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Dosages of prescribed ibuprofen in the EMA's THIN (UK) and IMS (FR, DE) data

Preliminary counts of recorded prescriptions in context of Article 31 referral

1. Dosages recorded in THIN

The following tabulations look only at ibuprofen medications with a recorded unit dose – tablets, capsules or sachets.

The intended dose is recorded in THIN for about 62.8% of prescriptions. Imputation of missing values was not done although this would be possible in some cases with some accuracy.

The table below shows mainly the commonly used intended doses but also includes the 3200 mg dose as, although rare, it was prescribed 1,211 times.

Table 1. Prescriptions by intended dose: UK (THIN entire dataset)

Intended	Frequency	Percentage	Cumulative Frequency	Cumulative Percentage
400	47,974	1.04	54,831	1.19
600	327,266	7.11	382,782	8.31
800	129,554	2.81	512,544	11.13
900	66,174	1.44	578,718	12.57
1,200	3,173,987	68.93	3,756,440	81.58
1,600	288,370	6.26	4,063,472	88.25
1,800	507,908	11.03	4,571,380	99.28
2,400	29,989	0.65	4,602,679	99.96
3,200	1,211	0.03	4,603,994	99.99
Frequency Missing = 2,735,455				

In addition to looking at intended doses it is possible to examine the intervals between prescriptions to see if these are less than would be expected on the basis of the prescribed quantities and intended dose. If so, this may indicate that patients are taking more than the doctor intended.

Doing this calculation, when it is possible, suggests that patients take more ibuprofen than intended over the period of a prescription on 19% of occasions. To some extent this may be an artefact as patients might return for a new prescription slightly early to avoid running out. If we only consider patients who appear to be taking 20% more than intended the figure appears to be about 10%. Split down by dose this appears as Table 2 below:

Table 2. Patients possibly taking 20% more than intended (THIN data)

Intended	No	Yes
400	30,195 (73.85%)	10,694 (26.15%)
600	197,969 (86.87%)	29,928 (13.13%)
800	90,416 (82.93%)	18,615 (17.07%)
900	40,369 (89.30%)	4,836 (10.70%)
1,200	2,078,583 (90.83%)	209,752 (9.17%)
1,600	213,125 (88.35%)	28,104 (11.65%)
1,800	359,244 (91.01%)	35,487 (8.99%)
2,400	22,962 (89.88%)	2,584 (10.12%)
3,200	918 (88.35%)	121 (11.65%)

From this it seems possible that some patients exceed the dosages by a significant margin. If we only consider patients who appear to be taking 20% more than intended then the figure for 2400 mg appears to be about 10%. For example, if possible dosages above 10000mg are excluded as probable outliers that may be due to errors in the data, the mean dosage among the 10% of patients who exceed the 2400mg intended dose by 20% or more is about 4000mg.

These figures are derived from the entire THIN dataset and it is reasonable to ask whether current prescribing and consumption is more cautious. The same calculations restricted to prescriptions beyond 01 Jan 2013 suggest that prescribing may have become more moderate. There were no prescriptions for 3200mg and 2400mg accounted for 0.3% rather than 0.65% of prescriptions. Levels of prescribing at 1800mg and 1600mg had also fallen slightly, apparently back to 1200mg which had risen to 74% from 69%:

Table 3. Prescriptions by intended dose: UK (THIN data after 01 Jan 2013)

Intended	Frequency	Percentage	Cumulative Frequency	Cumulative Percentage
400	1,546	1.22	1,750	1.39
600	8,665	6.86	10,432	8.26
800	2,570	2.04	13,005	10.30
900	2,124	1.68	15,129	11.98
1,200	93,284	73.88	108,491	85.93
1,600	4,100	3.25	113,248	89.70
1,800	12,605	9.98	125,853	99.68
2,400	396	0.31	126,258	100.00
Frequency Missing = 139,401				

This apparent moderation in intended doses was somewhat countered by a rise in patients who exceeded their intended dose by 20% or more to 15% from the previous 10%.

2. Dosages recorded in IMS France and IMS Germany

2.1. Results

The following substances, present in the product dictionaries of IMS France and Germany, were included in the analysis:

Table 4. Substances included

France	Germany
codeine + ibuprofen	dexibuprofen

France	Germany
ibuprofen	dexpanthenol + loperamide + ibuprofen
ibuprofen + levomenthol	ibuprofen
pseudoephedrine + ibuprofen	ibuprofen + polyurethane
	pseudoephedrine + ibuprofen

In line with the referral, dexibuprofen and combination products have been included.

Regarding the pharmaceutical form, only systemic forms have been included (Oral Topical, Topical, Dermatological, Haemorrhoidal, External, Ophthalmic, Otic, Nasal Topical, Lung Administration, Vaginal/Intra-uterine have, therefore, been excluded).

The following tables (5 and 6) show the number of prescriptions by different intended daily dosage as calculated by IMS for France and Germany, respectively.

Table 5. Prescriptions by intended dose: France

Intended	Frequency		Percentage		Percentage	
	All DB	2014	All DB	2014	(of the classifiable)	
100	594	51	0.03%	0.03%	0.05%	0.05%
150	180	12	0.01%	0.01%	0.02%	0.01%
200	10,658	799	0.49%	0.51%	0.92%	0.79%
250	673	41	0.03%	0.03%	0.06%	0.04%
300	26,637	1,412	1.21%	0.91%	2.31%	1.39%
350	859	40	0.04%	0.03%	0.07%	0.04%
400	66,969	5,141	3.05%	3.31%	5.80%	5.08%
450	679	38	0.03%	0.02%	0.06%	0.04%
500	6,776	328	0.31%	0.21%	0.59%	0.32%
600	142,024	10,288	6.48%	6.62%	12.30%	10.16%
700	11,724	615	0.53%	0.40%	1.02%	0.61%
750	1,782	121	0.08%	0.08%	0.15%	0.12%
800	127,895	14,091	5.83%	9.06%	11.08%	13.91%
900	10,780	457	0.49%	0.29%	0.93%	0.45%
1,000	8,632	934	0.39%	0.60%	0.75%	0.92%
1,200	700,573	63,368	31.94%	40.75%	60.69%	62.56%
1,400	484	17	0.02%	0.01%	0.04%	0.02%
1,500	647	77	0.03%	0.05%	0.06%	0.08%
1,600	26,328	2,139	1.20%	1.38%	2.28%	2.11%
1,800	867	30	0.04%	0.02%	0.08%	0.03%
2,000	3,220	692	0.15%	0.44%	0.28%	0.68%
2,400	3,782	323	0.17%	0.21%	0.33%	0.32%
3,000	473	141	0.02%	0.09%	0.04%	0.14%
3,600	192	8	0.01%	0.01%	0.02%	0.01%
4,000	839	126	0.04%	0.08%	0.07%	0.12%
Unclassifiable	273,703	16,485	12.48%	10.60%	100.00%	100.00%
Unknown	765,152	37,733	34.89%	24.26%		
Total	2,193,122	155,507	100.00%	100.00%		

In France the daily dosage is recorded for 65.1% of ibuprofen and dexibuprofen prescriptions in the whole database (from 1997); however, a further 12.5% have a calculated daily dosage that is not sensible and therefore will need to be revised and cleaned in order to be used. The 1,200 mg is the most prescribed dose (> 60% of prescriptions with a calculated and sensible dosage) followed by lower dosage. Higher doses are prescribed more rarely with above 2,400 mg being < 1% of prescriptions.

Table 6. Prescriptions by intended dose: Germany

Intended	Frequency		Percentage		Percentage	
	All DB	2014	All DB	2014	(of the classifiable)	
200	2,996	96	0.05%	0.01%	0.34%	0.07%
300	1,424	205	0.02%	0.02%	0.16%	0.14%
400	21,631	1,376	0.37%	0.15%	2.45%	0.97%
500	1,435	57	0.02%	0.01%	0.16%	0.04%
600	59,234	7,672	1.01%	0.82%	6.70%	5.39%
700	252	55	0.00%	0.01%	0.03%	0.04%
800	104,640	11,375	1.78%	1.21%	11.84%	7.99%
900	11,553	2,282	0.20%	0.24%	1.31%	1.60%
1,000	16,653	1,530	0.28%	0.16%	1.89%	1.07%
1,200	344,885	59,328	5.88%	6.32%	39.04%	41.67%
1,400	2,507	480	0.04%	0.05%	0.28%	0.34%
1,500	30,533	6,406	0.52%	0.68%	3.46%	4.50%
1,600	90,942	14,696	1.55%	1.56%	10.29%	10.32%
1,800	144,686	29,079	2.47%	3.10%	16.38%	20.42%
2,000	6,459	1,001	0.11%	0.11%	0.73%	0.70%
2,100	1,311	253	0.02%	0.03%	0.15%	0.18%
2,200	304	6	0.01%	0.00%	0.03%	0.00%
2,400	37,591	6,199	0.64%	0.66%	4.26%	4.35%
2,500	144		0.00%	0.00%	0.02%	0.00%
2,800	2,831	7	0.05%	0.00%	0.32%	0.00%
3,000	528	110	0.01%	0.01%	0.06%	0.08%
3,200	451	71	0.01%	0.01%	0.05%	0.05%
3,600	375	83	0.01%	0.01%	0.04%	0.06%
4,000	66	4	0.00%	0.00%	0.01%	0.00%
Unclassifiable	44,798	6,120	0.76%	0.65%	100.00%	100.00%
Unknown	4,933,991	790,706	84.17%	84.19%		
Total	5,862,220	939,197	100.00%	100.00%		

In Germany the vast majority of prescriptions (84.2%) do not have a calculated dosage. Of the prescriptions with a calculated and sensible dosage 1,200 mg is the most frequent followed by 1,800 mg and 800 mg. Higher doses are prescribed more frequently than in France, with 2,400 mg dosage being in the order of 4.3% of prescriptions with a calculated and sensible dosage. These data, however, need to be interpreted with caution due to the high percentage of missing values in the dataset.

3. Conclusions

From counts of intended prescribed dosages in all 3 datasets (UK, FR and DE), prescriptions of 2,400 mg of ibuprofen would appear to account for < 1% of all prescriptions. However, while preliminary further analyses in the THIN dataset suggest even this low baseline is decreasing since 01 Jan 2013, if patients are taking more than the intended amount, some patients may be taking very high doses.

IMS France data seems to support the possibility of further analysis; moreover duration can be investigated and we do not expect any major data quality issue on that.

IMS Germany data instead do not seem to support the same conclusion re. the possibility of further analysis due to the high proportion of missing values.