonary oedema (0535): 1; Coughing (0513): 1; Larynx oedema (0522): 2); **1810 (n 5):** (Anaphylactic shock (0713): 1; Anaphylactoid reaction (0714): 2; Temperature changed sensation (1705): 2); **Iotrolan (n 6): 100 (n 2):** (Dermatitis (0007): 1; Rash (0027): 1); **410 (n 2):** (Meningitis (0955): 2); **1040 (n 1):** (Flushing (0207): 1); **1300 (n 1):** (Face oedema (0602): 1); **Iotroxic acid (n 97): 100 (n 36):** (Bullous eruption (0871): 1; Rash maculo-papular (0030): 1; Sweating increased (0043): 4; Rash erythematous (0028): 5; Rash (0027): 5; Pruritus (0024): 8; Urticaria (0044): 12); **410 (n 4):** (Paraesthesia (0137): 1; Tremor (0154): 1; Hyperkinesia (0114): 1; Vertigo (0158): 1); **600 (n 20):** (Gastritis (0291): 1; Abdominal pain (0268): 1; Dyspepsia (0279): 1; Nausea (0308): 6; Vomiting (0228): 11); **1010 (n 7):** (Hypertension (0210): 1; Circulatory failure (0499): 2; Hypotension (0212): 4); **1030 (n 4):** (Tachycardia (0224): 1; Bradycardia (0208): 1; Cardiac arrest (0437): 2); **1040 (n 1):** (Cerebrovascular disorder (0445): 1); **1100 (n 16):** (Coughing (0513): 1; Asthma (1367): 1; Laryngismus (0520): 1; Respiratory depression (0144): 1; Bronchospasm (0511): 2; Larynx oedema (0522): 3; Dyspnoea (0514): 7); **1810 (n 9):** (Chest pain (0718): 1; Hyperpyrexia (0894): 1; Allergy (1058): 1; Anaphylactic shock (0713): 1; Allergic reaction (0712): 1; Temperature changed sensation (1705): 1; Rigors (0731): 1; Malaise (0728): 2); **Ioversol (n 105): 100 (n 53):** (Skin reaction localised (1650): 1; Skin disorder (0037): 1; Angioedema (0003): 1; Dermatitis (0007): 1; Rash maculo-papular

(0030): 2; Rash (0027): 9; Pruritus (0024): 9; Rash erythematous (0028): 11; Urticaria (0044): 18); **410 (n 1):** (Paraesthesia (0137): 1; **431 (n 4):** (Eye abnormality (0243): 1; Lacrimal gland disorder (0216): 1; Exophthalmos (0242): 1; Vision abnormal (0257): 1); **500 (n 1):** (Agitation (0163): 1); **600 (n 14):** (Increased stool urgency (1843): 1; Dysphagia (0280): 1; Nausea (0308): 3; Vomiting (0228): 9); **1010 (n 4):** (Hypertension (0210): 1; Cyanosis (0501): 1; Hypotension (0212): 2); **1030 (n 3):** (Bradycardia (0208): 1; AV block (0431): 1; Fibrillation ventricular (0440): 1); **1040 (n 8):** (Cerebral ischaemia (1987): 2; Flushing (0207): 6); **1100 (n 10):** (Bronchospasm (0511): 1; Throat tightness (1489): 1; Laryngitis (0521): 1; Larynx oedema (0522): 1; Coughing (0513): 2; Dyspnoea (0514): 4); **1230 (n 2):** (Purpura (0459): 1; Purpura thrombopenic thrombotic (0592): 1); **1810 (n 4):** (Malaise (0728): 2; Oedema (0398): 2); **1820 (n 1):** (Infusion site rash (2136): 1); 100 (n 6): **Ioxaglate meglumine/Ioxaglate sodium (n 21): 100 (n 6):** (Rash (0027): 1; Urticaria (0044): 1; Sweating increased (0043): 1; Rash erythematous (0028): 3; **410 (n 2):** (Headache (0109): 1; Tremor (0154): 1); **600 (n 5):** (Nausea (0308): 1; Vomiting (0228): 4); **1010 (n 3):** (Hypotension (0212): 1; Hypertension (0210): 2); **1100 (n 3):** (Coughing (0513): 1; Dyspnoea (0514): 2); **1810 (n 2):** (Chest pain precordial (0719): 1; Oedema periorbital (1009): 1); **Ioxaglic acid (n 2): 100 (n 1):** (Rash maculo-papular (0030): 1); **1100 (n 1):** (Dyspnoea (0514): 1); **Ioxitalamate meglumine/Ioxitalamate sodium (n 5): 410 (n 1):** (Tremor (0154): 1); **600 (n 1):** (Vomiting (0228): 1); **1100 (n 2):** (Dyspnoea (0514): 1; Larynx oedema (0522): 1); **1810 (n 1):** (Oedema periorbital (1009): 1); **Ioxitalamic acid (n 5): 100 (n 2):** (Pruritus (0024): 2); **1100 (n 2):** (Dyspnoea (0514): 2); **1810 (n 1):** (Malaise (0728): 1); **Meglumine amidotrizoate/Sodium amidotrizoate (n 87): 100 (n 19):** (Angioedema (0003): 1; Pruritus (0024): 1; Rash (0027): 2; Urticaria (0044): 6; Rash erythematous (0028): 9; 410 (n 4): (Dystonia (0068): 1; Faecal incontinence (0107): 1; Abscences (1208): 1; Hyperkinesia (0114): 1); 431 (n 1): (Mydriasis (0219): 1); 500 (n 2): (Agitation (0163): 1; Anxiety (0166): 1); **600 (n 9):** (Nausea (0308): 2; Vomiting (0228): 7); **1010 (n 10):** (Cyanosis (0501): 1; Hypertension (0210): 1; Circulatory failure (0499): 3; Hypotension (0212): 5); **1030 (n 4):** (Fibrillation atrial (0439): 1; Bradycardia (0208): 1; Cardiac arrest (0437): 2); **1040 (n 3):** (Cerebrovascular disorder (0445): 1; Flushing (0207): 2); **1100 (n 19):** (Coughing (0513): 1; Rhinitis (0539): 1; Larynx oedema (0522): 1; Hypoxia (0519): 2; Pulmonary oedema (0535): 3; Bronchospasm (0511): 4; Dyspnoea (0514): 7); **1300 (n 2):** (Renal pain (0621): 1; Urinary incontinence (0156): 1); **1810 (n 14):** (Oedema generalised (0400): 1; Allergic reaction (0712): 1; Oedema periorbital (1009): 1; Oedema (0398): 1; Pallor (0220): 1; Death (0722): 3; Syncope (0223): 6); **Metrizoic acid (n 3)**: **1010 (n 1):** (Hypotension (0212): 1); **1820 (n 2):** (Injection site reaction (0058): 2).

Appendix Nr 7.

Correlation clusters and confirmatory plots.

Relevant Matlab program.

We try to render this section as self contained as possible, by allowing some limited repeat of elements already discussed.

We have attempted to obtain an auto-classification of Iodinate Contrast Agents starting from tables of ADRs frequencies, where the rows represented categories of ADRs, and the columns-Agents.

In a first version, a clustering technique for the columns was used, based on the WILKS's Chi-Square statistic. In this technique, the WILKS's statistic square root gives the diameter of any subset of columns and in particular, a pair-wise column dissimilarity (a pseudo-distance) function.

The attraction of this approach is that it permits an objective clustering within the frame of a GABRIEL Simultaneous Testing Procedure. However, in spite of its appeal, this technique failed to correctly identify the sets of agents having close ADR profiles. The point which we missed was the fact that WILKS's statistic small values can originate also in configurations other than subtables with close ADR profiles (such as in the cases of tables where one or more of the agents have small ADR values throughout).

We had to change the inter-column pseudo-distance. The appropriate choice was to define this pseudo-distance in terms of the "brute correlation" of the two column vectors (brute in the sense that averages are not subtracted), that is in terms of their multidimensional cosine. This choice proved itself successful.

We proceed now with the description of **this alternative technique,** using **an exact inter-column distance function, based on the multidimensional cosine of the column vectors, that is on their "brute" correlation coefficient**.

Our data sets are contingency (rxc) tables $X = \{x_{ij} : i = 1,2,...,r; j = 1,2,...,c\}$, with nonnegative elements. The r rows correspond to ADRs and the c columns, to the drugs. Each combination (i, j) is a cell of the table, with which is associated the cell value x_{ij}, the value of the ADR i for the drug j. Denote by x_{i+} the sum of row i, by x_{+j} the sum of column j and by x_{++} the total sum of elements of X.

If one divides all the elements of column j by the column total x_{+j}, one obtains **the column j profile**, a vector of weights $\dfrac{x_{ij}}{x_{+j}}$ summing up to 1. Two columns have **the same profile** if and only if they have **proportional elements**, i.e. the elements of one column can be obtained from those of the other column by multiplying by the same nonzero factor. A table in which **all column profiles coincide**, has a multiplicative structure expressed by the relations

$$x_{ij} = \frac{x_{i+} x_{+j}}{x_{++}} : i = 1,2,...,r; j = 1,2,...,c .$$

Or, in other words, all column profiles coincide with the **marginal column profile**
$\{\dfrac{x_{i+}}{x_{++}} : i = 1,2,...,r\}$.

One introduces in the Euclidean Space R^r to which the column vectors belong, a **dissimilarity measure** d defined on pairs of vectors of this space, measuring the departure of the pair from the situation of having the same profile, i.e. from being proportional. If $a = (a_1,...,a_r)'$ and $b = (b_1,...,b_r)'$ are **two vectors of** R^r, then we define **their dissimilarity** $d(a,b)$ as:

$$d(a,b) = \sqrt{\dfrac{1 - \cos(a,b)}{2}} \quad ,$$

where $\cos(a,b)$, the **multidimensional cosine** of a,b, is given by:

$$\cos(a,b) = \dfrac{a'b}{\sqrt{(a'a)(b'b)}} = \dfrac{\sum_{i=1}^{r} a_i b_i}{\sqrt{\sum_{i=1}^{r} a_i^2} \sqrt{\sum_{i=1}^{r} b_i^2}} \ .$$

The measure $d(a,b)$ in general, takes values between 0 (for a,b proportional with a positive factor of proportionality, and their respective profiles identical) and 1 (for a,b proportional with a negative factor of proportionality). In our case, a,b are column vectors with non-negative coordinates, and $d(a,b)$ varies from 0 to $\dfrac{1}{\sqrt{2}}$ (for a,b orthogonal).

Most of the dissimilarity measures in use are not true distances. But **this dissimilarity measure** $d(a,b)$ **is a true distance.** One can prove that it satisfies the triangle property: for any vectors a,b,c, one has

$$d(a,b) \leq d(a,c) + d(c,b) .$$

We will call $d(a,b)$ simply **the distance between** a **and** b **.**

The **Diameter of a subtable** formed of columns is defined as the largest distance between two columns of the subtable. At one end, we have the diameter of the set X itself; on the other end, the diameters of the subtables formed of just two columns. In the latter case, the diameter is simply the distance between these two columns. In fact, even subtables of one single column may be considered, regarding such a subtable as containing two identical columns. Its diameter must obviously be taken as equal to zero. The diameter as a function defined over the subtables of columns, is **monotonic with respect to the relation of subtables inclusion:** if S_1 and S_2 are

subtables of columns such that $S_1 \subseteq S_2$, and $diam(S_1)$ and $diam(S_2)$ are their respective diameters, then $diam(S_1) \leq diam(S_2)$.

Let $\delta > 0$ be a **gauge** arbitrarily chosen. A subset S of columns is δ-**homogeneous** if $diam(S) \leq \delta$. Of course, the smaller is δ, the closer is S to a subset of columns having the same profile. This can be **checked by examining the pair-wise distances which must be all** $\leq \delta$**.** And since from the definition of the distance one obtains

$$\cos(a,b) = 1 - 2 * d^2(a,b),$$

the requirement that all pair-wise distances shall be $\leq \delta$, translates into **the condition that all pair-wise brute correlation should be** $\geq 1 - 2 * \delta^2$.

Given a gauge $\delta > 0$, our aim will be to **group the columns** (drugs in our case) **into clusters.** A cluster is a **maximal** δ-**homogeneous set of columns.** Being maximal, means being such that any larger subset including it will be non-homogeneous.

Assuming that we know how to split the columns into clusters for any given $\delta > 0$, we will try by playing with δ, to achieve a compromise between two opposite aims: to have **clusters as large as possible** on the one hand, and clusters **of as small a diameter as possible**, on the other hand.

Once this is done, the clusters will represent suggestions made by the statistician to the specialist, who will try to **find out the connection, if any, between the drugs (columns) which enter into the composition of each cluster.** It is clear that in this subsequent research, **only clusters containing at least two columns** (drugs) **are of interest.**

Our technique will consist mainly from constructing a **binary tree clustering based on a technique for optimally splitting a set into two subsets.**

We use a program written by us, following the elegant metaphoric explanation (which amounts to a pseudo-algorithm) given by **Leonard Kaufman and Peter J. Rousseeuw** in their book "**Finding Groups in Data,** An Introduction to Cluster Analysis", 1990, John Wiley [27], Chapter 6, Divisive Analysis, pp. 253-279.

In our implementation, the result of the algorithm is a table of the subsets obtained in the successive splitting into two, ordered on decreasing diameter. This table permits to tackle the problem formulated above.

As additional checking means, we use

a) **A graphical procedure whose result is an Euclidean Map** where the columns of the table are represented by markers, **the Euclidean distances between markers approximating the inter-column distances.** One starts from the matrix of column pair-wise dissimilarities (proper distances in our case), and by means of the Torgerson-Gower **Multi-Dimensional Scaling**, one

obtains a "**reification**", that is a set of points in an Euclidean space, whose pair-wise Euclidean distances approximate the pair-wise (dissimilarity) distances. The coordinates are ordered in decreasing importance, and the first two are used in the Euclidean Map which permits to see the cluster structure of the columns to an extent which **will confirm the clustering already obtained.**

This is true, provided the GOF (Goodness of Fit) given by the fist two dimensions is high enough. Otherwise, some of the pair-wise dissimilarities may be poorly approximated. In this latter case a successive examination of the plots for dimensions 3, 4 and so on may be of help.

b) The **minimal pair-wise distance** for each cluster, or equivalently **the maximal pair-wise brute correlation** thereof, which permit to get an idea of **the extent to which the clusters are homogeneous.**

In the program given below, one takes **a few values for the Gauge** (and the correponding values of the Brute Correlation) ; this choice is rather arbitrary. We have taken the values

Gauges   .825   .85   .90   .925   .95   .975

Correlations (brute)   .2958 .2739   .2236   .1936   .1581   .1118

For each one of these values, the splitting of the set of objects into maximal disjoint clusters is obtained. **All the obtained clusters, whether disjoint or not, are examined for maximal pair-wise correlation, and those with high enough values thereof are retained**.

Another relevant feature is the fact that for each value of Gauge, **the clusters have to be disjoint**. This may lead to the **loss of pairs of quite close objects (agents)**, which are **classified by the algorithm in different clusters**. A search for such pairs is provided for.

Befor applying the Clustering Program to a data matrix X, the sum of the values for each agent is

claculated, and the vector **scarce,** having as coordinates the indices of the agents with a small number of records, is formed. Implicitly, one obtains the vector **rich,** having as coordinates the

indices of the agents having a large number of records. The agents figuring in **scarce** are deleted and the analysis is done only for the agents figuring in **rich**. If there are no agents with too small

numbers of records, one will take for **scarce** the empty set: **scarce** = [ ].

The Clustering Program (written in MATLAB 5.3).

```
function TOTTABSUPL=ALLCLUSTERSFINAL(X,scarce)
% TOTTABSUPL=ALLCLUSTERSFINAL(X,scarce)
% INPUT: X(nxm), clustering involves rows
```

```
%       GAUGES and CORRELS chosen given INTERNALLY
%       scarce= 1xn vector of indices of "scarce" agents
% OUTPUT: Clusters and supplementary pairs for each GAUGE/CORREL; INTERNAL,
on screen
%          TOTTABSUPL= list of supplementary pairs as GLOBAL matrix
[n,m]=size(X); rich=setdiff(1:n,scarce); rich
X=X(rich,:);[n,m]=size(X);
DSQ=DSQ1A(X');
disp(' Follow up to four confirmatory plots');
rank=8; figure(1); [RR,GOF]=MDSCAL11A(DSQ,rank,rich');
CORRS=[.825 .85 .90 .925 .95 .975]';
GAUGES=sqrt(.5*(1-CORRS));
disp('GAUGES and CORRELATIONS');
disp(num2str([GAUGES CORRS]));
NGAUGES=length(GAUGES);
TOTTABSUPL=[]; TOTTABCL=[];
disp('==================================================');
for i=1:NGAUGES
  disp(['GAUGE     Nr     ',num2str(i),'     =     ',num2str(GAUGES(i)),'     CORREL=
',num2str(CORRS(i))]);
 [TABL,TABCL,TABSUPL]= ALLCLUSTERSF3A(X,GAUGES(i),DSQ,rich);
 TOTTABSUPL=[TOTTABSUPL;TABSUPL]; TOTTABCL=[TOTTABCL; TABCL];
  disp('==================================================');
end
TOTTABCL=UNIQUE(TOTTABCL,'rows');
TT=TOTTABSUPL;
if isempty(TT); TT=ones(0,3); end;
PAIRS=TT(:,1:2);
[nP,mP]=size(PAIRS);
indpairs=[];
for i=1:nP
  veci=zeros(1,n);veci(PAIRS(i,:))=ones(1,2);
  if prod(TOTTABCL*veci'-2)==0
    indpairs=[indpairs;0];
  else
    indpairs=[indpairs;1];
  end
end
indp=find(indpairs);
TOTTABSUPL=TOTTABSUPL(indp,:);
TOTTABSUPL=UNIQUE(TOTTABSUPL,'rows');
[vec,J]=sort(TOTTABSUPL(:,3));
TOTTABSUPL=TOTTABSUPL(J,:);
[nT,mT]=size(TOTTABSUPL);
for i=1:nT
  term=rich(TOTTABSUPL(i,1:2));
  TOTTABSUPL(i,1:2)=term;
```

```
end
disp('PAIRS of possible interest');
disp('Cols 1, 2= pair, Col 3= correlation');
M= TOTTABSUPL'; fprintf(1, '%6.0f  %6.0f %10.4f\n', M(1:3,1:nT));
[nu,nv]=size(TOTTABCL);
disp('Summary of clusters');
for i=1:nu
  veci=rich(find(TOTTABCL(i,:)));
  disp(['   ',num2str(veci)]);
end
%-------------------------------------------------------
function [TABL,TABCL,TABSUPL]= ALLCLUSTERSF3A(X,GAUGE,DSQ,indold)
% [TABL,TABCL,TABSUPL]= ALLCLUSTERSF3A(X,GAUGE,DSQ,indold)
% INPUT: X(nxm)= data matrix, the clustering is done on rows
%      GAUGE= such that DIAM<= GAUGE entails subset homogeneous
%      DSQ= matrix of pairwise dissimilarities (Dissimilarity Squared Root)
%      indold= vector(1xnrich) of rows X old indices (as rows in the larger matrix)
% OUTPUT: TABL=[DIAM, SPLIT, USED, PLACES] reduced then by deleting USED
%      each row of TABL corresponds to a retained subset
%      TABL(i,:)=[DIAM(i), SPLIT(i),PLACES(i)]
%      SUBSET=find(PLACES(i)); DIAM(i)=max pairwise DSQ ;
%      SPLIT(i)=1 if to split, and =0 if already cluster
%      USED(i)=1 if used, =0 if not yet used in order to split
%      PLACES(i)= 1xn vector 1/0, the ones show the rows involved
%      TABCL= 0/1 subset table for clusters with at least 2 elements
%      TABSUPL= table of possible pairs not found by clustering, and
%      their correlations (>= that corresponding to GAUGE)
[n,m]=size(X);
CORREL=GAUGEINV(GAUGE);
indi0=1:n; TEST=0;
DIAM=DIAMETER(1:n,DSQ);       SPLIT=1;       USED=0;       PLACES=ones(1,n);
TABL=[DIAM,1,0,PLACES];
while TEST<n+1
  if sum((TABL(:,2)==1).*(TABL(:,3)==0))==0; break; end
  icrt=min(find((TABL(:,2)==1).*(TABL(:,3)==0)));
  LINE=TABL(icrt,:); SPLIT=LINE(2); USED=LINE(3); PLACES=LINE(4:n+3);
  indi0=find(PLACES); % indi0
  if length(indi0)>1
   [ind1,ind2]= SPLITINTWO(indi0,DSQ); TABL(icrt,3)=1;
   DIAM1=DIAMETER(ind1,DSQ); SPLIT1=(DIAM1>=GAUGE); USED1=0;
   DIAM2=DIAMETER(ind2,DSQ); SPLIT2=(DIAM2>=GAUGE); USED2=0;
   PLACES1=zeros(1,n); PLACES1(ind1)=1;
   PLACES2=zeros(1,n); PLACES2(ind2)=1;
   LINE1=[DIAM1,SPLIT1,USED1,PLACES1];
   LINE2=[DIAM2,SPLIT2,USED2,PLACES2];
   TABL=[TABL;LINE1;LINE2];
  end
```

```
   indclust=find(TABL(:,2)==0);
   TEST=length(indclust);
end
TABL=flipud(UNIQUE(TABL,'rows'));
TABL(:,3)=[];
[r,c]=size(TABL);
indcl=find((TABL(:,1)>0).*(TABL(:,2)==0));
TABLCLUST=TABL(indcl,3:c);[rindcl,cindcl]=size(TABLCLUST);
for i=1:rindcl;
   vec=TABLCLUST(i,:);  indvec=indold(find(vec));  fprintf([' cluster ',num2str(i),' = ',num2str(indvec),'\n ']);
   diam=DIAMETER(find(vec),DSQ);  disp([' pairwise correls = at least ',num2str(GAUGEINV(diam))]);
end;
indcl=(sum(TABLCLUST')>1); TABCL=TABLCLUST(indcl,:);
[NRCL,M]=size(TABCL);
PAIRS0=zeros(M,M);
for i=1:NRCL
   vec=TABCL(i,:);
   PAIRS0=PAIRS0+vec'*vec;
end
PAIRS1=(GAUGEINV(DSQ)>=CORREL); PAIRS1=PAIRS1-diag(diag(PAIRS1));
SUPL=PAIRS1-PAIRS0;
TABSUPL=[];
for i=1:M-1
   for j=i+1:M
      vi=X(i,:); vj=X(j,:); vi=vi*pinv(sum(vi)); vj=vj*pinv(sum(vj));
      c0ij=corr0(vi,vj);
      if SUPL(i,j)==1; TABSUPL=[TABSUPL;[i,j,c0ij]];end;
   end
end
% if isempty(TABSUPL)
   % disp('No supplementary pairs to examine');
% else
   % disp('supplementary pairs to examine, and their correlations');
   % disp(num2str(TABSUPL));
% end


%------------------------------------------------------------
function S=DIAMETER(index,DSQ)
nindex=length(index);
if nindex==1
   S=0;
else
   S=0; for i=1:nindex-1; for j=i:nindex; S=max(S,DSQ(index(i),index(j)));end;end;
end
```

```
%------------------------------------------------------------
function RR=DSQ1A(X)
% RR=DSQ1A(X)
% INPUT: X(nxm)
% OUTPUT: RR(mxm)= matrix of columns dissimilarities
%           (columns are usually variates)
%      Here, RR(i,j)=(.5*(1-corrcoef0(X(:,i),X(:,j)))).^.5
RR=(.5*(1-corrcoef0(X))).^.5;
%------------------------------------------------------------
function R=corrcoef0(X)
% R=corrcoef0(X)
% INPUT: X= nxm matrix
% OUTPUT: R= m x m matrix of pair-columnwise corr0 values
%      R(i,j)=corr0(X(:,i),X(:,j))
[n,m]=size(X);
R=ones(m,m);
for i=1:m-1
  for j=i+1:m
    R(i,j)=corr0(X(:,i),X(:,j));
    R(j,i)=R(i,j);
  end
end
%-------------------------------------------------------------
function R=corr0(x,y)
% R=corr0(x,y)
% INPUT: x,y= n-vectors, both horizontal or both vertical
% OUTPUT: R= 'brute' correlation, where means are not subtracted
N12=sum(x.*y);
N1=sqrt(ssq(x)); N2=sqrt(ssq(y));
R= pinv(N1)*N12*pinv(N2);
%-------------------------------------------------------------
function CORR=GAUGEINV(GAUGE)
% CORR=GAUGEINV(GAUGE)
% INPUT: vector or matrix of values of GAUGE=sqrt((1-CORR)/2);
% CORR="brute" correlation
% OUTPUT: vector or matrix of values of CORR=1-2*GAUGE.^2
CORR=1-2*GAUGE.^2;
%-------------------------------------------------------------
function [INDI,INDE]= SPLITINTWO(INDI0,DSQ)
% [INDI,INDE]= SPLITINTWO(INDI0,DSQ)
% INPUT: INDI0= initial INDI with at least two elements
% DSQ(nxn)= matrix of dissimilarities
% OUTPUT: INDI,INDE= sets of indices of two clusters into
%      which INDI0 is split
% DSQ0=DSQ(INDI0,INDI0);
[n,p]=size(DSQ);
n0=length(INDI0);
```

```
if n0==2
  INDI=INDI0(1); INDE=INDI0(2);
else
INDI=INDI0; INDE=[];
for j=1:n0
  vec= internall0(INDI,DSQ);
  jmax=min(find(vec==max(vec)));
  INDImax=INDI(jmax);
  INDI= setdiff(INDI,INDImax);
  INDE= [INDE,INDImax]; INDE=sort(INDE);
  [diffs,vecint,vecext]=externall0(INDI,INDE,DSQ);
  if max(diffs)<=0
    break;
  end
end
end
%-------------------------------------------------------------
function  vec=internall0(indi,DSQ)
% vec=internall0(indi,DSQ)
% INPUT: indi(1xk)=columns involved, k>1; DSQ(nxn)=dissimilarities matrix
% OUTPUT: vec(1xk), vec(j)="average distance" of column j
%        to the other k-1 columns
% Subroutine form of internall
k=length(indi);
vec=zeros(1,k);
for j=1:k
  ind=setdiff(1:k,j);
  vec(j)=mean(DSQ(indi(j),indi(ind)));
end
%-------------------------------------------------------------
function [diffs,vecint,vecext]=externall0(indi,inde,DSQ)
% [diffs,vecint,vecext]=externall0(indi,inde,DSQ)
% INPUT: indi(1xkint), inde(1,kext), DSQ(nxn)= dissimilarities matrix
% OUTPUT: vecint(1xkint)= vector of distances of each col of MINT to the others in MINT
%        vecext(1xkint)= vector of distances of each col of MINT to the columns of MEXT
%        diffs= vecint-vecext
% Subroutine form of EXTERNALL
ki=length(indi);
ke=length(inde);
vecint=zeros(1,ki);
vecext=zeros(1,ki);
for j=1:ki
  ind= setdiff(1:ki,j);
  vecint(j)=mean(DSQ(indi(j),indi(ind)));
  vecext(j)=mean(DSQ(indi(j),inde));
end
diffs=vecint-vecext;
```

```
%-------------------------------------------------------------------
function [RR,GOF]=MDSCAL11A(DSQ,rank,indnew)
% [RR,GOF]=MDSCAL11A(DSQ,rank,indnew)
% INPUT: DSQ(n,n)= row-squared-distces matrix of unknown Y
%       indnew = vertical vector of indices replacing (1:n)' as markers
% OUTPUT: RR(n,rank)= 'Reification' of Y in an Euclidean
%       subspace of R^n, of dimension= rank (usually 2)
%       GOF= (cumsum(diag(D)))'/ssq(-.5*ga);
%       ga= inter effects of matrix DSQ of interrow
%         sq distces
%       Plots: 4 plots, each for two consec dimensions
%           rank= even
%           as subplot(2,2,h), h=1:min(rank,4)
[n,n1]=size(DSQ); rank=min(rank,n);
[mu,al,be,ga]=addest(DSQ);
[U,D,V]=svdrank(-.5*ga,rank); U=real(U); D=real(D); V=real(V);
RR=U*(D.^.5);
GOF=(cumsum(diag(D*D)))'/ssq(-.5*ga); GOF=real(GOF);
mark=num2str(indnew);
  for h=1:min(rank/2,4)
nc1=2*h-1; nc2=2*h; ncstr=num2str(h);
gofstr=[num2str(GOF(nc1)),' ',num2str(GOF(nc2))];
ncstr12=num2str([nc1,nc2]);
XM1=RR(:,nc1); YM1=RR(:,nc2);
% XM1=RR(indnew,nc1); YM1=RR(indnew,nc2);
subplot(2,2,h); plot(0,0,'w+', XM1,YM1,'w.');
title(['Comps ',ncstr12,' Cumpercs ',gofstr],'fontsize',8);
text(XM1,YM1,mark); axis('equal');
end
%----------------------------------------------------------------
function y=ssq(x)
% y=ssq(x)
% INPUT: matrix x (in particular, vector)
% OUTPUT: sum of squares y of elements of x
y=sum(sum(x.*x));
%----------------------------------------------------------------
function [mu,al,be,ga]=addest(Y)
% [mu,al,be,ga]=addest(Y)
% INPUT: Y(nxm)= complete data matrix
% OUTPUT: mu= gen. mean,
%       al(n)= row main effects estimates, as a (nx1) column
%       be(m)= col main effects estimates, as a (1xm) row
%    ga(nxm)= cell non-add-ty estimates (add. residuals)
[n,m]=size(Y);
mu=mean(mean(Y)); al=(mean(Y'))'-mu; be=mean(Y)-mu;
ga=Y-(mu*ones(n,m))-(al*ones(1,m))-(ones(n,1)*be);
%----------------------------------------------------------------
```

```
function [U,D,V,XEST,GOF]=svdrank(X,rank)
% [U,D,V,XEST,GOF]=svdrank(X,rank)
% INPUT: Data matr X(nxm), rank (of the SVD fit)
% OUTPUT: U(nxrank), D(rankxrank), V(mxrank)
%       XEST=U*D*V'; GOF=SQNORM(XEST)/SQNORM(X)
ind=(1:rank);
[u,d,v]=svd(X);
U=u(:,ind);
D=d(ind,ind);
V=v(:,ind);
XEST=U*D*V';
GOF=trace(XEST'*XEST)/trace(X'*X);
%----------------------------------------------------------------
```

Appendix Nr 8.

Data presentation, correlation clusters and confirmatory plots of SOCD frequencies of ATC-V08A -A, -B, -C and -D sub-class products together for the whole 40-year collection period (1968-2010) and for the two 20-year collections 1968-1989, and 1990-2010.

30 SOCD GROUPS:

1	100	11	700	21	1230
2	200	12	800	22	1300
3	300	13	900	23	1410
4	410	14	1010	24	1420
5	420	15	1020	25	1500
6	431	16	1030	26	1600
7	432	17	1040	27	1700
8	433	18	1100	28	1810
9	500	19	1210	29	1820
10	600	20	1220	30	1830

The SOCD groups of ADRs with codes 420 and 1600 contain in all 4 reports and will be eliminated. All the report numbers matrices will have 28 rows, for the 28 SOCD groups remaining after removal of groups 420 and 1600.

CLASSES A, B, C, D TOGETHER

Matrices

TABCD1(28x30) =[TA1,TB1,TC1,TD1] (years 1968-2010)

TABCD2(28x30) =[TA2,TB2,TC2,TD2] (years 1968-1989)

TABCD3(28x30) =[TA3,TB3,TC3,TD3] (years 1990-2010)

Nr of reports per contrast agent 1-9 (Class A):

Years\Drug	1	2	3	4	5	6	7	8	9
1968-2010	33	44648	9	101	936	165	14395	2223	1068
1968-1989	29	26017	9	87	659	123	7251	671	1031
1990-2010	4	18631	0	14	277	42	7144	1552	37

Drugs with few reports:

Years 1968-2010: 1, 3 and to a lesser extent 4, 6

Years 1968-1989: 1, 3 and to a lesser extent 4, 6

Years 1990-2010: 1, 3, 4, 6, 9

Nr of reports per contrast agent 10-21 (Class B)

Years\Drug	10	11	12	13	14	15	16	17	18	19	20	21
1968-2010	1629	4815	19870	4617	17716	434	19387	773	7570	5200	82	2012
1968-1989	0	0	2396	0	2053	0	193	8	0	1587	0	1939
1990-2010	1629	4815	17474	4617	15663	434	19194	765	7570	3613	82	73

Drugs with few reports:

Years 1968-2010: 20

Years 1968-1989: 10, 11, 13, 15, 17, 18, 20 and to a lesser extent 16

Years 1990-2010: 20, 21

Nr of reports per contrast agent 22-29 (Class C) and 30 (Class D):

Years\Drug	22	23	24	25	26	27	28	29	30	Total
1968-2010	2721	621	193	527	878	484	880	867	310	**155164**
1968-1989	2656	621	145	452	874	394	734	204	259	**50392**
1990-2010	65	0	48	75	4	90	146	663	51	**104772**

Drugs with few reports:

Years 1968-2010: none

Years 1968-1989: none

Years 1990-2010: 23, 26

The three tables above must be read as a single table with 3 rows and 30 columns. The rows

stand for TABCD1 (years 1968-2010), TABCD2 (years 1968-1989) and TABCD3 (years

1990-2010). The columns from 1 to 30 stand as follows:

Columns 1-9   for contrast agents 1-9   of class A,

Columns 10-21 for contrast agents 1-12 of class B,

Columns 22-29 for contrast agents 1- 8 of class C,

Column   30   for contrast agent   1   of class D.

We can write a table of correpondence as follows:

 Columns 1-9 correspond to Agents a1, a2, a3, a4, a5, a6, a7, a8, a9 of class A,

 Columns 10-21   ,,   ,,   ,,   b1, b2, b3, b4, b5, b6, b7, b8,b9,b10,b11,b12 of class B,

 Columns 22-29   ,,   ,,   ,,   c1, c2, c3, c4, c5, c6, c7, c8 of class C,

 Column   30 corresponds to Agent   d1 of class D.

 For instance, a cluster [3 5 10 19 20 28 30] is readily written as [a3, a5, b1, b10, b11, c7, d1].

The table values are total numbers of reports. For example, in column 22 (for agent 1 of class C),

2721= total number of reports for years 1968-2010,

2656= total number of reports for years 1968-1989,

   65= total number of reports for years 1990-2010

In column **Total (column 31)**, are given the totals of TABCD1, TABCD2 and TABCD3, that is **155164, 50392** and **104772** respectively.

In the following analyses, "scarce" will denote the set of contrast agents of small total number

of reports, which will not be included in the clustering operation.

==

YEARS 1968-2010 (data set TABCD1)

Groupings (Clusters and supplementary pairs of possible interest)

X=TABCD1'; scarce= [1 3 20]; ALLCLUSTERSFF3A(X, scarce);

Follow 4 confirmatory plots
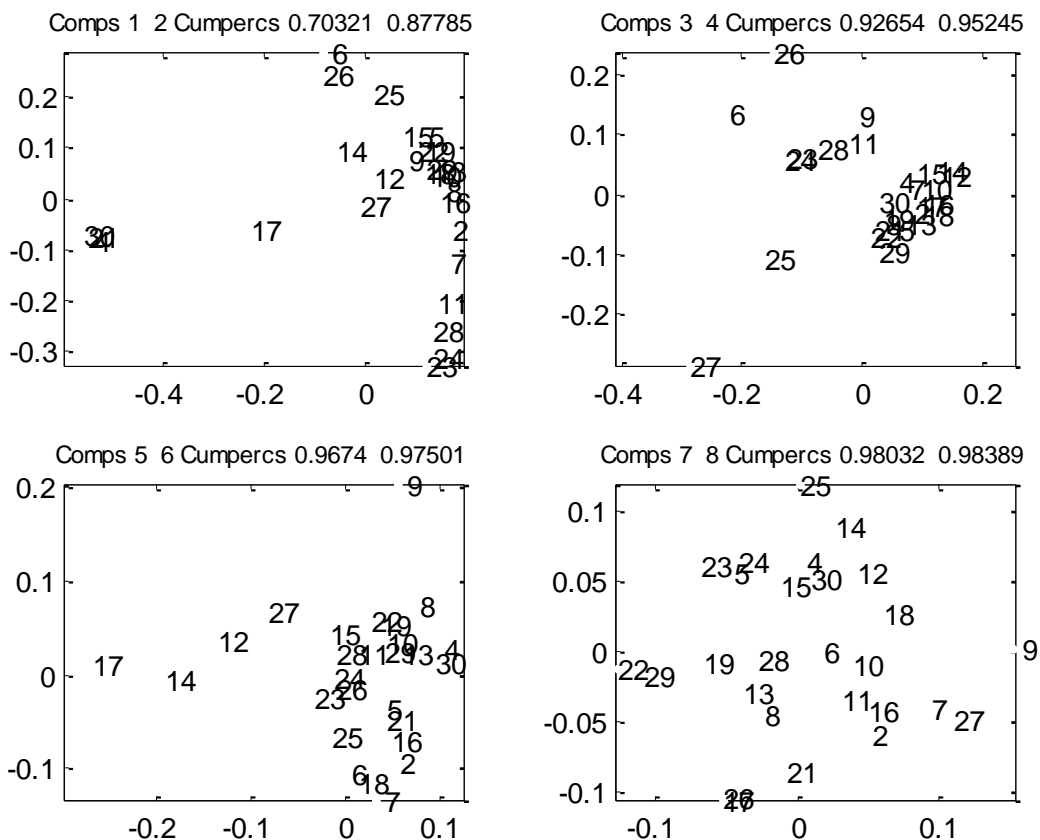
Comps 1 2 Cumpercs 0.70321 0.87785

Comps 3 4 Cumpercs 0.92654 0.95245

Comps 5 6 Cumpercs 0.9674 0.97501

Comps 7 8 Cumpercs 0.98032 0.98389

===

GAUGES(=MAX DIAMETERS) and CORRELATIONS(PAIRWISE AT LEAST=)

0.2958   0.825

0.27386   0.85

0.22361   0.9

0.19365   0.925

0.15811   0.95

0.1118   0.975

VALID THROUGHOUT

===

CLUSTERS:

cluster 1 =   9 14 25

  pairwise correls = at least 0.87831

cluster 2 =   2   5   7   8 10 11 12 13 15 16 18 19 22 29

pairwise correls = at least 0.90255

cluster 3 = 4 21 30

pairwise correls = at least 0.94437

cluster 4 = 23 24 28

pairwise correls = at least 0.98373

cluster 5 = 2 5 8 10 13 15 16 18 19 22 29

pairwise correls = at least 0.96184

cluster 6 = 7 11

pairwise correl = 0.97267

cluster 7 = 8 10 13 19 22 29

pairwise correls = at least 0.98096

cluster 8 = 2 16 18

pairwise correls = at least 0.98535

cluster 9 = 4 30

pairwise correl = 0.98567

cluster 10= 5 15

pairwise correl = 0.98668

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

11	28	0,9937	25	29	0,9430	28	29	0,9214
12	14	0,9883	16	28	0,9412	9	18	0,9191
14	15	0,9706	13	14	0,9411	8	14	0,9189
11	24	0,9692	14	22	0,9399	18	25	0,9189
11	23	0,9655	7	24	0,9389	2	23	0,9188
9	10	0,9650	9	22	0,9375	2	9	0,9182
7	28	0,9585	14	16	0,9372	2	14	0,9172
2	28	0,9580	9	16	0,9370	19	28	0,9146
9	15	0,9571	14	29	0,9343	12	17	0,9146
8	9	0,9564	9	12	0,9320	9	11	0,9130
5	25	0,9555	7	23	0,9314	10	25	0,9122
6	26	0,9524	5	9	0,9314	22	28	0,9097
9	19	0,9516	6	25	0,9309	8	24	0,9064
9	13	0,9509	13	28	0,9307	15	26	0,9040
22	25	0,9488	13	25	0,9305	18	28	0,9008
10	14	0,9477	9	29	0,9289	16	24	0,8989

14	18	0,9477	14	17	0,9287	12	28	0,8985
19	25	0,9457	15	25	0,9286	16	25	0,8980
5	14	0,9449	10	28	0,9279	7	9	0,8955
8	28	0,9441	2	24	0,9263	7	14	0,8933
14	19	0,9437	8	25	0,9218			

Summary of clusters

23 24 28

9 14 25

8 10 13 19 22 29

7 11

5 15

4 30

4 21 30

2 16 18

2 5 8 10 13 15 16 18 19 22 29

2 5 7 8 10 11 12 13 15 16 18 19 22 29

For comparison, clusters obtained for scarce = [ ]:

9 14

8 10 13 16 19 22 29

7 11

6 26

5 15

4 30

4 21 30

2 18

2 5 8 10 13 15 16 18 19 20 22 29

2 5 7 8 10 11 12 13 15 16 18 19 20 22 29

2 5 7 8 9 10 11 12 13 14 15 16 18 19 20 22 28 29

1 6 26

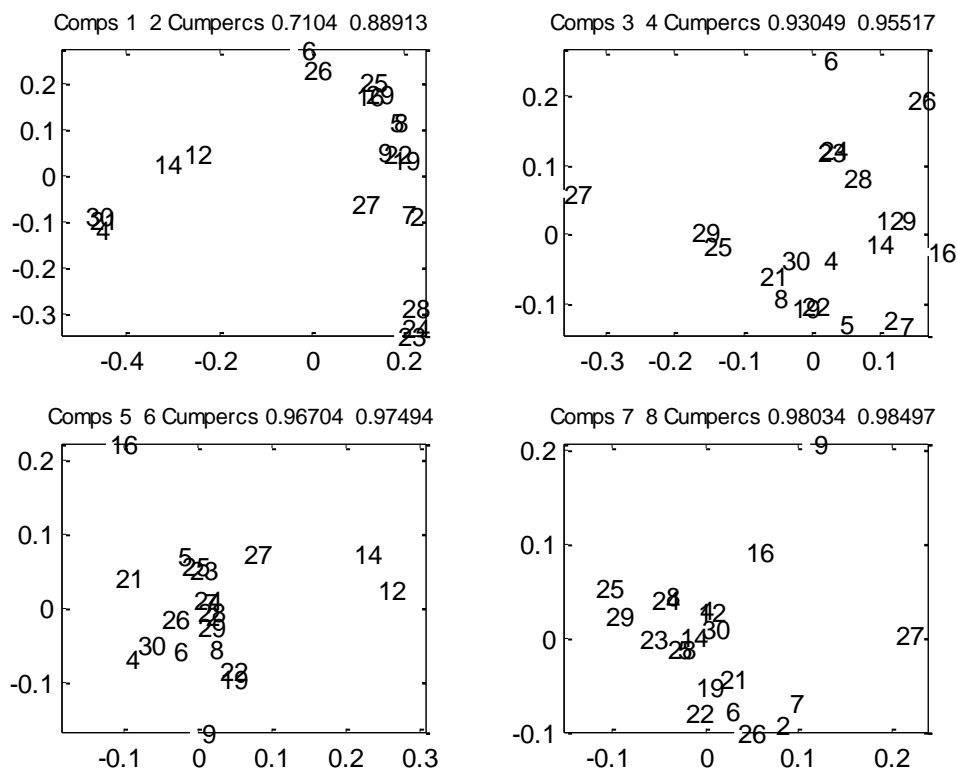===

YEARS 1968-1989 (data set TABCD2)

Groupings (Clusters and supplementary pairs of possible interest)

X=TABCD2'; scarce= [1 3 10 11 13 15 17 18 20]; ALLCLUSTERSFF3A(X, scarce);

Follow up to four confirmatory plots

Comps 1 2 Cumpercs 0.7104 0.88913

Comps 3 4 Cumpercs 0.93049 0.95517

Comps 5 6 Cumpercs 0.96704 0.97494

Comps 7 8 Cumpercs 0.98034 0.98497

===

CLUSTERS:

cluster 1 = 4 12 14 21 30

 pairwise correls = at least 0.82769

cluster 2 = 2 5 7 8 9 16 19 22 25 29

 pairwise correls = at least 0.86307

 cluster 3 = 23 24 28

 pairwise correls = at least 0.98614

 cluster 4 = 4 21 30

 pairwise correls = at least 0.93087

 cluster 5 = 12 14

 pairwise correls = 0.98387

 cluster 6 = 2 5 8 19 22

 pairwise correls = at least 0.9496

 cluster 7 = 25 29

 pairwise correls = 0.98829

 cluster 8 = 5 8 19 22

pairwise correls = at least 0.97366

cluster 9 =   4 30

pairwise correls = 0.97502

cluster 10 =   8 19 22

pairwise correls = at least 0.98209

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

6	25	0.8922
6	29	0.8939
7	23	0.8996
16	26	0.9008
7	24	0.9038
22	28	0.9053
2	23	0.9119
19	28	0.9142
2	24	0.9148
6	26	0.9407
7	28	0.9424
2	28	0.9539

Summary of clusters

25 29

23 24 28

12 14

8 19 22

5 8 19 22

4 30

4 21 30

4 12 14 21 30

2 5 8 19 22

2 5 7 8 9 16 19 22 25 29

For comparison, clusters obtained for scarce = [ ]:

25 29

23 24 28

16 26

12 14

8 19 22

5 8 19 22

4 30

4 21 30

4 12 14 21 30

2 5 8 19 22

1 2 5 7 8 9 19 22 25 29

==

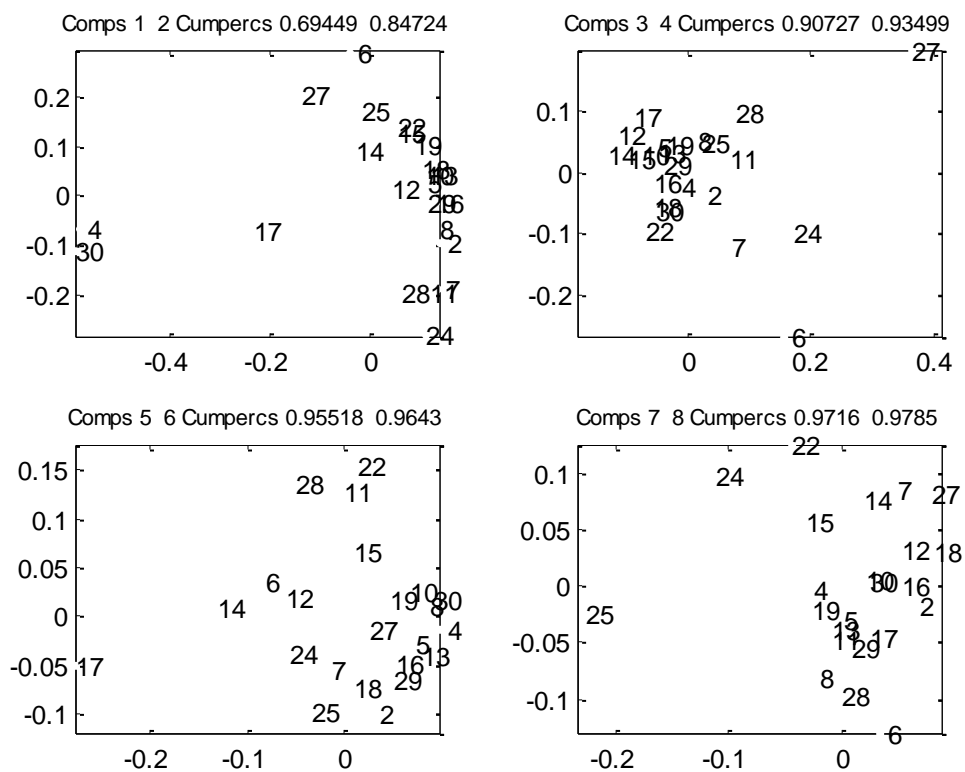**YEARS 1990-2010 (data set TABCD3)**

Groupings (Clusters and supplementary pairs of possible interest)

X=TABCD3'; scarce=[1 3 9 20 21 23 26]; ALLCLUSTERSFF3A(X,scarce);

Follow up to four confirmatory plots

==

CLUSTERS:

cluster 1 = 2 5 7 8 10 11 12 13 14 15 16 18 19 22 28 29

 pairwise correls = at least 0.84887

 cluster 2 = 4 30

 pairwise correls = 0.95895

 cluster 3 = 2 5 8 10 12 13 14 15 16 18 19 22 29

 pairwise correls = at least 0.91746

 cluster 4 = 7 11 28

 pairwise correls = at least 0.93946

 cluster 5 = 14 22

 pairwise correl = 0.94804

 cluster 6 = 5 8 10 12 13 15 16 18 19 29

 pairwise correls = at least 0.96246

 cluster 7 = 11 28

 pairwise correl = 0.98403

 cluster 8 = 12 18

 pairwise correl = 0.97703

 cluster 9 = 5 8 10 13 16 29

 pairwise correls = at least 0.98422

 cluster 10 = 15 19

 pairwise correl = 0.99091

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

7	24	0,9641	2	24	0,9386	8	24	0,9163
19	25	0,9604	25	29	0,9366	14	17	0,9157
15	25	0,9587	18	25	0,9356	2	25	0,9040
13	25	0,9545	12	25	0,9341	24	29	0,9030
11	24	0,9483	24	28	0,9308	16	24	0,8994
14	25	0,9454	16	25	0,9306	12	17	0,8993

5	25	0,9451	8	25	0,9200
10	25	0,9402	22	25	0,9197

Summary of clusters

15 19

14 22

12 18

11 28

7 11 28

5 8 10 13 16 29

5 8 10 12 13 15 16 18 19 29

4 30

2 5 8 10 12 13 14 15 16 18 19 22 29

2 5 7 8 10 11 12 13 14 15 16 18 19 22 28 29

For comparison, clusters obtained for scarce = [ ]:

21 30

15 18 19

14 20

14 20 22

11 28

7 11 28

5 8 10 13 16 29

5 8 10 13 15 16 18 19 29

4 21 30

2 12

2 5 8 10 12 13 15 16 18 19 29

2 5 8 10 12 13 14 15 16 18 19 20 22 29

2 5 7 8 10 11 12 13 14 15 16 18 19 20 22 28 29

==

Comments: The picture is less clear than in the case of classes A, B, C analyzed separately.

One would expect that the subsets yielded by the analysis be consistent with the classes A, B, C, D. One obtains nothing like this. At a second thought, one realizes that any agent, constrained no more to choose its pair within its own class, may find a closer (in the sense of correlation) pair agent outside this class.

TABCD2 is of smaller weight than TABCD1 and TABCD3.

The lists of non-cluster pairs are very long. Their "queues" should be rather examined, e.g.

those with correlations larger than .89.

For each one of the periods 1968-2010, 1968-1989 and 1990-2010, the clustering was done also for an empty scarce = [ ], that is without deleting agents. The summary of the clusters for each period in this case is displayed for each period immediately after the summary for the data with agents deleted, for comparison. The two sets of clusters are very similar, especially if, in the case of no deletion, one disregards the agents deleted in the alternative set.

Appendix Nr 9.

Data collection, correlation clusters and confirmatory plots of SADRs frequencies of ATC-V08A -A, -B, -C and -D sub-class products together for the whole 40-year collection period (1968-2010) and for the two 20-year collections 1968-1989, and 1990-2010. "Big Matrix" Data A, B, C, D together.

The matrices subject to clustering are obtained from the "BIG MATRIX" and are ABCD1(876x30), ABCD2(520x30) and ABCD3(818x30), for years 1968-2010, years 1968-1989 and years 1990-2010. They are obtained from the sub-matrices of the "BIG MATRIX" for the three periods considered, after deleting in each case the empty rows (for SOCD-ADRs which did not occur). The Agent totals for each one of the three sub-matrices were already obtained in SOCD-ADRs DATA A, B, C, D TOGETHER FINALA.doc, and consequently the same holds for the "scarce" subsets, which are valid here too.

==

"BIG MATRIX" all together Years 1968-2010

X=ABCD1'; scarce=[1 3 20]; ALLCLUSTERSFINAL(X,scarce)
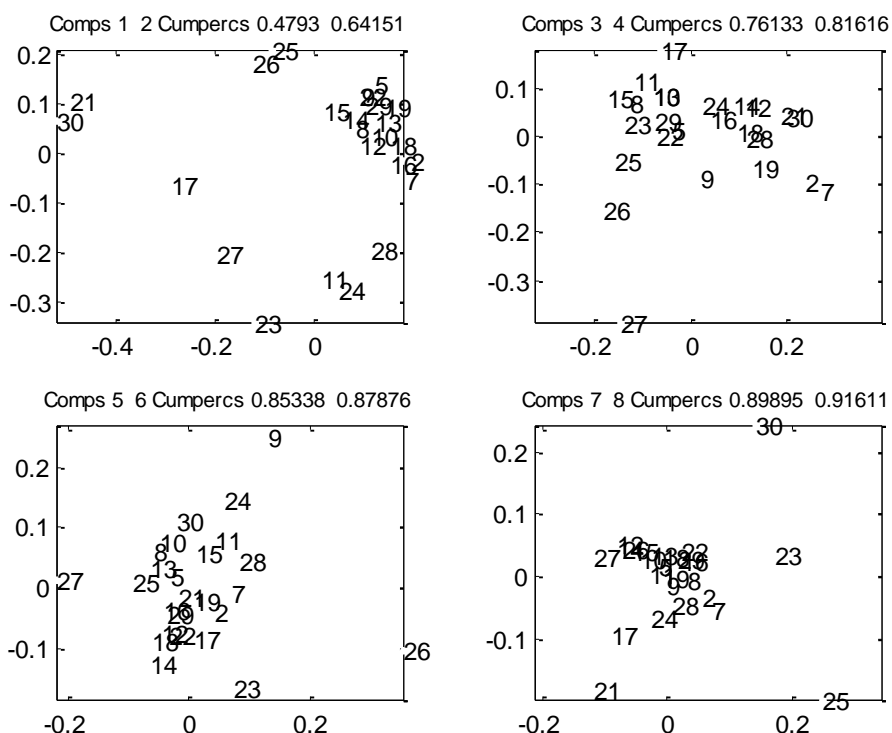
Follow 4 confirmatory plots

===

GAUGES(=MAX DIAMETERS) and CORRELATIONS(PAIRWISE AT LEAST=)

0.2958   0.825

0.27386   0.85

0.22361   0.9

0.19365   0.925

0.15811   0.95

0.1118   0.975

THESE VALUES ARE VALID THROUGHOUT

===

CLUSTERS:

cluster 1 =   5   8   10   12   13   14   16   18   19   22   29

 pairwise correls = at least 0.87517

 cluster 2 =   11   24

 pairwise correls = 0.91139

cluster 3 = 2 7 28

 pairwise correls = at least 0.91756

cluster 4 = 5 8 10 13 22 29

 pairwise correls = at least 0.92715

 cluster 5 = 12 14 16 18

 pairwise correls = at least 0.92748

 cluster 6 = 2 7

 pairwise correls = 0.98897

 cluster 7 = 12 14 18

 pairwise correls = at least 0.95742

 cluster 8 = 13 22 29

 pairwise correls = at least 0.95829

 cluster 9 = 22 29

 pairwise correls = 0.97753

 cluster 10 = 12 14

 pairwise correls = 0.98205

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

2	19	0,9589	7	19	0,9221	5	15	0,9083
2	18	0,9551	15	29	0,921	7	16	0,9079
2	16	0,9383	24	28	0,9189	7	12	0,9006
13	15	0,9365	16	28	0,9136	2	29	0,8978
2	12	0,9322	2	14	0,9131	12	28	0,8968
10	15	0,9265	8	15	0,9129	2	22	0,8936
7	18	0,9237	15	22	0,9116	2	13	0,8931

Summary of clusters

 22 29

13 22 29

12 14

12 14 18

12 14 16 18

11 24

5 8 10 13 22 29

5 8 10 12 13 14 16 18 19 22 29

2 7

2 7 28

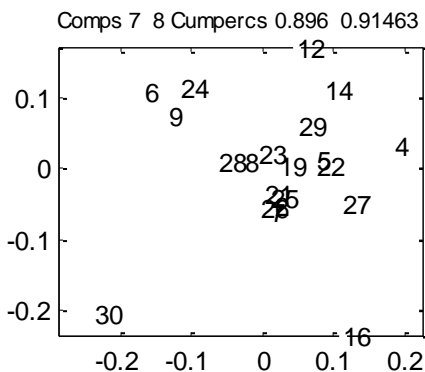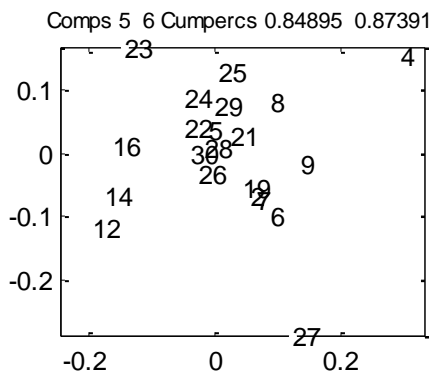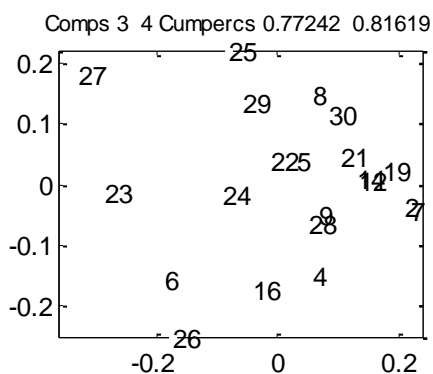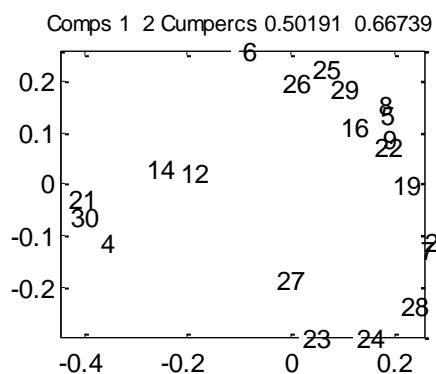===

"BIG MATRIX" all together Years 1968-1989

X=ABCD2'; scarce=[1 3 10 11 13 15 17 18 20]; ALLCLUSTERSFINALA(X,scarce);

Follow 4 confirmatory plots

===

CLUSTERS:

cluster 1 = 2 5 7 19 22

 pairwise correls = at least 0.83481

 cluster 2 = 25 29

 pairwise correls = 0.87654

 cluster 3 = 8 9

 pairwise correls = 0.89339

 cluster 4 = 12 14

 pairwise correls = 0.94056

 cluster 5 = 2 7 19

 pairwise correls = at least 0.94271

 cluster 6 = 5 22

 pairwise correls = 0.94375

 cluster 7 = 2 7

 pairwise correls = 0.99337

===

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

8	25	0.8972
5	29	0.8994
8	22	0.8995
5	8	0.9048
22	29	0.9078
7	28	0.9173
2	28	0.9300

Summary of clusters

 25 29

 12 14

8 9

5 22

2 7

2 7 19

2 5 7 19 22

===

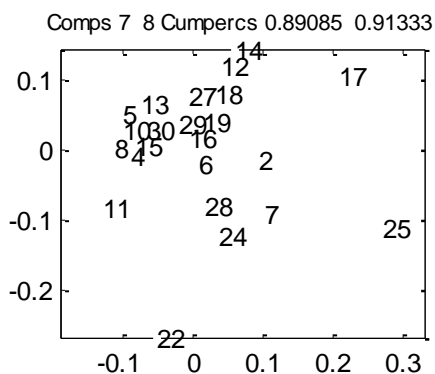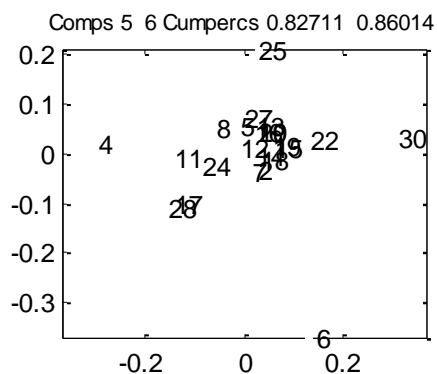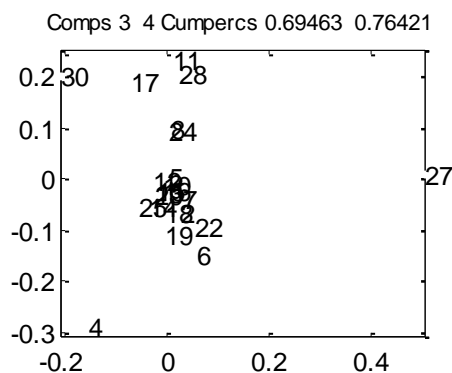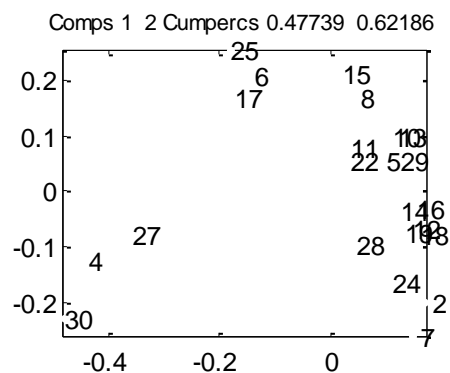**"BIG MATRIX" all together Years 1990-2010**

X=ABCD3'; scarce=[1 3 9 20 21 23 26]; ALLCLUSTERSFINALA(X,scarce);

Follow 4 confirmatory plots

===

CLUSTERS:

cluster 1 =   11 28

 pairwise correls = 0.86981

cluster 2 =   2 10 12 13 14 16 18 19 29

pairwise correls = at least 0.87603

cluster 3 =   5 8

  pairwise correls = 0.92494

cluster 4 =   10 12 13 14 16 18 29

  pairwise correls = at least 0.92344

cluster 5 =   2 19

  pairwise correls = 0.94588

cluster 6 =   10 13 16 29

  pairwise correls = at least 0.93913

cluster 7 =   12 14 18

  pairwise correls = at least 0.97058

cluster 8 =   10 13

  pairwise correls = 0.97856

cluster 9 =   12 14

  pairwise correls = 0.98184

==

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

2	7	0,9755	5	10	0,9212	7	12	0,9039
13	15	0,9365	15	29	0,9165	8	29	0,9036
5	13	0,9302	7	18	0,9112	7	16	0,8963
10	15	0,9265	5	12	0,9107	7	24	0,894
8	13	0,9252	5	29	0,9091	8	15	0,8928
8	11	0,9242	2	24	0,9071	7	19	0,8912
8	10	0,9223	5	19	0,9048	5	14	0,8907

Summary of clusters

  12 14

  12 14 18

  11 28

  10 13

  10 13 16 29

10 12 13 14 16 18 29

5 8

2 19

2 10 12 13 14 16 18 19 29

==

Comments: The picture is less clear than in the case of classes A, B, C analyzed separately.

One would expect that the subsets yielded by the analysis be consistent with the classes A, B, C, D. One obtains nothing like this. At a second thought, one realizes that any agent, constrained no more to choose its pair within its own class, may find a closer (in the sense of correlation) pair agent outside this class.

ABCD2 is of smaller weight than ABCD1 and ABCD3.

The subsets to study might be: the cluster [5 8 10 12 13 14 16 18 19 22 29], and the non-cluster pairs.

The lists of non-cluster pairs are very long. Their "queues" should be rather examined, and we have left only the pairs with correlations larger than .95.

The concordance between the results for SOCD and the "BIG MATRIX" A, B, C, D taken together, is poor.

==

...

WHO Collaborating Centre
for International Drug Monitoring
Box 1051, SE-751 40 Uppsala, Sweden

Tel: +46-18-65 60 60
Fax: +46-18-65 60 80
E-mail: info@who-umc.org

CAVEAT DOCUMENT

Accompanying statement to data released from the WHO Collaborating Centre

The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden receives summary clinical reports about individual suspected adverse reactions to pharmaceutical products from National Centres in countries participating in a Collaborative Programme. Only limited details about each suspected adverse reaction are received at the Centre. It is important that the limitations and qualifications which apply to the information and its use are understood.

The term "pharmaceutical product" is used instead of "drug" to emphasize that products marketed under one generic or trade name may vary in their content of active or other ingredients, both in time or from place to place.

The reports submitted to the Collaborating Centre in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event.

The reports, which are submitted to National Centres, come from both regulatory and voluntary sources. Some national Centres accept reports only from medical practitioners; other National Centres accept reports from a wider spectrum of health professionals. Some National Centres include reports from pharmaceutical companies in the information submitted to the Collaborating Centre; other National Centres do not.

The volume of reports for a particular pharmaceutical product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time, from product to product and country to country. Moreover, no information is provided on the number of patients exposed to the product.

Thus the sources of reports accepted by National Centres vary, as do the proportions.

A number of National Centres which contribute information to the Collaborating Centre make an assessment of the likelihood that a pharmaceutical product caused the suspected reaction. Other National Centres do not document such assessments on individual reports in the WHO data base.

Processing time varies from country to country. Reporting figures obtained from the Collaborating Centre may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between pharmaceutical products, may be misleading. The information tabulated in the accompanying printouts is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. Some describe such information as "raw data". Any use of this information must take into account at least the above.

Some National Centres which have authorized release of their information strongly recommend that anyone who intends to use it should contact them for interpretation.

Any publication, in whole or in part, of the obtained information must have published with it a statement:

(i)   of the source of the information,

(ii)   that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction,

(iii)   that the information does not represent the opinion of the World Health Organization.

Omission of these 3 statements may exclude the responsible person or organization from further information from the system.

References

[1]   Bernardi M, Bradu D, Di Sarra B, Galeazzi G. Marcucci M, Montecchiani G, Moretti V, Moroni L, Re L, Rossini L, Rossini P, Tonnini C. Ionic and nonionic contrast agents. A contribution by WHO-ITA and the Drug Documentation and Information Centre of Regione Marche. Pharmacologyonline Newsletter 2:497-517(2010).

[2]   De Martinis C, Rossini L. Some internal medicine and pharmacotoxicological clinical views and perspectives on global essentials, regionally protected, brand-name or unbranded equivalents, off-label and "me-too", neglected, repurposed, complementary, prescribed and/or distributed over-the-counter, differently marketed available or not counterfeit diagnostic, preventive and therapeutic medicinal products. Pharmacologyonline Newsletter 2:475-496(2010).

[3]   Farmaci sì, ma personalizzati. Maseri A, Gabaglio L. L'espresso February 3:126-127(2011); Becker RE, Greig NH. Scienceonline Review: Lost in translation-Neuropsychiatric drug development. Science 330:1449(2011).

[4]   Bradu D, Rossini L. Contrast agents – Iodinated products. Second WHO-ITA/ITA-OMS 2010 contribution on aggregated WHO system-organ class disorders and/or clustering based on reported adverse reactions/events. Pharmacologyonline Newsletter 2:727-753(2010).

[5]   Bradu D, Rossini L. Contrast agents – Paramagnetic gadolinium and manganese chelates and superparamagnetic iron-based products. Third WHO-ITA/ITA-OMS 2010 contribution using WHO system organ class disorders (SOCDs) and Adverse reaction and event preferred names (ADRs). Pharmacologyonline Newsletter 3:728-781(2010).

[6] Cf [2], p 481 and Reference [56], and pp 484-485.

[7] Rossini L. Il Polo Universitario Ospedaliero di Ancona: Il Servizio di Farmacologia e Tossicologia clinica. Written by Dean' invitation for Lettere dalla Facolta', Anno 2000. Atti Acc Marchigiana Scienze, Lettere, ed Arti, Ancona, 2007, in print; Rossini L. Didattica vissuta e aggiornamento della "Nuova Tabella XVIII". Atti Acc Marchigiana Scienze, Lettere ed Arti, Ancona   XXXVIII 1999-2000:323-342(2005); Rossini L. Drugs and the future. Pharmacologyonline 1:12-44(2005); Bernardi M, Galeazzi G, Lamura E, Piantelli F, Rendell J,

Rossini P, Rossini L. (Ecto)nucleotidase kinetics observed by 31P-NMR spectroscopy: resolution of signals. Pharmacol Res 36:353-361(1997); Rossini L. Sperimentazione dei Farmaci e Farmacovigilanza. Corso Monografico. New Entries in Pharmacology 1:3-22(1996); Rossini L, Bernardi M, Cavalieri L, Concettoni C, Galeazzi G, Gentili M, Moretti V, Moroni L, Pettinari F, Picchi L, Pigini P, Rossini P, Tonnini C, Violet C. Farmacovigilanza Internazionale: Uso ed abuso dei farmaci. Relazione 21.6.1991 at the Accademia Marchigiana Scienze Lettere ed Arti, Ancona. Memorie Acc March Sci Lettere Arti Ancona 29:151-198(1996); Di Sarra B, Piantelli F, Moretti V, Re L, Rossini L, Tonnini C. Physio-pharmaco-toxicological *in vivo* read-out: an interuniversity integrated analytical center. Issues, results and perspectives. Quaderni Marchigiani Medicina - Special Issue 20th Anniversary of Ancona University 5:183-185(1989); Moretti V, Concettoni C, Massaccesi E. L' accertamento analitico delle sostanze d' abuso. Esperienza del Servizio di Farmacologia e Tossicologia dell' Universita' degli Studi di Ancona, USL 12-Regione Marche. Quad March Med 5:119-125(1987); Rossini L. Sul rilevamento degli effetti indesiderati da farmaci nella fase IV: Suggerimenti al medico pratico. Federazione Medica 38:92-98(1985); Cingolani ML, Re L, Rossini L. The usefulness, in pharmacological classification, of complementary pattern-recognition techniques and structure modelling as afforded by the iterative collation of multiple-trial data in data banks. Pharmacol Res Commun 17:1-22(1985); Bradu D, Cingolani ML, Ferrante L, Re L, Rescigno A, Rossini L. A contribution to the advancement of the computational procedures as applied to the classification of drug and receptor congeners. Highlights in Receptor Chemistry. C Melchiorre & M Giannella Eds. Elsevier Science Publishers Amsterdam 251-294(1984); Re L, Rossini L. Electrophysiological analysis of the cholinergic effects of cimetidine and ranitidine. Pharmacol Res Commun 16:381-389(1984): Rossini L, Leone L. Sviluppo del Programma internazionale di Farmacovigilanza OMS nel nostro Paese. Rassegna Clinico Scientifica LIII:4-19(1977); Chance B, Mayer D, Rossini L. A time sharing instrument for direct readout of oxidation-reduction states in intracellular compartments in cardiac tissue. IEEE Trans Biomed Eng BME-17:118-121(1970) (See: Dutton PL. Retrospective: Britton Chance (1913-2010). Science Perspectives 330:1641(2010); Terzuolo CA, Chance B, Handelman E, Rossini L, Schmelzer P. Measurements of reduced pyridine nucleotides in a single neuron. Biochim Biophys acta 126:361-371(1966).

[8] Black JW. Pharmacology: Analysis and explorations. Br Med J 293:252-255(1986).

[9] Venulet J, Helling-Borda M. WHO's International Drug Monitoring – The formative years 1968-1975. Drug Safety 33:e1-e23(2010).

[10] Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income Countries: A questionaire-based analysis. Drug Safety7 33:689-703(2010).

For the References related to the iodinated contrast agents, the lists presented in the previous recent contributions (See: [1], and [4])) are upgraded in [11], why the Lists of those commun topics to the iodinated and the Gd-chelates (See: [5]) are upgrated in [12].

[11] Ahn S, Jung SY, Lee JP, Lee SJ. Properties of Iopamidol-incorporated poly(vynil alcohol) microparticle as an X-ray imaging flow tracer. J Phys Chem, B 115(5):889-901(2011); Interactions in iodinate contrast media solutions: 1. Thermodynamic Study. J Thermal Anal and Cal. Akadémiai Kiadó & Springer Science Publishers. ISSN 1572-8943. Issue Title: AICAT2010 Special Chapter; DOI 10 1007/s10973-010-1090-4. Pp 1-6. Online October 25(2010); Hallouard f, Anton N, Choquet P, Costantinesco A, Vandamme T. Iodinated blood pool contrast media for preclinical X-ray imaging applications. A review. Biomaterials 31(24):6249-6268(2010); Schoemig A, Wessely R. and Deutsches Herzzentrum Muenchen. Iodixanol vs. iomeprol to prevent contrast-induced nephropathy after coronary intervention (CONTRAST). Clinical Trials. Gov. Service US National Institutes of Health. March 12(2010); Hsu S-P, Tsai T-J, Chien C-T. Ioxitalamate induces renal tubular apoptosis via activation of renal efferent nerve-mediated adrenergic signaling, renin activity, and reactive oxigen species production in rats. Toxicol Sci 114:149-158(2010); Biondi-Zaccai G, Lotrionte M. A critical review of meta-analysis of adverse event contrast agents. Cap 6-Iodinated and Gadolinium contrast media, pp 31-39. In DHS Thomsen & JAW Webb Edts, Safety Issues and ESUR Guidlines, 2nd Revised Ed Springer 2009, pp 1-256. AL Baert & M Knauth Edts, Medical Radiology, Diagnostic Imaging Springer Series; Pan J-J, Draganov PV. Adverse reactions to iodinate contrast media administered at the time of endoscopic retrograde cholangiopancreatography (ERCP). Inflammation & Allergy – Drug Targets 8:17-20(2009); Weisbord SD. Iodinated contrast media and the kidney. Rev Cardiov Medicine 9, Suppl 1:514-523(2008); Belhadjali H, Bouzgarrou L, Youssef M, Njim L, Zill J. DRESS syndrome induced by sodium meglumine ioxitalamate. Allergy 63:786-787(2008); Lapi F, Cecchi E, Pedone C, Attanasio A, Banchelli G, Vannucci A, Di Pirro M, Moschini M, Berni V, Matucci R, Scalia A, Yendi E, Mugelli A. Pharmacoepidemiology and prescription. Safety aspects

of iodinate contrast media related to their physicochemical properties: a pharmacoepidemiology study in two Tuscan hospitals. Eur J Clin Pharmacol 64:723-737(2008); Thomsen HS, Morcos SK, Erley CM, et al. The ACTIVE Trial: comparison of the effects on renal function of iomeprol-400 and iodixanol-320 in patients with chronic kidney disease undergoing abdominal computed tomography. Invest Radiol 43:170-178(2008); Thomsen HS, Morcos SK, Barrett BJ. Contrast-induced nephropathy: the wheel has turned 360 degrees. Acta Radiol 49:646-657(2008); Nguyen SA, Suranyi P, Ravenel JG, et al. Iso-osmolality versus low-osmolality iodinate contrast medium at intravenous contrast-enhanced CT: effect on kiney function. Radiology 248:97-105(2008); Solomon KJ, Natarajan MK, Doucet S, et al. Cardiac angiography in renally impaired patients (CARE) study: a randomized double-blind trial at contrast-induced nephropathy in patients with chronic kidney disease. Circulation 115:3189-3196(2007); Katzberg RW, Barrett BJ. Risk of iodinate contrast material-induced nephropathy with intravenous administration. Radiology 243:622-628(2007); Barrett BJ, Katzberg RW, Thomsen HS, et al. Contrast-indiced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol. Invest Radiol 41:815-821(2006); Cademartiri F, de Monye C, Pugliese F, et al. High iodine concentration contrast material for non invasive multislice computer tomography coronary angiography. Iopromide 370 vs Iomeprol 400. Invest Radiol 41:349-352(2006); Tepel M, Aspelin P, Lameire N. Contrast-Induced nephropathy. A clinical and evidence-based approach. Circulation 1123:1799-1806(2006); Katzberg RW, Haller C. Contrast-induced nephrotoxicity: Clinical landscape. Kidney Intern 69:S3-S7.doi:10.1038/sj.ki.5000366(2006); Barrett BJ, Parfrey PC. Clinical practice. Preventing nephropathy induced by contrast medium. N Eng J Med 354:379-386(2006); Davidson C, Stacul F, McCullough PA, et al. Contrast medium use. Am J Cardiol 98:42K-58K(2006); Misaki T, Yamamoto K, Shimizu T, Narabayashi. Comparison of Iomeprol 300 and 350 mg/ml syringe preparations for contrast-enhanced helical computer tomography of the liver using bolus-tracking technology. Bull Osaka Med Coll 52:1-7(2006); Fleischmann D. Use of high concentration contrast media: principles and rationale-vascular district. Eur J Radiol 45 Suppl 1:588-593(2003); Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. New Eng J Med 348:491-499(2003); Stacul F. Contrast media. Current iodinate contrast media. Eur Radiol 11:690-697(2001); Dooley M, Blair J. Iomeprol: A review of its use as a contrast medium. Drugs 59:1169-1186(2000); Carraro M, Malalan F, Antonione R, et al. Effects of a dimeric vs a monomeric nonionic contrast medium on

renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. Eur Radiol 8:144-147(1998); Sovak M. The Harry W Fischer lecture: Contrast media – a meandering look. Acad Radiol 3:S241-S247(1996); Almen T. Visipaquer: a step forward – a historical review. Acta Radio 36(Suppl 399):S2-S18(1995); Krause W. Physicochemical parameters of X-ray contrast media. Invest Radiol 29:72-80(1994); New iodinated contrast agents. The physicochemical and biological properties of asymmetric dimers. Invest Radiol 29:S264-S266(1994); Eloy R, Corot C, Belleville J. Contrast media for angiography: Physicochemical properties, pharmacokinetics and biocompatibility. Clinical Materials 7:89-197(1991).

[12] Fourth Annual Symposium on Nephrogenic Systemic Fibrosis and Gadolinium-Based contrast agents. Full eBriefing by Megan Stephan at www.nyas.org/NSF-eB, The New York Academy of Sciences Magazine, Winter 2011:13; American Society of Health-System Pharmacists. Quick guide to contrast media:1- 14(2010); Thomsen DHS. Renal adverse effects. Contrast medium-induced nephropathy. Cap 9:61-foll. In Contrast media: Safety issues and ESUR guidelines, DHS Thomsen & JAW Webb Edts. 2nd Ed Springer Medical Radiology: Diagnostic Imaging, AL Baert & M Knauth Edts(2009); Ledneva E, Karle S, Launay-Vacher V, Janus N, Deray G. Renal safety of Gadolinium-based contrast media in patients with chronic renal insufficiency. Radiology 250:618-628(2009); Perez JD, Arita DY, Costa H, Casarini DE. Proteomic analyses of contrast media-treated mesangial cell. Open Proteomic J 2:1-7(2009); J Weinreb, Kuo P. Nephrogenic Systemic fibrosis. Magnetic Resonance Imaging Clinics North America 17:159-167(2009); Bellin M-F. MR contrast agents, the old and the new. Eur J Radiol 69:314-323(2006); Cyrus T, Winter PM, Caruthers SD, Wickline SA, Lanza GM. Magnetic resonance nanoparticles for cardiovascular molecular imaging and therapy. Expert Review Cardiov Therapy 3:705-715(2005); Lawyers at Anapol Schwartz. Introduction to Gadolinium litigation:1-21(2009); Kuhtz-Buschbeck JP, Ehrhardt K, Köhnlein S, Radtke W, Heintzen P. Gadopentetate dimeglumine and iodinate contrast media hemodynamic side effects after bolus injections in pigs. Invest Radiol 32:111-119(1997).

[13] Sharma SK. Iodinated contrast Media and contrast-induced nephropathy: Is there a preferred cost-effective agent?. J Invasive Cardiology 20:245-248(2008).

[14]   Bradu D, Rossini L. Iodinated and RMN Contrast Agents Reports sent from Italy in the WHO-Pharmacovigilance System over the first 40th years of the Programme. Sixth WHO-ITA/ITA-OMS 2010-2011 contribution. At work, in preparation (2011).

[15]   Faglia F. Economie sull' orlo del collasso. Corriere Medico 37;13: Medicina- Attualita', April 21 2011, p 10.

[16]   L' Italia e' sempre piu' multietnica: dall' estero il 6,5 per cento dei residenti. Corriere Medico 37;9: Sanita', March 23 2011, p 5.

 [17] Krall RL. A call to reorient healthcare. Science 332:177(2011); Schellekens H, Moors E, Leufkens HG. Drug regulatory systems must foster innovation. Science 332:174-175(2011); Hilbert M, López P. The world's technological capacity to store, comunicate, and compute information. Science 332:60-65(2011); Finlayson AET. Dealing with data: Fostering Fidelity; Greve M, Svenning J-C. Dealing with data: Preserve old collections; Los W, Wood J. Dealing with data: Upgrading Infrastructure; Severin AJ. Dealing with data: Training new scientists; Bolon B, Altrock B, Barthold SW, Baumgarth N, Besselsen D, et al.Advancing translational research. Science Letters 331:1515-1517(2011); Tenenbaum JB, Kemp C, griffiths TL, Goodman ND. How to grow a mind: Statistics, structure, and abstraction. Science Review 331:1279-1285(2011); Science Staff. Challenges and opportunities. Science 331:692-693; Science SPECIALSECTION Dealing with data 331:661-728(2011); Porter MA. Bounds and vision. Science 331:676-677(2011); Hanson B, Sugend A, Alberts B. Making data maximally available. Science Editorial 331:649(2011).

[18]   Kaiser J. NIH's second shop for tried-and-tested drugs. Science News&Analysis Biomedicine 332:1492(2011).

[19]   Marshall E. Unseen world of clinical trials emerges from US database. Science 333:145(2011); Roher B. To improve health care, experts look to cure clinical trials. Science AASASNews&Notes Medical Research 332:1518(2011).

[20] Leshner AI. Innovation needs novel thinking. Science editorial 332:1009(2011).

[21]   Schoeninger MJ, Bada JL, Masters PM, Bettinger RL, White TD. Unexamined bodies of evidence. Science 332:916(2011); Anonimous. Sciencenow, Scienceonline. Computer algorithm may speed drug discovery. Science 332:63(2011).

[22]   Bradu D, Rossini L. Biosimilar brandede iodiate contrast agents related to the largest number of report sto the WHO-Pharmacovigilance system over the first 40 years of the Programme. Fifth WHO-ITA/ITA-OMS 2010-2011 contribution. At work, in preparation (2011).

[23]   Bernardi M, Bradu D, Di Sarra B, Galeazzi G, Marcucci M, Montecchiani G, Moretti V, Moroni L, Re L, Rossini L, Rossini P, Tonnini C, Ionic and nozioni contrast agents. A contribution by WHO-ITA and the Drug Documentation and Information Centre of Regione Marche. Pharmacologyonline Newsletter 2:497-517(2010).

[24]   Rossini P, Rossini L. Experimental and clinical pharmacotoxicology 2009. Narrative update prevalently related to cognitive neurosciences. Pharmacologyonline Newsletter 3:443-457(2009).

[25]   Rossini L, Rossini P. Universita' Politecnica delle Marche and Marche Region, Italy: Medical Pharmacotoxicology today. Pharmacologyonline Newsletter 3:85-108(2008).

[26]   Rossini L, Rossini P. After the new "Year of Darwin". Pharmacologyonline Newsletter 1:754-771(2010).

[27]   Yaffe   MB.   Editorial   Guide: Living   by   the   numbers.   Scienceonline, www.sciencesignaling.org, www-sciencemag-org. Science 2009;326:1313.

[28]   Sahel JA. Commentary: Quality Versus Quantity – Assessing individual research performance.   Scienceonline/Scienceexpress/Sciencetranslationalmedicine   25   May issue:http//scim.ag/stm052511. Science 332:1003(2011).

[29] Rossini L. Pre- and post-marketing pharmacovigilance: The myths of the placebo effects and of the off-label use of drugs. Pharmacologyonline Newsletter 2:80-94(2008).