EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA study on prescribing of ibuprofen in the French primary care setting

EMA drug utilisation study using IMS Health electronic health records

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. PASS information

Title	EMA study on prescribing of ibuprofen in France primary care setting
Protocol version identifier	1.0
EU PAS Register No:	Study not yet registered
Active substance	Ibuprofen
Medicinal product(s):	Multiple
Procedure number:	EMEA/H/A-31/1401
Study initiator	EMA
Research question and objectives	The primary objective of the present analysis is to provide drug utilisation data on the exposure of high-dose ibuprofen prescribing (2,400 mg or above per day) in France in adults.
Authors	**Gianmario Candore, Jim Slattery, Kevin Blake**

Marketing authorisation holder

Marketing authorisation holder(s)	Multiple

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2. Responsible parties

Project lead: Gianmario Candore

Clinical lead: Kevin Blake

Statistical lead: Jim Slattery

Project Sign-off: Peter Arlett

3. Rationale and background

The present study has been undertaken in the context of the current European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) Article 31 review to evaluate the cardiovascular risks with systemic ibuprofen medicines. These risks concern high-dose ibuprofen (2,400 mg per day) taken regularly for long periods. Ibuprofen is usually taken at lower doses and for short periods of time.

4. Research question and objectives

The primary objective of the present analysis is to provide drug utilisation data on the exposure of high-dose ibuprofen prescribing (2,400 mg or above per day) in France in adults.

Furthermore, the duration of the prescription will be calculated to estimate the percentage of patients prescribed high-dose ibuprofen for long periods.

5. Research methods

5.1. Study design

Descriptive study based on an electronic health record (EHR) database. Preliminary counts were performed in IMS data from 2 EU Member States (France and Germany) however only the French data were considered sufficient to perform the required analyses on this occasion.

5.2. Study Population

This analysis includes all patients recorded in the France IMS database as having received a prescription of ibuprofen.

The study period includes all data available in IMS France; from 1st January 1997 to 30th June 2014.

5.3. Setting and data sources

The IMS Disease Analyser France database includes anonymised patient medical records collected through a representative panel of GPs in France. In addition to prescription records, the IMS databases include records of patients diagnoses, test results and demographic and lifestyle characteristics.

The France IMS database (version June 2014) contains a cumulative number of 3,889,629 patients with data from 1997.

5.4. Variables

Exposure: prescription of ibuprofen, found by searching for any "substance name" containing ibuprofen (codeine + ibuprofen, ibuprofen, ibuprofen + levomenthol and pseudoephedrine + ibuprofen were included in the analysis).

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

Daily Dosage: Dosing information comes from a structured field in the IMS disease analyser databases. This field is populated using the free text dose information provided by the prescriber.

Based on quality checking confirmed by IMS, we have relied on the dose information provided in the databases and have not done any calculations in-house. However, some values including decimal doses (e.g. 95.2381 mg) has been considered as 'Unclassifiable' and not considered further in the analysis.

Dosing has been presented both as in the original values and, for facilitating comparison, grouped into the following categories:

- ≤ 1200 mg
- 1200 - 2400 mg
- ≥ 2400 mg

Duration: duration information can be obtained in two ways in IMS database; i) in a structured data field as prescribed by the physician; ii) calculated based on the prescription information on the size of the pack, the number of packs and the daily dosage. The latter is considered the recommended way to calculate duration by IMS, in particular because ibuprofen is an on demand therapy.

Duration has then been created in SAS on data extracted from IMS disease analyser. Quality checks on the pack size and the number of packs prescribed didn't reveal any particular problem and all quantities described as packs have been multiplied with pack size and divided by the daily dosage to get duration for each prescription.

Sensitivity analysis using both ways to create duration didn't show any meaningful difference.

Treatment episode: in order to estimate the length of time each patient might have been taken ibuprofen, treatment episodes have been created. The following assumptions were made:

- since a patient can switch between different dosages, treatments that include only high dosage prescriptions have been considered (≥ 2400 mg);
- prescribing before the end date of the previous prescription has been treated by letting the duration left from the previous prescription be carried forward to the next. This means that a prescription lasting 14 days, being renewed 10 days later, would have the 4 days still left being added to the duration of the new prescription;
- prescribing after the end date of the previous prescription has been considered as a continued treatment episode if the date of prescription is within 3 days after the end date of the previous prescription. This "grace period" seems to be sensible for this kind of drug and would allow for patients having less than perfect adherence;
- a patient can have more than one therapy episode, all episodes have been counted;

- therapy episodes have been grouped in weeks as 1 - 7 days, 8 - 14 days, 15 - 21 days, 22 - 28 days, 29 - 25 days and more than 35 days (therapy durations might have been cut short by reaching the end of the study period or by starting before the study period, but given the short period of the episodes for the drug under study this has not impacted the analysis).

5.5. Study size

This study is a descriptive analysis of EHR data from IMS Health. No sample size or statistical precision calculation is performed.

5.6. Data management

Data extraction and management is performed in IMS Disease Analyser; analyses are performed using SAS 9.3.

5.7. Strengths and limitations of the research methods

- The IMS Disease Analyser maintains data collected through a representative panel of physicians which allows population-based analyses;
- Prescription records represent the most complete set of data in IMS Disease Analyser, which strengthen the analyses at prescription level. However, prescriptions of ibuprofen in hospital settings and in settings other than GP clinics in France will be missing. This might be relevant for low-dose ibuprofen usually obtained over the counter;
- Registration of patients with a GP is not a requirement of the national healthcare system in France; however, GPs are increasingly regarded as the primary point of contact for patients and their records can provide substantial information on the patient's medical history managed at primary care level.

6. Results

6.1. Daily dosage prescription of ibuprofen

More than 2 million prescriptions containing ibuprofen were recorded in IMS France. Table 1 shows the number split by different intended daily dosage as calculated by IMS Disease Analyser France. The most commonly prescribed daily dosages are highlighted in grey. To check whether current prescription and behaviour has changed over time, the same information is reported based on the entire databases and on the more recent complete year of data available (2013).

Table 1. Prescriptions by intended dose

Intended	Frequency		Percentage		Percentage (of the classifiable)	
	All Years	2013	All Years	2013	All Years	2013
100	594	103	0.03%	0.03%	0.05%	0.06%
150	180	20	0.01%	0.01%	0.02%	0.01%
200	10,658	2029	0.49%	0.51%	0.92%	1.14%
250	673	118	0.03%	0.03%	0.06%	0.07%

Intended	Frequency		Percentage		Percentage (of the classifiable)	
	All Years	2013	All Years	2013	All Years	2013
300	26,637	3,053	1.21%	0.91%	2.31%	1.72%
350	859	79	0.04%	0.03%	0.07%	0.04%
400	66,969	8,998	3.05%	3.31%	5.80%	5.06%
450	679	109	0.03%	0.02%	0.06%	0.06%
500	6,776	823	0.31%	0.21%	0.59%	0.46%
600	142,024	19,467	6.48%	6.62%	12.30%	10.95%
700	11,724	1291	0.53%	0.40%	1.02%	0.73%
750	1,782	593	0.08%	0.08%	0.15%	0.33%
800	127,895	22,697	5.83%	9.06%	11.08%	12.77%
900	10,780	1119	0.49%	0.29%	0.93%	0.63%
1,000	8,632	1565	0.39%	0.60%	0.75%	0.88%
1,200	700,573	110,572	31.94%	40.75%	60.69%	62.20%
1,400	484	59	0.02%	0.01%	0.04%	0.03%
1,500	647	93	0.03%	0.05%	0.06%	0.05%
1,600	26,328	3,466	1.20%	1.38%	2.28%	1.95%
1,800	867	81	0.04%	0.02%	0.08%	0.05%
2,000	3,220	720	0.15%	0.44%	0.28%	0.41%
2,400	3,782	441	0.17%	0.21%	0.33%	0.25%
3,000	473	120	0.02%	0.09%	0.04%	0.07%
3,600	192	15	0.01%	0.01%	0.02%	0.01%
4,000	839	138	0.04%	0.08%	0.07%	0.08%
Unclassifiable	273,703	31,476	12.48%	10.60%	100.00%	100.00%
Unknown	765,152	62,385	34.89%	24.26%		
Total	2,193,122	271,630	100.00%	100.00%		

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 had not been considered further in the analysis. 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. This pattern is confirmed with more recent data. It is worth to highlight as data quality seems to have improved since both the number of unknown and unclassifiable prescription are reduced in 2013.

Table 2 show the same information split by age group for the paediatric and adult population; highlighted in grey and amber the greatest difference between the two groups.

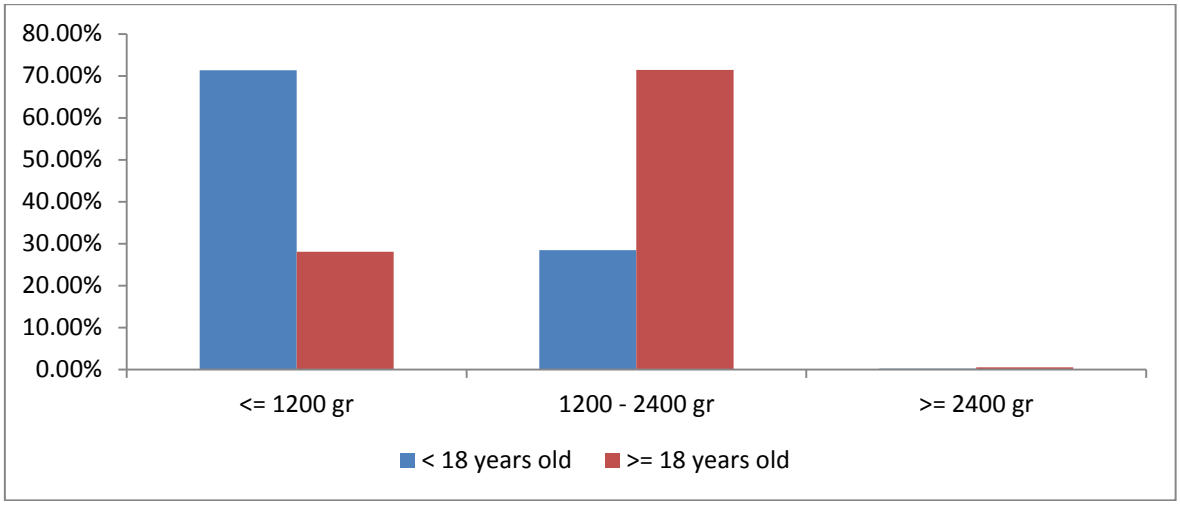
Table 2. Prescriptions by intended dose: age group split

Intended	Frequency <18 years old		Frequency ≥18 years old		Percentage (of the classifiable) <18 years old		≥18 years old	
	All Years	2013	All Years	2013	All Years	2013	All Years	2013
100	529	91	65	12	0.25%	0.28%	0.01%	0.01%
150	171	19	9	1	0.08%	0.06%	0.00%	0.00%
200	6,305	1200	4317	829	2.94%	3.65%	0.46%	0.57%
250	629	112	44	6	0.29%	0.34%	0.00%	0.00%
300	23,278	2,699	3,285	352	10.85%	8.20%	0.35%	0.24%
350	835	79	24	0	0.39%	0.24%	0.00%	0.00%
400	16,616	2,613	50,198	6,379	7.74%	7.94%	5.36%	4.41%
450	669	106	10	3	0.31%	0.32%	0.00%	0.00%
500	2,996	432	3765	391	1.40%	1.31%	0.40%	0.27%
600	75,061	10,830	66,422	8,610	34.98%	32.90%	7.10%	5.95%
700	2,951	503	8764	788	1.38%	1.53%	0.94%	0.54%
750	780	196	997	397	0.36%	0.60%	0.11%	0.27%
800	16,506	3,013	111,004	19,665	7.69%	9.15%	11.86%	13.59%

Intended	Frequency <18 years old		Frequency ≥18 years old		Percentage (of the classifiable) <18 years old		≥18 years old	
	All Years	2013	All Years	2013	All Years	2013	All Years	2013
900	3,891	414	6879	705	1.81%	1.26%	0.73%	0.49%
1,000	1,841	433	6775	1130	0.86%	1.32%	0.72%	0.78%
1,200	57,681	9,506	640,760	100,955	26.88%	28.88%	68.46%	69.78%
1,400	20	2	463	57	0.01%	0.01%	0.05%	0.04%
1,500	273	43	371	50	0.13%	0.13%	0.04%	0.03%
1,600	2,270	307	23,877	3,154	1.06%	0.93%	2.55%	2.18%
1,800	63	4	803	77	0.03%	0.01%	0.09%	0.05%
2,000	775	231	2440	489	0.36%	0.70%	0.26%	0.34%
2,400	187	30	3412	411	0.09%	0.09%	0.36%	0.28%
3,000	124	37	348	83	0.06%	0.11%	0.04%	0.06%
3,600	9	2	183	13	0.00%	0.01%	0.02%	0.01%
4,000	93	16	744	122	0.04%	0.05%	0.08%	0.08%
Total (classifiable)	214,553	32,918	935,959	144,679	100.00%	100.00%	100.00%	100.00%

Daily dosage distribution between age groups differ consistently: patients younger than 18 years old are mainly prescribed lower dosage of Ibuprofen compared to older patients. High dose of at least 2,400 mg are rare in both groups, even more in the younger group (see figure 1).

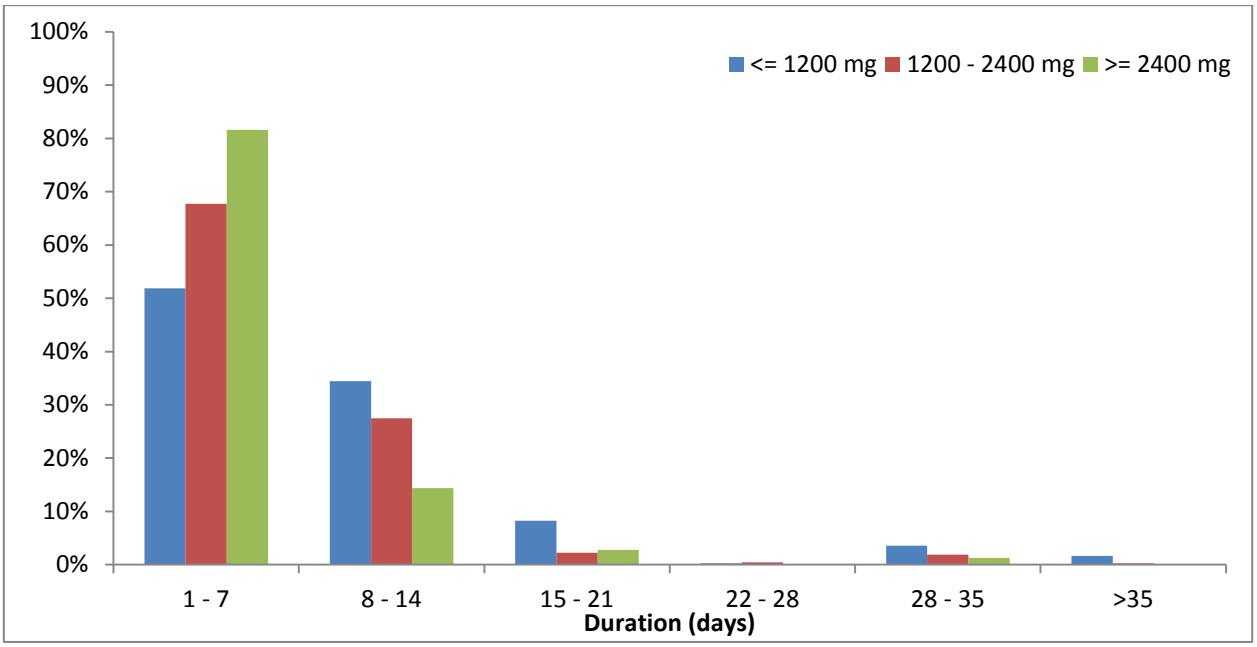
Figure 1. Prescription by intended dose: distribution by age group



6.2. Duration of ibuprofen prescriptions

The duration of each ibuprofen prescription is shown in figure 2 for adult patients only. Duration for lower dose groups is also reported to better contextualise the distribution of ibuprofen high-dosage.

Figure 2. Distribution of prescriptions duration by daily dosage group: adult population



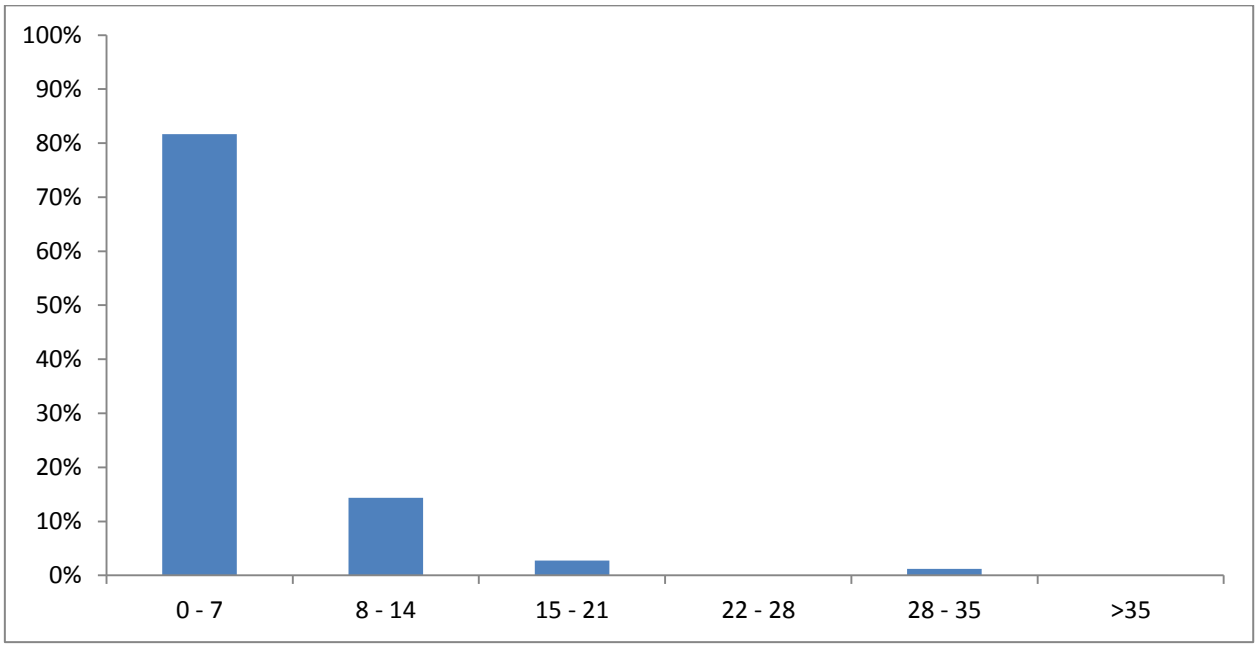
Results confirm that ibuprofen is usually taken for short period of time: in all three dosage groups very few prescriptions exceed the three weeks. Moreover, high-dose ibuprofen seems to be prescribed for a shorter period compared to lower dosage groups: more than 80% of prescriptions are for a week or less and 96% of prescriptions are for two weeks or less.

Focusing on the recorded prescriptions during 2013, a very similar distribution is found: the percentage of high-dose prescriptions within a week or less increase to almost 87%; the proportion of prescriptions in the period 15 – 21 days increases slightly as well (from 2.8% to 4%) but the absolute numbers are small.

6.3. Duration of ibuprofen treatment episodes

The duration of each high-dose ibuprofen treatment episode for the adult patients only is shown in figure 3.

Figure 3. Distribution of treatment episode duration for the high-dose prescriptions (≥ 2,400 mg): adult population



Results are almost identical to the distribution of prescriptions duration (figure 2) confirming that, for high-dose, i) ibuprofen is usually prescribed for a short period of time, only 4% of adult patients have it prescribed for longer than two weeks; ii) adult patients do not return to the physician to have a continuation of the therapy.

Focusing on the recorded prescriptions during 2013, very similar results are obtained.

7. Key findings

- Prescriptions of high-dose ibuprofen (≥ 2,400 mg) in the adult population account to appear for 0.36% of all ibuprofen prescriptions over the entire dataset (3412 prescriptions). Moreover, results from 2013 suggest this has decreased to 0.28% (411 prescriptions).
- Ibuprofen is usually taken for short period of time; 96% of prescriptions of high-dose ibuprofen are for two weeks or less. This result is confirmed even when creating treatment episodes

8. Plans for publicly communicating study results

The study will be registered in the ENCePP E-Register of Studies which currently serves as the EU PAS register referred in the Module VIII of the good pharmacovigilance practices (GVP) on post-authorisation studies.