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 Flupirtine 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
Protocol version identifier	Draft-Version 3.0
Date of last version of protocol	3 July 2015
EU PAS register number	Study not yet registered Registration is planned prior to study initiation once the protocol is final and approved by BfArM
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 (MAH) responsible for this study	LUPIN (EUROPE) LIMITED VictoriaCourt, BextonRoad Knutsford, Cheshire, WA16 OPF UK Hormosan Pharma GmbH – a Lupin Group Company Wilhelmshoeherstr. 106 60389 Frankfurt Germany
JointPASS	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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2. List 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
EU-PAS	European Post Authorisation Study
EWP	European Working Party
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
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
ICMJE	International Committee of Medical Journal Editors
INN	International Nonproprietary Name
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorization Holder
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over The Counter
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
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organization

3. Responsible parties

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IMS Health is a partner centre of the ENCePP scientific network which is coordinated by the European Medicines Agency. IMS is dedicated to excellence in research by adhering to the ENCePP Guide on Methodological Standards and promoting scientific independence and transparency.

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4. 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.

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 on 28June 2013 to restrict the use of oral Flupirtine medicines and suppositories as following:

- treatment of acute (short-term) pain in adults who cannot use other painkillers, such as non-steroidal anti-inflammatory drug (NSAIDs) and weak opioids
- treatment duration limited to not longer than 2 weeks
- after each full week of treatment patients' liver function should be checked
- treatment termination if any signs of liver problems occur
- contraindicated for patients with preexisting liver disease of alcohol abuse problems
- contraindicated for patients taking other medications known to cause liver problems

The recommendations follow a review by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) which looked into reported liver problems with Flupirtine, ranging from high liver-enzyme levels to liver failure. The PRAC evaluated the available data on liver safety, noting that there were no cases of liver failure or liver transplantation reported in patients who took the medicine for 2 weeks or less. The PRAC also reviewed the available data on the benefits of Flupirtine and concluded that, while there were data from studies in the treatment of acute pain, there were insufficient data to support its use in the treatment of long-term pain.

The CMDh agreed with the PRAC's conclusions and endorsed the PRAC's recommendations on the use of flupirtine-containing medicines. The CMDh position was sent to the European Commission (EC), which endorsed it and adopted a final legally binding decision valid throughout the EU on 5 September2013.

The reported outcomes were communicated to healthcare professionals by all Germany marketing authorisation holders (MAHs) via a joint Direct Healthcare Professional Communication (DHPC) distributed in July 2013.

The Summaries of Product Characteristics (SmPCs) for flupirtine-containing medicinal products have been revised accordingly by Lupin in February 2014 and MAHs marketing flupirtine-containing medicinal products in Germany in September/October 2013.

Additionally the PRAC requested that the MAHs should submit a risk management plan (RMP). The protocols of two studies - a drug utilisation study (DUS) and a PASS - should be submitted as part of the RMP.

This protocol covers a design for a DUS based on the information captured in longitudinal patient-level databases and has been set up accordingly to fulfill the conditions of the authority.

Research question and objectives

The aims of this study are 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 will display:

- Number of Flupirtine patients per specialty, per region (East/West Germany) and overall patients in the office
- Patient demography (age, gender and insurance status)
- Diagnoses, related to Flupirtine prescriptions
    - Diagnoses explicitly associated with Flupirtine prescriptions
    - Co-diagnoses associated with Flupirtine prescriptions
- Therapies, related to Flupirtine patients
    - Co-prescriptions received by Flupirtine patients
    - Further therapies received by Flupirtine patients
- Flupirtine exposure
    - Dosage and therapy duration
    - Prescription length
    - Number of Flupirtine prescriptions
    - Single and repeat prescriptions
    - relevant treatment patterns if available
- Contraindications for use of NSAIDs or weak opioids
- Long-term medications (>14 days) leading to contraindications for the use of Flupirtine
- Liverfunctions test, if available within 1 week after exposure to Flupirtine

Study design

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

The DUS will be carried out in Germany as more than 90% of total prescriptions for flupirtine-containing medicinal products of MAHs in European Union Member States were issued in Germany.

Population

The study will capture 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 (patient selection window) in the selected data sources will be included in the analysis. The analysis will consist of 2 time periods, the first one the year 2012 as time frame before and the second one the year 2014 as time frame after the SmPC revision.

Variables

The following variables will be extracted from the database:

- Prescription of a flupirtine-containing medicinal product
- Specialty and type of prescribing physician

- Demographical characteristics of patients treated with flupirtin (age, gender, insurance)
- Indication for Flupirtine treatment (reasons for prescription)
- Duration of Flupirtine treatment recommended by the physician
- Daily Flupirtine dose recommended by the physician
- Prescription length
- Concomitant prescriptions of drugs
- Co-diagnosis
- Liverfunction tests

Data sources
The following data sources will be used: IMS® Disease Analyzer (DA); primary care physician (PCP) and orthopaedist panels. Both panels cover more than 95% of all Flupirtine prescriptions in Germany.

Study size
All patients in the PCP and orthopaedist panel recorded during the analysis periods 2012 and 2014 of the IMS® DA will be considered for the study. The study size per period will 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.

Data analysis
The statistical analysis will be done descriptively and performed separately for each physician panel. All analyses will be stratified by incident and prevalent users. Missing values will be reported as missing and no imputation will be conducted. Descriptive tables will be made for all variables.

Milestones(planned)

Start of data collection (reference period):	January 1, 2012
End of data collection (reference period):	December 31, 2012
Start of data collection (assessment period):	January 1, 2014
End of data collection (assessment period):	December 31, 2014
Registration in the EU PAS register:	Registration is planned prior to study initiation once the protocol is final and approved by BfArM
Final study report:	February29, 2016

During the analysis time the following points and related time periods required have to be taken into account:

- Data will be available 6-8 weeks after end of data collection
- Data cleaning will last 2 weeks

- Statistical analysis, quality control and internal review will be performed within 6-8 weeks
- The study report will be created within 4 weeks

The start and end of data collection refers to the selection window for Flupirtine prescriptions. In addition a 12-month period before Flupirtine exposure start will be tracked. Additionally patients with at least 1 to 6 months follow up period after first exposure start date for each of both periods will be selected to obtain maximum information. For patients with longer observational period, the analysis will be performed until end of collection time if available.

5. Amendments and updates

None

6. Milestones

The study will start after the BfArM approval of the final study protocol.

Milestone: before and after SmPC review	Planned date
Start of data collection - Reference period	January , 1 2012
End of data collection - Reference period	December 31, 2012
Start of data collection – Assessment period	January 1, 2014
End of data collection - Assessment period	December 31, 2014
Registration in the EU PAS register	Registration is planned prior to study initiation once the protocol is final and approved by BfArM
Final report of study results	February 29, 2016

During the analysis time the following points and related time periods required have to be taken into account:

- Data will be available 6-8 weeks after end of data collection
- Data cleaning will last 2 weeks
- Statistical analysis, quality control and internal review will be performed within 6-8 weeks
- The study report will be created within 4 weeks

The start and end of data collection refers to the selection window for Flupirtine prescriptions. In addition a 12-month period before Flupirtine exposure start will be tracked. Additionally patients with at least 1 to 6 months follow up period after first exposure start date for each of both periods will be selected to obtain maximum information. For patients with longer observational period, the analysis will be performed until end of collection time if available.

7. Rationale and background

Flupirtine, a non opiotic analgetic 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 protocol covers a design for a DUS based on the information captured in longitudinal patient-level databases and has been designed to fulfill the conditions of the authority.

8. Research question and objectives

The Flupirtine DUS aims 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 will display 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)
    - Recommended Flupirtine treatment duration (by physicians)
    - Prescription length
    - 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
- Liverfunctions test performed within 1 week after Flupirtine exposure start

9. Research methods

9.1. Study design

This drug utilisation study for Flupirtine will employ 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 will be 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 will be set up as a pre-post design to compare flupirtine prescribing patterns (before and after the revision of SmPC).

9.2. Setting

The study will be 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) will be identified from selected database.

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

The study will include 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 will include:

- Incident user: 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 user: 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 will not be applied.

Study period
The selection of patients from the IMS® Disease Analyzer will be 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 will be 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 will be analysed for each patient for whom these data are available.

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

9.3. Variables

The following variables will be 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[iii]
- Flupirtine exposure
    - Number of Flupirtine prescriptions per patients during the observation period
    - Single use and repeated prescriptions
    - Treatment duration (by physician)
    - Dosage advice (by physician)
    - Prescription length (based on DDD or on physician's advice if available)
        - Co-diagnosis during study period
        - Concomitant prescription of drugs grouped by relevant ATC classes[ii]
- 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

9.4. Data Sources

The IMS® Disease Analyzer, aGerman longitudinal patient-level database will be 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 practices* 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' practice 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 will therefore be based on data from the PCP panel and the orthopaedist panel.

9.5. Study size

All patients in the PCP and orthopaedist panel of the IMS®DA fulfilling the selection criteria will be 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). As acute pain treatment has no seasonal impacts, the 12 months period and not a calendar year period is acceptable for feasibility appraisal.

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

Taking into account the sample sizes and a further 25% reduction for a hypothetical decrease in Flupirtine prescriptions over the planned observation period compared to the period evaluated in 2014, we expect that the minimum number of Flupirtine patients available for the analysis will be not lower than about 8,400 and 1,300 patients in the DA PCP and orthopaedist panel, respectively. The more data are available, the higher the level of confidence on any estimates, i.e. the smaller the width of the 95% confidence interval.

Similar Flupirtine patient counts for the DA database are expected for the 12-month selection window of the Flupirtine DUS.

The study size of the Flupirtine DUS is 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, so the study size of the planned 12-month patient selection window in the Flupirtine DUS may be slightly different.

The 12-month patient selection window is considered to be sufficient to provide representative for prescribing practices during the routine clinical use of flupirtine-containing medicinal products in Germany.

9.6. Data management

The study will be conducted according to IMS Health standard operating procedures (SOPs) of IMS Health. Data sets extracted from the database will be stored to allow future analysis if needed.

9.7 Data analysis

9.7.1 General remarks

Data from specialist panels will not be combined. The data will be analysed separately by panel (PCP and orthopaedist panel) and for the period before and after SmPC review.

All analyses will be stratified by incident and prevalent users.

Study tables will reference the data source used for each set of results. The data will be presented graphically where useful.

The statistical unit will be the patient (for information such as demographical and clinical characteristics, medical history, contraindications) and the Flupirtine prescription (for information such as indication, number of prescriptions, recommended treatment duration, concomitant drug prescriptions).

The statistical analysis will be done descriptively. Missing values will be reported as missing and no imputation will be conducted. Descriptive tables will be compiled for all variables. Continuous variables will be presented with counts, means, medians, standard deviations, and minimum and maximum values. Categorical variables will be presented in frequency tables. Rates and 95% confidence intervals will be provided when relevant.

Data will be analysed using the statistical software SAS (SAS Institute Inc., Cary, USA) with version 9.3 or above.

All results will be presented in tables. In addition, parameters addressing the primary objectives and eligible for a comparison of time periods (assessment period and reference period) with respect to the effect of risk minimisation measures (for example flupirtine treatment duration) will be presented graphically e.g. by displaying plots or bar charts.

The following section will describe the analyses and definitions used for the DA (**IMS® Disease Analyzer**) database.

9.7.2 EMR data (IMS® Disease Analyzer) – PCP and orthopaedist panel

Prevalent and incident patients

The entire analysis will be stratified by incident patients - defined as new patients, if no flupirtine containing products were dispensed for at least 12 months previous to the first Flupirtine treatment within each study period, and prevalent patients - defined as patients with at least one prescription of Flupirtine products 12 months prior to index date of first prescription within analysis period.

Flupirtine patients by specialty, by region (East/West Germany) and number of patients in the office

The number of Flupirtine patients per specialty will be analyzed, adding the region (East/West Germany) and overall number of patients within the office

Analyses:

- Number of Flupirtine patients per specialty including region (East/West Germany) and number of patients in the office

9.7.2.1 Patient characteristics of Flupirtine treated patients

The patient characteristics (age, gender, insurance private or SHI) of Flupirtine patients will be described.

- Number of patients within following age groups:
  - < 18 years
  - 18 to 29 years
  - 30 to 39 years
  - 40 to 49 years
  - 50 to 59 years
  - 60 to 69 years
  - 70 years and older

Analyses:

- Number and percentage of Flupirtine patients per age group, gender, insurance status(private or SHI insured)

Indication for flupirtine prescription

In order to describe the indication for flupirtine drugs all diagnoses related to the flupirtine prescriptions will be analysed.

- All diagnoses documented on the prescription of flupirtine will be defined as principal diagnosis.

As not for all prescriptions principal diagnoses will be available, additionally the following approaches will be chosen:

- If there is any disease associated with acute pain (Annex 3-ii) recorded in a time frame of 2 weeks around the date of prescription, this will be defined as associated diagnosis.
- If there is any disease associated with acute pain (Annex 3-ii) recorded in a 12 months history before the date of prescription, this will be defined as co-morbidity.

Principal diagnoses, associated diagnoses and co-morbidities will be analysed separately.

The findings of principal diagnoses will be grouped by diagnosis according to ICD-10 codes (selection of codes see Annex 3) including diseases associated with acute pain and chronic pain.

Analysis:

- Number and percentage of prescriptions, stratified by diagnosis (only principal diagnoses)
- Number and percentage of prescriptions associated with acute pain (principal diagnoses, associated diagnoses and co-morbidities)
- Number and percentage of prescriptions associated with chronic pain (only principal diagnoses)

Contraindication for the use of NSAIDs or weak opioids

The patients' history will be evaluated for medical events referencing to contraindications for NSAIDs or weak opioids (such as myocardial infarction or stroke) for a timeperiod of 12 months prior to first prescription of Flupirtine. Only patients with a history of at least 12 months will be included in this analysis.

Analyses:

- Number and percentage of patients identified as contraindicated of NSAIDs/weak opioid treatment (such as myocardial infarction or stroke)

Long-term medications leading to contraindications for Flupirtin

A therapy duration exceeding 14 days will be considered as long-term treatment within a year time span. A long-term treatment known to lead to contraindications for the use of Flupirtine will be analyzed

Analyses:

- Number and percentage of long-term therapies leading to contraindication of Flupirtine

Concomitant diseases of Flupirtine patients

Diseases are assumed to be concomitant, if prescription issued prior or after 2 weeks to Flupirtine treatment within study period.

Analyses:

- Number and percentage of patients with concomitant diseases during observation period, grouped by ICD codes

Therapies related to Flupirtine treatment
Patients treated with Flupirtine will be monitored by analyzing all co-prescriptions within the observation window of 12 months prior to Flupirtine treatment start, grouped by diagnosis according to ICD-10 codes [selection of codes see Annex 3 (ii)].

Analyses:

Number and percentage of patients receiving co-medication during 12 months prior to Flupirtine treatment start grouped by diagnosis according to ICD-10 codes [selection of codes see Annex 3 (ii)].

9.7.2.2 Flupirtine exposure

Flupirtine exposure will be defined as one or more prescriptions of Flupirtine. These prescriptions will be identified using the ATC code for Flupirtine or INN. The Flupirtine exposure start date (i.e. the cohort entry date) for each patient will be defined as the date of the first record of Flupirtine prescription during each of the defined twelve-month patient selection window.

Treatment duration
The treatment duration (in days) will be evaluated by using the recommended treatment duration by the physician. If this is not available, the treatment duration cannot be determined exactly as the dose recommendation “as required (pro re nata)” is very often given in the therapy of acute pain. Therefore, the percentage of patients with no information according to recommendation by the physician will be determined.

Prescription length
The prescription length (in days) will be determined as allows:

- For prescriptions with available information on recommended dose per day: from the prescription date plus the expected number of days of drug supply based on the package size and the recommended daily dose
- For all prescriptions without recommendation of dosage: from the prescription date plus the expected number of days of drug supply based on the package size and the DDD(400 mg / day)

The prescription length is therefore not necessarily identical to the treatment duration.

The following parameters will be considered in the analysis for each Flupirtine prescription:

- Date of prescription
- Recommended daily dose by physician
  Recommended treatment duration by physician

Analyses:

- Number and percentage of patients with prescriptions of a flupirtine-containing medicinal product during the 12-month patient selection window
- Treatment duration in days
- Prescription length
- Single use and repeated use

Treatment episodes

A treatment episode will be defined as one or more prescriptions (repeated prescriptions) of flupirtine with gaps between prescription length not more than 7 days. In the case the gap between the prescriptions is longer than 7 days it will be considered as two subsequent treatment episodes. The analysis of treatment episodes will consider prescription length based on DDD, because for all prescriptions this information will be available.

Analyses:

- Number and percentage of episodes
- Min, max, mean, median length of episodes
- Patients within each episode

9.7.2.3 Monitoring of liver function

For patients where liver function tests after Flupirtine exposure are available (within 1 week after Flupirtine prescription) the following tests will be analyzed in the PCP and orthopaedist panel. Although a feasibility check has shown that laboratory tests are more comprehensively covered in the PCP panel of the database than in the specialist panels, liver function test will also be monitored in the orthopaedist panel in order to ensure comprehensiveness of data.
However, the laboratory tests of the orthopaedist panel will only be included in the analysis in the case sufficient liver function test data are available. A minimum number of 100 laboratory test results per time period will be considered as sufficient.
As Flupirtine treated patients happen to have false positive Bilirubin results, Bilirubin will not be considered the analysis[21]

The proportion of prescriptions with at least one liver function tests within 1 week after prescription date of flupirtine will be estimated.

Liver function tests

- GOT
- GPT
- Gamma-GT
- AP
- Albumin

Analyses:

- Number and percentage of patients with test available
  Value of the test

9.7.2.4 Comparison of the patient/prescriptions of the two observational periods

The comparison of the patients/prescriptions of the two observational periods (assessment period and reference period) based on IMS® Disease Analyzer data will consider the following parameters. The comparisons will be performed separately by physician panel and will be stratified by incident and prevalent users:

- Number and percentage of patients with any diagnosis of disease contraindicated for NSAIDs or weak opioids
- Number and percentage of prescriptions with diagnosis associated with acute pain
- Number and percentage of patients with single and repeated flupirtine prescriptions within the defined time period
- Number and percentage of prescriptions with LFT monitoring during flupirtine treatment
- Length of treatment episodes
- Number and percentage of patients with at least one treatment episode longer than 14 days (based on DDD)

9.8. 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 will be extracted by a programmer with extensive programming and analysis experience with the LifeLink EMR data.

The following steps will be 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 will be reviewed and approved by senior staff at the IMS team.
- Programming Code Review: all programming code will be 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 will be reviewed by senior staff member of the COE Pharmacoepidemiology and Drug Safety at IMS.

9.9. Limitations of the research methods

IMS® Disease Analyzer is representative of Germany as a whole insofar as that the included practices 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 practices 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 will 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. Therefore, patients cannot be followed up across specialties and double counting of patients cannot be completely ruled out when analyzing more than one panel. It is planned to use of the PCP and the orthopaedist panels for this study.

For patients covered in the IMS® Disease Analyzer the medical history of patients will be evaluated for at least 12 months.

The duration of Flupirtine treatment (in days) will be evaluated using the treatment duration recommended by the physician. In cases where this information is not available, the treatment duration will be calculated using recommended dosage 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.

The length of prescription will be determined from the recommended daily dose by the physician (if available) or using the defined daily dose (DDD). The dose recommendation “on demand” will not be taken into account for the determination of prescription length.

9.10. Other aspects

None

10. Protection of human subjects

This study is non-interventional and based on secondary data use. No identifying data is collected in any of selected databases. These databases are set up following local law, including data privacy regulation.

Ethics Committee/Institutional Review Board approval is not necessary.

The study will follow the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE) 2007 and be in accordance with Guide on Methodological Standards in Pharmacoepidemiology of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).[13,14]

The study will comply with the definition of non-interventional (observational) studies provided in the Article 2(c) of Directive 2001/20/EC (definition of non-interventional/observational studies).[15] The study will follow the Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies (EMA 2012, Revision 2013) and the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E (ICH 2004) referring to the nature of non-interventional observational studies.[16,17]

11. Management and reporting of adverse events (AEs) / adverse reactions (ADRs)

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[18].

12. Plans for disseminating and communicating study results

The study will be registered in the EU-PAS register (currently the ENCePP e-register of studies).

The study report will be written in English, using the template included in the GVP Module VIII "Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies" (EMA/623947/2012)[19]. When reporting results of this study, the appropriate STROBE checklist (von Elm, 2007) will be followed[20].

The final study report will be communicated to BfArM.

Study results will be considered for publication and will follow the International Committee of Medical Journal Editors (ICMJE, 2010) guidelines. In addition, communication in appropriate scientific meetings will be considered.
Study results will be considered for publication and for presentation on scientific congresses.

13. References

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2. European Agency for the Evaluation of Medicinal Products: Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain (CPMP/EWP/612/00, 21 November 2002)
3. European Medicines Agency: PRAC recommends restricting the use of flupirtine-containing medicines. 14 June 2013, EMA/362055/2013
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6. Summary of Product Characteristics Flupirtinmaleat-Hormosan 100mh Hartkapseln, Dated February 2014
7. European Commission: Commission Implementing Decision of 5.9.2013 concerning, in the framework of Article 107i of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations of medicinal products for human use which contain the active substance “flupirtine”. Brussels, 5.9.2013, C (2013) 5788 final.
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13. International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology, Revision 2 April 2007. https://www.pharmacoepi.org/ [Access: October 2014]
14. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 3). EMA/95098/2010. Available at http://www.encepp.eu/standards_and_guidances [Access: October 2014]
15. European commission. Article 2(c) of Directive 2001/20/EC. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
16. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 1), EMA/813938/2011 Rev 1
17. European Agency for the Evaluation of Medicinal Products: Note for guidance on structure and content of clinical study reports CPMP/ICH/137/95
18. Guideline on good pharmacovigilance practices (GVP), Module VI – management and reporting of adverse reactions to medicinal products, EMA 873138/2011
19. European Agency for the Evaluation of Medicinal Products: Guidance for the format and content for the protocol of non-interventional post-authorisation safety studies, 26 September 2012, EMA/623947/2012.
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP for the STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4(10):e296
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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1-DHPC	Not applicable	July 2013	Direct Healthcare Professional Communication (DHPC): Einschränkungen der therapeutischen Zielgruppe und Begrenzung der Behandlungsdauer für Flupirtine-haltige Arzneimittel nach Bewertung des LebertoxizitätsrisikosText
2-Updated SmPC	Not applicable	July2014	Summary of Product Characteristics Flupirtinmaleat-Hormosan 100mg Hartkapseln, Dated July2014

Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

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

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	17
1.1.2 End of data collection[2]	☒	☐	☐	17

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1717
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Registration is planned prior to study initiation once the protocol is final and approved by BfArM

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1Why the study is conducted?(e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	13, 18
2.1.2 The objective(s) of the study?	☒	☐	☐	13, 20
2.1.3The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	13, 22
2.1.4Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	13, 20
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☒	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000	☐	☐	☒	

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)				

Comments:

Only descriptive statistics will be done, no statistical tests

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	13, 22
4.2 Is the planned study population defined in terms of:	☒	☐	☐	22
4.2.1 Study time period?	☒	☐	☐	23
4.2.2 Age and sex?	☒	☐	☐	22
4.2.3 Country of origin?	☒	☐	☐	22
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	22

Comments:

All patients with a record of Flupirtine prescription during the defined time period will be included

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured?(e.g. operational details for defining and categorising exposure)	☒	☐	☐	23
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	23
5.3 Is exposure classified according to time windows?(e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders?(e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers?(e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				15
8.1.1 Exposure?(e.g. pharmacy dispensing, general practice prescribing,claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	
8.1.2 Endpoints?(e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
	☐	☐	☒	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1.3 Covariates?				
8.2 Does the protocol describe the information available from the data source(s)on:				
8.2.1 Exposure?(e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	17, 20, 22, 23
8.2.2 Endpoints?(e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3Covariates?(e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	20
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	29
8.3.2Endpoints?(e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
8.3.3Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	29
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	14, 27
10.3 Are descriptive analyses included?	☒	☐	☐	14, 27
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methodsfor adjusting				

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	27
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27
11.3 Are methods of quality assurance described?	☒	☐	☐	31
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	32
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	32
12.2 Does the protocol discuss study feasibility?(e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	13, 26
12.3 Does the protocol address other limitations?	☒	☐	☐	32

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	33
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	13, 33

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☐	☒	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	33, 34
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	33, 34

Comments:

Name of the main author of the protocol: Silvia Dombrowski

Date: 24/09/2015

S. Dombrowski

Signature: _____

Annex 3. Additional information

i. List of flupirtine-containing medicinal products in Germany in 2014

Dolokadin 400mg Tabletten Retard
Flupirtinmaleat Winthrop® 400 mg Retardtabletten
Flupirtinmaleat Winthrop® 100 mg Hartkapseln
Flupigil® 100 mg Hartkapseln
Katadolon® S long
Katadolon®
Katadolon® Zäpfchen
Katadolon®Kinderzäpfchen
Katadolon® inject
Trancolong®
Trancopal® dolo
Trancopal® dolo Suppositorien

ii. 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