BIOSIMILAR BRANDED IODINATED CONTRAST AGENTS RELATED TO THE LARGEST NUMBER OF REPORTS TO THE WHO-PHARMACOVIGILANCE SYSTEM OVER THE FIRST 40 YEARS OF THE PROGRAMME.

FIFTH WHO-ITA/ITA-OMS 2010-2011 CONTRIBUTION

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Summary

Analysis of the side-events, and suspicious or confirmed adverse drug reactions (SADRs), accounting for a total of 67,232 reports, based on the model and on a Matlab program (as described in the fourth contribution of our current series) showed broadly inhomogeneous profiles of all of the 10 products categorized as "biosimilar" that have been the object of the largest number of reports in the first 40 years of the WHO Pharmacovigilance Programme. The analysis highlighted striking differences both when they were subdivided into system-organ class disorders (SOCDs) or studied together, and when they were analyzed in terms of five pairs of biosimilars and their respective, agreed, generic reference products. These conclusions add to the data, already reported by the authors, of the preclinical experiments and the pre-marketing conventional standardized clinical trials regulations.

Key words: WHO International Drug Monitoring, Pharmacovigilance Programme. Correlation objective autoclassificative and confirmatory clustering comparisons between couples of ATC-

V08A-A 8 Amidotrizoate, Iotalamate, Ioxitalamate and Metrizoate, and ATC-V08A-B 2 Ioxaglate "biosimilars".

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> **"The science of nature is based on possible necessity, religion on necessary possibility; ... the former aims to make obscure facts clear, whereas metaphysics aims to make clear facts obscure".** Georg Simmel, Posthumous Diary, edited by Massimo Cacciari. Nino Aragno Editore, Torino, 2011, pp 27 and 29.
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> **"*Evidence-based medicine* denies the existence of any criterion of truth outside its own logic, where it recognizes a plausible reason that it claims to be persuasive; it therefore denies the principle of choice, requiring an act of unlimited conformity, commensurate to the method, or mystical expression of the degree of uncertainty".** Ivan Cavicchi, La medicina della scelta. Bollati Boringhieri, Torino, 2000, pp 1-453.

Recently [1, 2] we stressed that *generic (*either *branded* and *unbranded)* medicinal products could constitute a global socio-economic issue, inspiring future drug utilization. However the question has not yet been conclusively addressed even in the WHO human pharmacotoxicology guidelines and Technical Reports. In fact, the WHO Model core and complementary Lists of Essential Drugs report the definition of *therapeutic equivalence*, *which has become the reference for generic drugs*, referring the reader to non-proprietary names for the identification of the active principles. The term may also indicate some *"biosimilars"*, although these criteria have become established with some perplexities and reservations, for example for *(proprietary) innovator original products*. Chemical and *pharmaceutical equivalence* of the generic products, and their *bioavailability*,

according to the Regulations of the European Medicine Agency (former EMEA, now EMA; Cf: [13], and Notes 2 and 3, in [2]) are declared as *population bioequivalent* to the *patented one, the originator/innovator,* or to the reference *generic, which by conventional statistics and methodology is a surrogate of real therapeutic equivalence*. An example of the latter entails product quality monitoring also after commercialization through the European post-marketing network (Eudravigilance), announced as in Reference [12] of [2], whose Directive 2010/84/EU, published on 31 December 2010, nevertheless does not appear to be more than a monitoring of "Suspected" Adverse Reactions (See Discussion Section and Reference [7] of the Fourth Note of the Series, in [3]).

In the past we have highlighted the lack of long-term comparisons of the profiles of suspected adverse reactions (SADRs; Cf [3], Second Note) to "biosimilar generics", the inadequacy of their analyses using surrogate biokinetic markers of choice (Cf Note 2 in [2], again, as above), the lack of studies even on physiologically frail individuals, as those residual, autoreferred features commonly yet adopted in biometric classifications (Cf [4]; Text, Reference [5] and 5. Appendices, Note Ia & b, Notes II & 3, in [5]). To no avail (See the introductory citation by SP Mel'gunov, in [3], Third). We have also explained why the same current clinical trials, which have been updated, should be abandoned for ethical reasons too (See p 25, in [1], and Sections 4 and 5, in [2]), and replaced and/or at least complemented by the best, wholly WHO-generated, still unique international Pharmacovigilance Programme network, jointly initiated and implemented since 1968.

We have analysed the complete database of the national SADRs for the ATC-V08A -A, -B, -C, and -D iodinated diagnostic contrast agent sub-classes sent to the International WHO Pharmacovigilance Programme over the first 40 years of its activity (in [3], Fourth). These SADRs are uniquely interesting because the products were originally expected to elicit no specific pharmacotoxicological effect. We have recently constructed an objective autoclassification model and have applied it to the reference products (*generic, branded pharmaceutical equivalent,* supposed *population bioequivalent/"biosimilar"* and even barely different "me too drugs") for which SADRs have been reported. Here the model was applied to those "biosimilar" products. The data are reported in Appendix 1 (ex Appendix 4, in [3], Fourth), for 10 of them 52 with the highest total frequencies indicated in brackets and in bold.

We are convinced that equivalent products may be equal in most but not all cases, for instance in terms of their therapeutic effects (i.e., [23], in [2]). We would like to help the "medical specialties to state the reasons for the intolerance … of an equivalent in prescriptions (Ruling n 13981/09 of December 30, 2009 of the Administrative Tribunal of Latium; Cf Appendix 1, in [2])". See p 26, in [1]: "Potentially different "class effects" are being recognized for each drug and dosage range, and for the sites and continuities of the effects of the various prescription rationales. In fact we still need to understand that the classification of potentially homogeneous profiles, that is to say, of the "class effects", on which our current pharmacological treatises are firmly based, is a nonsensical hypothesis of a theorem which has proved counterproductive. There are cases in which it has been ascertained that therapeutic substitution in the context of effects of classes which have been proved to be heterogeneous has drawn attention to the irrationality of this policy. This irrationality is thoroughly ignored by administrative measures dogmatically defined as socio-economic, which, in the absence of basic long-term studies, often surreptitiously invoke and impose the law of so-called "management savings". Prospective studies over adequate periods should therefore be conducted, alongside assessments of pharmacotoxicological and clinical cost-benefit ratios, through transparent computerization of databases relating to "incremental cost-effectiveness-efficiency indices", which management investigators should become familiar with and learn through high-level refresher courses".

1. Data mining.

It can be noted from the data reported in Appendix 1 that of the four VO8A sub-classes -A, -B, -C, and -D, "biosimilars" are present only for A (9 reference products) and B products (12 reference products): their presence is with 7 for A - with 30 "biosimilars"-, and 1 for B – with 2 only -, respectively. If the reference products accounting for less than 1000 total Reports and the "biosimilars" with less than 100 Reports in 40 years are excluded, there remain only 5 reference products and 10 "biosimilars" of the 2 subclasses (number of Reports in brackets): V08A-A: 1-Amidotrizoic acid (25,998), vs 2-Meglumine amidotrizoate/Sodium amidotrizoate (18,590); 3-Iotalamic acid (14,053) vs 4-Iotalamate meglumine/Iotalamate sodium (342); 5-Ioxitalamate acid (418) vs 6-Ioxitalamate meglumine/Ioxitalamate sodium (1,798); 7-Metrizoic acid (689) vs 8-Meglumine metrizoate/Calcium metrizoate (144), and V08A-B: 9-Ioxaglic acid (233) vs 10-Ioxaglate meglumine/Ioxaglate sodium (4,967). All these have been evidentiated in Appendix 1 in

bold, in the Following Table, and completely with the preferred name frequencies of any SADRs- codex in The Appendix 2.

SOCD-Code	1 - Amidotrizoic acid	2 -Meglumine amidotrizoate/Sodium amidotrizoate	3 - Iotalamic acid	4 - Iotalamate meglumine/Iotalamate sodium	5 - Ioxitalamic acid	6 - Ioxitalamate meglumine/Ioxitalamate sodium	7 - Metrizoic acid	8 - Meglumine metrizoate/Calcium metrizoate	9 - Ioxaglic acid	10 - Ioxaglate meglumine/Ioxaglate sodium	General Total & columns total
100	9,496	6,401	5,670	93	163	599	210	31	50	1,389	**24,102**
200	44	32	55		2	4				17	**154**
300		2									**2**
410	1,449	1,118	805	28	19	98	20	11	21	278	**3,847**
431	377	223	226	1	7	6	8	7	2	54	**911**
432	21	15	11			3	3			4	**57**
433	14	9	4			1				1	**29**
500	284	199	165	5	3	24	11	6	8	89	**794**
600	3,006	2,034	1,172	27	75	259	84	14	36	685	**7,392**
700	10	18	11			4	1	1	2	10	**57**
800	41	20	14		2	2			2	14	**95**
900	7	10	1				2			6	**26**
1010	1,210	1,256	545	20	25	104	18	5	16	384	**3,583**
1020	61	66	22	1		2	1		1	31	**185**
1030	814	842	299	29	12	49	21	1	7	212	**2,286**
1040	878	552	424	7	3	37	15	5	1	121	**2,043**
1100	3,955	2,408	2,369	42	42	221	98	8	29	605	**9,777**
1210	7	8	2		2		1			7	**27**
1220	17	14	10	1					1	7	**50**
1230	65	45	44	1	3	3	3			31	**195**
1300	1,029	615	454	6	3	38	11	2	7	226	**2,391**
1410	1	1									**2**
1420	11		1					2		2	**16**
1500	2	2				1					**5**
1700	6	1									**7**

1810	2,822	2,543	1,499	79	54	331	180	47	47	781	**8,383**
1820	354	140	237	2	2	12	2	4	1	7	**761**
1830	17	16	13		1				2	6	**55**
Total	**25,998**	**18,590**	**14,053**	**342**	**418**	**1,798**	**689**	**144**	**233**	**4,967**	**67,232**

1.2 BIOSIMILAR IODINATE CONTRAST AGENTS

We are examining 10 agents, subdivided into 5 pairs (Main Pairs) of possibly 'biosimilar' ones. Each pair contains an agent as acid and the same agent as a salt. Their possible 'biosimilarity' is 'aprioric', that is based on chemical grounds, before any clustering is attempted. They should behave in a similar manner as far as adverse reactions are concerned, and we expect them to have close adverse reactions profiles.

Table 1. Pairs, the 10 agents and totals reports over years 1968-2010.

Main Pair	Agent Nr	Agents Name	Total Reports
1	1	Amidotrizoic Acid	25,998
	2	Meglumine Amidotrizoate/ Sodium Amidotrizoate	18,590
2	3	Iotalamic Acid	14,053
	4	Iotalamate Meglumine/ Iotalamate Sodium	342
3	5	Ioxitalamic Acid	418
	6	Ioxitalamate Meglumine/ Ioxitalamate Sodium	1,798
4	7	Metrizoic Acid	689
	8	Meglumine Metrizoate/ Calcium Metrizoate	144
5	9	Ioxaglic Acid	233
	10	Ioxaglate Meglumine/ Ioxaglate Sodium	4,967

The collected information on ADRs reports is summarized in two datasets:

a) A (28x10) matrix IODSOCD10, where the 10 columns stand for the 10 agents, in the order in which they appear in Table 1, above and the 28 rows stand for the 28 groups of SOCD-ADRs, with the codes:

100	**200**	**300**	**410**	**431**	**432**	**433**
500	**600**	**700**	**800**	**900**	**1010**	**1020**
1030	**1040**	**1100**	**1210**	**1220**	**1230**	**1300**
1410	**1420**	**1500**	**1700**	**1810**	**1820**	**1830**

b) A (593x10) matrix IODADR10, more detailed, with the same 10 columns, and with rows standing each for an involved ADR.

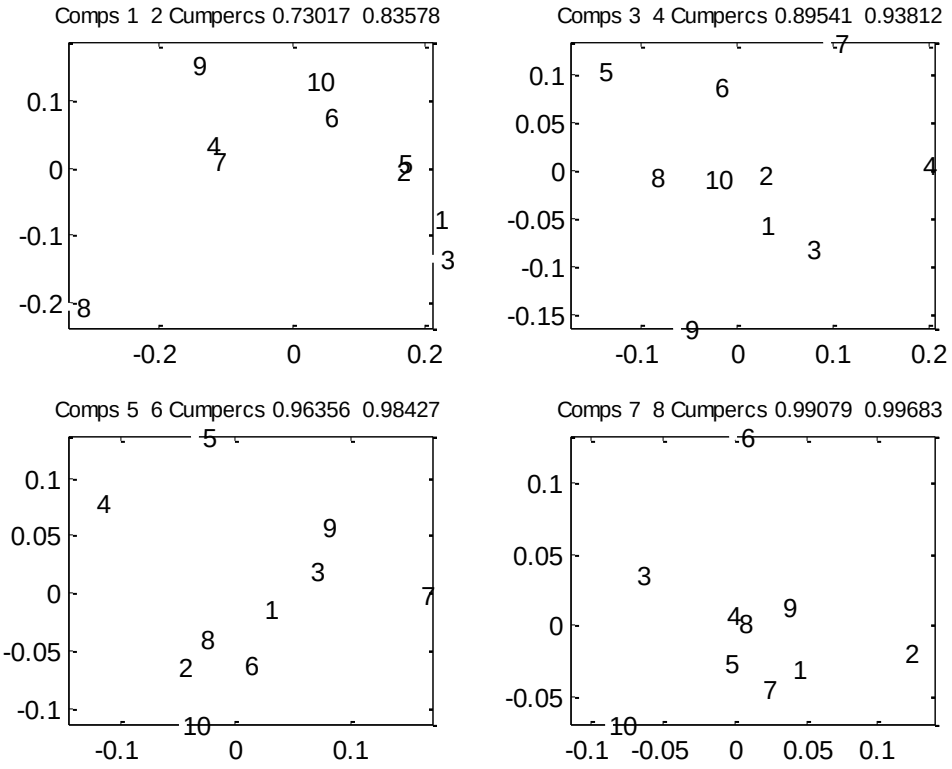
1.2.1.CLUSTERING ANALYSIS FOR THE MATRIX IODSOCD10

X=IODSOCD10'; scarce= [ ]; ALLCLUSTERSFINAL(X, scarce);

rich =

1 2 3 4 5 6 7 8 9 10

Follow **4 confirmatory plots**



GAUGES and CORRELATIONS

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 hold throughout

==========

CLUSTERS

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

pairwise correls = at least 0.86513

cluster 2 = 1 2 3 5 6 10

pairwise correls = at least 0.94621

cluster 3 = 4 7 9

pairwise correls = at least 0.95598

cluster 4 = 1 3 5

pairwise correls = at least 0.96195

cluster 5 = 2 6 10

pairwise correls = at least 0.98558

cluster 6 = 1 3

pairwise correls = at least 0.99466

==========

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

8	10	0.8625
6	8	0.8751
8	9	0.9150
4	8	0.9208
7	8	0.9319

==========

Summary of clusters

4 7 9

2 6 10

1 3

1 3 5

1 2 3 5 6 10

1 2 3 4 5 6 7 9 10

==========

Comments:

Cluster 1 (correlations $\geq .865$) **is not satisfactory, but puts in evidence the agent 8 which appears as a singleton, different from the rest. This gives the impression that no pair including 8 should be examined. As we will see, this impression is incorrect.**

Cluster2 (correlations ≥ 0.946) **and Cluster 3 (correlations** ≥ 0.956) **are quite good and exhaust the clustering, since the more precise Cluster4, Cluster5 and Cluster6 are all subsets of Cluster2.**

From the Main Pairs, (1 2) and (5 6) will be examined as subsets of Cluster2, and (7 8) is the best of the pairs of possible interest (correlation=0.932). **Main Pair** (3 4) **appears in the poorer Cluster1, and could be examined. In an analysis where only clusters are taken into account, the Main Pair (7 8) would be lost, since for any given gauge, the obtained clusters have to be disjoint.**

From the pairs of possible interest, pairs (8 9) and (4 8) of correlations 0.915 **and** 0.921**, respectively, may be examined too.**

Hence, from the 5 Main Pairs, only 3 (or 4) deserve further examination.

All this can be checked on the first confirmatory plot (for dimensions 1, 2).

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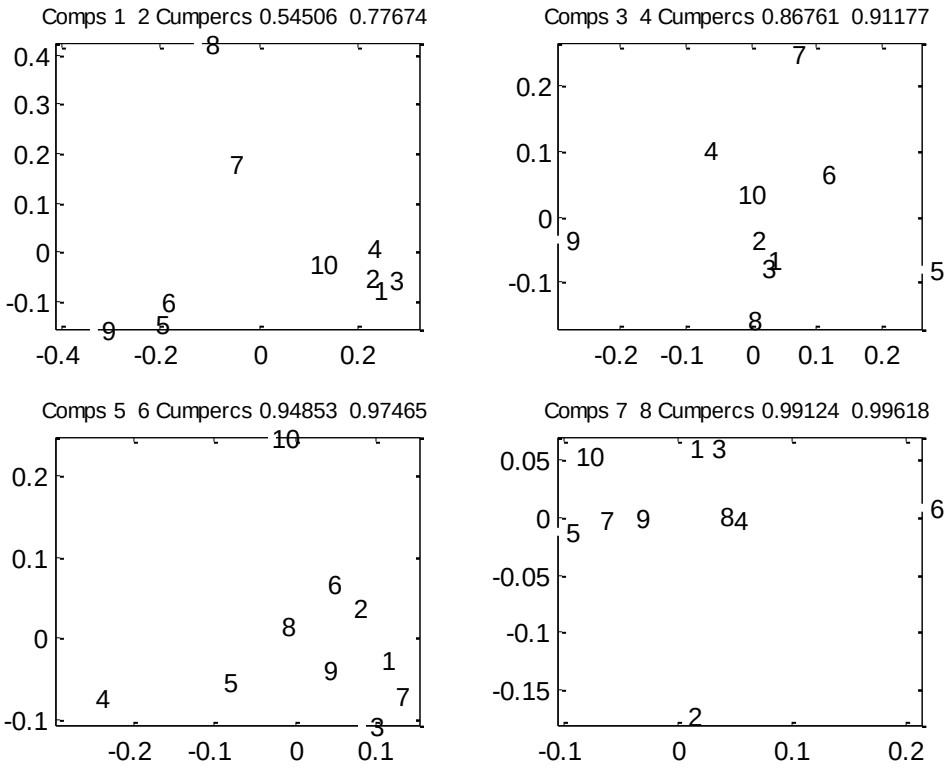
1.2.2. CLUSTERING ANALYSIS FOR MATRIX IODADR10

```
X=IODADR10'; scarce=[ ]; ALLCLUSTERSFINAL(X, scarce );
```

```
rich =

    1    2    3    4    5    6    7    8    9   10
```

Follow 4 confirmatory plots



GAUGES and CORRELATIONS

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 hold throughout

==========

CLUSTERS

cluster 1 = 1 2 3 4 10

pairwise correls = at least 0.9229

cluster 2 = 5 6

pairwise correl = 0.93288

cluster 3 = 1 2 3

pairwise correls = at least 0.98161

==========

PAIRS of possible interest

Cols 1, 2= pair, Col 3= correlation

1	**6**	**0.8291**
1	**7**	**0.8392**
2	**6**	**0.8451**
7	**8**	**0.8535**
2	**7**	**0.8607**
6	**9**	**0.8665**
6	**10**	**0.8731**
7	**10**	**0.8740**
6	**7**	**0.8793**

==========

Summary of clusters

5 6

1 2 3

1 2 3 4 10

==========

Comments.

The collection of clusters proposed here is more restricted than in the case of data set IODSOCD10.

A common skeleton is still present: Main Pairs (1,2) and (3,4) are subsets of Cluster1, Main Pair (5 6) is Cluster2 and Main Pair (7 8) is one of the pairs of possible interest, even if not on a high place. Hence, the same 4 Main Pairs appear in both data sets IODSOCD10 and IODADR10 as deserving examination, but with different motivations. Here too, the confirmatory plot for dimensions 1,2 displays the above findings. In the cases when close markers in this plot do not appear as pairs good candidates for examination, one can find the explanation by looking at the other 3 plots, where the corresponding markers are seen to be not such close.

Discussion.

As a temporary conclusion, our efforts will proceed along the lines set by our present and earlier contributions. We hope that these works, by exploring similarities in chemico-physical structure and bioavailability parameters, contrast agent cost-effectiveness (See [6] and Part 2 of the Discussion in [3], Fourth note) and actual phenotypic acute and delayed subchronic side-effects highlighted in the WHO-Pharmacovigilance Programme dataset, will contribute to establish whether the ATC-V08A –A, and -C subgroups, and their WHO-SOCD aggregation, among others (Cf [7, 8]), may be ameliorated by our objective autoclassification model, and constitute a first illustrative, original example of a different sort of sensibly coupled and/or multifaceted/multivariated complex human pathophysiological clinical and epidemiological objectively potentially disaggregated patterns of feed-back profiles between and within ordinarily used prototype biosimilar products.

It seems to us at this point, also on the basis of the present study, that even though personalized medicine is still immature, pre-clinical pharmacology and even more so that of clinical trials (as currenlty developed in relation to the so-called "relatively structured conventional bandwagon") find themselves in dire conditions, being of limited use in the way they are applied to socially as well as genetically diverse populations. It is therefore clear that it is essential to focus consistently and intensively on feed-back responses through application of a system that is both analytical and encompasses all cases of drug administration. This is clearly included in the scope of the evolution of the WHO Pharmacovigilance Programme, to which we have provided a contribution also through the present paper on biosimilar products.

Appendix Nr 1.

Nr of total SADRs (for the 30 SOCDs Classes and the 40 years global collection) of the 52 used and reported "biosimilars" of the V08A -A, B, C, and D sub-classes, and, in bold, those 10 presenting the highest total frequencies. 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 global 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 2.

For each "biosimilar" 10 products indicated in bold in the Appendix Nr 1., the total number of SADRs (in bold, in brackets) are listed, then the frequencies in rising order as aggregated in the WHO-standardized 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 for the 10 reviewed, selected products is 67,232.

N. 1 Amidotrizoic Acid (25,998); 100 (n 9,496): (Acne (0001):1; Otitis externa (0059):1; Stevens Johnson syndrome (0042):1; Piloerection (1071):1; Erythema nodosum (0015):1; Alopecia (0002):1; Livedo reticularis (1410):1; Melanosis (0019):1; Eczema (0012):1; Skin nodule (0061):1; Skin atrophy (0034):1; Rash pustular (0032):2; Fixed eruption (1249):2; Skin ulceration (0041):2; Urticaria acute (0045):3; Rash purpuric (0462):3; Skin exfoliation (1199):3; Nail disorder (0020):3; Skin necrosis (0060):3; Skin cold clammy (0932):4; Erythema multiforme (0014):4; Skin disorder (0037):7; Dermatitis exfoliative (0008):8; Dermatitis (0007):14; Rash follicular (0029):16; Skin discolouration (0036):16; Bullous eruption (0871):29; Angioedema (0003):92; Sweating increased (0043):150; Rash maculo-papular (0030):165; Rash erythematous (0028):206; Rash (0027):963; Pruritus (0024):1912; Urticaria (0044):5878); **200 (n 44)**: (Arthropathy (0065):1; Fracture (2190):1; Arthrosis (0066):1; Muscle weakness (1128):3; Myopathy (0074):3; Rhabdomyolysis (1210):3; Synovitis (0864):4; Myalgia (0073):6; Arthralgia (0063):22); **410 (n 1,449)**: (Meningism (0120):1; Meningitis (0955):1; Monoplegia (0122):1; Blindness cortical (1890):1; Ptosis (0142):1; Myasthenia gravis-like syndrome (1063):1; Dyskinesia tardive (1065):1; Myelitis (0123):1; Convulsions local (0096):1; Neuritis sensory (0129):1; Hyporeflexia (0850):1; Neuropathy peripheral (1313):1; Visual field defect (0159):2; Neuralgia (0124):2; Hemiparesis (0111):2; Ataxia (0088):2; Nystagmus (0131):2; Quadriplegia (0143):2; Paresis (0141):2; Cramps legs (0939):2; Gait abnormal (0108):2; Neurologic disorder NOS (2133):3; Hypotonia (0119):3; Hyperaesthesia (0113):3; Tetany (0152):3; Sensory disturbance (0148):3; EEG abnormal (0104):3; Anaesthesia mouth (1473):4; Spasm generalized (0149):4; Dystonia (0068):4; Dysaesthesia (1491):4; Paraplegia (0140):5; Oculogyric crisis (0132):5; Faecal incontinence (0107):5; Oedema cerebral (0891):6; Neuropathy (0130):6; Encephalopathy (0105):7; Aphasia (0087):9; Paralysis (0138):9; Hemiplegia (0112):20; Hypertonia (0116):27; Muscle contractions involuntary (0155):28; Speech disorder (0150):30; Hypoaesthesia (0117):38; Convulsions grand mal (0095):41; Vertigo (0158):43; Stupor (0151):55; Dysphonia (0103):73; Coma (0091):78; Headache (0109):134; Paraesthesia (0137):154; Tremor (0154):179; Convulsions (0093):191; Dizziness (0101):242); **431 (n 377)**: (Blepharitis (1007):1; Photophobia (0250):1; Miosis (0217):1; Scleritis (0255):2; Mydriasis (0219):3; Eye abnormality (0243):3; Diplopia (0241):6; Lacrimal gland disorder (0216):12; Blindness (0232):12; Eye pain (0244):13; Vision abnormal (0257):33; Lacrimation abnormal (1049):65; Conjunctivitis (0238):225); **432 (n 21)**: (Deafness (0258):2; Ear disorder NOS (1255):3; Ear ache (0260):8; Tinnitus (0264):8); **433 (n 14)**: (Parosmia (0265):1; Taste perversion (0267):13); **500 (n 284)**: (Depression (0172):1; Suicide attempt (2362):1; Impotence (0182):1; Delirium (0099):1; Neurosis (0189):1; Anorexia (0165):1; Personality disorder (0192):1; Drug abuse (0175):2; Emotional lability (0177):2; Catatonic reaction (0169):2; Hallucination (0179):2; Hysteria (0180):4; Depersonalization (0171):7; Thinking abnormal (0199):9; Aggressive reaction (0162):10; Amnesia (0164):10; Somnolence (0197):28; Nervousness (0188):32; Anxiety (0166):46; Agitation (0163):52; Confusion (0092):71); **600 (n 3,006)**: (Intestinal perforation (0754):1; Mucositis NOS (1351):1; Tenesmus (0231):1; Oesophageal ulceration haemorrhagic (0312):1; Constipation (0204):1; Oesophagitis (0309):1; Gastroenteritis (0293):1; Oesophagospasm (0310):1; Colitis (0271):1; Saliva altered (0758):1; Haemorrhage rectum (1014):1; Salivary gland pain (0326):1; Enanthema (0281):1; Teeth-

grinding (1086):1; Tooth disorder (0336):2; Gastritis (0291):2; Flatulence (0285):2; Salivary gland enlargement (0325):2; Tongue disorder (0330):3; GI haemorrhage (0294):3; Glossitis (0295):3; Hiccup (0300):3; Haematemesis (0297):4; Stomatitis (0327):4; Cheilitis (0270):4; Pancreatitis (0314):7; Peritonitis (0320):7; Saliva increased (0222):9; Dyspepsia (0279):11; Mouth dry (0218):23; Diarrhoea (0205):42; Tongue oedema (0331):58; Dysphagia (0280):102; Abdominal pain (0268):122; Nausea (0308):949; Vomiting (0228):1630); **700 (n 10)**: (Gallbladder disorder (0345):1; Hepatic function abnormal (0348):1; Hepatitis (0350):1; Bilirubinaemia (0339):1; Cholangitis (1576):2; Jaundice (0356):4); **800 (n 41)**: (Hyperglycaemia (0382):1; Oedema pharynx (1395):1; Hypoglycaemic reaction (0390):1; Dehydration (0370):1; Hyponatraemia (0392):1; Anion gap abnormal (1589):1; LDH increased (0394):1; Hypoglycaemia (0389):2; Acidosis respiratory (1465):2; Xerophthalmia (0943):2; Thirst (0405):2; Hypokalaemia (0391):2; Weight increase (0408):2; Hyperkalaemia (0383):6; Creatine phosphokinase increased (0791):7; Acidosis (0363):9); **900 (n 7)**: (Endocrine disorder NOS (1252):1; Hypothyroidism (0417):1; Hyperthyroidism aggravated (0416):1; Hyperthyroidism (0415):4); **1010 (n 1,210)**: (Cor pulmonale (1295):1; Aneurysm (0915):1; Cardiomegaly (1320):1; Cardiac failure left (0497):1; Cardiac failure right (0498):3; ECG abnormal specific (0503):4; Hypotension postural (0213):4; Pulse weak (1401):6; ECG abnormal (0502):7; Cardiac failure (0496):9; Heart disorder (0504):10; Hypertension (0210):108; Cyanosis (0501):151; Circulatory failure (0499):183; Hypotension (0212):721); **1020 (n 61)**: (Coronary artery disorder (0426):1; Thrombosis coronary (0488):1; Aortic stenosis (0424):1; Pericardial effusion (0910):1; Myocardial ischaemia (0429):2; Angina pectoris (0422):17; Myocardial infarction (0428):38); **1030 (n 814)**: (Adams Stokes syndrome (0432):1; Bundle branch block (0436):1; Heart block (0441):1; Fibrillation cardiac (0442):1; AV block complete (1378):2; Arrhythmia atrial (0434):2; Arrhythmia ventricular (0435):3; Tachycardia supraventricular (0229):4; AV block (0431):4; Fibrillation atrial (0439):5; Extrasystoles (0438):8; Tachycardia ventricular (0230):12; Fibrillation ventricular (0440):23; Arrhythmia (0433):26; Palpitation (0221):73; Bradycardia (0208):98; Tachycardia (0224):214; Cardiac arrest (0437):336); **1040 (n 878)**: (Ocular haemorrhage (1004):1; Arteriosclerosis (0771):1; Capillary fragility increased (0443):1; Subarachnoid haemorrhage (0463):1; Gangrene (0911):1; Thrombophlebitis leg deep (0472):1; Haemorrhage intracranial (1068):1; Cerebral infarction (1986):2; Thrombophlebitis superficial (0479):2; Thrombophlebitis arm superficial (0468):2; Thrombophlebitis deep (0470):3; Vascular disorder (0491):4; Cerebral ischaemia (1987):5; Cerebral haemorrhage (0444):5; Vasospasm (0226):6; Vasculitis (0085):6; Peripheral ischaemia (0454):11; Thrombophlebitis (0466):19; Cerebrovascular disorder (0445):29; Phlebitis (0455):63; Flushing (0207):151; Vasodilatation (0225):563); **1100 (n 3,955)**: (Sinusitis (0540):1; Respiratory tract haemorrhage (0538):1; Upper respiratory tract infection (0543):1; Bronchitis (0805):1; Pulmonary disorders (2032):1; Bradypnoea (0510):1; Pulmonary haemorrhage (0534):1; Hemothorax (1153):2; Atelectasis (1197):2; Respiratory distress syndrome (2252):2; Haemoptysis (0516):2; Epistaxis (0515):3; Pneumonia (0528):3; Pneumothorax (0531):3; Asthma (1367):3; Airways obstruction (1749):4; Sputum increased (0541):4; Laryngitis (0521):7; Respiratory insufficiency (0537):7; Hypoventilation (0518):10; Throat tightness (1489):11; Hypoxia (0519):12; Stridor (0542):13; Respiratory depression (0144):29; Hyperventilation (0517):31; Respiratory disorder (0536):50; Pulmonary oedema (0535):68; Apnoea (0507):188; Larynx oedema (0522):192; Laryngismus (0520):211; Pharyngitis (0523):230; Coughing (0513):249; Bronchospasm (0511):412; Rhinitis (0539):730; Dyspnoea (0514):1470); **1210 (n 7)**: (Anaemia hypochromic (0553):1; Anaemia haemolytic (0548):1; Haemolysis (0560):1; Erythrocytes agglutination (0559):1; Anaemia (0544):3); **1220 (n 17)**: Agranulocytosis (0570):1; Monocytosis

(0793):1; Lymphangitis (0580):1; Granulocytopenia (0572):1; Lymphopenia (0845):1; Leukocytosis (0576):2; Leucopenia (0908):2; Eosinophilia (0571):4; Lymphadenopathy (0577):4); **1230 (n 65)**: (Haemorrhage retroperitoneal (1214):1; Platelets abnormal (0589):1; Embolism arterial (0447):1; Thrombosis cerebral (0486):1; Haematoma (1353):1; Embolism - blood clot (0446):1; Prothrombin decreased (0590):1; Coagulation factor decreased (1122):2; Gingival bleeding (0930):2; Thrombosis mesenteric vessel (0489):2; Thrombosis (0481):2; Disseminated intravascular coagulation (1175):2; Thrombosis arterial (0482):2; Purpura thrombocytopenic (1348):3; Embolism pulmonary (0451):3; Thrombosis carotid (0485):3; Haemorrhage NOS (0452):4; Coagulation disorder (0586):5; Thrombocytopenia (0594):8); Purpura (0459):20; **1300 (n 1,029)**: (Nephrosclerosis (1177):1; Dysuria (0601):1; Urinary tract infection (0628):1; Nephritis (0607):1; Cystitis haemorrhagic (0600):1; Polyuria (0613):1; Bacteriuria (1956):1; Renal pain (0621):1; Nephrosis (0610):2; Creatinine clearance decreased (0598):2; Renal tubular disorder (0623):2; Renal failure chronic (2329):4; Nephropathy toxic (0609):7; Haematuria (0604):7; Urinary incontinence (0156):8; Anuria (0596):10; Oliguria (0612):11; Renal tubular necrosis (0624):11; Renal function abnormal (0619):15; Renal failure acute (0618):39; Azotaemia (2328):50; Face oedema (0602):853); **1410 (n 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 2)**: (Artery malformation (0676):2); **1700 (n 6)**: (Lymphoma-like disorder (0582):1; Thrombocythaemia (0593):1; Neoplasm NOS (1259):2; Carcinoma (0746):2); **1810 (n 2,822)**: (Influenza-like symptoms (1222):1; Multiple organ failure (1819):1; Therapeutic response increased (0874):1; Oedema dependent (0399):1; Leg pain (1439):1; Posture abnormal (2012):1; Medicine ineffective (1948):1; Therapeutic response decreased (0878):1; Scar (1522):1; Hypovolaemia (0929):2; Abdomen enlarged (0711):3; Chest pain substernal (0720):3; Hyperpyrexia (0894):3; Hyperpyrexia malignant (0893):4; Chest pain precordial (0719):4; Hypothermia (0727):6; Anaphylactic reaction (2237):8; Allergy (1058):9; Oedema mouth (1485):12; Oedema generalised (0400):12; Back pain (0717):16; Condition aggravated (0965):20; Asthenia (0716):25; Temperature changed sensation (1705):30; Fatigue (0724):31; Oedema peripheral (0401):40; Pallor (0220):43; Malaise (0728):54; Oedema periorbital (1009):86; Pain (0730):112; Fever (0725):133; Oedema (0398):135; Anaphylactic shock (0713):147; Syncope (0223):169; Rigors (0731):271; Death (0722):280; Allergic reaction (0712):291; Anaphylactoid reaction (0714):310; Chest pain (0718):554); **1820 (n 354)**: (Cellulitis (1372):1; Anaesthesia local (0062):1; Application site reaction (0047):2; Injection site mass (0055):5; Injection site necrosis (0056):12; Injection site inflammation (0054):30; Injection site pain (0057):119; Injection site reaction (0058):184); **1830 (n 17):** (Moniliasis (0741):1; Herpes zoster (0862):1; Infection (0736):5; Sepsis (0744):10);

n. 2 Meglumine amidotrizoate/Sodium amidotrizoate (18,590); 100 (n 6,401): (Pruritus genital (0026):1; Alopecia (0002):1; Pruritus ani (0025):1; Stevens Johnson syndrome (0042):1; Nail disorder (0020):1; Chloasma (0006):1; Skin nodule (0061):1; Eczema (0012):1; Erythema multiforme (0014):1; Rash follicular (0029):1; Hair texture abnormal (0855):1; Rash psoriaform (0031):1; Fixed eruption (1249):1; Rash purpuric (0462):1; Skin necrosis (0060):1; Rash pustular (0032):1; Dermatitis exfoliative (0008):3; Skin disorder (0037):3; Epidermal necrolysis (0013):4; Skin discolouration (0036):10; Bullous eruption (0871):11; Dermatitis (0007):12; Skin cold clammy (0932):13; Urticaria acute (0045):17; Rash maculo-papular (0030):108; Sweating increased (0043):117; Angioedema (0003):139; Rash erythematous (0028):399; Rash (0027):600; Pruritus (0024):949; Urticaria (0044):4000); **200 (n 32)**: (Fracture

pathological (0069):1; Muscle atrophy (0072):1; Fracture (2190):1; Skeletal pain (1347):1; Arthropathy (0065):1; Avascular necrosis bone (2222):1; Myopathy (0074):1; Arthrosis (0066):1; Myositis (0748):1; Arthritis (0064):2; Muscle weakness (1128):3; Synovitis (0864):4; Myalgia (0073):7; Arthralgia (0063):7); **300 (n 2)**: LE rash (0080):2); **410 (n 1,118)**: (Hypertension intracranial (0115):1; Tongue paralysis (0153):1; Abscences (1208):1; Arachnoiditis (1031):1; Torticollis (0077):1; Cerebellar syndrome (0089):1; Migraine (0121):1; CSF abnormal (0098):1; Monoplegia (0122):1; Ataxia (0088):1; Neuritis (0125):1; Paraplegia (0140):1; Neurologic disorder NOS (2133):1; Choreoathetosis (0090):1; Nystagmus (0131):1; Hyperkinesia (0114):2; Extrapyramidal disorder (0106):2; Gait abnormal (0108):2; Hypokinesia (0118):2; EEG abnormal (0104):2; Cerebral disorder (1960):2; Neuropathy (0130):3; Convulsions aggravated (0094):3; Cramps legs (0939):3; Neuralgia (0124):3; Sensory disturbance (0148):3; Dyskinesia (0102):3; Spasm generalized (0149):3; Visual field defect (0159):4; Quadriplegia (0143):4; Oculogyric crisis (0132):4; Convulsions local (0096):4; Dysaesthesia (1491):4; Hypotonia (0119):5; Encephalopathy (0105):5; Paresis (0141):5; Paralysis (0138):6; Tetany (0152):6; Aphasia (0087):7; Oedema cerebral (0891):7; Hemiparesis (0111):7; Dystonia (0068):8; Hemiplegia (0112):10; Faecal incontinence (0107):11; Vertigo (0158):14; Speech disorder (0150):15; Muscle contractions involuntary (0155):20; Hypertonia (0116):21; Hypoaesthesia (0117):28; Convulsions grand mal (0095):30; Stupor (0151):39; Dysphonia (0103):45; Coma (0091):83; Headache (0109):105; Dizziness (0101):126; Convulsions (0093):140; Paraesthesia (0137):152; Tremor (0154):155); **431 (n 223)**: (Scleritis (0255):1; Corneal ulceration (0240):1; Myopia (0248):1; Blindness temporary (1280):1; Retinal disorder (0251):2; Diplopia (0241):2; Blepharitis (1007):3; Lacrimal gland disorder (0216):4; Mydriasis (0219):4; Eye abnormality (0243):5; Eye pain (0244):6; Papilloedema (0249):6; Blindness (0232):13; Lacrimation abnormal (1049):20; Vision abnormal (0257):31; Conjunctivitis (0238):123); **432 (n 15)**: (Vestibular disorder (1126):1; Ear ache (0260):4; Deafness (0258):4; Tinnitus (0264):6); **433 (n 9)**: Taste perversion (0267):9); **500 (n 199)**: (Depression (0172):1; Hysteria (0180):1; Sleep disorder (0195):1; Insomnia (0183):1; Delirium (0099):1; Neurosis (0189):1; Apathy (0167):1; Psychosis (0193):1; Emotional lability (0177):2; Depersonalization (0171):2; Anorexia (0165):2; Amnesia (0164):4; Hallucination (0179):4; Aggressive reaction (0162):4; Thinking abnormal (0199):6; Nervousness (0188):19; Anxiety (0166):20; Somnolence (0197):35; Agitation (0163):42; Confusion (0092):51); **600 (n 2,034)**: (GI haemorrhage (0294):1; Haemorrhage rectum (1014):1; Colitis (0271):1; Increased stool urgency (1843):1; Enteritis (0282):1; Intestinal perforation (0754):1; Eructation (0283):1; Malabsorption (1025):1; Enanthema (0281):1; Melaena (0306):1; Tongue discolouration (0329):1; Oesophagospasm (0310):1; Enterocolitis (1324):1; Saliva altered (0758):1; Intestinal obstruction (0302):2; Hiccup (0300):2; Ileus (0214):2; Haematemesis (0297):2; Salivary gland pain (0326):2; Peritonitis (0320):3; Cheilitis (0270):3; Gastro-intestinal disorder NOS (1262):3; Tongue disorder (0330):4; Stomatitis (0327):4; Salivary gland enlargement (0325):5; Stomatitis ulcerative (0328):5; Amylase increased (1101):5; Tenesmus (0231):5; Dyspepsia (0279):6; Glossitis (0295):8; Pancreatitis (0314):10; Saliva increased (0222):10; Mouth dry (0218):16; Tongue oedema (0331):31; Dysphagia (0280):60; Diarrhoea (0205):90; Abdominal pain (0268):147; Nausea (0308):688; Vomiting (0228):907); **700 (n 18)**: (Gallbladder disorder (0345):1; Coma hepatic (0344):1; Biliary pain (0338):1; Cholecystitis (0342):1; Cholangitis (1576):1; Hepatorenal syndrome (1103):1; Hepatitis (0350):1; Hepatic failure (0933):2; Hepatic function abnormal (0348):4; Jaundice (0356):5); **800 (n 20)**: (Electrolyte abnormality (0374):1; Oedema pharynx (1395):1; Glucose tolerance abnormal (0376):1; Dehydration (0370):1; Weight decrease (0407):1; Alkalosis respiratory (0366):1; Hypocalcaemia (0387):1; Hyperglycaemia

(0382):2; Hypokalaemia (0391):2; Acidosis (0363):2; Hypoglycaemia (0389):2; Thirst (0405):2; Hyperkalaemia (0383):3); **900 (n 10)**: (Endocrine disorder NOS (1252):1; Diabetes insipidus (0411):1; Hypothyroidism (0417):1; Hyperthyroidism aggravated (0416):1; Hyperthyroidism (0415):6); **1010 (n 1,256)**: (Pulse weak (1401):1; Heart disorder (0504):2; Cardiac failure right (0498):3; ECG abnormal specific (0503):3; ECG abnormal (0502):14; Cardiac failure (0496):15; Hypertension (0210):108; Cyanosis (0501):146; Circulatory failure (0499):238; Hypotension (0212):726); **1020 (n 66)**: (Angina pectoris aggravated (0423):1; Pericarditis (0430):2; Myocardial ischaemia (0429):6; Coronary artery disorder (0426):7; Myocardial infarction (0428):23; Angina pectoris (0422):27); **1030 (n 842)**: (Extrasystoles (0438):2; Arrhythmia atrial (0434):2; Bundle branch block (0436):4; Arrhythmia ventricular (0435):4; AV block complete (1378):4; Adams Stokes syndrome (0432):5; Heart block (0441):7; AV block (0431):12; Fibrillation atrial (0439):14; Palpitation (0221):16; Tachycardia ventricular (0230):36; Arrhythmia (0433):40; Fibrillation ventricular (0440):100; Bradycardia (0208):125; Tachycardia (0224):218; Cardiac arrest (0437):253); **1040 (n 552)**: (Arteriosclerosis (0771):1; Pulmonary infarction (0458):1; Cerebral infarction (1986):1; Transient ischaemic attack (1694):1; Thrombophlebitis arm superficial (0468):1; Haemorrhage intracranial (1068):1; Thrombophlebitis deep (0470):1; Vascular disorder (0491):1; Thrombophlebitis leg deep (0472):1; Peripheral gangrene (0453):1; Thrombophlebitis leg superficial (0473):1; Cerebral ischaemia (1987):1; Thrombophlebitis superficial (0479):1; Cerebral haemorrhage (0444):2; Phlebitis superficial (0457):3; Gangrene (0911):3; Vasculitis (0085):3; Vasospasm (0226):8; Peripheral ischaemia (0454):13; Thrombophlebitis (0466):15; Cerebrovascular disorder (0445):20; Phlebitis (0455):37; Vasodilatation (0225):196; Flushing (0207):239); **1100 (n 2,408)**: (Yawning (0201):1; Upper respiratory tract infection (0543):1; Larynx pain (1648):1; Epistaxis (0515):1; Sputum increased (0541):1; Cheyne-Stokes respiration (1016):1; Atelectasis (1197):1; Sputum disorder (1976):1; Pulmonary haemorrhage (0534):1; Hypopnoea (1712):2; Respiratory distress syndrome (2252):2; Haemoptysis (0516):2; Pleural effusion (0524):2; Asthma (1367):3; Bronchitis (0805):3; Pneumonitis (1141):3; Bradypnoea (0510):3; Throat tightness (1489):5; Aspiration (1030):7; Hypoxia (0519):8; Pneumonia (0528):8; Hypoventilation (0518):12; Laryngitis (0521):13; Respiratory insufficiency (0537):14; Stridor (0542):20; Hyperventilation (0517):27; Respiratory depression (0144):32; Respiratory disorder (0536):44; Pulmonary oedema (0535):71; Pharyngitis (0523):71; Laryngismus (0520):109; Apnoea (0507):115; Larynx oedema (0522):132; Coughing (0513):162; Bronchospasm (0511):356; Rhinitis (0539):427; Dyspnoea (0514):746); **1210 (n 8)**: (Anaemia haemolytic (0548):2; Anaemia (0544):3; Haemolysis (0560):3); **1220 (n 14)**: (Leucopenia (0908):3; Lymphadenopathy (0577):3; Eosinophilia (0571):3; Leukocytosis (0576):5); **1230 (n 45)**: (Platelets abnormal (0589):1; Haemoperitoneum (0588):1; Disseminated intravascular coagulation (1175):1; Embolism arterial (0447):1; Purpura allergic (0460):1; Thrombosis retinal artery (0794):1; Thrombosis arterial (0482):1; Embolism limb (0449):1; Thrombosis mesenteric vessel (0489):1; Prothrombin decreased (0590):2; Embolism - blood clot (0446):2; Thrombosis cerebral (0486):3; Thrombocytopenia (0594):3; Thrombosis (0481):4; Purpura (0459):5; Haemorrhage NOS (0452):5; Coagulation disorder (0586):6; Embolism pulmonary (0451):6); **1300 (n 615)**: (Polyuria (0613):1; Micturition urgency (1497):1; Nephritis (0607):1; Creatinine clearance decreased (0598):1; Nephrosis (0610):1; Urethral disorder (0626):1; Renal calculus (0617):1; Nephropathy toxic (0609):2; Renal failure chronic aggravated (2330):2; Renal pain (0621):2; Urine abnormal (0629):2; Dysuria (0601):2; Urinary tract infection (0628):2; Urinary retention (0157):2; Micturition frequency (0606):3; Haematuria (0604):3; Anuria (0596):6; Renal failure chronic (2329):6; Oliguria (0612):10; Renal

tubular necrosis (0624):12; Urinary incontinence (0156):15; Renal function abnormal (0619):16; Azotaemia (2328):39; Renal failure acute (0618):59; Face oedema (0602):425); **1410 (n 1)**: (Priapism (0890):1; **1500 (n 2)**: (Artery malformation (0676):1; Chondrodystrophy (1120):1); **1700 (n 1)**: (Skin hypertrophy (0038):1; **1810 (n 2,543)**: (Halitosis (0990):1; Therapeutic response increased (0874):1; Hyperpyrexia (0894):1; Anaesthetic complication (2160):1; Hypovolaemia (0929):1; ESR increased (0723):1; Medicine ineffective (1948):1; Oedema dependent (0399):1; Multiple organ failure (1819):2; Anaphylactic reaction (2237):3; Chest pain substernal (0720):3; Hypothermia (0727):4; Oedema generalised (0400):5; Oedema mouth (1485):5; Abdomen enlarged (0711):6; Chest pain precordial (0719):8; Condition aggravated (0965):8; Influenza-like symptoms (1222):8; Fatigue (0724):13; Oedema peripheral (0401):19; Therapeutic response decreased (0878):19; Back pain (0717):21; Asthenia (0716):36; Temperature changed sensation (1705):45; Malaise (0728):46; Pain (0730):70; Pallor (0220):71; Syncope (0223):109; Oedema (0398):136; Allergic reaction (0712):148; Fever (0725):172; Anaphylactic shock (0713):202; Oedema periorbital (1009):203; Death (0722):219; Chest pain (0718):243; Rigors (0731):295; Anaphylactoid reaction (0714):416); **1820 (n 140)**: (Infusion site reaction (2137):1; Implantation complication (1035):1; Injection site mass (0055):1; Anaesthesia local (0062):1; Injection site infection (1910):2; Application site oedema (0048):2; Cellulitis (1372):3; Application site reaction (0047):5; Injection site necrosis (0056):7; Injection site inflammation (0054):15; Injection site pain (0057):38; Injection site reaction (0058):64); **1830 (n 16)**: (Immune system disorder (1903):1; Abscess (0887):1; Herpes zoster (0862):1; Infection (0736):5; Sepsis (0744):8);

n. 3 Iotalamic acid (14,053); 100 (n 5,670): (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):74; Rash erythematous (0028):86; Rash (0027):658; Pruritus (0024):953; Urticaria (0044):3781**); 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 805)**: (Hemianopia (0110):1; Hyperkinesia (0114):1; Brain stem disorder (0810):1; Meningism (0120):1; Convulsions local (0096):1; Myelitis (0123):1; CSF abnormal (0098):1; Neuralgia (0124):1; Upper motor neurone lesion (0892):1; Neuritis (0125):1; Cramps legs (0939):1; Oculogyric crisis (0132):1; Convulsions aggravated (0094):1; Ptosis (0142):1; Gait abnormal (0108):1; Tongue paralysis (0153):1; Hyperreflexia (0774):2; Oedema cerebral (0891):2; Vocal cord paralysis (0942):2; Coordination abnormal (0097):2; Paralysis flaccid (0139):2; EEG abnormal (0104):2; Paraplegia (0140):2; Faecal incontinence (0107):2; Paresis (0141):2; Neuropathy (0130):2; Quadriplegia (0143):2; Dystonia (0068):2; Tetany (0152):2; Visual field defect (0159):3; Dysaesthesia (1491):3; Hypotonia (0119):3; Ataxia (0088):3; Hemiparesis (0111):3; Dyskinesia (0102):5; Encephalopathy (0105):5; Paralysis (0138):7; Vertigo (0158):8; Hypertonia (0116):9; Aphasia (0087):11; Muscle contractions involuntary (0155):13; Speech disorder (0150):15; Hemiplegia (0112):17; Hypoaesthesia (0117):21; Stupor (0151):26; Convulsions grand mal (0095):26; Dysphonia (0103):28; Coma (0091):37; Headache (0109):58; Dizziness (0101):97; Convulsions (0093):98; Paraesthesia (0137):129; Tremor (0154):138); **431 (n 226)**: (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):144); **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 165)**: (Dreaming abnormal (1243):1; Anorexia (0165):1; Mental deficiency (0187):1; Hysteria (0180):1; Depersonalization (0171):4; Psychosis (0193):4; Thinking abnormal (0199):5; Hallucination (0179):7; Aggressive reaction (0162):8; Nervousness (0188):9; Amnesia (0164):10; Agitation (0163):21; Anxiety (0166):22; Somnolence (0197):27; Confusion (0092):44); **600 (n 1,172)**: (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):59; Nausea (0308):340; Vomiting (0228):635); **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 545)**: (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):63; Circulatory failure (0499):64; Cyanosis (0501):80; Hypotension (0212):319); **1020 (n 22)**: (Coronary artery disorder (0426):1; Myocarditis (1352):1; Myocardial ischaemia (0429):3; Angina pectoris (0422):6; Myocardial infarction (0428):11); **1030 (n 299)**: (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):6; Fibrillation ventricular (0440):7; Palpitation (0221):10; Arrhythmia (0433):11; Bradycardia (0208):42; Cardiac arrest (0437):101; Tachycardia (0224):110); **1040 (n 424)**: (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):4; Vasospasm (0226):7; Peripheral ischaemia (0454):10; Cerebral ischaemia (1987):10; Thrombophlebitis (0466):13; Cerebrovascular disorder (0445):31; Flushing (0207):55; Phlebitis (0455):67; Vasodilatation (0225):209); **1100 (n 2,369)**: (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):7; Respiratory depression (0144):13; Throat tightness (1489):14; Hyperventilation (0517):15; Stridor (0542):16; Laryngitis (0521):16; Pulmonary oedema (0535):28; Respiratory disorder (0536):34; Apnoea (0507):79; Laryngismus (0520):128; Larynx oedema (0522):129; Coughing (0513):178; Pharyngitis (0523):203; Bronchospasm (0511):240; Rhinitis (0539):563; Dyspnoea (0514):685); **1210 (n 2)**: (Haemolysis (0560):2; **1220 (n 10)**: (Eosinophilia (0571):2; Leucopenia (0908):3; Leukocytosis (0576):5); 1230 (n 44): (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):5; Purpura (0459):8; Coagulation disorder (0586):12); **1300 (n 454)**: (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):4; Azotaemia (2328):9; Urinary incontinence (0156):12; Renal function abnormal (0619):12; Renal failure acute (0618):14; Face oedema (0602):393); **1420 (n 1)**: (Salpingitis (0963):1; **1810 (n 1,499)**: (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):10; Oedema generalised (0400):13; Temperature changed sensation (1705):17; Malaise (0728):22; Oedema peripheral (0401):22; Back pain (0717):22; Oedema mouth (1485):24; Fatigue (0724):26; Pallor (0220):29; Anaphylactic shock (0713):53; Pain (0730):66; Oedema (0398):66; Fever (0725):66; Oedema periorbital (1009):71; Syncope (0223):80; Death (0722):110; Allergic reaction (0712):155; Anaphylactoid reaction (0714):173; Rigors (0731):189; Chest pain (0718):263); **1820 (n 237)**: (Injection site mass (0055):1; Injection site infection (1910):3; Application site reaction (0047):4; Injection site necrosis (0056):4; Injection site inflammation (0054):17; 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.4 Iotalamate meglumine/Iotalamate sodium (342); 100 (n 93): (Sweating increased (0043):2; Rash (0027):7; Pruritus (0024):8; Urticaria (0044):76); **410 (n 28)**: (EEG abnormal (0104):1; Muscle contractions involuntary (0155):1; Dizziness (0101):1; Speech disorder (0150):1; Neuropathy (0130):1; Nystagmus (0131):1; Dysphonia (0103):2; Tremor (0154):3; Headache (0109):4; Convulsions grand mal (0095):4; Convulsions (0093):4; Coma (0091):5); **431 (n 1)**: (Conjunctivitis (0238):1); **500 (n 5):** (Amnesia (0164):1; Confusion (0092):1; Personality disorder (0192):1; Agitation (0163):2); **600 (n 27)**: (Abdominal pain (0268):1; Nausea (0308):6; Vomiting (0228):20); **1010 (n 20)**: (Circulatory failure (0499):2; Cyanosis (0501):3; Hypertension (0210):3; Hypotension (0212):12); **1020 (n 1)**: (Myocardial infarction (0428):1; **1030 (n 29)**: (Arrhythmia (0433):1; Tachycardia ventricular (0230):1; Tachycardia (0224):3; Bradycardia (0208):5; Fibrillation ventricular (0440):9; Cardiac arrest (0437):10); 1040 (n 7): (Flushing (0207):1; Phlebitis (0455):1; Cerebral ischaemia (1987):1; Thrombophlebitis (0466):1; Cerebral infarction (1986):1; Vasodilatation (0225):2); **1100 (n 42)**: (Hypoxia (0519):1; Respiratory disorder (0536):1; Pulmonary oedema (0535):1; Pharyngitis (0523):2; Apnoea (0507):3; Larynx oedema (0522):4; Bronchospasm (0511):6; Dyspnoea (0514):12; Rhinitis (0539):12); **1220 (n 1)**: (Leucopenia (0908):1); 1230 (n 1): (Embolism pulmonary (0451):1); **1300 (n 6)**: (Anuria (0596):1; Renal failure acute (0618):2; Face oedema (0602):3); **1810 (n 79)**: (Fatigue (0724):1; Condition aggravated (0965):1; Malaise (0728):1; Oedema generalised (0400):1; Back pain (0717):1; Anaphylactoid reaction (0714):2; Syncope (0223):2; Oedema (0398):2; Oedema periorbital (1009):2; Fever (0725):4; Death (0722):5; Pain (0730):5; Chest pain (0718):8; Anaphylactic shock (0713):9; Rigors (0731):17; Allergic reaction (0712):18); **1820 (n 2)**: (Injection site inflammation (0054):2);

n. 5 Ioxitalamic acid (418); 100 (n 163): (Erythema multiforme (0014):1; Skin cold clammy (0932):1; Fixed eruption (1249):1; Angioedema (0003):2; Sweating increased (0043):2; Rash maculo-papular (0030):9; Rash erythematous (0028):16; Pruritus (0024):31; Urticaria (0044):48; Rash (0027):52); **200 (n 2)**: (Muscle weakness (1128):1; Myalgia (0073):1); **410 (n 19)**: (Headache (0109):1; Hypertonia (0116):1; Meningism (0120):1; Dizziness (0101):2; Paraesthesia (0137):2; Convulsions (0093):3; Coma (0091):3; Tremor (0154):6); **431 (n 7)**: (Photopsia

(1172):1; Vision abnormal (0257):2; Lacrimal gland disorder (0216):4); **500 (n 3)**: (Nervousness (0188):1; Amnesia (0164):1; Somnolence (0197):1); **600 (n 75)**: (Mouth dry (0218):1; Saliva increased (0222):1; Flatulence (0285):1; Abdominal pain (0268):3; Vomiting (0228):27; Nausea (0308):42); **800 (n 2)**: (Hyponatraemia (0392):1; LDH increased (0394):1); **1010 (n 25)**: (Hypotension postural (0213):1; Cyanosis (0501):2; Circulatory failure (0499):2; Hypertension (0210):7; Hypotension (0212):13); **1030 (n 12)**: (Fibrillation ventricular (0440):1; Palpitation (0221):2; Cardiac arrest (0437):4; Tachycardia (0224):5); **1040 (n 3)**: (Flushing (0207):3); **1100 (n 42)**: (Apnoea (0507):1; Respiratory insufficiency (0537):1; Hyperventilation (0517):1; Aspiration (1030):1; Pharyngitis (0523):1; Respiratory disorder (0536):1; Respiratory depression (0144):2; Bronchospasm (0511):4; Coughing (0513):7; Dyspnoea (0514):23); **1210 (n 2)**: (Anaemia haemolytic, angiopathic (1740):1; Haemolysis (0560):1); **1230 (n 3)**: (Purpura thrombocytopenic (1348):1; Haemorrhage NOS (0452):1; Thrombocytopenia (0594):1); **1300 (n 3)**: (Face oedema (0602):3); **1810 (n 54)**: (Fatigue (0724):1; Chest pain (0718):1; Drug level increased (1281):1; Pallor (0220):1; Pain (0730):1; Allergic reaction (0712):2; Oedema (0398):2; Death (0722):2; Malaise (0728):3; Temperature changed sensation (1705):3; Anaphylactoid reaction (0714):4; Anaphylactic reaction (2237):5; Syncope (0223):6; Rigors (0731):7; Anaphylactic shock (0713):15); **1820 (n 2)**: (Injection site mass (0055):1; Injection site pain (0057):1); **1830 (n 1)**: (Sepsis (0744):1);

n. 6 Ioxitalamate meglumine/Ioxitalamate sodium (1,798); 100 (n 599): (Heat rash (1469):1; Urticaria acute (0045):1; Fixed eruption (1249):1; Rash purpuric (0462):1; Skin exfoliation (1199):1; Rash vesicular (1443):1; Bullous eruption (0871):2; Skin necrosis (0060):3; Erythema multiforme (0014):4; Skin discolouration (0036):10; Eczema (0012):11; Sweating increased (0043):21; Angioedema (0003):32; Rash maculo-papular (0030):43; Pruritus (0024):88; Rash erythematous (0028):90; Rash (0027):100; Urticaria (0044):189; **200 (n 4)**: (Avascular necrosis bone (2222):1; Myalgia (0073):1; Arthralgia (0063):1; Myopathy (0074):1); **410 (n 98)**: (Myasthenia gravis-like syndrome (1063):1; Neuralgia (0124):1; Visual field defect (0159):1; Neurologic disorder NOS (2133):1; Dysphonia (0103):1; Oedema cerebral (0891):1; Hemiplegia (0112):1; Paralysis (0138):1; Hypertension intracranial (0115):1; Paraplegia (0140):1; Convulsions grand mal (0095):1; Speech disorder (0150):1; Hyperaesthesia (0113):1; Tetany (0152):1; Hemiparesis (0111):1; Vertigo (0158):1; Hypotonia (0119):1; Tongue paralysis (0153):2; Coma (0091):4; Muscle contractions involuntary (0155):4; Spasm generalized (0149):5; Hypoaesthesia (0117):7; Dizziness (0101):8; Paraesthesia (0137):10; Convulsions (0093):11; Headache (0109):12; Tremor (0154):18); **431 (n 6)**: (Eye pain (0244):1; 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 24)**: (Breath holding (0752):1; Amnesia (0164):1; Apathy (0167):1; Confusion (0092):2; Nervousness (0188):2; Somnolence (0197):7; Anxiety (0166):10); **600 (n 259)**: (Haematemesis (0297):1; Diarrhoea bloody (1382):1; Enterocolitis (1324):1; Stomatitis (0327):1; Saliva increased (0222):1; Dysphagia (0280):2; Tongue oedema (0331):2; Mouth dry (0218):5; Diarrhoea (0205):7; Abdominal pain (0268):9; Vomiting (0228):84; Nausea (0308):145); **700 (n 4)**: (SGPT increased (0360):1; Hepatocellular damage (0353):1; SGOT increased (0359):2); **800 (n 2)**: (Hyponatraemia (0392):1; **1010 (n 104)**: (Cardiac failure (0496):2; Heart disorder (0504):2; Hypertension (0210):9; Cyanosis (0501):14; Circulatory failure (0499):25; Hypotension (0212):52); 1020 (n 2): (Angina pectoris (0422):2); **1030 (n 49)**: (Fibrillation cardiac (0442):3; Arrhythmia (0433):3; Palpitation (0221):4; Bradycardia (0208):7; Cardiac arrest (0437):10; Tachycardia (0224):21); **1040 (n 37)**: (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):24); **1100 (n 221)**: (Hemothorax (1153):1; Bronchospasm paradoxical (1490):1; Laryngitis (0521):1; Aspiration (1030):1; Hypoxia (0519):2; Throat tightness (1489):3; Apnoea (0507):3; Respiratory insufficiency (0537):3; Laryngismus (0520):4; Pulmonary oedema (0535):4; Pharyngitis (0523):4; Larynx oedema (0522):6; Respiratory disorder (0536):7; Respiratory depression (0144):9; Rhinitis (0539):17; Bronchospasm (0511):21; Coughing (0513):30; Dyspnoea (0514):104); **1230 (n 3)**: (Embolism cerebral (0448):1; Disseminated intravascular coagulation (1175):1; Purpura (0459):1); **1300 (n 38)**: (Anuria (0596):1; Renal function abnormal (0619):2; Azotaemia (2328):4; Renal failure acute (0618):13; Face oedema (0602):18); **1500 (n 1)**: (Abortion (0634):1); **1810 (n 331)**: (Pain (0730):1; Oedema generalised (0400):1; Unexpected therapeutic effect (0735):1; Oedema mouth (1485):2; Asthenia (0716):4; Back pain (0717):5; Fatigue (0724):6; Allergy (1058):6; Anaphylactic reaction (2237):8; Oedema (0398):8; Oedema periorbital (1009):9; Pallor (0220):10; Death (0722):10; Malaise (0728):13; Syncope (0223):16; Chest pain (0718):17; Fever (0725):18; Temperature changed sensation (1705):30; Allergic reaction (0712):36; Rigors (0731):40; Anaphylactoid reaction (0714):44; Anaphylactic shock (0713):46); **1820 (n 12)**: (Injection site inflammation (0054):1; Application site oedema (0048):1; Injection site pain (0057):1; Injection site reaction (0058):3; Injection site necrosis (0056):6);

n. 7 Metririzoic acid (689); 100 (n 210): (Rash psoriaform (0031):1; Erythema multiforme (0014):1; Skin necrosis (0060):1; Urticaria acute (0045):2; Angioedema (0003):6; Sweating increased (0043):7; Pruritus (0024):14; Rash erythematous (0028):15; Skin discolouration (0036):21; Rash (0027):25; Urticaria (0044):117); **410 (n 20)**: (Dizziness (0101):1; Convulsions grand mal (0095):1; Convulsions (0093):1; Paralysis (0138):1; Tremor (0154):2; Coma (0091):3; Headache (0109):4; Paraesthesia (0137):7); **431 (n 8)**: (Vision abnormal (0257):2; Conjunctivitis (0238):6); **432 (n 3)**: (Tinnitus (0264):3); **500 (n 11)**: (Amnesia (0164):1; Psychosis (0193):1; Confusion (0092):2; Anxiety (0166):7); **600 (n 84)**: (Dysphagia (0280):1; Diarrhoea (0205):1; Dyspepsia (0279):1; Saliva increased (0222):1; Vomiting (0228):24; Nausea (0308):56); **700 (n 1)**: (Hepatic function abnormal (0348):1); **900 (n 2)**: (Goitre (0414):1; Sialoadenitis (0986):1); **1010 (n 18)**: (Cardiac failure (0496):1; Cyanosis (0501):2; Circulatory failure (0499):3; Hypotension (0212):12); **1020 (n 1)**: (Myocardial infarction (0428):1); **1030 (n 21)**: (Fibrillation atrial (0439):1; Arrhythmia ventricular (0435):1; Fibrillation ventricular (0440):1; Bradycardia (0208):2; Palpitation (0221):3; Cardiac arrest (0437):6; Tachycardia (0224):7); **1040 (n 15)**: (Thrombophlebitis arm (0467):1; Thrombophlebitis superficial (0479):1; Thrombophlebitis deep (0470):1; Phlebitis (0455):1; Thrombophlebitis leg deep (0472):1; Thrombophlebitis arm deep (0505):2; Flushing (0207):8); **1100 (n 98)**: (Pharyngitis (0523):1; Hypoventilation (0518):1; Respiratory depression (0144):1; Pulmonary oedema (0535):1; Stridor (0542):2; Larynx oedema (0522):3; Bronchospasm (0511):6; Rhinitis (0539):12; Coughing (0513):13; Dyspnoea (0514):58); **1210 (n 1)**: (Haemolysis (0560):1); **1230 (n 3)**: (Purpura allergic (0460):1; Thrombocytopenia (0594):2); **1300 (n 11)**: (Nephrosis (0610):1; Oliguria (0612):1; Face oedema (0602):9); **1810 (n 180)**: (Malaise (0728):1; Back pain (0717):1; Oedema periorbital (1009):1; Pain (0730):1; Oedema peripheral (0401):1; Chest pain (0718):2; Sudden death (1134):2; Oedema (0398):3; Fatigue (0724):3; Temperature changed sensation (1705):4; Fever (0725):5; Syncope (0223):6; Rigors (0731):8; Death (0722):16; Allergic reaction (0712):28; Anaphylactoid reaction (0714):47; Anaphylactic shock (0713):51); **1820 (n 2)**: (Injection site reaction (0058):2);

n. 8 Meglumine metrizoate/Calcium metrizoate (144); 100 (n 31) (Angioedema (0003):1; (Pruritus (0024):1; (Rash (0027):4; (Rash erythematous (0028):4; Urticaria (0044):21); **410 (n 11)**: (EEG abnormal (0104):1; (Muscle contractions involuntary (0155):1; (Coma (0091):1; (Headache (0109):2; (Hemiparesis (0111):3; Dizziness (0101):3); **431 (n 7)**: (Blindness (0232):2; Vision abnormal (0257):5); **500 (n 6)**: (Personality disorder (0192):1; (Hallucination (0179):1; (Confusion (0092):2; Anxiety (0166):2); **600 (n 14)**: (Diarrhoea (0205):1; (Vomiting (0228):5; Nausea (0308):8); **700 (n 1)**: (Jaundice (0356):1; **1010 (n 5)**: (Cyanosis (0501):1; (Circulatory failure (0499):2; Hypotension (0212):2); **1030 (n 1)**: (Bradycardia (0208):1); **1040 (n 5)**: (Thrombophlebitis leg deep (0472):1; (Cerebral infarction (1986):1; (Thrombophlebitis superficial (0479):1; (Cerebrovascular disorder (0445):1; Vasospasm (0226):1); **1100 (n 8)**: (Pharyngitis (0523):1; (Rhinitis (0539):1; (Bronchospasm (0511):2; Dyspnoea (0514):4); **1300 (n 2)**: (Face oedema (0602):1; Renal function abnormal (0619):1); **1420 (n 2)**: (Salpingitis (0963):2); **1810 (n 47)**: (Syncope (0223):1; (Oedema (0398):1; (Fever (0725):1; (Allergic reaction (0712):2; (Death (0722):3; (Rigors (0731):3; (Anaphylactic shock (0713):14; Anaphylactoid reaction (0714):22); **1820 (n 4)**: (Injection site necrosis (0056):2; Injection site reaction (0058):2);

n. 9 Ioxaglic acid (233); 100 (n 50): (Angioedema (0003):2; Sweating increased (0043):2; Pruritus (0024):4; Rash maculo-papular (0030):6; Rash (0027):7; Urticaria (0044):13; Rash erythematous (0028):16); **410 (n 21)**: (Nystagmus (0131):1; Oedema cerebral (0891):1; Coma (0091):1; Hemiplegia (0112):1; Dizziness (0101):1; Speech disorder (0150):1; Paresis (0141):1; Paraesthesia (0137):2; Vertigo (0158):2; Aphasia (0087):2; Headache (0109):4; Tremor (0154):4); **431 (n 2)**: (Blindness temporary (1280):1; Diplopia (0241):1); **500 (n 8)**: (Euphoria (0178):1; Anxiety (0166):1; Nervousness (0188):1; Confusion (0092):2; Somnolence (0197):3); **600 (n 36)**: (Amylase increased (1101):1; Pancreatitis (0314):2; Abdominal pain (0268):7; Vomiting (0228):10; Nausea (0308):16); **700 (n 2)**: (SGOT increased (0359):1; SGPT increased (0360):1); **800 (n 2)**: (Lipase increased (1621):2); **1010 (n 16)**: (Cyanosis (0501):2; Hypotension (0212):14); 1020 (n 1): (Myocardial ischaemia (0429):1); **1030 (n 7)**: (Palpitation (0221):1; Cardiac arrest (0437):3; Tachycardia (0224):3); **1040 (n 1)**: (Flushing (0207):1); **1100 (n 29)**: (Apnoea (0507):1; Rhinitis (0539):2; Larynx oedema (0522):2; Bronchospasm (0511):3; Coughing (0513):6; Dyspnoea (0514):15); **1220 (n 1)**: (Lymphoedema (0581):1); **1300 (n 7)**: (Micturition disorder (0605):1; Nephropathy toxic (0609):1; Renal failure acute (0618):1; Face oedema (0602):4); **1810 (n 47)**: (Chest pain precordial (0719):1; Oedema generalised (0400):1; Pain (0730):1; Pallor (0220):2; Allergic reaction (0712):2; Chest pain (0718):2; Anaphylactic shock (0713):2; Oedema periorbital (1009):2; Hyperpyrexia (0894):3; Malaise (0728):4; Anaphylactoid reaction (0714):4; Fever (0725):5; Syncope (0223):5; Rigors (0731):6; Temperature changed sensation (1705):7); **1820 (n 1)**: (Injection site reaction (0058):1); **1830 (n 2)**: (Healing impaired (0896):2);

n. 10 Ioxaglate meglumine/Ioxaglate sodium (4,967); 100 (n 1,389): (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):20; Rash maculo-papular (0030):25; Angioedema (0003):44; Rash erythematous (0028):79; Rash (0027):134; Pruritus (0024):195; Urticaria (0044):858); **200 (n 17)**: (Synovitis (0864):1; Muscle weakness (1128):2; Myalgia (0073):2; Myopathy (0074):4; Arthralgia (0063):4; Arthritis (0064):4);

410 (n 278): (Vocal cord paralysis (0942):1; Oculogyric crisis (0132):1; Brain stem disorder (0810):1; Oedema cerebral (0891):1; Hemianopia (0110):1; Paralysis (0138):1; Vertigo (0158):1; Paraplegia (0140):1; Hyperkinesia (0114):1; Quadriplegia (0143):1; Encephalomyelitis (0974):1; Tongue paralysis (0153):1; Hypoaesthesia (0117):2; EEG abnormal (0104):2; Ataxia (0088):2; Nystagmus (0131):2; Encephalopathy (0105):2; Hypertonia (0116):3; Paresis (0141):3; Aphasia (0087):3; Dysaesthesia (1491):3; Hemiplegia (0112):4; Neuropathy (0130):5; Stupor (0151):5; Muscle contractions involuntary (0155):6; Dysphonia (0103):6; Speech disorder (0150):7; Hemiparesis (0111):9; Dizziness (0101):11; Convulsions grand mal (0095):17; Coma (0091):24; Convulsions (0093):28; Paraesthesia (0137):33; Headache (0109):34; Tremor (0154):55); **431 (n 54)**: (Miosis (0217):1; Diplopia (0241):2; Lacrimal gland disorder (0216):2; Eye pain (0244):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 89)**: (Euphoria (0178):1; Delirium (0099):1; Thinking abnormal (0199):1; Paranoid reaction (0190):1; Insomnia (0183):1; Aggressive reaction (0162):2; Psychosis (0193):2; Amnesia (0164):3; Nervousness (0188):4; Anxiety (0166):5; Hallucination (0179):6; Somnolence (0197):8; Agitation (0163):18; Confusion (0092):36); **600 (n 685)**: (Mucositis NOS (1351):1; Haematemesis (0297):1; Oesophagospasm (0310):1; Saliva increased (0222):1; Peritonitis (0320):1; 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):16; Nausea (0308):238; Vomiting (0228):391); **700 (n 10)**: (Hepatitis cholestatic (0351):1; Bilirubinaemia (0339):1; Hepatorenal syndrome (1103):1; Hepatic enzymes increased (1346):1; Hepatitis (0350):2; SGOT increased (0359):2; SGPT increased (0360):2); **800 (n 14)**: (Hypervolaemia (1178):1; Hyperglycaemia (0382):1; Hypoproteinaemia (0827):1; Xerophthalmia (0943):1; Ketosis (0393):1; Acidosis (0363):2; Oedema pharynx (1395):2; Hyperkalaemia (0383):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 384)**: (Hypertension pulmonary (0211):1; ECG abnormal specific (0503):2; ECG abnormal (0502):3; Cardiac failure right (0498):3; Cardiac failure (0496):4; Cyanosis (0501):23; Circulatory failure (0499):43; Hypertension (0210):45; Hypotension (0212):260); **1020 (n 31)**: (Pericardial effusion (0910):1; Myocardial ischaemia (0429):3; Coronary artery disorder (0426):4; Thrombosis coronary (0488):4; Angina pectoris (0422):6; Myocardial infarction (0428):13); **1030 (n 212)**: (Bundle branch block (0436):1; Torsade de pointes (1431):1; Tachycardia supraventricular (0229):1; AV block (0431):1; Arrhythmia ventricular (0435):4; Fibrillation atrial (0439):4; Arrhythmia (0433):9; Fibrillation ventricular (0440):13; Tachycardia ventricular (0230):15; Bradycardia (0208):44; Cardiac arrest (0437):48; Tachycardia (0224):71); **1040 (n 121)**: (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):18; Cerebrovascular disorder (0445):21; Vasodilatation (0225):64); **1100 (n 605)**: (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; Larynx oedema (0522):9; Respiratory disorder (0536):11; Respiratory depression (0144):12; Pharyngitis (0523):12; Hypoxia (0519):17; Laryngismus (0520):27;

Apnoea (0507):28; Coughing (0513):42; Pulmonary oedema (0535):45; Bronchospasm (0511):86; Rhinitis (0539):101; Dyspnoea (0514):176); **1210 (n 7)**: (Haemolysis (0560):2; Anaemia (0544):5); **1220 (n 7)**: (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 226)**: (Creatinine clearance decreased (0598):1; Dysuria (0601):1; Renal failure chronic (2329):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):39; Renal failure acute (0618):50; Face oedema (0602):75); **1420 (n 2)**: (Uterine spasm (0667):2); **1810 (n 781):** (Chest pain precordial (0719):1; Drug interaction (2356):1; Allergy aggravated (1027):1; Hyperpyrexia malignant (0893):1; Serum sickness (0733):1; Hypothermia (0727):2; Fatigue (0724):3; Oedema mouth (1485):3; Asthenia (0716):4; Temperature changed sensation (1705):4; Oedema peripheral (0401):5; Allergy (1058):5; Anaphylactic reaction (2237):7; Condition aggravated (0965):8; Pallor (0220):8; Back pain (0717):11; Oedema (0398):13; Pain (0730):14; Malaise (0728):15; Syncope (0223):18; Oedema periorbital (1009):20; Chest pain (0718):52; Allergic reaction (0712):64; Death (0722):68; Rigors (0731):90; Fever (0725):97; Anaphylactic shock (0713):121; Anaphylactoid reaction (0714):144); **1820 (n 7)**: (Anaesthesia local (0062):1; Injection site inflammation (0054):2; Injection site pain (0057):2; Injection site reaction (0058):2); **1830 (n 6)**: (Sepsis (0744):6).

Appendix Nr 3.

The code-number of the SOCD-SADRs effectively appearing in the 10 iodinated contrast agents "biosimilar" products indicated in bold in the Appendix Nr 1.

LIST OF 593 ADRs INVOLVED IN IODADR10

1	2	3	6	7	8
12	13	14	15	19	20
22	24	25	26	27	28
29	30	31	32	34	36
37	38	41	42	43	44
45	47	48	54	55	56
57	58	59	60	61	62
63	64	65	66	68	69
72	73	74	77	78	80

85	86	87	88	89	90
91	92	93	94	95	96
97	98	99	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	129	130
131	132	137	138	139	140
141	142	143	144	148	149
150	151	152	153	154	155
156	157	158	159	162	163
164	165	166	167	169	171
172	175	177	178	179	180
182	183	187	188	189	190
192	193	195	197	199	201
204	205	207	208	210	211
212	213	214	216	217	218
219	220	221	222	223	224
225	226	227	228	229	230
231	232	238	240	241	243
244	246	247	248	249	250
251	255	257	258	260	264
265	267	268	270	271	279
280	281	282	283	285	291
293	294	295	297	300	302
306	308	309	310	312	314
320	325	326	327	328	329
330	331	336	338	339	342
344	345	348	350	351	353

356	359	360	363	366	370
374	376	382	383	387	389
390	391	392	393	394	398
399	400	401	405	407	408
411	414	415	416	417	422
423	424	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
465	466	467	468	470	472
473	479	481	482	485	486
487	488	489	491	494	496
497	498	499	501	502	503
504	505	507	510	511	513
514	515	516	517	518	519
520	521	522	523	524	528
531	534	535	536	537	538
539	540	541	542	543	544
548	553	559	560	570	571
572	576	577	580	581	582
586	588	589	590	592	593
594	596	598	600	601	602
604	605	606	607	609	610
612	613	617	618	619	621
623	624	626	628	629	631
632	634	639	655	667	669
676	711	712	713	714	716

717	718	719	720	722	723
724	725	727	728	730	731
733	735	736	741	744	746
748	750	752	754	758	771
774	779	791	793	794	805
808	810	827	845	850	855
862	864	871	874	876	877
878	887	890	891	892	893
894	896	908	910	911	912
915	929	930	932	933	938
939	942	943	955	963	965
974	986	990	993	1004	1007
1009	1014	1016	1025	1027	1030
1031	1035	1038	1049	1058	1063
1065	1068	1071	1086	1101	1103
1120	1122	1123	1126	1128	1134
1141	1153	1172	1175	1177	1178
1197	1199	1208	1210	1214	1222
1243	1249	1252	1255	1259	1262
1280	1281	1295	1303	1313	1320
1324	1346	1347	1348	1351	1352
1353	1367	1368	1372	1378	1382
1395	1398	1401	1410	1431	1439
1443	1447	1460	1465	1469	1473
1485	1489	1490	1491	1496	1497
1522	1576	1589	1621	1648	1694
1705	1712	1721	1738	1740	1749
1819	1831	1839	1843	1890	1903
1910	1948	1956	1960	1976	1986

1987	2012	2032	2086	2129	2133
2137	2160	2190	2222	2237	2252
2328	2329	2330	2356	2362	----

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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.

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