Drug utilisation study (DUS) on flupirtine-containing medicinal products

Retrospective drug utilisation study using patient-level databases to characterise prescribing practices of flupirtine-containing medicinal products during routine clinical use and assess the main reasons for prescription by representative groups of prescribers

DUS information

Title	**Drug utilisation study (DUS) on flupirtine-containing products:** **Retrospective drug utilisation study using patient-level databases to characterise prescribing practices of flupirtine-containing drugs during routine clinical use and assess the main reasons for prescription by representative groups of prescribers.**
Version identifier of the final study report	Final-Version 2.0
Date of last version of the final study report	28. August 2017
EU PAS register number	ENCEPP/SDPP/12241
Active substance	Flupirtine (INN) Pharmacotherapeutic group: non-opioid, non-NSAID, non-steroidal analgesic ATC code: N02BG07
Medicinal product	Flupirtine-containing medicinal products
Product reference	n/a
Procedure number	DE/H/3428/001/DC DE/H/3430/001/DC
Marketing authorisation holder(s)	LUPIN (EUROPE) LIMITED VictoriaCourt, BextonRoad Knutsford, Cheshire, WA16 OPF UK Hormosan Pharma GmbH – a Lupin Group Company Wilhelmshoeherstr. 106 60389 Frankfurt Germany
Joint PASS	No
Research question and objectives	Characterisation of prescribing practices of flupirtine-containing medicinal products during routine clinical use and assessment of the main reasons for prescriptions by representative groups of prescribers
Country(-ies) of study	Germany
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1. Abstract

Title

Drug utilisation study (DUS) on flupirtine-containing medicinal products.

Retrospective drug utilisation study using patient-level databases to characterise prescribing practices of flupirtine-containing medicinal products during routine clinical use and assess the main reasons for prescription by representative groups of prescribers.

Keywords

Flupirtine-containing medical products, prescribing practices, reason for prescription, hepatotoxicity, short term use.

Rationale and background

Due to a rising number of hepatotoxicity reactions during treatment with flupirtine-containing products the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) recommended in June 2013 to restrict the use of oral Flupirtine medicines and suppositories. Flupirtine was restricted to treatment of acute pain for patients contraindicated for NSAIDs/weak opioids and duration of treatment not longer than 2 weeks. Furthermore, liver function tests after full week of treatment were recommended.

Research question and objectives

The aims of this study were to characterise prescribing practices for flupirtine-medicinal products during routine clinical use and to evaluate co-prescriptions and therapies of patients treated with Flupirtine products before and after the revision of the SmPC.
The analysis displayed the number of Flupirtine patients, patients' demography, diagnosis related to Flupirtine prescriptions, therapies and co-therapies, details on Flupirtine exposure, contraindications for use of NSAIDs/weak opioids, long term medications leading to contraindications for use of Flupirtine and liver function tests.

Study design

This study was implemented using a longitudinal patient level Electronic Medical Records (EMR) database for Germany, IMS® Disease Analyzer.

Setting

The study captured patients in the outpatient setting. All patients who have received at least one prescription for a flupirtine-containing product within a defined 12-month period were included in the analysis.

Subjects and study Size, including dropouts

All patients in the primary care physician (PCP) and orthopaedist panel meeting the selection criteria and recorded during the analysis periods 2012 and 2014 (before and after the SmPC revision) of the IMS® DA were considered for the study. The study size per period was planned to include approximately 1,300 patients treated with Flupirtine in the orthopaedist panel of the IMS® DA database and approximately 8,400 patients treated in the PCP panel.

Variables and data sources

The variables used for the analysis were, specialty, demographic data, diagnosis, therapy duration, therapy length and dosage, co-diagnosis and co-treatments, liver function tests.
Data source: PCP and orthopaedist panels of the IMS® Disease Analyzer (DA).

Results

All results refer to the total groups composed of patients who have received Flupirtine prescriptions by GPs and orthopaedists.
In total, 21,714 patients with Flupirtine prescriptions were available for the analysis in the reference period 2012, 19,674 patients for the assessment period 2014. In 2012, 18,443 were classified as incident and 3,271 as prevalent patients. In 2014, 17,023 were classified as incident and 2,651 as prevalent patients.

Almost 40% of all Flupirtine patients in the reference period 2012 (39.7%) and the assessment period 2014 (39.9%) were diagnosed contraindicated for the use of NSAIDs or weak opioids

The main reason in the reference period 2012 to prescribe flupirtine-containing medical products was the diagnosis "Dorsalgia" (ICD10 M54) in 28.2% of prescriptions. A similar distribution was found in the assessment period 2014 (25.0%).

For both periods, the median length of episodes was 14 days for all patient groups. In the reference period 2012, the mean length of episode was 24.4 days and 18.3 days in the assessment period. In the reference period 2012, 51.7% of prescriptions had a treatment length ≤14days, 64.2% in incident group and 19.7% in the prevalent group. In the assessment period 2014, the corresponding figures were 70.0%, 77.6% and 41.1%.

During the reference period 2012, 76.8% of flupirtine prescriptions were prescribed as single prescriptions. During the assessment period 2014, the single use was more frequent than in 2012, 83.1% of flupirtine prescriptions were prescribed as single prescription. The majority of flupirtine prescriptions in the total group and the incident group were single prescriptions in both time periods, whereas in prevalent patients the majority of flupirtine prescriptions was repeated prescriptions.

In the reference period 2012, for 6.4% of flupirtine prescriptions a LFT record within 1 week after prescription date was recorded in the study groups. In the assessment period 2014, slightly higher values of about 8% were observed.

Discussion

The findings suggest that Flupirtine was mainly prescribed for muscoskeletal disorders, in particular back pain (dorsalgia), in Germany. This was observed for the 12-month time period before and for the 12-month time period after the restriction of use in 2013. More single use and short-term use (up to 14 days) indicate desired extent changes in the prescribing behaviour of physicians following the revision of the SmPC. However, changes were not observed regarding all requirements for the prescription of flupirtine. Monitoring of liver function was done in a small proportion of flupirtine users before and remained low, although slightly increased, even after the revision of SmPC. The proportion of patients diagnosed to be contraindicated for the use of NSAIDs or weak opioids remained on the same level.

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2. GermanyList of abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
COE	Center of Excellence
CPMP	Committee for Proprietary Medicinal Products
CTCAE	Common Terminology Criteria for Adverse Events
DA	IMS® Disease Analyzer
DDD	Daily Defined Dose
DHPC	Direct Healthcare Professional Communication
DILI	Drug Induced Liver Injury
DUS	Drug Utilization Study
EC	European Commission
EMA	European Medicines Agency
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EWP	European Working Party
GP	General Practitioner
GVP	Good Pharmacovigilance Practices
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Version 2014, German Modification
INN	International Nonproprietary Name
MAH	Marketing Authorization Holder
NSAID	Non-Steroidal Anti-Inflammatory Drug
PASS	Post Authorisation Safety Study
PCP	Primary Care Physician
PRAC	Pharmacovigilance Risk Assessment Committee
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RWES	Real World Evidence Solutions
SAS	Statistical Analysis Systems
SmPC	Summary of Product Characteristics
SNEPCO	Selective Neuronal Potassium Channel Opener
SOC	System Organ Class
SOP	Standard Operating Procedure
WHO	World Health Organization

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5. Milestones

Milestone: before and after SmPC review	Planned date	Actual date	Comments
Start of data collection - Reference period	January 1, 2012	January 1, 2012	none
End of data collection - Reference period	December 31, 2012	December 31, 2012	none
Start of data collection – Assessment period	January 1, 2014	January 1, 2014	none
End of data collection - Assessment period	December 31, 2014	December 31, 2014	none
Start of data extraction for analysis	November 2, 2015	November 2, 2015	none
End of data extraction for analysis	November 9, 2015	November 9, 2015	none
Registration in the EU PAS register	ENCEPP/SDPP/12241 *February 2, 2016*	ENCEPP/SDPP/12241 *February 2, 2016*	none
Final report of study results	February 29, 2016	February 29, 2016	none

6. Rationale and background

Flupirtine, a non opioticanalgetic drug for acute and chronic pain relief was first introduced in the European Union in 1984 as an alternative analgesic to opioids and NSAIDs. During the use of this selective neuronal potassium channel opener (SNEPCO) other pharmacological impacts such as a reduction in muscle tension have been observed.

The German Federal Institute for Drugs and Medical Devices (BfArM) induced an urgent union procedure under Article 107i of Directive 2001/83/EC on February, 28th 2013 and signalized its intention to restrict the use of all flupirtine-containing medications to short term treatment of acute pain and to withdraw the indication of use in chronic pain[1].

This intention from BfArM was based on a rising number of observed liver effects spontaneously reported during Flupirtine treatment while evaluating pharmacovigilance data. The effects range from asymptomatic liver enzyme elevation to fatal liver failure or liver transplantation were received. BfArM reported a total number of 954 records in their German adverse drug reaction database for Flupirtine including 330 reports for the system organ class (SOC) hepatic and biliary disorders (according to Common Terminology Criteria for AEs, CTCAE).Liver failure was reported in 49 cases including 12 cases with fatal outcome and 3 cases with liver transplantation. Flupirtine treatment lasted 60 days in average. In 25 of the above 49 cases (51%) a co medication with potential hepatotoxic effect was administered.

The growing number of Flupirtine prescriptions in Germany and thus the steadily increasing patient exposure was embraced to be associated with the rising number of reported Adverse Drug Reactions (ADRs). Additionally, a lack of the minimum requirement in the efficacy data of Flupirtine of at least three months treatment in controlled clinical studies for mild to moderately severe chronic nociceptive pain was denunciated by the BfArM[2].

Considering the above safety concerns and further consideration of the current evidence for the efficacy of Flupirtine in the treatment of acute and chronic pain, the BfArM came to the conclusion, that the benefit-risk balance was potentially favourable in acute pain, implementing strict treatment restrictions (e.g. treatment duration limited to 2 weeks, frequent liver tests) and unfavourable in the treatment of chronic pain.

The PRAC initiated a subsequent benefit-risk evaluation and considered that the controlled clinical studies required by the Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain (CPMP/EWP/612/00, issued 21 November 2002) for long-term treatment of chronic pain are not available for flupirtine-containing medicinal products[2].Based on the fact of observed liver effects recorded during long-treatment with Flupirtine and on the absence of controlled long-term clinical studies, the PRAC noted that the management of chronic pain is no longer favourable in terms of the benefit-risk balance for flupirtine-containing medicinal products. The PRAC adopted a recommendation on 13 June2013 under the provisions of article 107i of Directive 2001/83/EC[3].

Taking the currently available data into account, the PRAC decided that the benefit-risk balance for flupirtine-containing products is favourable in the treatment of acute pain, subject to implementation of the following risk minimisation measures[4]:

- Limitation of indication to acute pain in adults if treatment with other analgesics (e.g. NSAIDs, weak opioids) is contraindicated.
- Restriction of Flupirtine use to a maximum of two weeks of treatment.
- Contraindication of Flupirtine in patients with pre-existing liver disease or alcohol abuse.
- Contraindication of Flupirtine in patients concomitantly taking other medications which are known to cause Drug Induced Liver Injury (DILI).
- Weekly liver function tests during treatment and discontinuation in the case of abnormal liver function tests or clinical symptoms.

The PRAC imposed a DHPC, which was distributed on 15 July 2013, in order to communicate the outcome of the PRAC/EMA decision to healthcare professionals[5].
The SmPCs for flupirtine-containing medicinal products have been revised accordingly by Lupin in February 2014 and MAHS marketing flupirtine-containing medicinal products in September/October 2013[6].The educational material was distributed in February 2015.

Patients and prescribers have been provided with joint educational material according to the PRAC request, prepared jointly by all German MAHs. The educational material, the DUS and a PASS protocol are parts of the RMP.

As of 5 September 2013, the European Commission implemented the decision (C (2013) 5788 final) with the majority opinion of the CMD(h) addressed to all member states based on the PRAC's recommendation[7].

Additionally the PRAC requested that the MAHs should submit a risk management plan (RMP) within 3 months after the EC decision. The protocols of two studies - a drug utilization study (DUS) and a PASS should be submitted as part of the RMP.

Hormosan Pharma GmbH launched Flupirtinmaleat-Hormosan 100 mg Hartkapseln in Germany on 31 July 2012, but the marketing of the product was stopped in January 2013. This decision was taken because of commercial and not for safety reasons. Any other MAs held by Lupin Group of companies with in EU have not been launched yet. Therefore an extension of deadline for submitting the RMP (including the outline of DUS, PASS and educational material) was received by the Reference Member State (RMS) authority BfArM on 29 November 2013 as the products are currently not marketed.

This report presents the results of the DUS covering a one year period (2012) before and a one year period (2014) after the restriction of flupirtine use.

7. Research question and objectives

The Flupirtine DUS aimed to characterise prescribing practices of flupirtine-medicinal products during routine clinical use and to assess the main reasons for prescription by representative groups of prescribers.

The analysis was displayed by specialty and by prevalent/incident status:

- Number of prescribing physicians
- Region of office (East/West Germany)
- Number of overall patients in the office
- Number of patients with at least one flupirtine-containing product
- Patient characteristics: age, gender, insurance status, indication for Flupirtine prescription
- Flupirtine exposure:
    - Number of Flupirtine prescriptions per patient during the 12-month observation period
    - Recommended daily Flupirtine dose (by physicians, if available)
    - Recommended Flupirtine treatment duration (by physicians, if available)
    - Treatment duration (Prescription length by physician, if available)
    - Indications related to the Flupirtine prescription
- Co diagnosis within analysis period
- Concomitant prescription of drugs grouped by relevant ATC classes (Annex 3- ii)
- Administered long-term medications (>14 days) leading to contraindication use of Flupirtine
- Contraindications for use of NSAIDs or weak opioids
- Treatment patterns if available
- Liverfunction test performed within 1 week after Flupirtine exposure start

8. Amendments and updates

None

9. Research methods

9.1. Study design

This drug utilisation study for Flupirtine employed an analysis using a longitudinal database in Germany:

- Patient level electronic medical record (EMR) data (IMS® Disease Analyzer)

The IMS® Disease Analyzer provides both drug use data and information about patients' clinical characteristics, including indication, co-morbidities and laboratory tests in separate physician panels.

The study was carried out in Germany as more than 90% of total prescriptions of flupirtine-containing medicinal products of MAHs in European Union Member States were issued in Germany.
The study was set up as a pre-post design to compare Flupirtine prescribing patterns before and after the revision of SmPC.

9.2. Setting

The study was conducted in the outpatient setting in Germany.

Study population
All patients with a record of Flupirtine prescription during the defined 12-month periods (patient selection window) were identified from selected database.

The study included both single users and recurrent users of flupirtine-containing medicinal products.

The study included two cohorts of patients:

- patients initiated on Flupirtine treatment after the review of SmPC in Germany
- patients treated with Flupirtine before the review of SmPC in Germany

The two cohorts included:

- Incident group: patients who had one or more Flupirtine prescriptions during the one-year observational period, but no Flupirtine prescription for at least 12 months prior to the first Flupirtine prescription during the observational period
- Prevalent group: patients who had one or more Flupirtine prescriptions during the one-year observational period and at least one Flupirtine prescription during the 12 months prior to the first Flupirtine prescription during the observational period

Inclusion criteria:
Eligible patients must have at least one prescription of Flupirtine (exposure) during the defined 12-month observational period.

Exclusion criteria:
Exclusion criteria were not applied.

Study period
The selection of patients from the IMS® Disease Analyzer was carried out in two defined 12-month periods from January 1, 2012to December 31, 2012 and January 1, 2014 to December 31, 2014, respectively (patient selection window). The date of the first prescription fill in each period was defined as the exposure start date.

Pre-exposure period:
In order to obtain information about medical history before Flupirtine exposure start, a time period of at least 12 months prior to the individual Flupirtine exposure start date was analysed for each patient for whom these data were available.

Follow-up:
A follow-up period of one to six months after the exposure start date was monitored for all patients, and till the end of analysis period for whom these data were available.

Analysis period:
Analysis period 2012 covered the entire year 2012, from 01.01.2012 to 31.12. 2012 (reference period in this analysis).
The analysis period 2014 included the entire year 2014, from 01.01.2014 to 31.12.2014, respectively (assessment period in this analysis).

9.3. Subjects

The study captured patients in the outpatient setting in Germany. All patients who have received at least one prescription for a flupirtine-containing product within a defined 12-month period were included in the analysis, covering the time periods 2012 and 2014, which was before and after the revision of SmPC.

9.4. Variables

The following variables were derived from the data sources.

IMS® Disease Analyzer – PCP and orthopaedist panels

- Number of prescribing physicians
- Region of office (East/West Germany)
- Number of overall patients in the office
- Number of patients with at least one prescription of flupirtine-containing medicinal product
- Patient characteristics
    - Age
    - Gender
    - Insurance status (private or SHI insured)
    - Indication for Flupirtine exposure
- Flupirtine exposure
    - Number of Flupirtine prescriptions per patients during the observational period
    - Single use and repeated prescriptions
    - Treatment duration (by physician)
    - Dosage advice (by physician)
    - Treatment duration (Prescription length based on physician's advice if available)
    - Co-diagnosis during study period
    - Concomitant prescription of drugs grouped by relevant ATC classes
    - Long-term medications (>14 days) leading to contraindication for Flupirtine
    - Diseases contraindicated for NSAIDs and weak opioids
    - Liverfunction tests - as far as available within 1 week after Flupirtine exposure

Definition treatment duration:
The doctor enters the recommended dosage to the EMR, and hence the treatment duration is calculated. This assumption always is based on the fact, that the prescribed package is used continuously from prescription date until end of provided amount of drug. The recommended treatment duration is only available in a part of prescriptions.

Definition treatment episode:
Treatment episodes were calculated taking all Flupirtine prescriptions per patient per analysis period into account. Single prescriptions were evaluated as one episode. Repeated - two or more - subsequent prescriptions were summarised to one episode, if the gap between those prescriptions was $\leq$ 7 days. The length of this episode was then the time period of first day of the first prescription until last day of drug supply of the last prescription based on DDD (400mg/day).

As the recommended treatment duration – by physician - is only available in a part of prescriptions, the analysis of treatment episodes is based on strength, pack size and DDD per single flupirtine prescription. In case the DDD algorithm is applied, treatment duration and prescription length is identical. For this report we have used treatment duration as overall term, because of the mixture of prescription length (based on DDD) and treatment duration recommended by the physician. Prescription length was used as a parameter to calculate treatment duration.

9.5. Data sources and measurement

The IMS® Disease Analyzer, a German longitudinal patient-level database was used as data source for the Flupirtine utilization study.

IMS® Disease Analyzer

IMS® Disease Analyzer is a database which continuously receives anonymised data reported from approximately 3,000 office-based physicians* (including specialists such as cardiologists, gynaecologists, neurologists, orthopaedists, or urologists) representing approximately 2.4% of all offices* in Germany. The database contains longitudinal data from more than 11 million observational profiles documented over the last 3 years.

The data are generated directly from the electronic medical records of the panel physicians' office via standardized interfaces and provide daily routine information on patients' diseases and therapies.

The main parameters routinely collected in the IMS® Disease Analyzer database are presented in Table 1. The lag time of data availability is 6 weeks.

The IMS® Disease Analyzer PCP panel consists of 1,141 PCPs (general practitioners [GPs] and internists without subspecialty) and 177 orthopaedists selected using a pre-specified random plan as described by Becher et al. (2009) in their paper verifying the validity and representativeness of the IMS® Disease Analyzer patient database in Germany[8].

* No personal data but exclusively anonymous information (in accordance with § 3 Abs. 6 "Bundesdatenschutzgesetz" – German Federal Data Protection Act).

Table 1: Variables included in the IMS® Disease Analyzer database

Category	Nature of data	Variables
Patient data	Characteristics	Age, sex, insurance(private or SHI insured)
	Diagnoses	Date of diagnosis, ICD-10, original text, co-morbidity, laboratory tests and results
	Therapy	Date of visit, product and quantity, molecule, ATC, dosage scheme, co-prescription

The German IMS® Disease Analyzer database has been previously used to answer a wide range of research questions[9,10,11,12]. In addition, the IMS® Disease Analyzer database is used by the European Medicines Agency (EMA) as one of its resources for answering research questions.

A preliminary investigation showed that most of patients who had received Flupirtine prescriptions in the IMS® DA were documented in the PCP panel and the orthopaedist panel (about 95%). For the time period from August 2011 to July 2013 nearly 54,000 patients with at least one Flupirtine prescription were recorded in the DA database including about 39,000 Flupirtine patients treated by PCPs and about 15,000 Flupirtine patients treated by orthopaedists. The current DUS was therefore based on data from the PCP panel and the orthopaedist panel.

9.6. Bias

9.6.1. Assessment of selection bias

The datasource IMS® Disease Analyzer is based on a representative selection of offices and patients in cooperation with statistical offices and proved in several publications. No major selection bias is expected in the analyses based on data from this source.

No meaningful selection biases caused by the restriction of some analyses to patients with available 12-month history prior to index is expected. Such restrictions are standard practice in healthcare database studies.

9.6.2. Assessment of information bias

The DUS analysis is based on data entries provided by primary care physicians and orthopaedists. The input of their daily work documentation is anonymised and submitted to IMS Health. No data correction or data manipulation is performed. This might cause information bias.

9.6.3. Misclassification bias

The IMS® Disease Analyzer is completely anonymised. The verification of the information with source data is not possible. Misclassification bias cannot be excluded if study participants are not classified correctly with regard to selected patient characteristics, exposure or outcome parameters.

All above mentioned biases apply for all both study periods.

9.7. Study size

All patients in the PCP and orthopaedist panel of the IMS®DA fulfilling the selection criteria were considered for the study.
A preliminary count of patients treated with Flupirtine over a 12-month period (July 2013 to June 2014) gave the sample sizes for the selected IMS® DA panels (presented in Table 2).

Table 2: Number of patients with Flupirtine-containing prescriptions in the IMS® Disease Analyzer from July 2013 to June 2014

IMS® DA Panel	Number of Flupirtine patients	Number of Flupirtine patients with at least 12 months history	Number of Flupirtine patients with at least12 months history (25% reduction)
PCP	14,743	11,284	8,463
Orthopaedist	4,635	1,821	1,365

The study size of the Flupirtine DUS was expected to range from approximately 1,300Flupirtine patients in the orthopaedist panel of the IMS® DA database. The study size is based on the number of patients with Flupirtine prescriptions in the 12-month period from July 2013 to June 2014.
The 12-month patient selection window was considered to be sufficient to provide representative for prescribing practices during the routine clinical use of flupirtine-containing medicinal products in Germany.

9.8. Data transformation

Data entered by the physician was not corrected or changed. Any additional calculations were based on methodologies agreed in the SAP.

9.9. Statistical methods

9.9.1. Main summary measures

The statistical measures consist of mean, median, minimum, maximum, standard deviation, total count and percentages.

9.9.2. Main statistical methods

Only descriptive analyses were performed, no statistical tests were applied.

Additional statistical methods were not implemented.

9.9.3. Missing values

Missing values were not replaced.

They were not included in the analysis and listed as "amount of missing values" where necessary.

9.9.4. Sensitivity analyses

The analyses of concomitant diagnosis were performed based on patients with and without traceable history of 12 months prior to first prescription of Flupirtine, which means, that patients naive to the database (without a documented history prior to the analysis) were also analysed regarding diagnosis associated with Flupirtine prescriptions.

This analysis gave additional validation to the codiagnosis and health status of Flupirtine treated patients, disregarding if patients' history was recorded on the database or not.

9.9.5. Amendments to the statistical analysis plan

The list of diseases contraindicated for the use of NSAIDs or weak opioids was extended as the predefined list of contraindicated diseases turned out to be not detailed and not comprehensive enough to provide a complete picture. The extended list is attached in the Annex as Appendix 2-iii to this report.

The verbatim entry of therapy duration entered by physician was not used in the analysis. Preliminary analyses have shown that a recommendation by physicians for a treatment duration is rarely given for flupirtine. More often treatment "on demand" is recorded. Therefore, a treatment duration based on the dosage advice given by the physician was considered for the analysis in addition to the analysis based on DDD.

The SAP specified a default set of table layout, however, the tables' numbering was adapted to the EMA template chapters and expanded in regards of table amount. For that reason, the tables are not presented in this report in the same order as provided with the SAP.

9.10. Quality control

Data quality control is conducted at several levels.

At database level:
The quality unit of the IMS production department continuously verifies the quality of its numerous panels in terms of panel representativeness, consistency of collected data, and validation of coding of physicians' verbatim.

At study level:
All parts of the study from protocol development to the reporting of results are conducted according to IMS SOPs.

Data for analysis was extracted by a programmer with extensive programming and analysis experience with the LifeLink EMR data.

The following steps were undertaken to ensure quality and accuracy of all programming developed during the course of the study:

- Methodology Review: the statistical analysis plan and accompanying table shells were reviewed and approved by senior staff at the IMS team.
- Programming Code Review: all programming code was developed by a senior programmer with extensive programming and analysis experience with the LifeLink EMR data.
- Statistical Review: all results tables produced during the study were reviewed by senior staff member of the COE Pharmacoepidemiology and Drug Safety at IMS.

10. Results

All results presented in the report refer to the total group composed of patients managed by general practitioners (PCP) and orthopaedists, with remarks to speciality where necessary. Results for the PCP panel and the orthopaedist panel are provided in the Annex 3.

Results considering ICD10 codes or WHOATC codes are limited to top 10 findings in the report. For a detailed overview of all diagnosis or treatment results please refer to "supplemental tables" provided in the Annex 1 chapter stand alone documents.

10.1. Participants

All patients treated with flupirtine-containing medical products within 2012 or 2014 meeting the inclusion criteria were included into the study (Figure 1.) In total, 21,714 out of 3,446,052 patients had received Flupirtine prescriptions in 2012 and 19,674 out of 3,974,155 patients in 2014. In both periods, the percentage of patients with a traceable history for at least 12 months prior to the index date (which is the first prescription date of Flupirtine of each analysis period) was 71.5% in 2012 and 71.3% in 2014.

Flupirtine was prescribed by 1,227 physicians at 971 offices in 2012 and by 1,492 physicians at 1,181 offices in 2014. The number of patients receiving flupirtine prescriptions per office was 22 patients in 2012 and 16 patients in 2014. The prescriber characteristics are depicted in Table 3.

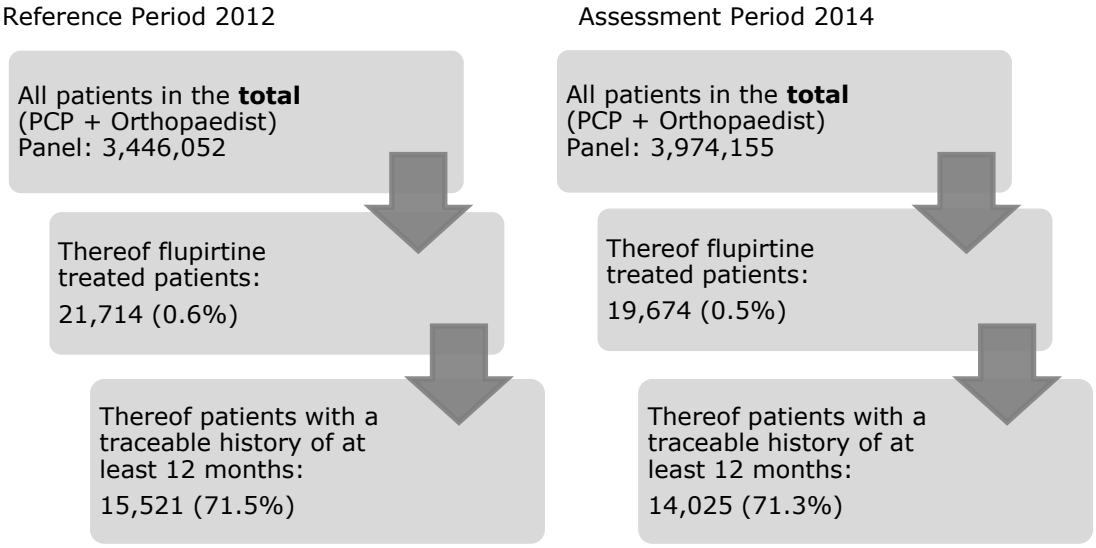

Figure 1. Patient flow in the total study population (PCP and orthopaedist panel)

Table 3: Prescriber characteristics – Total

Parameter			Reference period	Assessment period
Number of physicians		n	1227	1492
Number of offices		n	971	1181
Region of office				
	West Germany	n (%*)	762 (78.5%)	942 (79.8%)
	East Germany	n (%*)	209 (21.5%)	239 (20.2%)
Number of patients at office		n	3446052	3974155
		mean (SD)	2459 (1615)	2723 (1809)
		median	2130	2344
		min-max	2-22043	57-27008
Number of patients at office with at least one Flupirtine prescription		n	21714	19674
		mean (SD)	22 (43.1)	16(44.3)
		median	10	6
		min-max	1-652	1-1121

*% based on total number of offices; (Source: IMS® DA, panel)

10.2. Descriptive data

Out of 21,714 patients analysed in the reference period 2012, 18,443 were classified as incident and 3,271 as prevalent patients. Out of 19,674 patients analysed in the assessment period 2014, 17,023 were classified as incident and 2,651 as prevalent patients.

The demographical characteristics are specified in Table 4.

The mean age of Flupirtine patients in 2012was 54.6 years in the total group, 53.7 years in the incident group and 60.0 years in the prevalent group .The patients in 2014 had a mean age of 52.7 years in the total group, 51.7 years in the incident group and 59.1 years in the prevalent group.

Looking at 2012, the largest percentage of patients with Flupirtine prescriptions in the total group(23.5%) was between 50 years and 59 years. The same pattern was observed in the incident group with 23.4% of patients in this age group. Whereas in the prevalent group the largest percentage of patients receiving flupirtine prescriptions was the age group >70 years (29.9%).
The assessment period (2014) showed similar distributions. Patients in the total group and the incident group were most frequent aged 50-59 years (24.8% and 24.7%, respectively). In the prevalent group had the largest percentage of patients was >70 years old (27.3%).

The percentage of patients<18years was below< 0.5% in both time periods.

Almost two-third of all patients was female in both analysis periods (62.8% in 2012 and 59.6% in 2014).

In terms of insurance status, the vast majority of patients was statutory insured in both periods (87.6% in 2012 and87.2% in 2014).

Table 4**:** Demographic characteristics –Total

Parameter			**Reference period**			**Assessment period**		
			Total	**Incident**	**Prevalent**	**Total**	**Incident**	**Prevalent**
			N = 21714	**N = 18443**	**N = 3271**	**N = 19674**	**N = 17023**	**N = 2651**
Age		mean (SD)	54.61 (16.16)	53.67 (16.15)	59.96 (15.18)	52.71 (16.03)	51.71 (15.90)	59.12 (15.43)
		median	54	53	59	52	51	58
		min-max	5-96	5-96	10-96	3-98	3-98	15-98
Age. grouped								
	< 18 years	n (%)	80 (0.4%)	76 (0.4%)	4 (0.1%)	79 (0.4%)	76 (0.4%)	3 (0.1%)
	18-29 years	n (%)	1375 (6.3%)	1308 (7.1%)	67 (2.0%)	1575 (8.0%)	1507 (8.9%)	68 (2.6%)
	30-39 years	n (%)	2307 (10.6%)	2112 (11.5%)	195 (6.0%)	2470 (12.6%)	2286 (13.4%)	184 (6.9%)
	40-49 years	n (%)	4763 (21.9%)	4175 (22.6%)	588 (18.0%)	4308 (21.9%)	3830 (22.5%)	478 (18.0%)
	50-59 years	n (%)	5111 **(23.5%)**	4314 **(23.4%)**	797 (24.4%)	4875 **(24.8%)**	4198 **(24.7%)**	677 (25.5%)
	60-69 years	n (%)	3402 (15.7%)	2771 (15.0%)	631 (19.3%)	2950 (15%)	2439 (14.3%)	511 (19.3%)
	≥ 70 years	n (%)	4655 (21.4%)	3676 (19.9%)	979 **(29.9%)**	3408 (17.3%)	2684 (15.8%)	724 **(27.3%)**
Gender								
	Male	n (%)	8064 (37.1%)	7005 (38.0%)	1059 (32.4%)	7930 (40.3%)	6987 (41%)	943 (35.6%)
	Female	n (%)	13644 (62.8%)	11432 (62%)	2212 (67.6%)	11735 (59.6%)	10027 (58.9%)	1708 (64.4%)
Insurance status								
	SHI	n (%)	19019 (87.6%)	16030 (86.9%)	2989 (91.4%)	17153 (87.2%)	14763 (86.7%)	2390 (90.2%)
	Private insurance	n (%)	2695 (12.4%)	2413 (13.1%)	282 (8.6%)	2521 (12.8%)	2260 (13.3%)	261 (9.8%)

N=total number of patients; (Source: IMS® DA, panel)

10.3. Outcome data

10.3.1. Diseases leading to contraindications for NSAIDs or weak opioids

Almost 40% of all patients receiving flupirtine prescriptions in the assessment period 2012 were diagnosed contraindicated for the use of NSAIDs or weak opioids (39.7% in total group and 38.2% in incident group). This number were similar in 2014- 39.9% in total group and 38.0% in the incident group. The percentage were similar in the prevalent group 46.0% to 48.6% from 2012 to 2014.

This analysis was performed only within a time period of 12 months prior to the first Flupirtine prescription, disregarding all diagnoses the patient had had prior to that time span. An individual time period of 12 months prior to each patients' first Flupirtine prescription (index date) was analysed for each periods. Additionally, only patients with an available history of at least 12 months prior to first Flupirtine prescription were considered for this analysis. The results are displayed in Table 5. The diseases are specified in Annex 2-iii.

Table 5**:** Medical history – NSAIDs/weak opioids treatment contraindicated patients within 12 months prior to first Flupirtine prescription- Total

Parameter		**Reference period**			**Assessment period**		
		Total N = 21714	**Incident** N = 18443	**Prevalent** N = 3271	**Total** N = 19674	**Incident** N = 17023	**Prevalent** N = 2651
Patients with a 12 months history		**N[1] = 15521**	**N[1] = 12461**	**N[1] = 3060**	**N[1] = 14025**	**N[1] = 11526**	**N[1] = 2499**
Number and percentage of patients identified as contraindicated of NSAIDs/weak opioids treatment the year before index date	n (%[2])	6166 (39.7%)	4757 (38.2%)	1409 (46.0%)	5590 (39.9%)	4376 (38.0%)	1214 (48.6%)

N=total number of patients
[1:] total number of patients with available history
[2]: % based on total number of patients within available history
(Source: IMS® DA, panel)

10.3.2. Long-term medications leading to contraindications for Flupirtine

The percentage of long-term therapies (Appendix 2-ii) leading to contraindication for flupirtine-use ranged at a value of around 0.1%for all groups and both time periods. As above, the analysis was restricted to the time period 12 months prior to the first Flupirtine prescription and for patients with an available history of at least 12 months prior to index date. The results are summarized in Table 6.

Table 6: Medical history – Long-term medications leading to contraindications for Flupirtine patients within 12 months prior to first Flupirtine treatment - Total

Parameter		**Reference period**			**Assessment period**		
		Total N = 21714	**Incident** N =18443	**Prevalent** N =3271	**Total** N = 19674	**Incident** N =17023	**Prevalent** N =2651
Patients with a 12 months history		**N[1] = 15521**	**N[1] = 12461**	**N[1] = 3060**	**N[1] = 14025**	**N[1] = 11526**	**N[1] = 2499**
Number and percentage of long-term therapies leading to contraindication of Flupirtine	n (%[2])	18 (0.1%)	12 (0.1%)	6 (0.2%)	11 (0.1%)	10 (0.1%)	1 (0.04%)

N=total number of patients
1: total number of patients with available history
2: % based on total number of patients within available history;
(Source: IMS® DA, panel)

10.3.3. Indication for Flupirtine prescription

A split to flupirtine patients with acute only, chronic only and both pain diagnosis shows in the reference period 2012 10,541 patients (48.5%) and 9,857 patients (50.1%) in the assessment period 2014 diagnosed with acute pain in total group. Out of those, 64.5% (6,795 patients) had a principal pain diagnoses linked to the flupirtine prescription in the reference period and 63.8% (6,285 patients) in the assessment period. 3,746 patients (35.5%) in 2012 and 3,572 patients (36.2%) in 2014 were diagnosed with associated pain diagnosis. All results are shown in Table 7 (total) and in Table 31 (all specialties).

Table 7: Acute Patients only, by principal and associated diagnosis - TOTAL

	Reference period 2012						**Assessment period 2014**					
	Total		**Incident**		**Prevalent**		**Total**		**Incident**		**Prevalent**	
Diagnosis	N	%	N	%	N	%	N	%	N	%	N	%
Total (PCP + Ortho)												
Flupirtine N1	21,714	%	18,443	%	3,271	%	19,674	%	17,023	%	2,651	%
Total acute patients N2	10,541	(48.5%)	8,835	(47.9%)	1,706	(52.2%)	9,857	(50.1%)	8,426	(49.5%)	1,431	(54.0%)
Out of those:												
Principal*	6,795	(64.5%)	5,514	(62.4%)	1,281	(75.1%)	6,285	(63.8%)	5,212	(61.9%)	1,073	(75.0%)
Associated*	3,746	(35.5%)	3,321	(37.6%)	425	(24.9%)	3,572	(36.2%)	3,214	(38.1%)	358	(25.0%)

N= distinct number of patients with at least one **acute** pain diagnosis, no chronic pain
N1= total number of flupirtine patients
%: based on total number of flupirtine patients (N1)
*:%based on total number of patients from speciality (N2)
(Source: IMS® DA. panel)

With only chronic pain 340 patients (1.6%) were diagnosed in the reference and 277 patients (1.4%) in the assessment period. 75.0% (255 patients) of all these total chronic pain patients had a principal diagnosis in the reference period and 62.8% (174 patients) in the assessement period. 25.0% (85 patients) in 2012 and 37.2% (103 patients) in 2014 had a associated pain diagnosis. The patient count is displayed in Table 8 (Total) and Table 32 (all specialties).

Table 8: Chronic Patients only, by principal and associated diagnosis (Total)

	Reference period 2012						**Assessment period 2014**					
	Total		**Incident**		**Prevalent**		**Total**		**Incident**		**Prevalent**	
Diagnosis	N	%	N	%	N	%	N	%	N	%	N	%
Total (PCP + Ortho)												
Flupirtine N1	21,714	%	18,443	%	3,271	%	19,674	%	17,023	%	2,651	%
Total chronic patients N2	340	(1.6%)	224	(1.2%)	116	(3.5%)	277	(1.4%)	177	(1.0%)	100	(3.8%)
Out of those:												
Principal*	255	(75.0%)	159	(71.0%)	96	(82.8%)	174	(62.8%)	103	(58.2%)	71	(71.0%)
Associated*	85	(25.0%)	65	(29.0%)	20	(17.2%)	103	(37.2%)	74	(41.8%)	29	(29.0%)

N= distinct number of patients with at least one **chronic** pain diagnosis, no acute pain
N1= total number of flupirtine patients
%: based on total number of flupirtine patients (N1)
*:%based on total number of patients from speciality (N2)
(Source: IMS® DA. panel)

The patient count for both acute and chronic pain diagnosis related to flupirtine prescription was 911 patients (4.2%) in reference and 828 patients (4.2%) in assessment period. Thereof 723 patients (79.4%) in 2012 and 600 patients (72.5%) in 2014 were linked to a principal chronic or acute pain diagnosis. 188 patients (20.6%) in reference period vs. 228 patients (27.5%) in assessment period had associated pain diagnosis. The results are displayed in Table 9 (Total) and Table 33 (all specialities).

Table 9: Acute and chronic pain, by principal and associated diagnosis

	Reference period 2012						**Assessment period 2014**					
	Total		**Incident**		**Prevalent**		**Total**		**Incident**		**Prevalent**	
Diagnosis	N	%	N	%	N	%	N	%	N	%	N	%
Total (PCP + Ortho)												
Flupirtine N1	21,714	%	18,443	%	3,271	%	19,674	%	17,023	%	2,651	%
Total acute/ chronic patients N2	911	4.2%	556	3.0%	355	10.9%	828	4.2%	536	3.1%	292	11.0%
Out of those:												
Principal*	723	79.4%	416	74.8%	307	86.5%	600	72.5%	353	65.9%	247	84.6%
Associated*	188	20.6%	140	25.2%	48	13.5%	228	27.5%	183	34.1%	45	15.4%

N= distinct number of patients with **acute and chronic** pain diagnosis
N1= total number of flupirtine patients
%: based on total number of flupirtine patients (N1)
*:%based on total number of patients from speciality (N2)
(Source: IMS® DA. panel)

Almost all top 10 diagnoses linked to the prescriptions of Flupirtine were within the group of "Diseases of the musculoskeletal system and connective tissue" (M00-M99). In both reference (2012) and assessment (2014) period the share of patients with linked diagnosis to a flupirtine prescription was 53.5% in total. The results are displayed in Table 34 in the result tables section.

The main reason in 2012 to prescribe flupirtine-containing medical products was the principal diagnosis "Dorsalgia" (ICD10 M54; 28.2%) in the total group. This diagnosis (M54) was recorded in 24.9% of incident patients and in 47.2% of prevalent patients. .

A similar distribution was found for the assessment period 2014. The principal diagnosis "Dorsalgia" (ICD10 M54) was documented in 25.0% of patients in the total group, in 22.8% of patients in the incident group and in 38.9% of patients in the prevalent group.

In the prevalent group also the diagnosis "Pain, unspecified" (ICD10 code R52) were recorded frequently, 28.6% in 2012 and 23.4% in 2014.

The results are presented in Table 10.

Patients with Flupirtine prescriptions not directly linked to a diagnosis were evaluated in a different way. For each of such unlinked Flupirtine prescriptions a time period of 2 weeks around the prescription date was investigated to identify acute or chronic pain diagnosis previously defined (see SAP and in the Annex 2-i in this report).

These results were similar to the results presented for the principal diagnosis.

In the reference period 2012, "Dorsalgia" with a share of 27.4% was the most frequent diagnosis of the acute pain diagnosis group in total group. In the incident group and prevalent group this acute diagnosis was found in 29.0% of patients and 18.3% of patients, respectively. A similar pattern was observed for the assessment period 2014: in the total group 26.3% of patients, in the incident group 27.6% of patients and in the prevalent group 17.5% of patients.

The assessment of predefined chronic pain diagnoses identified the diagnosis "Pain, unspecified" (ICD 10 R52.2) as the most frequent diagnosis associated with Flupirtine prescriptions.

The reference period 2012 showed in group total a share of 2.0%, in incident group 1.5% and in the prevalent group 4.8%. For the assessment period 201 similar shares were found with 2.4% of patients in total group, 1.5% of patients in incident group and 8.3% of patients in the prevalent group.

Table 10**:** Medical history – Indication for Flupirtine prescription (ICD-10 codes), during analysis period- Total

Parameter		**Reference period**			**Assessment period**		
		Total	**Incident**	**Prevalent**	**Total**	**Incident**	**Prevalent**
		N = 21714	**N = 18443**	**N = 3271**	**N = 19674**	**N = 17023**	**N = 2651**
Principal diagnosis*							
DORSALGIA: M54	n (%)	**6131 (28.2%)**	**4586 (24.9%)**	**1545 (47.2%)**	**4921 (25.0%)**	**3889 (22.8%)**	**1032 (38.9%)**
OTHER DORSOPATHIES NEC: M53	n (%)	1588 (7.3%)	1006 (5.5%)	582 (17.8%)	1164 (5.9%)	777 (4.6%)	387 (14.6%)
PAIN NEC:R52	n (%)	1452 (6.7%)	515 (2.8%)	**937 (28.6%)**	949 (4.8%)	328 (1.9%)	**621 (23.4%)**
INTERVERT DISC DISORDER: M51	n (%)	996 (4.6%)	650 (3.5%)	346 (10.6%)	869 (4.4%)	571 (3.4%)	298 (11.2%)
SPONDYLOSIS: M47	n (%)	930 (4.3%)	568 (3.1%)	362 (11.1%)	902 (4.6%)	666 (3.9%)	236 (8.9%)
OTHER SOFT TISSIUE DISORDER NEC: M79	n (%)	806 (3.7%)	480 (2.6%)	326 (10.0%)	571 (2.9%)	297 (1.7%)	274 (10.3%)
BIOMECHAN LESIONS NEC: M99	n (%)	724 (3.3%)	659 (3.6%)	65 (2.0%)	779 (4.0%)	704 (4.1%)	75 (2.8%)
OTHER DISORDERS OF MUSCLE: M62	n (%)	661 (3.0%)	518 (2.8%)	143 (4.4%)	775 (3.9%)	636 (3.7%)	139 (5.2%)
CERVICAL DISC DISORDERS: M50	n (%)	280 (1.3%)	183 (1.0%)	97 (3.0%)	161 (0.8%)	87 (0.5%)	74 (2.8%)
GONARTHROSIS(KNEE): M17	n (%)	224 (1.0%)	119 (0.6%)	105 (3.2%)	160 (0.8%)	66 (0.4%)	94 (3.5%)
Associated with acute pain							
DORSALGIA: M54	n (%)	**5942 (27.4%)**	**5342 (29.0%)**	**600 (18.3%)**	**5169 (26.3%)**	**4704 (27.6%)**	**465 (17.5%)**
BIOMECHAN LESIONS NEC: M99	n (%)	1493 (6.9%)	1400 (7.6%)	93 (2.8%)	1692 (8.6%)	1600 (9.4%)	92 (3.5%)
INTERVERT DISC DISORDER:M51	n (%)	1219 (5.6%)	1102 (6%)	117 (3.6%)	1007 (5.1%)	908 (5.3%)	99 (3.7%)
OTHER DORSOPATHIES NEC: M53	n (%)	1216 (5.6%)	1093 (5.9%)	123 (3.8%)	792 (4%)	692 (4.1%)	100 (3.8%)
SPONDYLOSIS: M47	n (%)	1185 (5.5%)	1058 (5.7%)	127 (3.9%)	871 (4.4%)	787 (4.6%)	84 (3.2%)
OTHER DISORDERS OF MUSCLE: M62	n (%)	659 (3.0%)	596 (3.2%)	63 (1.9%)	789 (4.0%)	736 (4.3%)	53 (2.0%)
SPINAL OSTEOCHONDROSIS: M42	n (%)	344 (1.6%)	301 (1.6%)	43 (1.3%)	268 (1.4%)	247 (1.5%)	21 (0.8%)
OTHER SPONDYLOPATHIES: M48	n (%)	336 (1.5%)	265 (1.4%)	71 (2.2%)	193 (1.0%)	156 (0.9%)	37 (1.4%)
UNK/UNSP CAUSE MORBIDITY: R69	n (%)	280 (1.3%)	245 (1.3%)	35 (1.1%)	239 (1.2%)	205 (1.2%)	34 (1.3%)
GONARTHROSIS(KNEE): M17	n (%)	275 (1.3%)	214 (1.2%)	61 (1.9%)	156 (0.8%)	109 (0.6%)	47 (1.8%)
Associated with chronic pain							
OTHER CHRONIC PAIN: R522	n (%)	**427 (2.0%)**	**271 (1.5%)**	**156 (4.8%)**	**470 (2.4%)**	**250 (1.5%)**	**220 (8.3%)**
PERSIS SOMATORM PAIN DIS: F454	n (%)	62 (0.3%)	58 (0.3%)	4 (0.1%)	91 (0.5%)	62 (0.4%)	29 (1.1%)
CHRONIC INTRACTABLE PAIN: R521	n (%)	54 (0.2%)	41 (0.2%)	13 (0.4%)	48 (0.2%)	36 (0.2%)	12 (0.5%)
PERSONALTIY CHANGES: F628	n (%)	23 (0.1%)	22 (0.1%)	1 (0.0%)	6 (0.0%)	5 (0.0%)	1 (0.0%)

N=total number of patients ;(Source: IMS® DA, panel)
*NEC: not elsewhere classified

10.3.4. Concomitant diseases of Flupirtine patients

The overall amount of patients with concomitant acute or chronic pain disease (based on annex i) was 11,854 (76.4%) in reference period and 11,061 patients (78.9%) in the assessment period – both total values. Results are displayed in Table 11.

Table 11: Number and percentage of patients with concomitant **acute or chronic pain** diagnosis based on annex (i), two weeks around flupirtine prescription (linked/principal diagnoses are not included)

	Reference period 2012						**Assessment period 2014**					
	Total		**Incident**		**Prevalent**		**Total**		**Incident**		**Prevalent**	
	N	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**
Total	n=15,521		n=12,461		n=3,060		n=14,025		n=11,526		n=2,499	
	11,854	(76.4%)	9,668	(77.6%)	2,186	(71.4%)	11,061	(78.9%)	9,229	(80.1%)	1,832	(73.3%)
PCP	n=12,402		n=9,933		n=2,469		n=11,918		n=9,741		n=2,177	
	9,364	(75.5%)	7,632	(76.8%)	1,732	(70.1%)	9,340	(78.4%)	7,775	(79.8%)	1,565	(71.9%)
Ortho	n=3,119		n=2,528		n=591		n=2,107		n=1,785		n=322	
	2,490	(79.8%)	2,036	(80.5%)	454	(76.8%)	1,721	(81.7%)	1,454	(81.5%)	267	(82.9%)

N=Distinct number of patients with acute or chronic pain related diagnosis within 2 weeks around flupirtine Rx.
n=Number of patients with an available history of at least 12 months prior to first flupirtine prescription
%1: based on n
(Source: IMS® DA. panel)

The overall view at all concomitant diseases – not limited to pain diagnosis - for Flupirtine patients with an available history of at least 12 months (Table 12) showed a picture, where again "Dorsalgia" (ICD10 code M54) was the most frequent diagnosis.
In 2012, dorsalgia (ICD-10 M54) was recorded for 44.5% patients in the total group, 46.7% of patients in the incident group and 35.6% of patients in the prevalent group.
In 2014, this diagnosis was recorded for 47.1% of patients in the total group, 49.2% of patients in the incident group and 37.5% of patients in the prevalent group.
Patients already linked to a primary diagnosis for the treatment of Flupirtine were not included in this analysis.

Table 12: Medical history – Concomitant diseases of Flupirtine patients 2 weeks before and after Flupirtine prescription- Total

Parameter			Reference period			Assessment period		
			Total	Incident	Prevalent	Total	Incident	Prevalent
			N = 21714	N = 18443	N = 3271	N = 19674	N = 17023	N = 2651
Patients with a 12 months history			**N[1] = 15521**	**N[1] = 12461**	**N[1] = 3060**	**N[1] = 14025**	**N[1] = 11526**	**N[1] = 2499**
	ICD Level 3							
Co-diagnosis								
	DORSALGIA: M54	n (%[2])	6902 (44.5%)	5814 (46.7%)	1088 (35.6%)	6609 (47.1%)	5672 (49.2%)	937 (37.5%)
	ESSENTIAL (PRIMARY) HYPERTENSION: I10	n (%[2])	2088 (13.5%)	1403 (11.3%)	685 (22.4%)	1631 (11.6%)	1143 (9.9%)	488 (19.5%)
	OTHER DORSOPATHIES NEC:M53	n (%[2])	1632 (10.5%)	1292 (10.4%)	340 (11.1%)	1417 (10.1%)	1146 (9.9%)	271 (10.8%)
	BIOMECHAN LESIONS NEC: M99	n (%[2])	1558 (10.0%)	1391 (11.2%)	167 (5.5%)	1640 (11.7%)	1488 (12.9%)	152 (6.1%)
	INTERVERT DISC DISORDER: M51	n (%[2])	1302 (8.4%)	1028 (8.2%)	274 (9%)	1133 (8.1%)	909 (7.9%)	224 (9.0%)
	SPONDYLOSIS: M47	n (%[2])	1189 (7.7%)	926 (7.4%)	263 (8.6%)	1085 (7.7%)	879 (7.6%)	206 (8.2%)
	PAIN NEC:R52	n (%[2])	1152 (7.4%)	711 (5.7%)	441 (14.4%)	999 (7.1%)	638 (5.5%)	361 (14.4%)
	OTHER DISORDERS OF MUSCLE: M62	n (%[2])	1040 (6.7%)	887 (7.1%)	153 (5.0%)	1228 (8.8%)	1069 (9.3%)	159 (6.4%)
	OTHER SOFT TISSIUE DISORDER NEC: M79	n (%[2])	948 (6.1%)	712 (5.7%)	236 (7.7%)	809 (5.8%)	658 (5.7%)	151 (6%)
	DEPRESSIVE EPISODE: F32	n (%[2])	653 (4.2%)	387 (3.1%)	266 (8.7%)	483 (3.4%)	271 (2.4%)	212 (8.5%)

N=total number of patients
1: total number of patients with available history
2: % based on total number of patients within available history
(Source: IMS® DA, panel)

10.3.5. Therapies related to Flupirtine treatment

In order to assess concomitant therapies during the treatment with flupirtine-containing medical products, two approaches were applied.

For the first approach, treatments pre-defined as acute or chronic pain therapies (Appendix 2-i) were analysed within 12 months prior to the treatment start with Flupirtine.

The second approach considered all available treatments prescribed during the analysis period. The findings are described below and in Table 14.

First approach: *Analysis based on predefined acute and chronic pain treatments in patient history (time prior to Flupirtine exposure)*

The overall amount of patients – first approach - with treatment related to pain (based on annex ii) was 5,303 (34.2%) in reference period and 4,616 patients (32.9%) in the assessment period – both total values. Results are displayed in Table 13.

Table 13: Number and percentage of overall patients with pain therapies based on annex (ii) related to flupirtine.

	Reference period 2012						Assessment period 2014					
	Total		Incident		Prevalent		Total		Incident		Prevalent	
	N	%1	N	%1	N	%1	N	%1	N	%1	N	%1
Total	n=15,521		n=12,461		n=3,060		n=14,025		n=11,526		n=2,499	
	5,303	(34.2%)	3,956	(31.7%)	1,347	(44.0%)	4,616	(32.9%)	3,462	(30.0%)	1,154	(46.1%)
PCP	n=12,402		n=9,933		n=2,469		n=11,918		n=9,741		n=2,177	
	4,407	(35.5%)	3,256	(32.8%)	1,151	(46.6%)	3,943	(33.1%)	2,918	(30.0%)	1,025	(47.1%)
Ortho	n=3,119		n=2,528		n=591		n=2,107		n=1,785		n=322	
	896	(28.7%)	700	(27.7%)	196	(33.2%)	673	(31.9%)	544	(30.5%)	129	(40.1%)

N=Distinct number of patients with acute or chronic pain related diagnosis within 2 weeks around flupirtine Rx.
n=Number of patients with an available history of at least 12 months prior to first flupirtine prescription
%1: based n
(Source: IMS® DA. panel)

In the detailed view by WHO ATC codes in the reference period 2012 10.2% of the total group had received treatment with the NSAID ibuprofen (ATC M01AE01) within the year prior to flupirtine exposure start. The corresponding figures were 9.9% for the incident group and 11.1% for prevalent group.

For the assessment period 2014 a similar distribution was found. In the total group 9.9% of patients had received the NSAID ibuprofen (ATC M01AE01) within 1 year before flupirtine exposure start, in the incident and prevalent group 9.6% and 11.6%, respectively.

This analysis was limited to the predefined acute and chronic pain treatment (listed in the Appendix 2-i) and also to a group of patients with traceable history of at least 12 months prior to the analysis periods

Second approach: *Analysis of all drug treatments prescribed during analysis period (entire time within reference and assessment period)*

The analysis considering any concomitant treatment during observational period revealed a similar pattern. The NSAID ibuprofen (WHO ATC M01AE01) was the predominant co-therapy. In 2012, this therapy had a share of 28.3% in the total group, 28.7% share in the incident group and 26.4% in the prevalent group. In the 2014, this therapy had a share of 31.0% in the total group, 31.4% in the incident group and 28.3% share in the prevalent group.

Results for both approaches by ATC codes are displayed in Table 14.

Table 14: Therapies related to Flupirtine treatment by ATC code - Total

Parameter			Reference period			Assessment period		
			Total N = 21714	Incident N = 18443	Prevalent N = 3271	Total N = 19674	Incident N = 17023	Prevalent N = 2651
Patients with a 12 months history			**N[1] = 15521**	**N[1] = 12461**	**N[1] = 3060**	**N[1] = 14025**	**N[1] = 11526**	**N[1] = 2499**
Therapies associated with acute or chronic pain within12 months prior flupirtine exposure	**WHO ATC**							
	IBUPROFEN: M01AE01	n (%[2])	1579 (10.2%)	1238 (9.9%)	341 (11.1%)	1390 (9.9%)	1101 (9.6%)	289 (11.6%)
	DICLOFENAC: M01AB05	n (%[2])	1135 (7.3%)	888 (7.1%)	247 (8.1%)	841 (6.0%)	653 (5.7%)	188 (7.5%)
	METAMIZOLE SODIUM: N02BB02	n (%[2])	1005 (6.5%)	710 (5.7%)	295 (9.6%)	897 (6.4%)	637 (5.5%)	260 (10.4%)
	TETRAZEPAM: M03BX07	n (%[2])	517 (3.3%)	421 (3.4%)	96 (3.1%)	160 (1.1%)	94 (0.8%)	66 (2.6%)
	TRAMADOL: N02AX02	n (%[2])	372 (2.4%)	243 (2.0%)	129 (4.2%)	259 (1.8%)	167 (1.4%)	92 (3.7%)
	TILIDIN: N02AX51	n (%[2])	351 (2.3%)	223 (1.8%)	128 (4.2%)	281 (2.0%)	182 (1.6%)	99 (4.0%)
	ETORICOXIB: M01AH05	n (%[2])	299 (1.9%)	224 (1.8%)	75 (2.5%)	281 (2.0%)	218 (1.9%)	63 (2.5%)
	TELPERISONE: M03BX04	n (%[2])	210 (1.4%)	167 (1.3%)	43 (1.4%)	110 (0.8%)	79 (0.7%)	31 (1.2%)
	PANTOPRAZOLE: A02BC02	n (%[2])	180 (1.2%)	137 (1.1%)	43 (1.4%)	211 (1.5%)	155 (1.3%)	56 (2.2%)
	ZOLPIDEM: N05CF02	n (%[2])	148 (1.0%)	102 (0.8%)	46 (1.5%)	117 (0.8%)	80 (0.7%)	37 (1.5%)
Concomitant prescriptions within analysis period								
	IBUPROFEN : M01AE01	n (%)	6150 (28.3%)	5288 (28.7%)	862 (26.4%)	6092 (31.0%)	5341 (31.4%)	751 (28.3%)
	METAMIZOLE SODIUM: N02BB02	n (%)	4748 (21.9%)	3887 (21.1%)	861 (26.3%)	4730 (24.0%)	3966 (23.3%)	764 (28.8%)
	DICLOFENAC: M01AB05	n (%)	4243 (19.5%)	3680 (20.0%)	563 (17.2%)	3631 (18.5%)	3198 (18.8%)	433 (16.3%)
	PANTOPRAZOLE: A02BC02	n (%)	4034 (18.6%)	3175 (17.2%)	859 (26.3%)	4134 (21.0%)	3332 (19.6%)	802 (30.3%)
	OMEPRAZOLE: A02BC01	n (%)	1971 (9.1%)	1499 (8.1%)	472 (14.4%)	1583 (8.0%)	1227 (7.2%)	356 (13.4%)
	LEVOTHYROXINE SODIUM: H03AA01	n (%)	1963 (9.0%)	1538 (8.3%)	425 (13.0%)	1849 (9.4%)	1493 (8.8%)	356 (13.4%)
	SIMVASTATIN: C10AA01	n (%)	1723 (7.9%)	1298 (7.0%)	425 (13.0%)	1251 (6.4%)	937 (5.5%)	314 (11.8%)
	METOCLOPRAMIDE: A03FA01	n (%)	1681 (7.7%)	1289 (7.0%)	392 (12.0%)	1033 (5.3%)	830 (4.9%)	203 (7.7%)
	TETRAZEPAM: M03BX07	n (%)	1591 (7.3%)	1392 (7.5%)	199 (6.1%)	18 (0.1%)	12 (0.1%)	6 (0.2%)
	ETORICOXIB: M01AH05	n (%)	1513 (7.0%)	1295 (7.0%)	218 (6.7%)	1510 (7.7%)	1297 (7.6%)	213 (8.0%)

N=total number of patients
[1] : total number of patients with available history
[2]: % based on total number of patients within available history
(Source: IMS® DA, panel)

10.3.6. Exposure

10.3.6.1. Treatment Duration

In the reference period 2012, information on the treatment duration (calculated based on the recommended dosage, see Definitions in section 9.4. Variables, Definition treatment duration) was available in 28.8% of all prescriptions in the total group, in 30.7% of patients in the incident group and in 24.8% in the prevalent group. In the assessment period 2014 the percentage of prescriptions with available treatment duration was 24.8% in total group, 31.6% in the incident group and 21.5% in the prevalent group.

The total number of prescriptions with available treatment duration was the basis for the following results, where the duration of treatment per prescription was evaluated.

In the reference period 2012, out of 10,207 prescriptions in the total group, 51.7% had a treatment length ≤14days; out of 7,342 prescriptions in incident group, 64.2% had treatment length ≤14days and out of 2,865 prescriptions in the prevalent group, 19.7% had a treatment length ≤14days.

In the assessment period 2014, out of 9,110 prescriptions in total group, 70.0% had treatment length ≤14days.

Out of 7,200 prescriptions in incident group, 77.6% had a treatment length ≤14days was and out of 1,910 prescriptions in the prevalent group, 41.1% had a treatment length ≤14days.

Overall, the percentage of patients receiving short-term flupirtine treatment increased from 2012 to 2014 in all patient groups.

The findings are summarised in Table 15.

Table 15: Exposure to Flupirtine - treatment duration based on recommended dosage provided by the physician - Total

Parameter			**Reference period**			**Assessment period**		
			Total N = 34793	**Incident N = 23404**	**Prevalent N = 11389**	**Total N = 28505**	**Incident N = 19781**	**Prevalent N = 8724**
Number and percentage of prescriptions with information concerning treatment duration available								
	yes	n (%)	10207 (29.3%)	7342 (31.4%)	2865 (25.2%)	9110 (32.0%)	7200 (36.4%)	1910 (21.9%)
	no	n (%)	24586 (70.7%)	16062 (68.6%)	8524 (74.8%)	19395 (68.0%)	12581 (63.6%)	6814 (78.1%)
Recommended treatment duration			**N[1] = 10207**	**N[1] = 7342**	**N[1] = 2865**	**N[1] = 9110**	**N[1] = 7200**	**N[1] = 1910**
	≤ 14 days	n (%[2])	5276 (51.7%)	4711 (64.2%)	565 (19.7%)	6374 (70.0%)	5589 (77.6%)	785 (41.1%)
	> 14 days	n (%[2])	4931 (48.3%)	2631 (35.8%)	2300 (80.3%)	2736 (30.0%)	1611 (22.4%)	1125 (58.9%)

N=total number of prescriptions
[1] : total number of prescriptions with recommended treatment duration
[2] : % based on total number of prescriptions with recommended treatment duration
(Source: IMS® DA, panel)

10.3.6.2. Treatment Episodes

Length of treatment episodes

During the reference period 2012, the median length of episodes was 14 days for all patient groups; the mean length of episode was 24.4 days in total group, 19.4 days in incident group and 37.1 days in prevalent group.

During the assessment period 2014, the median length of episodes of 14 days for all patient groups was found to be same in the reference period (14 days). The mean length reduced to 18.3 days in total group, 15.0 days in incident group and 28.1 days in prevalent group.

Number of treatment episodes greater or ≤ 14 days

In the reference period 2012, 76.8% of episodes were short term (≤ 14 days) in the total group, 82.4% in the incident group and 62.6% in the prevalent group. In the reference period 2014, 86.4% of episodes were short term (≤ 14 days) in the total group, 92.0% in the incident and 69.9% in the prevalent group.

The length of episodes of flupirtine exposure more than 14 days decreased in each group of assessment period 2014, especially in the prevalent group when compared with the reference period 2012.

Results for both outcomes are presented in Table 16.

Table 16: Exposure to Flupirtine – Formulation and length of episodes – Total

Parameter		**Reference period**			**Assessment period**		
		Total	**Incident**	**Prevalent**	**Total**	**Incident**	**Prevalent**
		N = 29320	**N = 21049**	**N = 8271**	**N = 24995**	**N = 18711**	**N = 6284**
Length of treatment episodes based on DDD (in days)							
	mean (SD)	24.4 (34.6)	19.4 (21.6)	37.1 (53.3)	18.3 (23.8)	15.0 (12.1)	28.1 (41.2)
	median	14	14	14	14	14	14
	min-max	0.25* -435	0.25* -316	0.25* -435	1.8-417	1.8-313.5	1.8-417
Length of Episodes ≤ 14 days or > 14 days based on DDD							
	≤ 14 days	22521 (76.8%)	17345 (82.4%)	5176 (62.6%)	21601 (86.4%)	17206 (92.0%)	4395 (69.9%)
	> 14 days	6799 (23.2%)	3704 (17.6%)	3095 (37.4%)	3394 (13.6%)	1505 (8.0%)	1889 (30.1%)

N=total number of episodes
*: the duration of 0.25 days results out of the DDD calculation of product:
"Katadolon Inject Ampullen 1 St Teva GmbH PZN: 567646, 100mg"
(Source: IMS® DA, panel)

10.3.6.3. Single and Repeated Use

The results regarding single and repeated flupirtine use are displayed in

Table 17.

Prescriptions per patient per month

In the reference period 2012 and the assessment period 2014, the median number of Flupirtine prescriptions per patient was 1 per month in all groups.

In 2012, the mean value of prescriptions per patient was 1.1 per month in total group, 1.0 in incident group and 1.1 in the prevalent group.

In 2014, the mean value of prescriptions per patient was 1.0 per month in total, 1.0 in incident group and 1.1 in the prevalent group.

Single vs. repeated prescriptions

During the reference period 2012, 76.8% of Flupirtine prescriptions were prescribed as single prescriptions in total group; the corresponding figures for the incident group and the prevalent group were 83.5% and 39.0%, respectively.

During the assessment period 2014, 83.1% of Flupirtine prescriptions were prescribed as single prescriptions in total group; the corresponding figures for the incident group and the prevalent group were 89.2% and 43.7%, respectively.

In both periods, single prescriptions were more frequently observed than repeated prescriptions in total groups and incident groups. Whereas repeated prescriptions were more frequent than single prescriptions in the prevalent groups.

Table 17: Exposure to Flupirtine- Number and frequency of prescriptions – Total

Parameter			**Reference period**			**Assessment period**		
			Total	**Incident**	**Prevalent**	**Total**	**Incident**	**Prevalent**
			N = 21714	**N = 18443**	**N = 3271**	**N = 19674**	**N = 17023**	**N = 2651**
Number of prescriptions per patient per month		mean (SD)	1.1 (0.2)	1.0 (0.2)	1.1 (0.2)	1.0 (0.2)	1.0 (0.2)	1.1 (0.2)
		median	1	1	1	1	1	1
		min-max	1-3.6	1-3.5	1-3.7	1-4.5	1-4.0	1-4.5
Number of single and repeated prescriptions								
	Single	n (%)	16674 (76.8%)	15399 (83.5%)	1275 (39.0%)	16351 (83.1%)	15192 (89.2%)	1159 (43.7%)
	Repeat	n (%)	5040 (23.2%)	3044 (16.5%)	1996 (61.0%)	3323 (16.9%)	1831 (10.8%)	1492 (56.3%)

N=total number of patients; (Source: IMS® DA, panel)

10.3.6.4. Monitoring of Liver Function

The percentage of prescriptions with at least one LFT within 1 week after Flupirtine prescription was summarized in Table 18.

In the reference period 2012 for 6.4% of all Flupirtine prescriptions at least 1 LFT was performed in the total group. The corresponding figures for the incident group and the prevalent group were 6.5% and 6.4%, respectively.

A similar pattern was observed in the assessment period 2014 -total: 7.9%; incident: 7.8%; prevalent: 8.2%. In the prevalent patient group the percentage increased by 1.8% from the reference period to the assessment period.

Table 18: Liver Function Test - Total

Parameter		**Reference period**			**Assessment period**		
		Total	**Incident**	**Prevalent**	**Total**	**Incident**	**Prevalent**
		N = 34793	**N = 23404**	**N = 11389**	**N = 28505**	**N = 19781**	**N = 8724**
Prescriptions with at least one liver function test within 1 week after Flupirtine prescription	n (%)	2240 (6.4%)	1510 (6.5%)	730 (6.4%)	2263 (7.9%)	1547 (7.8%)	716 (8.2%)

N=total number of **prescriptions**
(Source: IMS® DA, panel)

10.3.7. Comparison of reference and assessment period

10.3.7.1. Number and percentage of patients with any diagnosis of disease contraindicated for NSAIDs or weak opioids prior to flupirtine exposure start

The percentage of patients contraindicated for the use of NSAIDs or weak opioids before Flupirtine treatment remained almost unchanged in the total group and incident group before and after the revision of SmPC. In 2012, the percentage was 39.7% in the total group and 38.2% in the incident group (Figure 2. **)**. In 2014, the percentage was 39.9% in the total group and 38.0% in the incident group.

The percentage of patients in the prevalent group with a disease contraindicated for the use of NSAIDs/weak opioids increased slightly from 46.0% in 2012 to 48.6% in 2014.

This analysis was done for the timeperiod12monthsbeforethefirst Flupirtine prescription and was performed for patients with an available history of at least 12 months prior to first Flupirtine prescription only.

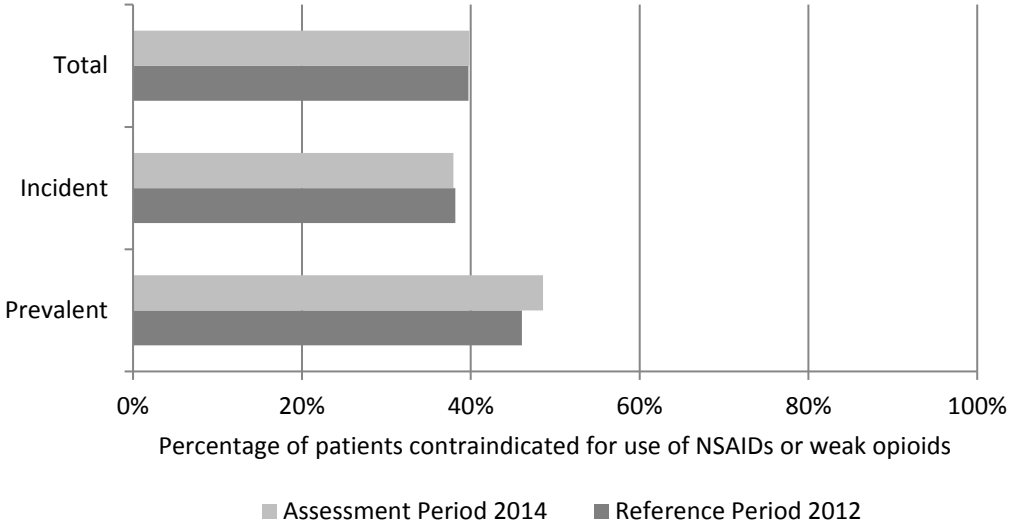

Figure 2. Comparison of contraindicated patients for the use of NSAIDs/weak opioids before Flupirtine start

(Source: IMS® DA, panel)

10.3.7.2. Percentage of principal diagnosis for Flupirtine prescriptions

The comparison below (Figure 3.) is focused on the most frequent diagnoses, dorsalgia for Flupirtine prescriptions linked to a certain diagnosis (principal diagnosis).
The percentage of the acute pain diagnosis M54 (dorsalgia) decreased in all groups (total: 28.2% in 2012 vs. 25.0% in 2014),

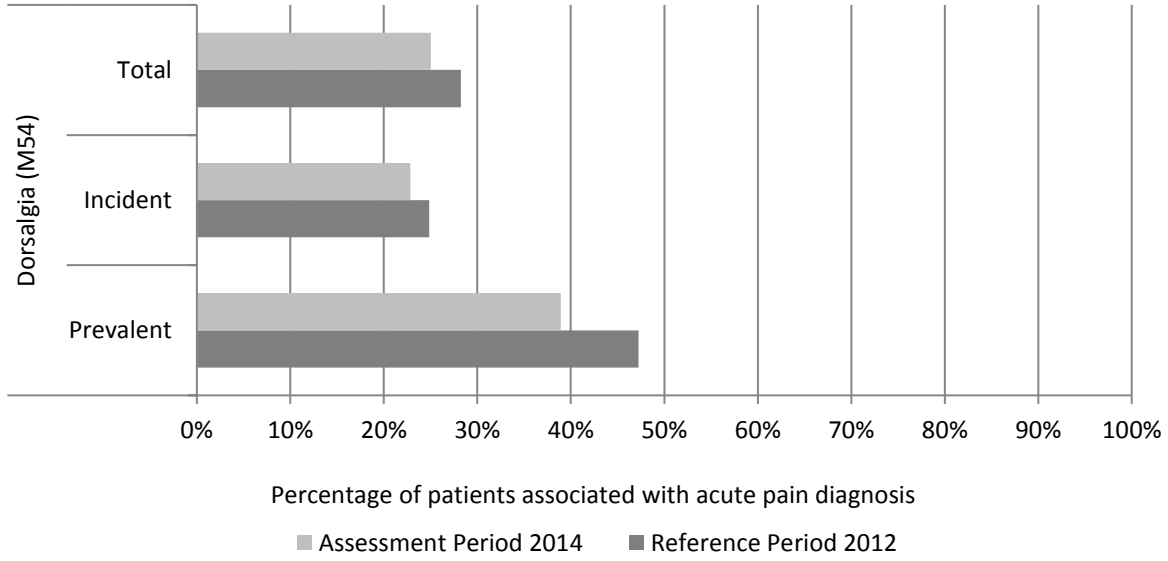

Figure 3. Comparison of percentage of principal diagnosis for Flupirtine prescriptions

(Source: IMS® DA, panel)

10.3.7.3. Percentage of Flupirtine prescriptions with diagnosis associated with acute pain

The comparison below (Figure 4.)is focused on the two most frequent acute pain diagnoses, dorsalgia and biomechanical lesions associated with flupirtine prescriptions.
The percentage of the acute pain diagnosis M54 (dorsalgia) decreased in all groups (total: 27.4% in 2012 vs. 26.3% in 2014), while the diagnosis M99 (biomechanical lesions, not elsewhere classified) raised in comparison of 2012 to 2014 in all groups (total: 6.9% in 20142 vs. 8.6% in 2014)

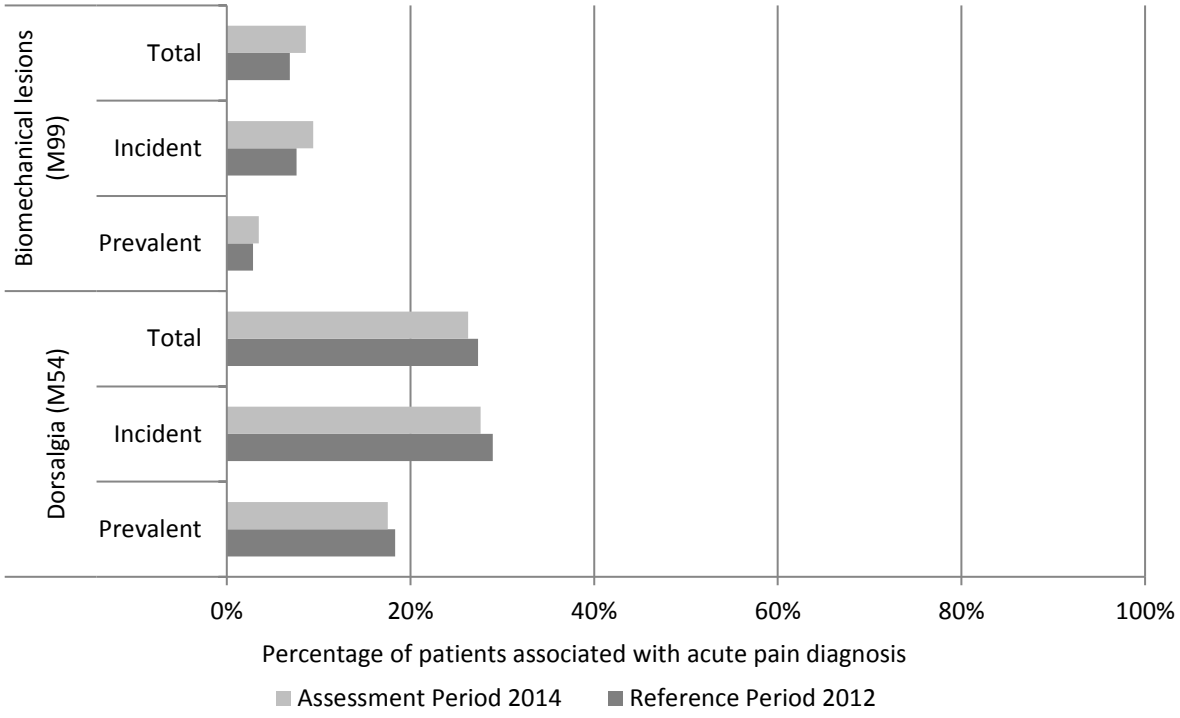

Figure 4. Comparison of percentage of Flupirtine prescriptions with diagnosis associated with acute pain

(Source: IMS® DA, panel)

10.3.7.4. Number and percentage of patients with single and repeated Flupirtine prescriptions within the defined time period

In total study group, the percentage of patients with single flupirtine prescriptions increased from 76.8% in the reference period 2012to 83.1% in the assessment period2014 (See Figure 5.).

This increase was also found for both subgroups of incident users and prevalent users.

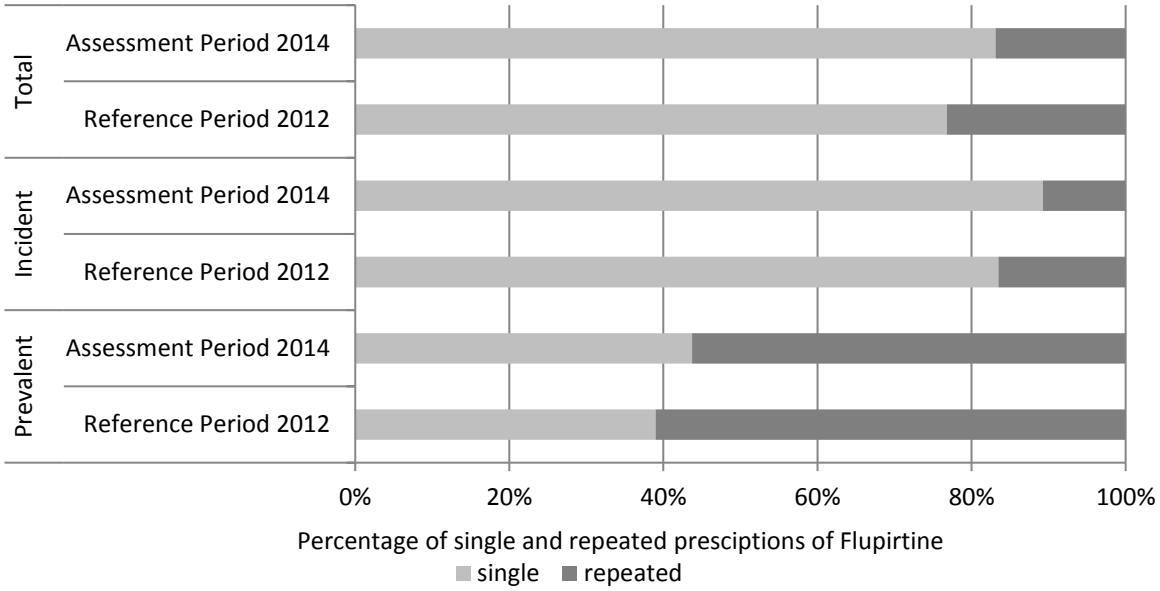

Figure 5. Comparison of percentage of single and repeated prescriptions of Flupirtine

(Source: IMS® DA, panel)

10.3.7.5. Percentage of prescriptions with LFT monitoring during Flupirtine treatment

The percentage of prescriptions with LFTmonitoring was slightly higher in the total group (6.4% vs.7.9%), in the incident group (6.5% vs. 7.8%) and in the prevalent patient group (6.4% vs.8.2%). (Compare Figure 6.).

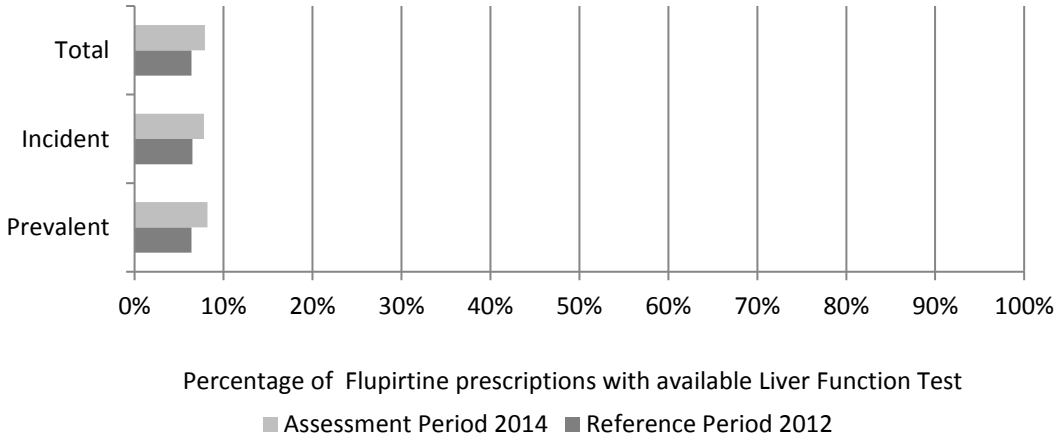

Figure 6. Comparison of percentage of performed Liver Function Tests

(Source: Source: IMS® DA, panel)

10.3.7.6. Length of treatment episodes (based on DDD)

The mean length of treatment episodes decreased in the total group and in both subgroups (see Figure 7.).

The mean episode length in the total group was 24.4 days in the reference period 2012 and 18.3 days in the assessment period 2014.

The incident group showed a mean length of 19.4 days in the reference period 2012 and 15.0 days in the reference period 2014. The corresponding figures for the prevalent group were 37.0 days and 28.0 days, respectively.

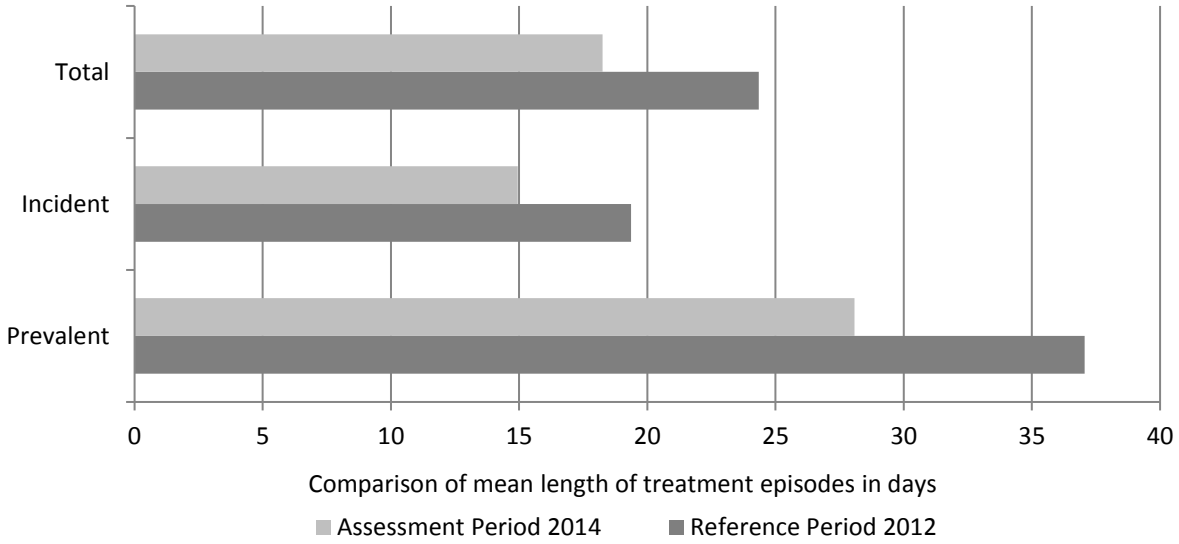

Figure 7. Comparison of mean length of treatment episodes in days

(Source: IMS® DA, panel)

10.3.7.7. Percentage of patients with at least one treatment episode longer than 14 days (based on DDD)

The percentage of patients with treatment episodes longer than 14 days decreased after the SmPC revision in both subgroups and in the total study group (Figure 8.).

The percentage of mean episodes with length >14 days was reduced in the total group from 23.2% to 13.6%; in the incident group from 17.6% to 8.0% and in the prevalent patients group from 37.4% to 30.1% (year 2012 to 2014).

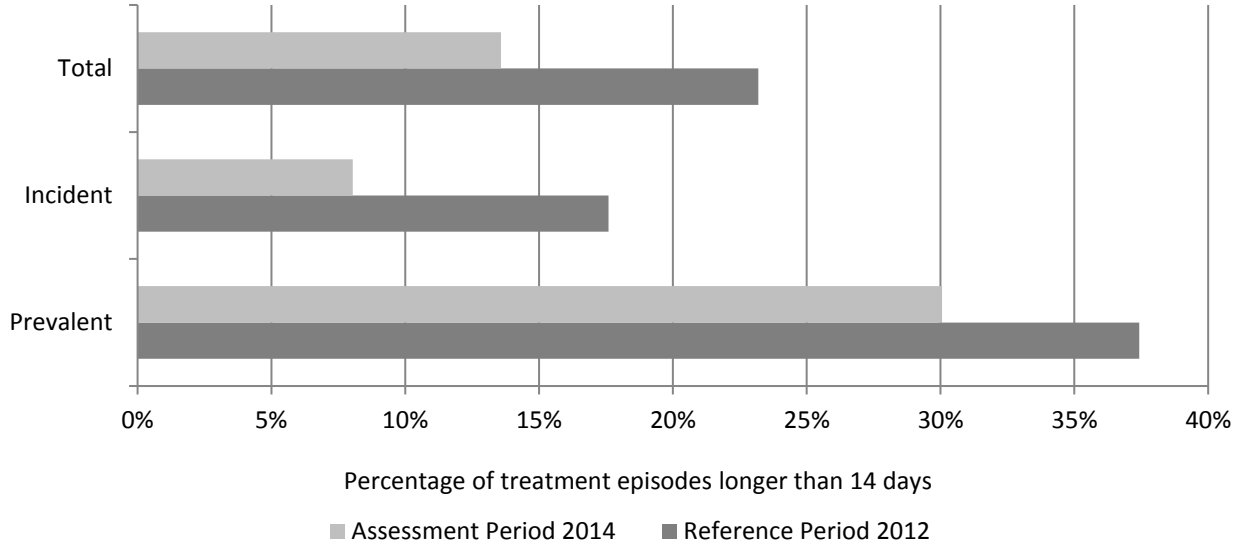

Figure 8. Comparison of treatment episodes >14 days

(Source: IMS® DA, panel)

10.4. Main results

No hypotheses were tested. The results of the descriptive analyses are presented in section 10.2and section 10.3.

10.5. Other analyses

None.

10.6. Adverse events/adverse reactions

Not applicable, as the study will be carried out by secondary use of already collected data.

According to the current guidelines of the International Society for Pharmacoepidemiology (ISPE) (2007, Section VI) and the EMA Guideline on Good Pharmacovigilance Practices (GVP): Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA, 2012b, Section VI: C.1.2.1), non-interventional studies which are based on secondary use of data do not require reporting of adverse events [13].

11. Discussion

11.1. Key results

In total, 21,714 patients with Flupirtine prescriptions were available for the analysis of the reference period 2012 and 19,674 patients for the assessment period 2014.

In both periods the vast majority of patients were incident user. In the reference 2012, 18,443 (84.9%) were classified as incident and 3,271 (15.1%) as prevalent patients. In the assessment period 2014, 17,023 (86.5%) were classified as incident and 2,651 (13.5%) as prevalent patients.

The mean age of Flupirtine patients in 2012 was 54.6 years and 52.7 years in 2014. Almost two-third of all patients was female in both analysis periods (62.8% in 2012 and 59.6% 2014).

Almost 40% of all Flupirtine patients in the reference period were diagnosed contraindicated for the use of NSAIDs or weak opioids (total group: 39.7%, incident group: 38.2%, prevalent group: 46.0%). A similar pattern was found for the assessment period (total group: 39.9%; incident group: 38.0%, prevalent group: 48.6%).

Almost all top 10 diagnoses linked to the prescriptions of Flupirtine belong to the group of "Diseases of the musculoskeletal system and connective tissue" (M00-M99) in the reference period and the assessment period. The main reason in the reference period 2012 to prescribe flupirtine-containing medical products was the diagnosis "Dorsalgia" (ICD10 M54) in 28.2% of prescriptions in the total study group and the incident group (24.9%). In the prevalent group this diagnosis was documented for nearly 50% of prescriptions (47.2%). A similar distribution was found for the total study group (25.0%) and the incident group (22.8%) in the assessment period 2014, whereas this diagnosis was less frequent (38.9%) in the prevalent patients compared to 2012.

Prior to Flupirtine exposure start patients have received treatment with NSAIDs and weak opioids. In the reference period 2012, the percentages ranged up to 10% for the single substance classes in the total group for the most frequent prescribed NSAID ibuprofen (ATC M01AE01). The same was observed for the incident and the prevalent group. For the assessment period 2014, a similar distribution was found for all study groups. In the total group the NSAID ibuprofen (ATC M01AE01) was with up to 10% the most frequent prescribed NSAID in the total group.

Overall, a similar picture was observed when considering any concomitant treatment during the respective time periods for analysis, entire year 2012 for the patients receiving flupirtine in 2012 and entire year 2014 for the patients receiving flupirtine in 2014. The NSAID ibuprofen (ATC M01AE01) was the dominant substance class with a percentage for the total group of 28.3% in the reference period 2012 (28.7% in the incident, 26.4% in the prevalent group) and 31.0% in the assessment period (in the incident group: 31.4%, in the prevalent group: 28.3%). Ibuprofen was followed by metamizole sodium(N02BB02) with 21.9% in the reference period 2012 (21.1% in the incident, 26.3% in the prevalent group) and 24.0% in the assessment period 2014 (23.3% in the incident, 28.8% in the prevalent group), diclofenac(M01AB05) with 19.5% in 2012(20.0% in the incident, 17.2% in the prevalent group)and 18.5% in 2014 (18.8% in the incident, 16.3% in the prevalent group), and pantoprazole(A02BC02) with 18.6% in 2012 (17.2% in the incident, 26.3% in the prevalent group)and 21.0% in 2014(19.6% in the incident, 30.3% in the prevalent group), respectively.

In the reference period 2012, the percentage of prescriptions with information on the dosage recommended by the physician, which was the basis for the calculation of treatment duration, was available in 28.8% of all prescriptions in the total group, in 30.7% in the incident group and in 24.8% in the prevalent group. In the assessment period 2014, the corresponding figures were 31.6% in the total group, 36.0% in the incident group and 21.5% in the prevalent group. In the reference period 2012, out of 10,207 prescriptions in the total group, 51.7% had a treatment length ≤14days. The corresponding figures for the incident group and the prevalent group were 64.2% out of 7,342 prescriptions and 19.7% out of 2,865 prescriptions, respectively. In the assessment period 2014, the percentages of prescriptions with a treatment duration ≤14days was higher compared to the reference period 2012 (total group: 70.0% out of 9,110 prescriptions, incident group: 77.6% out of 7,200 prescriptions, prevalent group: 41.1% out of 1,910 prescriptions).

A same pattern was found with respect to the calculation of short-term episodes based on DDD. In the reference period 2012, short-term episodes (≤ 14 days) were found in 76.8% of patients in the total group, in 82.4% in the incident group and 62.6% in the prevalent group. In the assessment period 2014, the percentage of patients with short-term episodes were larger than in the reference period with 86.4% in the total group, 92.0% in the incident and 69.9% in the prevalent group.

For both periods, the median length of episodes was 14 days for all patient groups. In the reference period 2012, the mean length of episode was 24.4 days in the total group, 19.4 days in the incident group and 37.1 in prevalent group. In the assessment period 2014, the mean length of flupirtine treatment episodes was lower (total group: 18.3 days, incident group: 15.0 days, prevalent group: 28.1 days in prevalent group).

During the reference period 2012, 76.8% of flupirtine prescriptions were prescribed as single prescriptions in the total group, 83.5% of prescriptions in the incident group and 39.0% in the prevalent group. During the assessment period 2014, the single use was more frequent than in 2012. In the total group 83.1% of flupirtine prescriptions were prescribed as single prescription, the incident group 89.2% and in the prevalent group had a share of 43.7%. The majority of flupirtine prescriptions in the total group and the incident group were single prescriptions in both time periods, whereas in prevalent patients the majority of flupirtine prescriptions was repeated prescriptions.

In the reference period 2012, for 6.5% of flupirtine prescriptions a LFT record within 1 week after prescription date was recorded in the study groups. In the assessment period 2014, slightly higher values of about 8% were observed.

11.2. Limitations

IMS® Disease Analyzer is representative of Germany as a whole insofar as that the included offices are selected to adequately reflect geographic coverage and differences between urban and rural locations. This database contains information from approximately 3,000 office-based physicians (including specialists) who represent approximately 2.4% of all offices in Germany. The balance of various specialties in the IMS® Disease Analyzer does not, however, exactly reflect the balance in Germany. The lack of data from Flupirtine-prescribing oncologists will limit only to some extent the representativeness of results. For the characterization and comparison of the prescribing practice, however, this does not pose a problem.

The limitations of the IMS® Disease Analyzer are those of a provider-sourced EMR database. Patients seeking care outside the EMR practice setting does not have that utilisation recorded in the database. One of the main reasons for data documentation is reimbursement purposes. In the IMS® Disease Analyzer patients cannot be tracked across panels and across offices. Therefore, patients cannot be followed up across specialties as well as offices and double counting of patients cannot be completely ruled out when more than one panel is considered for the analysis as it was done for the DUS Flupirtine.

This has also to be considered for the assessment of the indication for flupirtine, medical history and the treatment with NSAIDs and weak opioids. An underreporting of diagnoses and drug treatment cannot be completely ruled out. However, the analysis of associated diagnoses for treatment of Flupirtine was performed for two groups, on a group of patients with available history of at least 12 months and on a group of patients not limited to available history. Overall, the results were quite similar.

The analysis of patients identified as contraindicated of NSAIDs/weak opioids treatment was performed only within a time period of 12 months prior to the first Flupirtine prescription, disregarding if the patient had had any relevant diagnosis before that time span. Taking additionally into account, that an unbroken documentation on all patients' diseases or treatments will probably

not be recorded in orthopaedists' EMR, the percentage of patients contraindicated for the use of NSAIDs/weak opioids before Flupirtine start is very likely underestimated.

The duration of Flupirtine treatment (in days) was calculated using recommended dosage advice by the physician. The dose recommendation "on demand (pro re nata)" is very often given in the therapy of acute pain, acute pain episodes, and acute pain exacerbations which occur repeatedly. Therefore, the actual treatment duration is often shorter compared to the length of prescription.

This information on recommended daily dose by the physician was not available for two/third of Flupirtine prescriptions. This percentage was expected following findings preliminary investigations. In order to overcome this limitation the length was episodes was determined using the defined daily dose (DDD). For the calculation the following assumptions were taken into account: 1) the entire package was used, and no unit was left; 2) the episodes composed of 2 or more separate consecutive prescriptions including a gap of up to 7 days of treatment gap. This conservative approach leads very likely to an overestimation of the length of episodes and hence to an underestimation of the percentage of use up to 14 days.

11.3. Interpretation

The current report presents results of a retrospective Flupirtine drug utilization study in Germany. The DUS - as part of the risk management plan (RMP) - was requested by the PRAC due to the implemented restrictions of use after the revision of the SmPC in 2013. The restrictions of use include limitation of the indication to acute pain, treatment duration was recommended to be used at a maximum of two weeks and after each full week of treatment a liver function test should be performed.

The primary objective of this DUS was to evaluate the prescribing practice of flupirtine-containing medicinal products during routine clinical use and to assess the main reasons for prescriptions by representative groups of prescribers. The study was based on longitudinal data routinely recorded in the German longitudinal electronic patient-level database (IMS® Disease Analyzer). The PCP panel and the orthopaedist panel of IMS® Disease Analyzer were selected as a relevant data source for the analysis, because preliminary analyses had shown that 95% of all Flupirtine prescriptions recorded in this database were issued by PCPs or orthopaedists. For the study two one year periods, one before the restriction of use (2012) and one after the restriction of use (2014) was considered for the analysis.

Dorsalgia (ICD10: M54) is the most frequent principal diagnosis (around 25%) flupirtine-containing medical products were prescribed for before and after the restriction of use. The vast majority of all diagnoses during the both one-year analysis periods - disregarding if directly linked with the Flupirtine prescription, associated with acute pain or classified as concomitant diseases –belonged to the group "Diseases of the musculoskeletal system and connective tissue" (ICD-10 M00-M99), which is in line with the therapeutic area of Flupirtine to treat pain such as pain associated with muscle tension or pain following orthopaedic surgery or injuries.

Flupirtine is indicated for treatment of pain, when other non-steroidal anti-inflammatory drugs can not be used. Respective contraindications were identified for 40% of patients. However, the number of patients contraindicated for the use of NSAIDs and weak opioids is likely underestimated, because only the time period 12 months before the Flupirtine prescription was considered. Furthermore, it has to be considered that the documentation at specialists like orthopaedists is often not so comprehensive than at PCPs.

The percentage of patients with a treatment duration up to 14 days was 51.7% in 2012 and 70.0% in the year after the revision of the SmPC document. The share of single prescriptions rose by value of 6.3% from 76.8% (2012) to 83.1% (2014).
The findings regarding length of treatment and distribution of single versus repeated use suggest changes in the prescribing behaviour of physicians in 2014 compared to 2012.

Also the finding that the number of patients treated with Flupirtine as well as the number of Flupirtine prescriptions has decreased from 2012 to 2014 although the number of overall patients at the offices has increased, point into the direction that in 2014 the patient group eligible for Flupirtine and frequency of prescriptions is considered with respect to the revised SmPC.

There is a slight increase of liver function tests recorded in 2014, however, the test is recommended only after a full week of treatment and the laboratory values are not likely to be recorded at an

orthopaedist office, as the follow up might be scheduled at the PCP office. Therefore, findings regarding monitoring of liver function by laboratory tests has to be assessed carefully.

11.4. Generalisability

This DUS presents results on use of Flupirtine in real life setting in Germany based on data from a large patient level electronic database (IMS® Disease Analyzer) which is designed to be representative for Germany.

The analyses were conducted on a very large patient basis. No restrictions with regard to demographic characteristics, insurance status, co-diagnosis, region, or other, which could affect the external validity of results, were applied.

Taking the known limitations of the database into consideration the findings are considered to be generalisable for Germany.

12. Other information

None

13. Conclusion

The findings suggest that Flupirtine was mainly prescribed for muscoskeletal disorders, in particular back pain (dorsalgia), in Germany. This was observed for the 12-month time period before and for the 12-month time period after the restriction of use in 2013. More single use and short-term use (up to 14 days) indicate changes in the prescribing behaviour of physicians following the revision of the SmPC. However, changes were not observed regarding all requirements for the prescription of flupirtine. Monitoring of liver function was done in a small proportion of flupirtine users before and remained low, although slightly increased, even after the revision of SmPC. The proportion of patients diagnosed to be contraindicated for the use of NSAIDs or weak opioids remained on the same level.

14. References

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14. Fachinformation MEDA Pharma GmbH & Co. KG, Product Flupigil® 100 mg Hartkapseln, Status as of October 2013

Appendices

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1. Protocol of the Study	Version 3.1	25. September 2015	DUS Flupirtine study protocol
2. Statistical Analysis Plan	Version 1.0	25. September 2015	Lupin DUS Flupirtine SAP Version 1.0
3. SmPC	Version 1.0	25. September 2015	Summary of Product Charactersitics
4. Supplemental Tables	Version 1.0	15. February 2016	Supplemantal Tables

Annex 2. Additional information

i-Diseases associated with acute pain, acute pain episodes, acute pain exacerbations (selection)

G20-G26 Extrapyramidal and movement disorders
G20 Parkinson disease
G21 Secondary Parkinsonism
G22 Parkinsonism in diseases classified elsewhere
G23 Other degenerative diseases of basal ganglia

G35-G37 Demyelinating diseases of the central nervous system
G35 Multiple sclerosis

G40-G47 Episodic and paroxysmal disorders
G44 Other headache syndromes

M15-M19 Arthrosis
M15 Polyarthrosis
M16 Coxarthrosis [arthrosis of hip]
M17 Gonarthrosis [arthrosis of knee]
M18 Arthrosis of first carpometacarpal joint
M19 Other arthrosis

M40-M43 Deforming dorsopathies
M40 Kyphosis and lordosis
M41 Scoliosis
M42 Spinal osteochondrosis
M43 Other deforming dorsopathies

M45-M49 Spondylopathies
M45 Ankylosing spondylitis
M46 Other inflammatory spondylopathies
M47 Spondylosis
M48 Otherspondylopathies
M49 Spondylopathies in diseases classified elsewhere

M50-M54 Other dorsopathies
M50 Cervical disc disorders
M51 Other intervertebral disc disorders
M53 Otherdorsopathies, not elsewhere classified
M54 Dorsalgia

M60-M63 Disorders of muscles
M60 Myositis
M61 Calcification and ossification of muscle
M62 Other disorders of muscle
M63 Disorders of muscle in diseases classified elsewhere

M95-M99 Other disorders of the musculoskeletal system and connective tissue
M95 Other acquired deformities of musculoskeletal system and connective tissue
M96 Postprocedural musculoskeletal disorders, not elsewhere classified
M99 Biomechanical lesions, not elsewhere classified

R50-R69 General symptoms and signs
R51 Headache
R52 Pain, not elsewhere classified

Source:

- ICD-10-GM Version 2014, Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme 10. Revision, German Modification Version 2014, http://www.dimdi.de/static/de/klassi/icd-10-gm/kodesuche/onlinefassungen/htmlgm2014/. Access 20.08.2014
- Source: http://apps.who.int/classifications/icd10/browse/2010/en

ii-List of ICD codes and ATC classes for long term medication leading to contraindication for Flupirtine (therapies linked to this diagnosis)

Liver diseases

Disease of liver: K70 - K77

K70 Alcoholic liver disease
K71 Toxic liver disease
K72 Hepatic failure, not elsewhere classified
K73 Chronic hepatitis, not elsewhere classified
K74 Fibrosis and cirrhosis of liver
K75 Other inflammatory liver diseases
K76 Other diseases of liver
K77 Liver disorders in diseases classified elsewhere

Other liver diseases:

A06.4 Amoebic liver abscess
B15-B19 Viral hepatitis
E83.0 Wilson-Disease
E83.1 Haemochromatosis
E85 Amyloidosis
G93.7 Reye syndrome
I82.0 Budd-Chiari syndrome
K83.0 Cholangitis
P78.8 Other specified perinatal digestive system disorders
R16.0 Hepatomegaly, not elsewhere classified
R17 Unspecified jaundice
Q44.6 Cystic disease of liver
WHO ATC code:
A05BA:
Drug used in liver therapy

Alcohol abuse
F10 Mental and behavioural disorders due to alcohol

WHO ATC codes:
N07BB01, N07BB03, N07BB04, N07BB05: Drugs used in alcohol dependence

iii- Preexisting diseases leading to contraindications for non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids

Weak Opioids:

Description	ICD-10 code	ICD text
Hypersensitivity to codeine sulfate or any component of the product	T88.7	Unspecified adverse effect of drug or medicament
Respiratory depression in the absence of resuscitative equipment	R06.8	Other and unspecified abnormalities of breathing
Acute or severe bronchial asthma or hypercarbia	J45 J46	Asthma Status asthmaticus
Paralytic Ileus	K56.0	Paralytic Ileus
Raised Intracranial tension	G93.2	Benign intracranial hypertension

NSAIDs:

Description	ICD-10 code	ICD text
Allergy to aspirin or any NSAID	T88.7	Unspecified adverse effect of drug or medicament
Bleeding peptic ulcer	K27.0 K27.4	Peptic ulcer, site unspecified – acute with haemorrhage - chronic or unspecified with haemorrhage
Kidney disease	N00-N08 N10-N16 N17-N19	Glomerular disease Renal tubulo-interstitial diseases Renail failure
Past transient ischemic attack (excluding aspirin)	G45	Transient cerebral ischaemic attacks and related syndromes
Past stroke (excluding aspirin)	I60-I64	
Past myocardial infarction (excluding aspirin)	I21 I22	Acute myocardial infarction Subsequent myocardial infarction
Ischaemic Heart Disease (excluding aspirin)	I20-I25	

The list of diseases leading to contrainidictions for NSAID/weak opioids was extended by the following codes:

ICD3	Description
D56-D59, D65-D69	Anemia/ Coagulation defects
E03, E05, E10-E14, E73, E78, E86	Disorders of thyroid gland
E12	Glomerular disease
F11-F19	Mental and behavioral disorders due to psychoactive substance use
F99	Unspecified mental disorder
G40-G41, G46	Episodic and paroxysmal disorders
I27	Pulmonary heart disease and diseases of pulmonary circulation
I46	Cardiac arrest
I50	Heart failure
I65-I69	Cerebrovascular diseases
I73	Diseases of arteries, arterioles and capillaries
I95	Hypotension
J33, J43, J96,	Diseases of the respiratory system
J45	Asthma
J46	Status asthmaticus
K20, K25-K29	Diseases of esophagus, stomach and duodenum
K50-K52	Noninfective enteritis and colitis
K56 -K57	Other diseases of intestines
K80, K82	Disorders of gallbladder, biliary tract and pancreas
L26	Dermatitis and eczema
L51	Urticaria and erythema
M30-M36	Systemic connective tissue disorders
N35	Urethral structure
N40	Enlarged prostate
R56	Convulsions, not elsewhere classified
R57	Shock, not elsewhere classified
R60	Edema, not elsewhere classified
S00-S09	Injuries to the head

Annex 3. Result tables

I. IMS® Disease Analyzer

All tables will be provided for all IMS® Disease Analyzer panels separately.

Table 19: Prescriber characteristics – Total

Parameter			Reference period	Assessment period
Number of physicians		n	1227	1492
Number of offices		n	971	1181
Region of office				
	West Germany	n (%*)	762 (78.5%)	942 (79.8%)
	East Germany	n (%*)	209 (21.5%)	239 (20.2%)
Number of patients at office		n	3446052	3974155
		mean (SD)	2459 (1615)	2723 (1809)
		median	2130	2344
		min-max	2-22043	57-27008
Number of patients at office with at least one Flupirtine prescription		n	21714	19674
		mean (SD)	22 (43.1)	16(44.3)
		median	10	6
		min-max	1-652	1-1121

*% based on total number of offices; (Source: IMS® DA. panel)

Table 20: Prescriber characteristics – PCP

Parameter			Reference period	Assessment period
Number of physicians		N	1060	1295
Number of offices		N	847	1033
Region of office				
	West Germany	n (%*)	661 (78.0%)	820 (79.4%)
	East Germany	n (%*)	186 (22.0%)	213 (20.6%)
Number of patients at office		n	2622976	3011627
		mean (SD)	2162 (1068)	2386 (1192)
		median	2013	2206
		min-max	2-9698	57-14366
Number of patients with at least one Flupirtine prescription at office		n	15350	14940
		mean (SD)	18.12 (25.79)	14.46 (25.05)
		median	9	6
		min-max	1-256	1-246

*% based on total number of offices; (Source: IMS® DA. panel)

Table 21.: Prescriber characteristics – Ortopaedist

Parameter			Reference period	Assessment period
Number of physicians		N	167	197
Number of offices		N	124	148
Region of office				
	West Germany	n (%*)	101 (81.5%)	122 (82.4%)
	East Germany	n (%*)	23 (18.5%)	26 (17.6%)
Number of patients at office		n	823076	962528
		mean (SD)	4378 (2804)	4885(3125)
		median	3852	4136
		min-max	2-22043	1081-27008
Number of patients with at least one Flupirtine prescription at office		n	6364	4734
		mean (SD)	51.3 (95.24)	31.98 (105.15)
		median	19	6
		min-max	1-652	1-1121

*% based on total number of offices; (Source: IMS® DA. panel)

Table 22**:** Demographic characteristics –Total

Parameter			**Reference period**			**Assessment period**		
			Total	**Incident**	**Prevalent**	**Total**	**Incident**	**Prevalent**
			N = 21714	**N = 18443**	**N = 3271**	**N = 19674**	**N = 17023**	**N = 2651**
Age		mean (SD)	54.61 (16.16)	53.67 (16.15)	59.96 (15.18)	52.71 (16.03)	51.71 (15.90)	59.12 (15.43)
		median	54	53	59	52	51	58
		min-max	5-96	5-96	10-96	3-98	3-98	15-98
Age. grouped								
	< 18 years	n (%)	80 (0.4%)	76 (0.4%)	4 (0.1%)	79 (0.4%)	76 (0.4%)	3 (0.1%)
	18-29 years	n (%)	1375 (6.3%)	1308 (7.1%)	67 (2.0%)	1575 (8.0%)	1507 (8.9%)	68 (2.6%)
	30-39 years	n (%)	2307 (10.6%)	2112 (11.5%)	195 (6.0%)	2470 (12.6%)	2286 (13.4%)	184 (6.9%)
	40-49 years	n (%)	4763 (21.9%)	4175 (22.6%)	588 (18.0%)	4308 (21.9%)	3830 (22.5%)	478 (18.0%)
	50-59 years	n (%)	5111 **(23.5%)**	4314 **(23.4%)**	797 (24.4%)	4875 **(24.8%)**	4198 **(24.7%)**	677 (25.5%)
	60-69 years	n (%)	3402 (15.7%)	2771 (15.0%)	631 (19.3%)	2950 (15%)	2439 (14.3%)	511 (19.3%)
	≥ 70 years	n (%)	4655 (21.4%)	3676 (19.9%)	979 **(29.9%)**	3408 (17.3%)	2684 (15.8%)	724 **(27.3%)**
Gender								
	Male	n (%)	8064 (37.1%)	7005 (38.0%)	1059 (32.4%)	7930 (40.3%)	6987 (41%)	943 (35.6%)
	Female	n (%)	13644 (62.8%)	11432 (62%)	2212 (67.6%)	11735 (59.6%)	10027 (58.9%)	1708 (64.4%)
Insurance status								
	SHI	n (%)	19019 (87.6%)	16030 (86.9%)	2989 (91.4%)	17153 (87.2%)	14763 (86.7%)	2390 (90.2%)
	Private insurance	n (%)	2695 (12.4%)	2413 (13.1%)	282 (8.6%)	2521 (12.8%)	2260 (13.3%)	261 (9.8%)

N=total number of patients; (Source: IMS® DA. panel)

Table 23**:** Demographic characteristics –PCP

Parameter			**Reference period**			**Assessment period**		
			Total N = 15350	**Incident N = 12746**	**Prevalent N = 2604**	**Total N = 14940**	**Incident N = 12664**	**Prevalent N = 2276**
Age		mean (SD)	54.76 (16.64)	53.67 (16.64)	60.15 (15.55)	52.69 (16.40)	51.53 (16.27)	59.16 (15.60)
		median	54	53	59	52	51	58
		min-max	5-96	5-96	10-96	3-98	3-98	15-98
Age. grouped								
	< 18 years	n (%)	75 (0.5%)	71 (0.6%)	4 (0.2%)	65 (0.4%)	63 (0.5%)	2 (0.1%)
	18-29 years	n (%)	1023 (6.7%)	966 (7.6%)	57 (2.2%)	1271 (8.5%)	1210 (9.6%)	61 (2.7%)
	30-39 years	n (%)	1640 (10.7%)	1477 (11.6%)	163 (6.3%)	1930 (12.9%)	1766 (13.9%)	164 (7.2%)
	40-49 years	n (%)	3294 (21.5%)	2836 (22.3%)	458 (17.6%)	3180 (21.3%)	2784 (22.0%)	396 (17.4%)
	50-59 years	n (%)	3509 (22.9%)	2893 (22.7%)	616 (23.7%)	3631 (24.3%)	3035 (24.0%)	596 (26.2%)
	60-69 years	n (%)	2332 (15.2%)	1839 (14.4%)	493 (18.9%)	2201 (14.7%)	1773 (14.0%)	428 (18.8%)
	≥ 70 years	n (%)	3457 (22.5%)	2654 (20.8%)	803 (30.8%)	2655 (17.8%)	2030 (16.0%)	625 (27.5%)
Gender								
	Male	n (%)	5736 (37.4%)	4888 (38.3%)	848 (32.6%)	6064 (40.6%)	5233 (41.3%)	831 (36.5%)
	Female	n (%)	9610 (62.6%)	7854 (61.6%)	1756 (67.4%)	8872 (59.4%)	7427 (58.6%)	1445 (63.5%)
Insurance status								
	SHI	n (%)	13657 (89%)	11274 (88.5%)	2383 (91.5%)	13352 (89.4%)	11289 (89.1%)	2063 (90.6%)
	Private insurance	n (%)	1693 (11%)	1472 (11.5%)	221 (8.5%)	1588 (10.6%)	1375 (10.9%)	213 (9.4%)

N=total number of patients; (Source: IMS® DA. panel)

Table 24**:** Demographic characteristics – Orthopaedist

Parameter			**Reference period**			**Assessment period**		
			Total N = 6364	**Incident N = 5697**	**Prevalent N = 667**	**Total N = 4734**	**Incident N = 4359**	**Prevalent N = 375**
Age		mean (SD)	54.25 (14.94)	53.67 (14.99)	59.19 (13.65)	52.77 (14.84)	52.25 (14.77)	58.88 (14.38)
		median	54	53	59	52	52	59
		min-max	14-94	14-94	18-93	10-94	10-94	15-93
Age. grouped								
	< 18 years	n (%)	5 (0.1%)	5 (0.1%)	0 (0%)	14 (0.3%)	13 (0.3%)	1 (0.3%)
	18-29 years	n (%)	352 (5.5%)	342 (6%)	10 (1.5%)	304 (6.4%)	297 (6.8%)	7 (1.9%)
	30-39 years	n (%)	667 (10.5%)	635 (11.1%)	32 (4.8%)	540 (11.4%)	520 (11.9%)	20 (5.3%)
	40-49 years	n (%)	1469 (23.1%)	1339 (23.5%)	130 (19.5%)	1128 (23.8%)	1046 (24%)	82 (21.9%)
	50-59 years	n (%)	1602 (25.2%)	1421 (24.9%)	181 (27.1%)	1244 (26.3%)	1163 (26.7%)	81 (21.6%)
	60-69 years	n (%)	1070 (16.8%)	932 (16.4%)	138 (20.7%)	749 (15.8%)	666 (15.3%)	83 (22.1%)
	≥ 70 years	n (%)	1198 (18.8%)	1022 (17.9%)	176 (26.4%)	753 (15.9%)	654 (15%)	99 (26.4%)
Gender								
	Male	n (%)	2328 (36.6%)	2117 (37.2%)	211 (31.6%)	1866 (39.4%)	1754 (40.2%)	112 (29.9%)
	Female	n (%)	4034 (63.4%)	3578 (62.8%)	456 (68.4%)	2863 (60.5%)	2600 (59.6%)	263 (70.1%)
Insurance status								
	SHI	n (%)	5362 (84.3%)	4756 (83.5%)	606 (90.9%)	3801 (80.3%)	3474 (79.7%)	327 (87.2%)
	Private insurance	n (%)	1002 (15.7%)	941 (16.5%)	61 (9.1%)	933 (19.7%)	885 (20.3%)	48 (12.8%)

N=total number of patients; (Source: IMS® DA. panel)

Table 25**:** Medical history – NSAIDs/weak opioids treatment contraindicated patients within 12 months prior to first Flupirtine prescription - Total

Parameter		**Reference period**			**Assessment period**		
		Total N = 21714	**Incident** N = 18443	**Prevalent** N = 3271	**Total** N = 19674	**Incident** N = 17023	**Prevalent** N = 2651
Patients with a 12 months history		**N[1] = 15521**	**N[1] = 12461**	**N[1] = 3060**	**N[1] = 14025**	**N[1] = 11526**	**N[1] = 2499**
Number and percentage of patients identified as contraindicated of NSAIDs/weak opioids treatment the year before index date	n (%[2])	6166 (39.7%)	4757 (38.2%)	1409 (46.0%)	5590 (39.9%)	4376 (38.0%)	1214 (48.6%)

N=total number of patients
[1] : total number of patients with available history
[2] : % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 26**:** Medical history – NSAIDs/weak opioids treatment contraindicated patients within 12 months prior to first Flupirtine prescription - PCP

Parameter		**Reference period**			**Assessment period**		
		Total N = 15350	**Incident** N = 12746	**Prevalent** N = 2604	**Total** N = 14940	**Incident** N = 12664	**Prevalent** N = 2276
Patients with a 12 months history		**N[1] = 12402**	**N[1] = 9933**	**N[1] = 2469**	**N[1] = 11918**	**N[1] = 9741**	**N[1] = 2177**
Number and percentage of patients identified as contraindicated of NSAIDs/weak opioids treatment the year before index date	n (%[2])	6023 (48.6%)	4645 (46.8%)	1378 (55.8%)	5494 (46.1%)	4295 (44.1%)	1199 (55.1%)

N=total number of patients
[1] : total number of patients with available history
[2] : % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 27**:** Medical history – NSAIDs/weak opioids treatment contraindicated patients within 12 months prior to first Flupirtine prescription - Orthopaedist

Parameter		**Reference period**			**Assessment period**		
		Total N = 6364	**Incident** N = 5697	**Prevalent** N = 667	**Total** N = 4734	**Incident** N = 4359	**Prevalent** N = 375
Patients with a 12 months history		**N[1] = 3119**	**N[1] = 2528**	**N[1] = 591**	**N[1] = 2107**	**N[1] = 1785**	**N[1] = 322**
Number and percentage of patients identified as contraindicated of NSAIDs/weak opioids treatment the year before index date	n (%[2])	143 (4.6%)	112 (4.4%)	31 (5.2%)	96 (4.6%)	81 (4.5%)	15 (4.7%)

N=total number of patients
[1] : total number of patients with available history
[2] : % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 28: Medical history – Long-term medications leading to contraindications for Flupirtine patients within 12 months prior to first Flupirtine treatment - Total

Parameter		Reference period			Assessment period		
		Total N = 21714	**Incident** N = 18443	**Prevalent** N = 3271	**Total** N = 19674	**Incident** N = 17023	**Prevalent** N = 2651
Patients with a 12 months history		**N[1] = 15521**	**N[1] = 12461**	**N[1] = 3060**	**N[1] = 14025**	**N[1] = 11526**	**N[1] = 2499**
Number and percentage of long-term therapies leading to contraindication of Flupirtine	n (%[2])	18 (0.1%)	12 (0.1%)	6 (0.2%)	11 (0.1%)	10 (0.1%)	1 (0.0%)

N=total number of patients
[1] : total number of patients with available history
[2] : % based on total number of patients within available history; (Source: IMS® DA. panel)

Table 29: Medical history – Long-term medications leading to contraindications for Flupirtine patients within 12 months prior to first Flupirtine treatment - PCP

Parameter		Reference period			Assessment period		
		Total N = 15350	**Incident** N = 12746	**Prevalent** N = 2604	**Total** N = 14940	**Incident** N = 12664	**Prevalent** N = 2276
Patients with a 12 months history		**N[1] = 12402**	**N[1] = 9933**	**N[1] = 2469**	**N[1] = 11918**	**N[1] = 9741**	**N[1] = 2177**
Number and percentage of long-term therapies leading to contraindication of Flupirtine	n (%[2])	18 (0.1%)	12 (0.1%)	6 (0.2%)	11 (0.1%)	10 (0.1%)	1 (0.0%)

N=total number of patients
[1] : total number of patients with available history
[2] : % based on total number of patients within available history; (Source: IMS® DA. panel)

Table 30: Medical history – Long-term medications leading to contraindications for Flupirtine patients within 12 months prior to first Flupirtine treatment - Orthopaedist

Parameter		Reference period			Assessment period		
		Total N = 6364	**Incident** N = 5697	**Prevalent** N = 667	**Total** N = 4734	**Incident** N = 4359	**Prevalent** N = 375
Patients with a 12 months history		**N[1] = 3119**	**N[1] = 2528**	**N[1] = 591**	**N[1] = 2107**	**N[1] = 1785**	**N[1] = 322**
Number and percentage of long-term therapies leading to contraindication of Flupirtine	n (%[2])	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N=total number of patients
[1] : total number of patients with available history
[2] : % based on total number of patients within available history; (Source: IMS® DA. panel)

Table 31: Acute Patients only, by speciality and by principal and associated diagnosis

	Reference period 2012						Assessment period 2014					
	Total		Incident		Prevalent		Total		Incident		Prevalent	
Diagnosis	N	%	N	%	N	%	N	%	N	%	N	%
Total (PCP + Ortho)												
Flupirtine N1	21,714	%	18,443	%	3,271	%	19,674	%	17,023	%	2,651	%
Total acute patients N2	10,541	(48.5%)	8,835	(47.9%)	1,706	(52.2%)	9,857	(50.1%)	8,426	(49.5%)	1,431	(54.0%)
Out of those:												
Principal*	6,795	(64.5%)	5,514	(62.4%)	1,281	(75.1%)	6,285	(63.8%)	5,212	(61.9%)	1,073	(75.0%)
Associated*	3,746	(35.5%)	3,321	(37.6%)	425	(24.9%)	3,572	(36.2%)	3,214	(38.1%)	358	(25.0%)
PCP												
Flupirtine N1	15,350	%	12,746	%	2,604	%	14,940	%	12,664	%	2,276	%
PCP acute patients N2	8,161	(53.2%)	6,886	(54.0%)	1,275	(49.0%)	8,232	(55.1%)	7,047	(55.6%)	1,185	(52.1%)
Out of those:												
Principal*	5,343	(65.5%)	4,370	(63.5%)	973	(76.3%)	5,198	(63.1%	4,337	(61.5%)	861	(72.7%)
Associated*	2,818	(34.5%)	2,516	(36.5%)	302	(23.7%)	3,034	(36.9%)	2,710	(38.5%)	324	(27.3%)
Ortho												
Flupirtine N1	6,364	%	5,697	%	667	%	4,734	%	4,359	%	375	
Ortho acute patients N2	2,380	(37.4%)	1,949	(34.2%)	431	(64.6%)	1,625	(34.3%)	1,379	(31.6%)	246	(65.6%)
Out of those:												
Principal*	1,452	(61.0%)	1,144	(58.7%)	308	(71.5%)	1,087	(66.9%)	875	(63.5%)	212	(86.2%)
Associated*	928	(39.0%)	805	(41.3%)	123	(28.5%)	538	(33.1%)	504	(36.5%)	34	(13.8%)

N= distinct number of patients with at least one **acute** pain diagnosis, no chronic pain
N1= total number of flupirtine patients
%: based on total number of flupirtine patients (N1)
*:%based on total number of patients from speciality (N2)
(Source: IMS® DA. panel)

Table 32: Chronic Patients only, by speciality and by principal and associated diagnosis

	Reference period 2012						Assessment period 2014					
	Total		Incident		Prevalent		Total		Incident		Prevalent	
Diagnosis	N	%	N	%	N	%	N	%	N	%	N	%
Total (PCP + Ortho)												
Flupirtine N1	21,714	%	18,443	%	3,271	%	19,674	%	17,023	%	2,651	%
Total chronic patients N2	340	(1.6%)	224	(1.2%)	116	(3.5%)	277	(1.4%)	177	(1.0%)	100	(3.8%)
Out of those:												
Principal*	255	(75.0%)	159	(71.0%)	96	(82.8%)	174	(62.8%)	103	(58.2%)	71	(71.0%)
Associated*	85	(25.0%)	65	(29.0%)	20	(17.2%)	103	(37.2%)	74	(41.8%)	29	(29.0%)
PCP												
Flupirtine N1	15,350	%	12,746	%	2,604	%	14,940	%	12,664	%	2,276	%
PCP chronic patients N2	320	(2.1%)	210	(1.6%)	110	(4.2%)	258	(1.7%)	162	(1.3%)	96	(4.2%)
Out of those:												
Principal*	245	(76.6%)	154	(73.3%)	91	(82.7%)	163	(63.2%)	95	(58.6%)	68	(70.8%)
Associated*	75	(23.4%)	56	(26.7%)	19	(17.3%)	95	(36.8%)	67	(41.4%)	28	(29.2%)
Ortho												
Flupirtine N1	6,364	%	5,697	%	667	%	4,734	%	4,359	%	375	%
Ortho chronic patients N2	20	(0.3%)	14	(0.2%)	6	(0.9%)	19	(0.4%)	15	(0.3%)	4	(1.1%)
Out of those:												
Principal*	10	(50.0%)	5	(35.7%)	5	(83.3%)	11	(57.9%)	8	(53.3%)	3	(75.0%)
Associated*	10	(50.0%)	9	(64.3%)	1	(16.7%)	8	(42.1%)	7	(46.7%)	1	(25.0%)

N= distinct number of patients with at least one **chronic** pain diagnosis, no acute pain
N1= total number of flupirtine patients
%: based on total number of flupirtine patients (N1)
*:%based on total number of patients from speciality (N2)
(Source: IMS® DA. panel)

Table 33: Acute and chronic Patients, by speciality and by principal and associated diagnosis

	Reference period 2012						Assessment period 2014					
	Total		Incident		Prevalent		Total		Incident		Prevalent	
Diagnosis	N	%	N	%	N	%	N	%	N	%	N	%
Total (PCP + Ortho)												
Flupirtine N1	21,714	%	18,443	%	3,271	%	19,674	%	17,023	%	2,651	%
Total acute/chronic patients N2	911	4.2%	556	3.0%	355	10.9%	828	4.2%	536	3.1%	292	11.0%
Out of those:												
Principal*	723	79.4%	416	74.8%	307	86.5%	600	72.5%	353	65.9%	247	84.6%
Associated*	188	20.6%	140	25.2%	48	13.5%	228	27.5%	183	34.1%	45	15.4%
PCP												
Flupirtine N1	15,350	%	12,746	%	2,604	%	14,940	%	12,664	%	2,276	%
PCP acute/chronic patients N2	835	5.4%	495	3.9%	340	13.1%	769	5.1%	490	3.9%	279	12.3%
Out of those:												
Principal*	685	82.0%	385	77.8%	300	88.2%	570	74.1%	332	67.8%	238	85.3%
Associated*	150	18.0%	110	22.2%	40	11.8%	199	25.9%	158	32.2%	41	14.7%
Ortho												
Flupirtine N1	6,364	%	5,697	%	667	%	4,734	%	4,359	%	375	%
Ortho acute/chronic patients N2	76	1.2%	61	1.1%	15	2.2%	59	1.2%	46	1.1%	13	3.5%
Out of those:												
Principal*	38	50.0%	31	50.8%	7	46.7%	30	50.8%	21	45.7%	9	69.2%
Associated*	38	50.0%	30	49.2%	8	53.3%	29	49.2%	25	54.3%	4	30.8%

N= distinct number of patients with **acute and chronic** pain diagnosis
N1= total number of flupirtine patients
%: based on total number of flupirtine patients (N1)
*:%based on total number of patients from speciality (N2)
(Source: IMS® DA. panel)

Table 34***:*** *Medical history – Indication for Flupirtine prescription (ICD-10 codes), during analysis period- Total; Patients with at least one linked diagnosis to flupirtine prescription*

	Reference period 2012						***Assessment period 2014***					
	Total		***Incident***		***Prevalent***		***Total***		***Incident***		***Prevalent***	
	N	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***
Total	11,497	(53.5%)	9,478	(51.4%)	2,019	(61.7%)	10,531	(53.5%)	8,892	(52.2%)	1,639	(61.8%)
PCP	8,522	(55.5%)	6,895	(54.1%)	1,627	(62.5%)	7,971	(53.4%)	6,599	(52.1%)	1,372	(60.3%)
Ortho	2,975	(46.7%)	2,583	(45.3%)	392	(58.8%)	2,560	(54.1%)	2,293	(52.6%)	267	(71.2%)

N=total number of patients with linked flupirtine prescription;(Source: IMS® DA, panel)
%: based on total number of flupirtine patients
(Source: IMS® DA. panel)

Table 35**:** Medical history – Indication for Flupirtine prescription (ICD-10 codes) during analysis period- Total

Parameter		**Reference period**			**Assessment period**		
		Total	**Incident**	**Prevalent**	**Total**	**Incident**	**Prevalent**
		N = 21714	**N = 18443**	**N = 3271**	**N = 19674**	**N = 17023**	**N = 2651**
Principal diagnosis*							
DORSALGIA: M54	n (%)	**6131 (28.2%)**	**4586 (24.9%)**	**1545 (47.2%)**	**4921 (25.0%)**	**3889 (22.8%)**	**1032 (38.9%)**
OTHER DORSOPATHIES NEC: M53	n (%)	1588 (7.3%)	1006 (5.5%)	582 (17.8%)	1164 (5.9%)	777 (4.6%)	387 (14.6%)
PAIN NEC: R52	n (%)	1452 (6.7%)	515 (2.8%)	**937 (28.6%)**	949 (4.8%)	328 (1.9%)	**621 (23.4%)**
INTERVERT DISC DISORDER: M51	n (%)	996 (4.6%)	650 (3.5%)	346 (10.6%)	869 (4.4%)	571 (3.4%)	298 (11.2%)
SPONDYLOSIS: M47	n (%)	930 (4.3%)	568 (3.1%)	362 (11.1%)	902 (4.6%)	666 (3.9%)	236 (8.9%)
OTHER SOFT TISSIUE DISORDER NEC: M79	n (%)	806 (3.7%)	480 (2.6%)	326 (10.0%)	571 (2.9%)	297 (1.7%)	274 (10.3%)
BIOMECHAN LESIONS NEC: M99	n (%)	724 (3.3%)	659 (3.6%)	65 (2.0%)	779 (4.0%)	704 (4.1%)	75 (2.8%)
OTHER DISORDERS OF MUSCLE: M62	n (%)	661 (3.0%)	518 (2.8%)	143 (4.4%)	775 (3.9%)	636 (3.7%)	139 (5.2%)
CERVICAL DISC DISORDERS: M50	n (%)	280 (1.3%)	183 (1.0%)	97 (3.0%)	161 (0.8%)	87 (0.5%)	74 (2.8%)
GONARTHROSIS(KNEE): M17	n (%)	224 (1.0%)	119 (0.6%)	105 (3.2%)	160 (0.8%)	66 (0.4%)	94 (3.5%)
Associated with acute pain							
DORSALGIA: M54	n (%)	**5942 (27.4%)**	**5342 (29.0%)**	**600 (18.3%)**	**5169 (26.3%)**	**4704 (27.6%)**	**465 (17.5%)**
BIOMECHAN LESIONS NEC: M99	n (%)	1493 (6.9%)	1400 (7.6%)	93 (2.8%)	1692 (8.6%)	1600 (9.4%)	92 (3.5%)
INTERVERT DISC DISORDER: M51	n (%)	1219 (5.6%)	1102 (6%)	117 (3.6%)	1007 (5.1%)	908 (5.3%)	99 (3.7%)
OTHER DORSOPATHIES NEC: M53	n (%)	1216 (5.6%)	1093 (5.9%)	123 (3.8%)	792 (4%)	692 (4.1%)	100 (3.8%)
SPONDYLOSIS: M47	n (%)	1185 (5.5%)	1058 (5.7%)	127 (3.9%)	871 (4.4%)	787 (4.6%)	84 (3.2%)
OTHER DISORDERS OF MUSCLE: M62	n (%)	659 (3.0%)	596 (3.2%)	63 (1.9%)	789 (4.0%)	736 (4.3%)	53 (2.0%)
SPINAL OSTEOCHONDROSIS: M42	n (%)	344 (1.6%)	301 (1.6%)	43 (1.3%)	268 (1.4%)	247 (1.5%)	21 (0.8%)
OTHER SPONDYLOPATHIES: M48	n (%)	336 (1.5%)	265 (1.4%)	71 (2.2%)	193 (1.0%)	156 (0.9%)	37 (1.4%)
UNK/UNSP CAUSE MORBIDITY: R69	n (%)	280 (1.3%)	245 (1.3%)	35 (1.1%)	239 (1.2%)	205 (1.2%)	34 (1.3%)
GONARTHROSIS(KNEE): M17	n (%)	275 (1.3%)	214 (1.2%)	61 (1.9%)	156 (0.8%)	109 (0.6%)	47 (1.8%)
Associated with chronic pain							
OTHER CHRONIC PAIN: R522	n (%)	**427 (2.0%)**	**271 (1.5%)**	**156 (4.8%)**	**470 (2.4%)**	**250 (1.5%)**	**220 (8.3%)**
PERSIS SOMATORM PAIN DIS: F454	n (%)	62 (0.3%)	58 (0.3%)	4 (0.1%)	91 (0.5%)	62 (0.4%)	29 (1.1%)
CHRONIC INTRACTABLE PAIN: R521	n (%)	54 (0.2%)	41 (0.2%)	13 (0.4%)	48 (0.2%)	36 (0.2%)	12 (0.5%)
PERSONALTIY CHANGES: F628	n (%)	23 (0.1%)	22 (0.1%)	1 (0.0%)	6 (0.0%)	5 (0.0%)	1 (0.0%)

N=total number of patients;(Source: IMS® DA. panel)
*NEC: not elsewhere classified

Table 36**:** Medical history – Indication for Flupirtine prescription (ICD-10 codes) during analysis period- PCP

Parameter		Reference period			Assessment period		
		Total N = 15350	Incident N = 12746	Prevalent N = 2604	Total N = 14940	Incident N = 12664	Prevalent N = 2276
Principal diagnosis*							
DORSALGIA: M54	n (%)	4600 (30.0%)	3360 (26.4%)	1240 (47.6%)	4111 (27.5%)	3199 (25.3%)	912 (40.1%)
OTHER DISORDERS OF MUSCLE: R52	n (%)	1422 (9.3%)	494 (3.9%)	928 (35.6%)	926 (6.2%)	314 (2.5%)	612 (26.9%)
OTHER DORSOPATHIES NEC: M53	n (%)	921 (6%)	624 (4.9%)	297 (11.4%)	813 (5.4%)	560 (4.4%)	253 (11.1%)
OTHER DISORDERS OF MUSCLE: M62	n (%)	748 (4.9%)	421 (3.3%)	327 (12.6%)	620 (4.1%)	345 (2.7%)	275 (12.1%)
INTERVERT DISC DISORDER: M51	n (%)	726 (4.7%)	411 (3.2%)	315 (12.1%)	517 (3.5%)	249 (2.0%)	268 (11.8%)
BIOMECHAN LESIONS NEC: M99	n (%)	661 (4.3%)	350 (2.7%)	311 (11.9%)	448 (3.0%)	259 (2.0%)	189 (8.3%)
OTHER SOFT TISS DISORDER NEC:. M79	n (%)	568 (3.7%)	435 (3.4%)	133 (5.1%)	706 (4.7%)	574 (4.5%)	132 (5.8%)
SPONDYLOSIS: M47	n (%)	523 (3.4%)	475 (3.7%)	48 (1.8%)	528 (3.5%)	484 (3.8%)	44 (1.9%)
OTHER JOINT DISORDERS NEC: M25	n (%)	223 (1.5%)	139 (1.1%)	84 (3.2%)	116 (0.8%)	49 (0.4%)	67 (2.9%)
CERVICAL DISC DISORDERS: M50	n (%)	178 (1.2%)	141 (1.1%)	37 (1.4%)	101 (0.7%)	87 (0.7%)	14 (0.6%)
Associated with acute pain							
DORSALGIA: M54	n (%)	4028 (26.2%)	3568 (28.0%)	460 (17.7%)	4121 (27.6%)	3720 (29.4%)	401 (17.6%)
BIOMECHAN LESIONS NEC: M99	n (%)	638 (4.2%)	582 (4.6%)	56 (2.2%)	944 (6.3%)	860 (6.8%)	84 (3.7%)
INTERVERT DISC DISORDER: M51	n (%)	621 (4.0%)	547 (4.3%)	74 (2.8%)	563 (3.8%)	488 (3.9%)	75 (3.3%)
OTHER DORSOPATHIES NEC: M53	n (%)	586 (3.8%)	494 (3.9%)	92 (3.5%)	560 (3.7%)	478 (3.8%)	82 (3.6%)
OTHER DISORDERS OF MUSCLE: M62	n (%)	414 (2.7%)	366 (2.9%)	48 (1.8%)	511 (3.4%)	466 (3.7%)	45 (2.0%)
SPONDYLOSIS: M47	n (%)	411 (2.7%)	346 (2.7%)	65 (2.5%)	387 (2.6%)	322 (2.5%)	65 (2.9%)
SLEEP DISORDERS: G47	n (%)	196 (1.3%)	137 (1.1%)	59 (2.3%)	228 (1.5%)	138 (1.1%)	90 (4.0%)
OTHER DISORDERS OF MUSCLE R52	n (%)	193 (1.3%)	141 (1.1%)	52 (2.0%)	194 (1.3%)	147 (1.2%)	47 (2.1%)
UNK/UNSP CAUSE MORBID: R69	n (%)	180 (1.2%)	147 (1.2%)	33 (1.3%)	208 (1.4%)	174 (1.4%)	34 (1.5%)
GONARTHROSIS(KNEE): M17	n (%)	144 (0.9%)	99 (0.8%)	45 (1.7%)	98 (0.7%)	63 (0.5%)	35 (1.5%)
Associated with chronic pain							
OTHER CHRONIC PAIN: R522	n (%)	381 (2.5%)	233 (1.8%)	148 (5.7%)	427 (2.9%)	210 (1.7%)	217 (9.5%)
PERSIS SOMATORM PAIN DIS: F454	n (%)	53 (0.3%)	41 (0.3%)	12 (0.5%)	47 (0.3%)	36 (0.3%)	11 (0.5%)
CHRONIC INTRACTABLE PAIN: R521	n (%)	41 (0.3%)	37 (0.3%)	4 (0.2%)	75 (0.5%)	49 (0.4%)	26 (1.1%)
PERSONALTIY CHANGES: F628	n (%)	23 (0.1%)	22 (0.2%)	1 (0.0%)	6 (0.0%)	5 (0.0%)	1 (0.0%)

N=total number of patients;(Source: IMS® DA. panel)
*NEC: not elsewhere classified

Table 37**:** Medical history – Indication for Flupirtine prescription (ICD-10 codes) during analysis period- Orthopaedist

Parameter		**Reference period**			**Assessment period**		
		Total	**Incident**	**Prevalent**	**Total**	**Incident**	**Prevalent**
		N = 6364	**N = 5697**	**N = 667**	**N = 4734**	**N = 4359**	**N = 375**
Principal diagnosis*							
DORSALGIA: M54	n (%)	1531 (24.1%)	1226 (21.5%)	305 (45.7%)	810 (17.1%)	690 (15.8%)	120 (32%)
OTHER DORSOPATHIES NEC: M53	n (%)	667 (10.5%)	382 (6.7%)	285 (42.7%)	351 (7.4%)	217 (5.0%)	134 (35.7%)
SPONDYLOSIS: M47	n (%)	269 (4.2%)	218 (3.8%)	51 (7.6%)	454 (9.6%)	407 (9.3%)	47 (12.5%)
INTERVERT DISC DISORDER: M51	n (%)	248 (3.9%)	229 (4.0%)	19 (2.8%)	249 (5.3%)	226 (5.2%)	23 (6.1%)
BIOMECHAN LESIONS NEC: M99	n (%)	201 (3.2%)	184 (3.2%)	17 (2.5%)	251 (5.3%)	220 (5.0%)	31 (8.3%)
SHOULDER LESIONS: M75	n (%)	116 (1.8%)	102 (1.8%)	14 (2.1%)	80 (1.7%)	61 (1.4%)	19 (5.1%)
OTHER DISORDERS OF MUSCLE: M62	n (%)	93 (1.5%)	83 (1.5%)	10 (1.5%)	69 (1.5%)	62 (1.4%)	7 (1.9%)
OTH SOFT TISS DIS NEC: M79	n (%)	80 (1.3%)	69 (1.2%)	11 (1.6%)	54 (1.1%)	48 (1.1%)	6 (1.6%)
SPINAL OSTEOCHONDROSIS: M42	n (%)	73 (1.1%)	53 (0.9%)	20 (3.0%)	54 (1.1%)	41 (0.9%)	13 (3.5%)
GONARTHROSIS(KNEE): M17	n (%)	63 (1.0%)	41 (0.7%)	22 (3.3%)	80 (1.7%)	43 (1.0%)	37 (9.9%)
Associated with acute pain							
DORSALGIA: M54	n (%)	1914 (30.1%)	1774 (31.1%)	140 (21.0%)	1048 (22.1%)	984 (22.6%)	64 (17.1%)
BIOMECHAN LESIONS NEC: M99	n (%)	855 (13.4%)	818 (14.4%)	37 (5.5%)	748 (15.8%)	740 (17.0%)	8 (2.1%)
SPONDYLOSIS: M47	n (%)	774 (12.2%)	712 (12.5%)	62 (9.3%)	484 (10.2%)	465 (10.7%)	19 (5.1%)
OTHER DORSOPATHIES NEC M53	n (%)	630 (9.9%)	599 (10.5%)	31 (4.6%)	232 (4.9%)	214 (4.9%)	18 (4.8%)
INTERVERT DISC DISORDER: M51	n (%)	598 (9.4%)	555 (9.7%)	43 (6.4%)	444 (9.4%)	420 (9.6%)	24 (6.4%)
OTHER DISORDERS OF MUSCLE: M62	n (%)	245 (3.8%)	230 (4.0%)	15 (2.2%)	278 (5.9%)	270 (6.2%)	8 (2.1%)
SPINAL OSTEOCHONDROSIS: M42	n (%)	244 (3.8%)	221 (3.9%)	23 (3.4%)	170 (3.6%)	169 (3.9%)	1 (0.3%)
OTHER SPONDYLOPATHIES: M48	n (%)	203 (3.2%)	167 (2.9%)	36 (5.4%)	88 (1.9%)	82 (1.9%)	6 (1.6%)
CERVICAL DISC DISORDERS: M50	n (%)	162 (2.5%)	142 (2.5%)	20 (3.0%)	130 (2.7%)	122 (2.8%)	8 (2.1%)
OTH DEFORMING DORSOPATHY: M43	n (%)	134 (2.1%)	130 (2.3%)	4 (0.6%)	92 (1.9%)	89 (2.0%)	3 (0.8%)
Associated with chronic pain							
OTHER CHRONIC PAIN: R522	n (%)	46 (0.7%)	38 (0.7%)	8 (1.2%)	43 (0.9%)	40 (0.9%)	3 (0.8%)

N=total number of patients;(Source: IMS® DA. panel)
*NEC: not elsewhere classified

Table 38: Number and percentage of patients with concomitant **acute or chronic pain** diagnosis based on annex (i), two weeks around flupirtine prescription (linked/principal diagnoses are not included)

	Reference period 2012						**Assessment period 2014**					
	Total		**Incident**		**Prevalent**		**Total**		**Incident**		**Prevalent**	
	N	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**
Total	n=15,521		n=12,461		n=3,060		n=14,025		n=11,526		n=2,499	
	11,854	(76.4%)	9,668	(77.6%)	2,186	(71.4%)	11,061	(78.9%)	9,229	(80.1%)	1,832	(73.3%)
PCP	n=12,402		n=9,933		n=2,469		n=11,918		n=9,741		n=2,177	
	9,364	(75.5%)	7,632	(76.8%)	1,732	(70.1%)	9,340	(78.4%)	7,775	(79.8%)	1,565	(71.9%)
Ortho	n=3,119		n=2,528		n=591		n=2,107		n=1,785		n=322	
	2,490	(79.8%)	2,036	(80.5%)	454	(76.8%)	1,721	(81.7%)	1,454	(81.5%)	267	(82.9%)

N=Distinct number of patients with acute or chronic pain related diagnosis within 2 weeks around flupirtine Rx.
n=Number of patients with an available history of at least 12 months prior to first flupirtine prescription
%1: based on n
(Source: IMS® DA. panel)

Table 39: Medical history – Concomitant diseases of Flupirtine patients 2 weeks before and after Flupirtine prescription- Total

Parameter		Reference period			Assessment period		
		Total	Incident	Prevalent	Total	Incident	Prevalent
		N = 21714	N = 18443	N = 3271	N = 19674	N = 17023	N = 2651
Patients with a 12 months history		**N[1] = 15521**	**N[1] = 12461**	**N[1] = 3060**	**N[1] = 14025**	**N[1] = 11526**	**N[1] = 2499**
ICD Level 3							
Co-diagnosis							
DORSALGIA: M54	n (%[2])	6902 (44.5%)	5814 (46.7%)	1088 (35.6%)	6609 (47.1%)	5672 (49.2%)	937 (37.5%)
ESSENTIAL (PRIMARY) HYPERTENSION: I10	n (%[2])	2088 (13.5%)	1403 (11.3%)	685 (22.4%)	1631 (11.6%)	1143 (9.9%)	488 (19.5%)
OTHER DORSOPATHIES NEC: M53	n (%[2])	1632 (10.5%)	1292 (10.4%)	340 (11.1%)	1417 (10.1%)	1146 (9.9%)	271 (10.8%)
BIOMECHAN LESIONS NEC: M99	n (%[2])	1558 (10.0%)	1391 (11.2%)	167 (5.5%)	1640 (11.7%)	1488 (12.9%)	152 (6.1%)
INTERVERT DISC DISORDER: M51	n (%[2])	1302 (8.4%)	1028 (8.2%)	274 (9.0%)	1133 (8.1%)	909 (7.9%)	224 (9.0%)
SPONDYLOSIS: M47	n (%[2])	1189 (7.7%)	926 (7.4%)	263 (8.6%)	1085 (7.7%)	879 (7.6%)	206 (8.2%)
PAIN NEC:R52	n (%[2])	1152 (7.4%)	711 (5.7%)	441 (14.4%)	999 (7.1%)	638 (5.5%)	361 (14.4%)
OTHER DISORDERS OF MUSCLE: M62	n (%[2])	1040 (6.7%)	887 (7.1%)	153 (5.0%)	1228 (8.8%)	1069 (9.3%)	159 (6.4%)
OTHER SOFT TISSIUE DISORDER NEC: M79	n (%[2])	948 (6.1%)	712 (5.7%)	236 (7.7%)	809 (5.8%)	658 (5.7%)	151 (6.0%)
DEPRESSIVE EPISODE: F32	n (%[2])	653 (4.2%)	387 (3.1%)	266 (8.7%)	483 (3.4%)	271 (2.4%)	212 (8.5%)

N=total number of patients
[1]: total number of patients with available history
[2]: % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 40: Medical history – Concomitant diseases of Flupirtine patients 2 weeks before and after Flupirtine prescription- PCP

Parameter		Reference period			Assessment period		
		Total	Incident	Prevalent	Total	Incident	Prevalent
		N = 15350	N = 12746	N = 2604	N = 14940	N = 12664	N = 2276
Patients with a 12 months history		**N[1] = 12402**	**N[1] = 9933**	**N[1] = 2469**	**N[1] = 11918**	**N[1] = 9741**	**N[1] = 2177**
ICD Level 3							
Co-diagnosis							
DORSALGIA: M54	n (%[2])	5557 (44.8%)	4701 (47.3%)	856 (34.7%)	5784 (48.5%)	4984 (51.2%)	800 (36.7%)
ESSENTIAL (PRIMARY) HYPERTENSION: I10	n (%[2])	2074 (16.7%)	1389 (14.0%)	685 (27.7%)	1618 (13.6%)	1130 (11.6%)	488 (22.4%))
BIOMECHAN LESIONS NEC: M99	n (%[2])	963 (7.8%)	863 (8.7%)	100 (4.1%)	1209 (10.1%)	1085 (11.1%)	124 (5.7%)
OTHER DORSOPATHIES NEC: M53	n (%[2])	1114 (9.0%)	908 (9.1%)	206 (8.3%)	1094 (9.2%)	911 (9.4%)	183 (8.4%)
OTHER DISORDERS OF MUSCLE: M62	n (%[2])	818 (6.6%)	693 (7.0%)	125 (5.1%)	1077 (9.0%)	933 (9.6%)	144 (6.6%)
PAIN NEC: R52	n (%[2])	1067 (8.6%)	646 (6.5%)	421 (17.1%)	939 (7.9%)	592 (6.1%)	347 (15.9%)
INTERVERT DISC DISORDER: M51	n (%[2])	983 (7.9%)	748 (7.5%)	235 (9.5%)	841 (7.1%)	655 (6.7%)	186 (8.5%)
OTHER SOFT TISSIUE DISORDER NEC: M79	n (%[2])	853 (6.9%)	639 (6.4%)	214 (8.7%)	743 (6.2%)	601 (6.2%)	142 (6.5%)
SPONDYLOSIS: M47	n (%[2])	747 (6.0%)	567 (5.7%)	180 (7.3%)	673 (5.6%)	522 (5.4%)	151 (6.9%)
DIS-LIPOPROT MET/LIPIDM. E78	n (%[2])	625 (5.0%)	380 (3.8%)	245 (9.9%)	515 (4.3%)	335 (3.4%)	180 (8.3%)

N=total number of patients
[1]: total number of patients with available history
[2]: % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 41: Medical history – Concomitant diseases of Flupirtine patients 2 weeks before and after Flupirtine prescription- Orthopaedist

Parameter		Reference period			Assessment period		
		Total	Incident	Prevalent	Total	Incident	Prevalent
		N = 6364	N = 5697	N = 667	N = 4734	N = 4359	N = 375
Patients with a 12 months history		**N[1] = 3119**	**N[1] = 2528**	**N[1] = 591**	**N[1] = 2107**	**N[1] = 1785**	**N[1] = 322**
ICD Level 3							
Co-diagnosis							
DORSALGIA:M54	n (%[2])	1345 (43.1%)	1113 (44.0%)	232 (39.3%)	825 (39.2%)	688 (38.5%)	137 (42.5%)
BIOMECHAN LESIONS NEC: M99	n (%[2])	595 (19.1%)	528 (20.9%)	67 (11.3%)	431 (20.5%)	403 (22.6%)	28 (8.7%)
OTHER DORSOPATHIES NEC: M53	n (%[2])	518 (16.6%)	384 (15.2%)	134 (22.7%)	323 (15.3%)	235 (13.2%)	88 (27.3%)
SPONDYLOSIS: M47	n (%[2])	442 (14.2%)	359 (14.2%)	83 (14.0%)	412 (19.6%)	357 (20.0%)	55 (17.1%)
INTERVERT DISC DISORDER: M51	n (%[2])	319 (10.2%)	280 (11.1%)	39 (6.6%)	292 (13.9%)	254 (14.2%)	38 (11.8%)
OTHER DISORDERS OF MUSCLE: M62	n (%[2])	222 (7.1%)	194 (7.7%)	28 (4.7%)	151 (7.2%)	136 (7.6%)	15 (4.7%)
SHOULDER LESIONS: M75	n (%[2])	205 (6.6%)	163 (6.4%)	42 (7.1%)	161 (7.6%)	138 (7.7%)	23 (7.1%)
SPINAL OSTEOCHONDROSIS: M42	n (%[2])	191 (6.1%)	154 (6.1%)	37 (6.3%)	116 (5.5%)	103 (5.8%)	13 (4.0%)
GONARTHROSIS(KNEE): M17	n (%[2])	140 (4.5%)	104 (4.1%)	36 (6.1%)	97 (4.6%)	60 (3.4%)	37 (11.5%)
OTHER SPONDYLOPATHIES. M48	n (%[2])	128 (4.1%)	100 (4.0%)	28 (4.7%)	121 (5.7%)	104 (5.8%)	17 (5.3%)

N=total number of patients
1: total number of patients with available history
2: % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 42: Number and percentage of overall patients with pain therapies based on annex (ii) related to flupirtine.

	Reference period 2012						**Assessment period 2014**					
	Total		**Incident**		**Prevalent**		**Total**		**Incident**		**Prevalent**	
	N	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**	**N**	**%1**
Total	n=15,521		n=12,461		n=3,060		n=14,025		n=11,526		n=2,499	
	5,303	(34.2%)	3,956	(31.7%)	1,347	(44.0%)	4,616	(32.9%)	3,462	(30.0%)	1,154	(46.1%)
PCP	n=12,402		n=9,933		n=2,469		n=11,918		n=9,741		n=2,177	
	4,407	(35.5%)	3,256	(32.8%)	1,151	(46.6%)	3,943	(33.1%)	2,918	(30.0%)	1,025	(47.1%)
Ortho	n=3,119		n=2,528		n=591		n=2,107		n=1,785		n=322	
	896	(28.7%)	700	(27.7%)	196	(33.2%)	673	(31.9%)	544	(30.5%)	129	(40.1%)

N=Distinct number of patients with acute or chronic pain related diagnosis within 2 weeks around flupirtine Rx.
n=Number of patients with an available history of at least 12 months prior to first flupirtine prescription
%1: based n
(Source: IMS® DA. panel)

Table 43: Therapies related to Flupirtine treatment - Total

Parameter			Reference period			Assessment period		
			Total	Incident	Prevalent	Total	Incident	Prevalent
			N = 21714	N = 18443	N = 3271	N = 19674	N = 17023	N = 2651
Patients with a 12 months history			**N[1] = 15521**	**N[1] = 12461**	**N[1] = 3060**	**N[1] = 14025**	**N[1] = 11526**	**N[1] = 2499**
Therapies associated with acute or chronic pain within 12 months prior flupirtine exposure	**WHO ATC**							
	IBUPROFEN: M01AE01	n (%[2])	1579 (10.2%)	1238 (9.9%)	341 (11.1%)	1390 (9.9%)	1101 (9.6%)	289 (11.6%)
	DICLOFENAC: M01AB05	n (%[2])	1135 (7.3%)	888 (7.1%)	247 (8.1%)	841 (6.0%)	653 (5.7%)	188 (7.5%)
	METAMIZOLE SODIUM: N02BB02	n (%[2])	1005 (6.5%)	710 (5.7%)	295 (9.6%)	897 (6.4%)	637 (5.5%)	260 (10.4%)
	TETRAZEPAM: M03BX07	n (%[2])	517 (3.3%)	421 (3.4%)	96 (3.1%)	160 (1.1%)	94 (0.8%)	66 (2.6%)
	TRAMADOL: N02AX02	n (%[2])	372 (2.4%)	243 (2.0%)	129 (4.2%)	259 (1.8%)	167 (1.4%)	92 (3.7%)
	TILIDIN: N02AX51	n (%[2])	351 (2.3%)	223 (1.8%)	128 (4.2%)	281 (2.0%)	182 (1.6%)	99 (4.0%)
	ETORICOXIB: M01AH05	n (%[2])	299 (1.9%)	224 (1.8%)	75 (2.5%)	281 (2.0%)	218 (1.9%)	63 (2.5%)
	TELPERISONE: M03BX04	n (%[2])	210 (1.4%)	167 (1.3%)	43 (1.4%)	110 (0.8%)	79 (0.7%)	31 (1.2%)
	PANTOPRAZOLE: A02BC02	n (%[2])	180 (1.2%)	137 (1.1%)	43 (1.4%)	211 (1.5%)	155 (1.3%)	56 (2.2%)
	ZOLPIDEM: N05CF02	n (%[2])	148 (1.0%)	102 (0.8%)	46 (1.5%)	117 (0.8%)	80 (0.7%)	37 (1.5%)
Concomitant prescriptions within analysis period								
	IBUPROFEN : M01AE01	n (%)	6150 (28.3%)	5288 (28.7%)	862 (26.4%)	6092 (31.0%)	5341 (31.4%)	751 (28.3%)
	METAMIZOLE SODIUM: N02BB02	n (%)	4748 (21.9%)	3887 (21.1%)	861 (26.3%)	4730 (24.0%)	3966 (23.3%)	764 (28.8%)
	DICLOFENAC: M01AB05	n (%)	4243 (19.5%)	3680 (20.0%)	563 (17.2%)	3631 (18.5%)	3198 (18.8%)	433 (16.3%)
	PANTOPRAZOLE: A02BC02	n (%)	4034 (18.6%)	3175 (17.2%)	859 (26.3%)	4134 (21.0%)	3332 (19.6%)	802 (30.3%)
	OMEPRAZOLE: A02BC01	n (%)	1971 (9.1%)	1499 (8.1%)	472 (14.4%)	1583 (8.0%)	1227 (7.2%)	356 (13.4%)
	LEVOTHYROXINE SODIUM: H03AA01	n (%)	1963 (9.0%)	1538 (8.3%)	425 (13.0%)	1849 (9.4%)	1493 (8.8%)	356 (13.4%)
	SIMVASTATIN: C10AA01	n (%)	1723 (7.9%)	1298 (7.0%)	425 (13.0%)	1251 (6.4%)	937 (5.5%)	314 (11.8%)
	METOCLOPRAMIDE: A03FA01	n (%)	1681 (7.7%)	1289 (7.0%)	392 (12.0%)	1033 (5.3%)	830 (4.9%)	203 (7.7%)
	TETRAZEPAM: M03BX07	n (%)	1591 (7.3%)	1392 (7.5%)	199 (6.1%)	18 (0.1%)	12 (0.1%)	6 (0.2%)
	ETORICOXIB: M01AH05	n (%)	1513 (7.0%)	1295 (7.0%)	218 (6.7%)	1510 (7.7%)	1297 (7.6%)	213 (8.0%)

N=total number of patients
[1]: total number of patients with available history
[2]: % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 44: Therapies related to Flupirtine treatment - PCP

Parameter			Reference period			Assessment period		
			Total	Incident	Prevalent	Total	Incident	Prevalent
			N = 15350	N = 12746	N = 2604	N = 14940	N = 12664	N = 2276
Patients with a 12 months history			**N[1] = 12402**	**N[1] = 9933**	**N[1] = 2469**	**N[1] = 11918**	**N[1] = 9741**	**N[1] = 2177**
Therapies associated with acute or chronic pain within 12 months prior flupirtine exposure	**WHO ATC**							
	IBUPROFEN : M01AE01	n (%[2])	1302 (10.5%)	1010 (10.2%)	292 (11.8%)	1215 (10.2%)	951 (9.8%)	264 (12.1%)
	DICLOFENAC: M01AB05	n (%[2])	953 (7.7%)	741 (7.5%)	212 (8.6%)	724 (6.1%)	557 (5.7%)	167 (7.7%)
	METAMIZOLE SODIUM: N02BB02	n (%[2])	881 (7.1%)	617 (6.2%)	264 (10.7%)	802 (6.7%)	567 (5.8%)	235 (10.8%)
	TETRAZEPAM: M03BX07	n (%[2])	424 (3.4%)	344 (3.5%)	80 (3.2%)	128 (1.1%)	73 (0.7%)	55 (2.5%)
	TRAMADOL: N02AX02	n (%[2])	316 (2.5%)	203 (2%)	113 (4.6%)	221 (1.9%)	144 (1.5%)	77 (3.5%)
	TILIDIN: N02AX51	n (%[2])	306 (2.5%)	195 (2%)	111 (4.5%)	244 (2%)	151 (1.6%)	93 (4.3%)
	ETORICOXIB:M01AH05	n (%[2])	244 (2%)	183 (1.8%)	61 (2.5%)	222 (1.9%)	168 (1.7%)	54 (2.5%)
	TELPERISONE: M03BX04	n (%[2])	165 (1.3%)	129 (1.3%)	36 (1.5%)	81 (0.7%)	58 (0.6%)	23 (1.1%)
	PANTOPRAZOLE: A02BC02	n (%[2])	153 (1.2%)	115 (1.2%)	38 (1.5%)	187 (1.6%)	132 (1.4%)	55 (2.5%)
	ZOLPIDEM: N05CF02	n (%[2])	148 (1.2%)	102 (1%)	46 (1.9%)	117 (1%)	80 (0.8%)	37 (1.7%)
Concomitant prescriptions within analysis period	IBUPROFEN : M01AE01	n (%)	4642 (30.2%)	3925 (30.8%)	717 (27.5%)	4838 (32.4%)	4164 (32.9%)	674 (29.6%)
	METAMIZOLE SODIUM: N02BB02	n (%)	3809 (24.8%)	3040 (23.9%)	769 (29.5%)	3795 (25.4%)	3086 (24.4%)	709 (31.2%)
	PANTOPRAZOLE: A02BC02	n (%)	3752 (24.4%)	2920 (22.9%)	832 (32%)	3839 (25.7%)	3055 (24.1%)	784 (34.4%)
	DICLOFENAC: M01AB05	n (%)	3210 (20.9%)	2738 (21.5%)	472 (18.1%)	2662 (17.8%)	2288 (18.1%)	374 (16.4%)
	LEVOTHYROXINE SODIUM: H03AA01	n (%)	1958 (12.8%)	1533 (12%)	425 (16.3%)	1846 (12.4%)	1490 (11.8%)	356 (15.6%)
	OMEPRAZOL: A02BC01	n (%)	1775 (11.6%)	1326 (10.4%)	449 (17.2%)	1295 (8.7%)	953 (7.5%)	342 (15%)
	SIMVASTATIN: C10AA01	n (%)	1720 (11.2%)	1295 (10.2%)	425 (16.3%)	1250 (8.4%)	936 (7.4%)	314 (13.8%)
	METOCLOPRAMIDE: A03FA01	n (%)	1663 (10.8%)	1273 (10%)	390 (15%)	1024 (6.9%)	822 (6.5%)	202 (8.9%)
	RAMIPRIL: C09AA05	n (%)	1473 (9.6%)	1145 (9%)	328 (12.6%)	1237 (8.3%)	952 (7.5%)	285 (12.5%)
	BISOPROLOL:C07AB07	n (%)	1387 (9%)	1061 (8.3%)	326 (12.5%)	1203 (8.1%)	952 (7.5%)	251 (11%)

N=total number of patients
[1]: total number of patients with available history
[2]: % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 45: Therapies related to Flupirtine treatment - Orthopaedist

Parameter			Reference period			Assessment period		
			Total	Incident	Prevalent	Total	Incident	Prevalent
			N = 6364	N = 5697	N = 667	N = 4734	N = 4359	N = 375
Patients with a 12 months history			**N[1] = 3119**	**N[1] = 2528**	**N[1] = 591**	**N[1] = 2107**	**N[1] = 1785**	**N[1] = 322**
Therapies associated with acute or chronic pain within 12 months prior flupirtine exposure	**WHO ATC**							
	IBUPROFEN : M01AE01	n (%[2])	277 (8.9%)	228 (9%)	49 (8.3%)	175 (8.3%)	150 (8.4%)	25 (7.8%)
	DICLOFENAC: M01AB05	n (%[2])	182 (5.8%)	147 (5.8%)	35 (5.9%)	117 (5.6%)	96 (5.4%)	21 (6.5%)
	METAMIZOLE SODIUM: N02BB02	n (%[2])	124 (4.0%)	93 (3.7%)	31 (5.2%)	95 (4.5%)	70 (3.9%)	25 (7.8%)
	TETRAZEPAM: M03BX07	n (%[2])	93 (3.0%)	77 (3.0%)	16 (2.7%)	32 (1.5%)	21 (1.2%)	11 (3.4%)
	TRAMADOL: N02AX02	n (%[2])	56 (1.8%)	40 (1.6%)	16 (2.7%)	38 (1.8%)	23 (1.3%)	15 (4.7%)
	ETORICOXIB:M01AH05	n (%[2])	55 (1.8%)	41 (1.6%)	14 (2.4%)	59 (2.8%)	50 (2.8%)	9 (2.8%)
	TELPERISONE: M03BX04	n (%[2])	45 (1.4%)	38 (1.5%)	7 (1.2%)	29 (1.4%)	21 (1.2%)	8 (2.5%)
	TILIDIN: N02AX51	n (%[2])	45 (1.4%)	28 (1.1%)	17 (2.9%)	37 (1.8%)	31 (1.7%)	6 (1.9%)
	DEXAMETHASONE: H02AB02	n (%[2])	28 (0.9%)	22 (0.9%)	6 (1.0%)	25 (1.2%)	20 (1.1%)	5 (1.6%)
	PANTOPRAZOLE: A02BC02	n (%[2])	27 (0.9%)	22 (0.9%)	5 (0.8%)	24 (1.1%)	23 (1.3%)	1 (0.3%)
Concomitant prescriptions within analysis period								
	IBUPROFEN : M01AE01	n (%)	1508 (23.7%)	1363 (23.9%)	145 (21.7%)	1254 (26.5%)	1177 (27%)	77 (20.5%)
	DICLOFENAC: M01AB05	n (%)	1033 (16.2%)	942 (16.5%)	91 (13.6%)	969 (20.5%)	910 (20.9%)	59 (15.7%)
	METAMIZOLE SODIUM: N02BB02	n (%)	939 (14.8%)	847 (14.9%)	92 (13.8%)	935 (19.8%)	880 (20.2%)	55 (14.7%)
	ETORICOXIB:M01AH05	n (%)	397 (6.2%)	362 (6.4%)	35 (5.2%)	343 (7.2%)	312 (7.2%)	31 (8.3%)
	TETRAZEPAM: M03BX07	n (%)	371 (5.8%)	337 (5.9%)	34 (5.1%)	4 (0.1%)	2 (0.0%)	2 (0.5%)
	TRAMADOL: N02AX02	n (%)	347 (5.5%)	291 (5.1%)	56 (8.4%)	215 (4.5%)	192 (4.4%)	23 (6.1%)
	PANTOPRAZOLE: A02BC02	n (%)	282 (4.4%)	255 (4.5%)	27 (4.0%)	295 (6.2%)	277 (6.4%)	18 (4.8%)
	TILIDIN: N02AX51	n (%)	280 (4.4%)	234 (4.1%)	46 (6.9%)	252 (5.3%)	226 (5.2%)	26 (6.9%)
	OMEPRAZOL: A02BC01	n (%)	196 (3.1%)	173 (3.0%)	23 (3.4%)	288 (6.1%)	274 (6.3%)	14 (3.7%)
	DEXAMETHASONE: H02AB02	n (%)	193 (3.0%)	176 (3.1%)	17 (2.5%)	165 (3.5%)	159 (3.6%)	6 (1.6%)

N=total number of patients
[1]: total number of patients with available history
[2]: % based on total number of patients within available history
(Source: IMS® DA. panel)

Table 46: Exposure to Flupirtine - treatment duration based on recommended dosage provided by the physician - Total

Parameter			Reference period			Assessment period		
			Total N = 34793	Incident N = 23404	Prevalent N = 11389	Total N = 28505	Incident N = 19781	Prevalent N = 8724
Number and percentage of prescriptions with information concerning treatment duration available								
	yes	n (%)	10207 (29.3%)	7342 (31.4%)	2865 (25.2%)	9110 (32.0%)	7200 (36.4%)	1910 (21.9%)
	no	n (%)	24586 (70.7%)	16062 (68.6%)	8524 (74.8%)	19395 (68.0%)	12581 (63.6%)	6814 (78.1%)
Recommended treatment duration			**N[1] = 10207**	**N[1] = 7342**	**N[1] = 2865**	**N[1] = 9110**	**N[1] = 7200**	**N[1] = 1910**
	≤ 14 days	n (%[2])	5276 (51.7%)	4711 (64.2%)	565 (19.7%)	6374 (70.0%)	5589 (77.6%)	785 (41.1%)
	> 14 days	n (%[2])	4931 (48.3%)	2631 (35.8%)	2300 (80.3%)	2736 (30.0%)	1611 (22.4%)	1125 (58.9%)

N=total number of prescriptions
[1] : total number of prescriptions with recommended treatment duration
[2] : % based on total number of prescriptions with recommended treatment duration
(Source: IMS® DA. panel)

Table 47: Exposure to Flupirtine - treatment duration based on recommended dosage provided by the physician - PCP

Parameter			Reference period			Assessment period		
			Total N = 26532	Incident N = 16630	Prevalent N = 9902	Total N = 22748	Incident N = 14854	Prevalent N = 7894
Number and percentage of prescriptions with information concerning treatment duration available								
	yes	n (%)	7422 (29.3%)	4829 (31.4%)	2593 (25.2%)	6833 (32.0%)	5081 (34.4%)	1752 (21.9%)
	no	n (%)	19110 (70.7%)	11801 (68.6%)	7309 (74.8%)	15915 (68.0%)	9773 (63.6%)	6142 (78.1%)
Recommended treatment duration			**N[1] = 7422**	**N[1] = 4829**	**N[1] = 2593**	**N[1] = 6833**	**N[1] = 5081**	**N[1] = 1752**
	≤ 14 days	n (%[2])	3701 (49.9%)	3217 (66.6%)	484 (18.7%)	4474 (65.5%)	3798 (74.7%)	676 (38.6%)
	> 14 days	n (%[2])	3721 (50.1%)	1612 (33.4%)	2109 (81.3%)	2359 (34.5%)	1283 (25.3%)	1076 (61.4%)

N=total number of prescriptions
[1:] total number of prescriptions with recommended treatment duration
[2]: % based on total number of prescriptions with recommended treatment duration
(Source: IMS® DA. panel)

Table 48 Exposure to Flupirtine - treatment duration based on recommended dosage provided by the physician - Orthopaedist

Parameter			Reference period			Assessment period		
			Total N= 8261	Incident N= 6774	Prevalent N= 1487	Total N= 5757	Incident N= 4927	Prevalent N= 830
Number and percentage of prescriptions with information concerning treatment duration available								
	yes	n (%)	2785 (33.7%)	2513 (37.1%)	272 (18.3%)	2277 (39.6%)	7200 (43.0%)	1910 (19.0%)
	no	n (%)	5476 (66.3%)	4261 (62.9%)	1215 (81.7%)	3480 (60.4%)	12581 (57.09%)	6814 (81.0%)
Recommended treatment duration			**N[1] = 2785**	**N[1] = 2513**	**N[1] = 272**	**N[1] = 2277**	**N[1] = 2119**	**N[1] = 158**
	≤ 14 days	n (%[2])	1575 (56.6%)	1494 (59.5%)	81 (29.8%)	1900 (83.4%)	1791 (84.5%)	109 (69%)
	> 14 days	n (%[2])	1210 (43.4%)	1019 (40.5%)	191 (70.2%)	377 (16.6%)	328 (15.5%)	49 (31.0%)

N=total number of prescriptions
[1:] total number of prescriptions with recommended treatment duration
[2]: % based on total number of prescriptions with recommended treatment duration
(Source: IMS® DA. panel)

Table 49: Exposure to Flupirtine – Formulation and length of episodes – Total

Parameter		Reference period			Assessment period		
		Total N = 29320	Incident N = 21049	Prevalent N = 8271	Total N = 24995	Incident N = 18711	Prevalent N = 6284
Length of treatment episodes based on DDD (in days)							
	mean (SD)	24.4 (34.6)	19.4 (21.6)	37.1 (53.3)	18.3 (23.8)	15.0 (12.1)	28.1 (41.2)
	median	14	14	14	14	14	14
	min-max	0.25* -435	0.25* -316	0.25* -435	1.8 -417	1.8 -313.5	1.8 -417
Length of Episodes ≤ 14 days or > 14 days based on DDD							
	≤ 14 days	22521 (76.8%)	17345 (82.4%)	5176 (62.6%)	21601 (86.4%)	17206 (92.0%)	4395 (69.9%)
	> 14 days	6799 (23.2%)	3704 (17.6%)	3095 (37.4%)	3394 (13.6%)	1505 (8.0%)	1889 (30.1%)

N=total number of episodes
*: the duration of 0.25 days results out of the DDD calculation of product:
"Katadolon Inject Ampullen 1 St Teva GmbH PZN: 567646. 100mg"
(Source: IMS® DA. panel)

Table 50: Exposure to Flupirtine – Formulation and length of episodes – PCP

Parameter		Reference period			Assessment period		
		Total N = 21737	Incident N = 14730	Prevalent N = 7007	Total N = 19519	Incident N = 13980	Prevalent N = 5539
Length of treatment episodes based on DDD (in days)							
	mean (SD)	26.01 (37.57)	20.17 (23.37)	38.30 (54.85)	18.99 (25.99)	14.95 (12.63)	29.21 (42.82)
	median	14	14	14	14	14	14
	min-max	0.25*-435	0.25*-316	0.25*-435	1.8-417	1.8-313.5	1.8-417
Length of Episodes ≤ 14 days or > 14 days based on DDD							
	≤ 14 days	16371 (75.3%)	12037 (81.7%)	4334 (61.8%)	16659 (85.3%)	12857 (92.0%)	3802 (68.6%)
	> 14 days	5366 (24.7%)	2693 (18.3%)	2673 (38.1%)	2860 (14.7%)	1123 (8.0%)	1737 (31.4%)

N=total number of episodes
*: the duration of 0.25 days results out of the DDD calculation of product:
"Katadolon Inject Ampullen 1 St Teva GmbH PZN: 567646. 100mg"
(Source: IMS® DA. panel)

Table 51: Exposure to Flupirtine – Formulation and length of episodes – Orthopaedist

Parameter		Reference period			Assessment period		
		Total N = 7583	Incident N = 6319	Prevalent N = 1264	Total N = 5176	Incident N = 4731	Prevalent N = 745
Length of treatment episodes based on DDD (in days)							
	mean (SD)	19.59 (23.50)	17.47 (16.41)	30.19 (42.82)	15.61 (13.21)	14.98 (10.36)	19.66 (24.14)
	median	14	14	14	14	14	14
	min-max	1.8-421	1.8-266	3.7-421	1.8-329	1.8-188	3.75-329
Length of Episodes ≤ 14 days or > 14 days based on DDD							
	≤ 14 days	6150 (81.1%)	5308 (84.0%)	842 (66.6%)	4642 (89.7%)	4349 (91.9%)	593 (79.6%)
	> 14 days	1433 (18.9%)	1011 (16.0%)	422 (33.4%)	534 (10.3%)	382 (8.1%)	152 (20.4%)

N=total number of episodes
*: the duration of 0.25 days results out of the DDD calculation of product:
"Katadolon Inject Ampullen 1 St Teva GmbH PZN: 567646. 100mg"
(Source: IMS® DA. panel)

Table 52: Exposure to Flupirtine- Number and frequency of prescriptions – Total

Parameter			Reference period			Assessment period		
			Total N = 21714	Incident N = 18443	Prevalent N = 3271	Total N = 19674	Incident N = 17023	Prevalent N = 2651
Number of prescriptions per patient per month		mean (SD)	1.1 (0.2)	1.0 (0.2)	1.1 (0.2)	1.0 (0.2)	1.0 (0.2)	1.1 (0.2)
		median	1	1	1	1	1	1
		min-max	1-3.6	1-3.5	1-3.7	1-4.5	1-4.0	1-4.5
Number of single and repeated prescriptions								
	Single	n (%)	16674 (76.8%)	15399 (83.5%)	1275 (39.0%)	16351 (83.1%)	15192 (89.2%)	1159 (43.7%)
	Repeat	n (%)	5040 (23.2%)	3044 (16.5%)	1996 (61.0%)	3323 (16.9%)	1831 (10.8%)	1492 (56.3%)

N=total number of patients; (Source: IMS® DA. panel)

Table 53: Exposure to Flupirtine- Number and frequency of prescriptions – PCP

Parameter			Reference period			Assessment period		
			Total N = 15350	Incident N = 12746	Prevalent N = 2604	Total N = 14940	Incident N = 12664	Prevalent N = 2276
Number of prescriptions per patient per month		mean (SD)	1.09 (0.25)	1.07 (0.22)	1.13 (0.28)	1.08 (0.25)	1.04 (0.17)	1.17 (0.35)
		median	1	1	1	1	1	1
		min-max	1-3.7	1-3.5	1-3.7	1-4.5	1-4	1-4.5
Number of single and repeated prescriptions								
	Single	n (%)	11417 (74.4%)	10503 (82.4%)	914 (35.1%)	12224 (81.8%)	11259 (88.9%)	965 (42.4%)
	Repeat	n (%)	3933 (25.6%)	2243 (17.6%)	1690 (64.9%)	2716 (18.2%)	1405 (11.1%)	1311 (57.6%)

N=total number of patients; (Source: IMS® DA. panel)

Table 54: Exposure to Flupirtine- Number and frequency of prescriptions – Orthopaedist

Parameter			Reference period			Assessment period		
			Total N = 6364	Incident N = 5697	Prevalent N = 667	Total N = 4734	Incident N = 4359	Prevalent N = 375
Number of prescriptions per patient per month		mean (SD)	1.03 (0.18)	1.04 (0.18)	1.04 (0.14)	1.03(0.15)	1.02(0.15)	1.05(0.15)
		median	1	1	1	1	1	1
		min-max	1-3	1-3	1-3	1-3	1-3	1-2
Number of single and repeated prescriptions								
	Single	n (%)	5257 (82.6%)	4896 (85.9%)	361 (54.1%)	4127 (87.2%)	3933 (90.2%)	194 (51.7%)
	Repeat	n (%)	1107 (17.4%)	801 (14.1%)	306 (45.9%)	607 (12.8%)	426 (9.8%)	181 (48.3%)

N=total number of patients; (Source: IMS® DA. panel)

Table 55: Liver Function Test - Total

Parameter		Reference period			Assessment period		
		Total	Incident	Prevalent	Total	Incident	Prevalent
		N = 34793	N = 23404	N = 11389	N = 28505	N = 19781	N = 8724
Prescriptions with at least one liver function test within 1 week after Flupirtine prescription	n (%)	2240 (6.4%)	1510 (6.5%)	730 (6.4%)	2263 (7.9%)	1547 (7.8%)	716 (8.2%)

N=total number of **prescriptions**
(Source: IMS® DA. panel)

Table 56: Liver Function Test - PCP

Parameter		Reference period			Assessment period		
		Total	Incident	Prevalent	Total	Incident	Prevalent
		N = 26532	N = 16630	N = 9902	N = 22748	N = 14854	N = 7894
Prescriptions with at least one liver function test within 1 week after Flupirtine prescription	n (%)	2212 (8.3%)	1482 (8.9%)	730 (7.4%)	2258 (9.9%)	1542 (10.4%)	716 (9.1%)

N=total number of **prescriptions**
(Source: IMS® DA. panel)

Table 57: Liver Function Test - Orthopaedist

Parameter		Reference period			Assessment period		
		Total	Incident	Prevalent	Total	Incident	Prevalent
		N = 8261	N = 6674	N = 1487	N = 5757	N = 4927	N = 830
Prescriptions with at least one liver function test within 1 week after Flupirtine prescription	n (%)	28 (0.3%)	28 (0.4%)	0 (0.0%)	5 (0.1%)	5 (0.1%)	0 (0.0%)

N=total number of **prescriptions**
(Source: IMS® DA. panel)