PASS information

Title	Post-Authorisation Safety Study (PASS) for Flupirtine – Effect of Risk Minimisation Measures in Germany
Protocol version identifier	Version 3.0
Date of last version of protocol	July 01, 2015
EU PAS register number	Study not registered; registration planned after approval of the protocol 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	Not applicable
Procedure number	DE/H/3428/001/DC DE/H/3430/001/DC
Marketing authorisation holder(s) responsible for this study	Lupin (Europe) Limited Victoria Court, Bexton Road Knutsford, Cheshire, WA16 OPF UK Hormosan Pharma GmbH – a Lupin Group Company Wilhelmshoeherstr. 106 60389 Frankfurt Germany
Joint PASS	No
Research question and objectives	Evaluation of the impact of the introduction of risk minimisation measures (DHPC and updated SmPC) for flupirtine on the prescription behaviour of physicians
Country(-ies) of study	Germany
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2. List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
ALAT	Alanine Aminotransaminase
AP	Alkaline Phosphatase
ASAT	Aspartate Aminotransaminase
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
DA	IMS® Disease Analyzer
DDD	Defined Daily Dose
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilisation 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
GGT	Gamma-Glutamyl Transpeptidase, Gamma-Glutamyl-Transferase
GLDH	Glutamate Dehydrogenase
GP	General Practitioner
GVP	Good Pharmacovigilance Practices
ICD	International Statistical Classification of Diseases and Related Health Problems, Version 2014, German Modification
INN	International Nonproprietary Name
LFT	Liver Function Test
LRx	IMS® Longitudinal Prescription database
MAH	Marketing authorization holder
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over The Counter
PASS	Post-Authorization Safety Study
PCP	Primary Care Physician
QPPV	Qualified Person for Pharmacovigilance
PRAC	Pharmacovigilance Risk Assessment Committee
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
RMS	Reference Member State
RWES	Real World Evidence Solutions
SAS	Statistical Analysis Systems
SHI	Statutory Health Insurance
SmPC	Summary of Product Characteristics
SNEPCO	Selective Neuronal Potassium Channel Opener
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

Post-Authorisation Safety Study (PASS) for Flupirtine – Effect of Risk Minimisation Measures in Germany

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 28 June 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 must be stopped in any patient with abnormal liver function tests results or symptoms of liver disease
- 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 September 2013.

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 PASS based on the information captured in longitudinal patient-level EMR and prescription databases and has been set up accordingly to fulfill the conditions of the authority.

Research question and objectives

The PASS flupirtine aims to evaluate the impact of the implementation of risk minimisation measures (RMMs) (DHPC and updated SmPC) on the prescription behaviour of physicians in Germany.

The **primary objectives** of this study are therefore to describe for patients who have received flupirtine before and after implementation of risk minimization measures to:

- Estimate the proportion of patients with pre-existing liver disease or alcohol abuse problems
- Estimate the proportion of patients with pre-treatment with NSAIDs and weak opioids
- Estimate the proportion of patients with contraindications for NSAIDs and weak opioids
- Describe diagnoses related to the flupirtine prescription (indication)
- Evaluate the flupirtine treatment duration
- Estimate the proportion of patients with single and repeated flupirtine prescriptions within a defined time period
- Estimate the proportion of prescriptions with concomitant use of drugs known to have potential hepatotoxic effect
- Estimate the proportion of prescriptions with liver function test (LFT) monitoring during flupirtine treatment

The **secondary objective** of this study is to:

- Compare the length of treatment or proportions observed for each of the objectives listed above in the patients initiating flupirtine since implementation of RMMs to treatment length or proportions observed in the patients treated with flupirtine before the implementation of RMMs.

Study design

This is a retrospective cohort study with pre-post design (before and after implementation of risk minimisation measures) using a longitudinal patient level Electronic Medical Records (EMR) database and a longitudinal patient level prescription database for Germany.

Population

The study will be conducted in the outpatient setting in Germany.

All patients who have received at least one prescription for a flupirtine-containing product from 01 April 2012 to 31 March 2013 (reference period) and from 01 April 2015 to 31 March 2016 (assessment period) will be included in the analysis.

Variables

The following variables will be extracted from the databases: number of patients with flupirtine prescriptions, speciality of prescribing physician, demographical characteristics, medical history, co-morbidities, indication for flupirtine treatment, flupirtine prescription information (formulation, strength, package size, recommended daily dose and duration), pre-treatment with NSAIDs or weak opioids before flupirtine exposure start, concomitant use of contraindicated drugs and liver monitoring performance.

Data sources

The following data sources will be used: primary care physician (PCP) and orthopaedist panels of IMS® Disease Analyzer (DA) as well as IMS® Longitudinal Prescription (LRx) database.

Study size

All patients in the PCP and the orthopaedist panel of the IMS® Disease Analyzer and all prescriptions covered in the IMS® LRx database recorded in the reference period (01 April 2012 to 31 March 2013) and the assessment period (01 April 2015 to 31 March 2016) will be considered for the study. The study size for the reference period will include approximately 6200 flupirtine patients (orthopaedist panel of the IMS® DA) to about 370,000 flupirtine patients (IMS® LRx). The study size expected for the assessment period will include at least approximately 3,300 flupirtine patients (orthopaedist panel of the IMS® DA) to about 142,000 flupirtine patients (IMS® LRx).

Data analysis

The statistical analysis will be done descriptively and performed separately by database, per physician panel and per observational period. 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. Confidence intervals (95%) around estimates before and after the implementation minimization measures will be calculated. For comparison of patients initiating on flupirtine since the implementation of RMMs with patients treated with flupirtine before the implementation appropriate statistical tests will be used.

Milestones

Start of data collection – reference period:	April 1, 2012
End of data collection – reference period:	March 31, 2013
Start of data collection – assessment period:	April 1, 2015
End of data collection – assessment period:	March 31, 2016
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:	December 31, 2016

The duration of about 7 months between the end of data collection for the assessment period and the delivery of the final report is necessary because 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

5. Amendments and updates

None

6. Milestones

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

Milestone	**Planned date**
Start of data collection – Reference period	April 1, 2012
End of data collection - Reference period	March 31, 2013
Start of data collection – Assessment period	April 1, 2015
End of data collection - Assessment period	March 31, 2016
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	December 31, 2016

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 and a one month follow-up will be considered.

The duration of about 7 months between the end of data collection for the assessment period and the delivery of the final report is necessary because 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

7. Rationale and background

Flupirtine, a non-opiate analgesic 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 28 February 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 on an average. In 25 of the 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 June 2013 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 month after the EC decision. The protocols of two studies - a drug utilisation 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 PASS based on the information captured in longitudinal patient-level EMR and prescription databases and has been set up accordingly to fulfill the conditions of the authority.

8. Research question and objectives

The PASS flupirtine aims to evaluate the impact of the implementation of RMMs (DHPC and updated SmPC) on the prescription behaviour of physicians in Germany.

The **primary objectives** of this study are therefore to describe for patients who have received flupirtine before and after implementation of risk minimisation measures to:

- Estimate the proportion of patients with pre-existing liver disease or alcohol abuse problems
- Estimate the proportion of patients with pre-treatment with NSAIDs and weak opioids
- Estimate the proportion of patients with contraindications for NSAIDs and weak opioids
- Describe diagnoses related to the flupirtine prescription (indication)
- Evaluate the flupirtine treatment duration
- Estimate the proportion of patients with single and repeated flupirtine prescriptions within a defined time period
- Estimate the proportion of prescriptions with concomitant use of drugs known to have potential hepatotoxic effect
- Estimate the proportion of prescriptions with LFT monitoring during flupirtine treatment

The **secondary objective** of this study is to:

- Compare the length of treatment or proportions observed for each of the objectives listed above in the patients initiating flupirtine since implementation of RMMs to treatment length or proportions observed in the patients treated with flupirtine before the implementation of RMMs.

9. Research methods

9.1. Study design

This PASS for flupirtine will employ a cohort analysis with a pre-post design (before and after the implementation of RMMs) using two types of databases in Germany:

- Patient level EMR data (IMS® Disease Analyzer)
- Patient level prescription data (IMS® LRx)

The use of two databases provides complementary information to address the study objectives. The IMS® Disease Analyzer provides both drug use data and information about patients' clinical characteristics, including indication, co-morbidities and laboratory tests in separate outpatient physician panels. IMS® LRx captures about 60% of all statutory health insurance (SHI) prescriptions and information across all physician specialties in the outpatient setting.

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.

9.2. Setting

This study will be conducted in the outpatient setting in Germany.

Study population

Any patients who have a record of flupirtine prescription in the defined time periods of interest will be identified from selected databases. The study will include both first users and recurrent users of flupirtine.

The study will include two cohorts of patients:

- patients initiated on flupirtine treatment after the implementation of RMMs
- patients treated with flupirtine before the implementation of RMMs

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 of 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 first flupirtine prescription of the observational period

Inclusion criteria:

- Eligible patients must have at least one prescription for flupirtine (exposure) in the defined time periods.

Exclusion criteria will not be applied.

Study time period

The inclusion periods for the cohorts depends on the timing of the implementation of RMMs (DHPC, revised version of SmPCs, and distribution of educational material) in Germany.

- Reference period: flupirtine prescriptions received; April 2012 to March 2013
- Assessment period: flupirtine prescriptions received April 2015 to March 2016

In order to provide information on co-morbidities a time period of 12 months before the individual exposure start date will be analyzed for patients with available history of 12 months.
For all patients a minimum follow-up of at least one month after exposure start date will be taken into account. Patients will be followed over the individual available follow-up time ranging from a minimum of 1 month up to a maximum of 13 months.
Therefore, the overall study observation period covers the time period between April 2011 to April 2013 for the reference period and April 2014 to April 2016 for the assessment period.

The exposure start date for each patient will be defined as the date of the first record of the flupirtine prescription within the selection window.

9.3. Variables

The following variables will be considered in the PASS flupirtine.

IMS Disease Analyzer (PCP and orthopaedist panel)

- Prescribing physician
    - Region (West and East Germany)
    - Number of patients in office
- Patient characteristics
    - Age
    - Gender
    - Insurance (private or SHI insured)
    - Diagnosis related to the flupirtine prescription (indication)

    - Diagnoses coded by ICD-10 codes to describe co-morbidities at or prior to exposure start date
        - Liver diseases
        - Alcohol dependence
        - Diseases contraindicated for NSAIDs and weak opioids
    - Pain treatment prior to flupirtine exposure start
        - NSAIDs
        - Weak opioids
- Flupirtine exposure
    - Formulation (retard, immediate release, other)
    - Package size of flupirtine prescriptions
    - Strength of flupirtine prescriptions
    - Single use and repeated prescriptions
    - Prescription length (based on recommended daily dose, if available, or deduced from package size, strength and defined daily dose DDD)
    - Treatment duration (based on recommended duration, if available)
- Concomitant prescriptions of medicines known to have a potential hepatotoxic effect
- Performance of liver function tests during flupirtine treatment

<u>IMS® LRx</u>

- Prescribing physicians
    - Specialty
    - Region
- Patient characteristics
    - Age
    - Gender
    - Pain treatment prior to flupirtine exposure start
        - NSAIDs
        - Weak opioids
- Flupirtine exposure
    - Formulation (retard, immediate release, other)
    - Package size of flupirtine prescriptions
    - Strength of flupirtine prescriptions
    - Single use and repeated prescriptions
    - Prescription length
- Concomitant prescriptions of medicines known to have a potential hepatotoxic effect

9.4. Data Sources

Two German longitudinal patient-level databases will be used as data sources for the flupirtine PASS study.

IMS® Disease Analyzer
IMS® Disease Analyzer is a database which continuously receives anonymised data (in accordance with §3 Abs. 6 "Bundesdatenschutzgesetz" – German Federal Data Protection Act) 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 standardised 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.

Information on OTC/self-medication drugs is available in the database if these are prescribed by physicians. Some OTC drugs like some NSAIDs (for example ibuprofen) may be taken according to physician's recommendation. In this case the "green" prescription form may be used.

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]

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

Category	Nature of data	Variables
Patient data	Characteristics	Age, sex, insurance
	Diagnoses	Date of diagnosis, ICD-10 codes, original text, co-morbidity, referrals, laboratory tests and results
	Therapy	Date of visit, product and quantity, molecule, ATC codes, 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 found that most of patients who had received flupirtine prescriptions in the IMS® DA were documented in the PCP panel (including GPs and internists) and the orthopaedist panel (about 92% of patients and 95% of prescriptions). For the time period from August 2011 to July 2013 nearly 52,000 patients with at least one flupirtine prescription were recorded in the DA database including about 35,000 flupirtine patients treated by PCPs and about 13,000 flupirtine patients treated by orthopaedists. The PASS flupirtine will therefore be based on data from the PCP panel and the orthopaedist panel.

IMS® Longitudinal prescription database (LRx)
The IMS® longitudinal patient-level drug prescription (LRx) database is based on retail pharmacy data and provides information on dispensed drugs. IMS® LRx data include age, gender, drug information, and specialty of prescribing physician. The unique patient identifier allows patients to be tracked across all physician specialties in the outpatient setting (including prescriptions issued by hospital outpatient departments). Data are gathered from the SHI market in Germany on a monthly basis.

LRx data are not linked to EMR databases. This database will be analysed separately to provide a comprehensive description of the treatment pathway of flupirtine patients and concomitant drugs in Germany through the description of all prescriptions issued for each patient regardless of the specialty of the prescribing physician.

The advantage of IMS® LRx is its broad coverage (about 12,800 pharmacies representing about 60% of SHI prescriptions across Germany) and longitudinal follow-up, which makes it possible to analyse treatment patterns, discontinuation rates and switch patterns. IMS® LRx data in Germany have been available since 2008.

9.5. Study size

All patients in the PCP and orthopaedist panel of the IMS® Disease Analyzer and all prescriptions covered in the IMS® LRx database fulfilling the selection criteria will be considered for the study.

In the IMS® DA, ca. 15,500 patients in the PCP panel and ca. 6,200 patients in the orthopaedist panel were recorded with flupirtine prescriptions in the12-month reference period (April 2012 to March 2013), in the 12-month period from March 2014 to February 2015 ca. 12,400 patients and 4,300 patients, respectively. Assuming theoretically the same reduction (23%) from the reference period (April 2012 to March 2013) to the 12-month period starting in March 2014 to February 2015 (most recent data available) ca. 9,500 patients in the PCP panel with flupirtine prescriptions and 3,300 in the orthopaedist panel for the assessment period (April 2015 to March 2016) are expected for the sample size of the study.

The IMS® LRx database covers 60% of all statutory health insurance prescriptions in Germany, consequently considerable more prescriptions than in the IMS® DA database are available. The LRx database includes all outpatient specialties and covers therefore all flupirtine prescribing specialties in Germany. In a 12-month

period before the implementation of RMMs (January 2012 to December 2012) approximately 370,000 patients are available for analysis. In the period January 2014 to December 2014 approximately 230,000 patients are available in the database. Assuming in accordance to the approach described for the IMS® Disease Analyzer database a theoretically reduction of 38% about 142,000 patients are expected for the assessment period (April 2015 to March 2016) of the study.

Therefore, the 12-month data collection period for the reference and the assessment period is considered as to be sufficient to provide meaningful results regarding the prescription behaviour of physicians before and after the implementation of RMMs for flupirtine-containing products in Germany.

9.6. Data management

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

9.7. Data analysis

9.7.1 General remarks

Data from both databases will not be combined. The data will be analysed separately by data source (IMS® Disease Analyzer and IMS® LRx) and by panel (PCP and orthopaedist panel).

The analyses described below will be conducted for both study cohorts: patients who had received the flupirtine prescription before the implementation of RMMs and patients who had received the flupirtine prescription after the implementation of RMMs.

All analyses will be stratified by incident and prevalent users.

The statistical unit will be the patient (for information such as demographical and clinical characteristics, medical history) and the flupirtine prescription (for information such as indication, package size, strength, number of prescriptions, recommended treatment duration, concomitant drug prescriptions, liver function tests).

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.

Confidence intervals (95%) around estimates before and after the implementation of RMMs will be calculated. For comparison of patients initiating on flupirtine since the implementation of RMMs with patients treated with flupirtine before the implementation appropriate statistical tests will be used. Continuous variables will be assessed for normal distribution. For continuous variables following the normal

distribution, the Student t-test will be applied. Whereas, when the assumption of normality is violated, non-parametric tests such as Mann-Whitney U or Kruskal-Wallis will be applied.
For categorical variables, according to the absolute frequency of the variable in the response category, the Chi-square or the exact Fisher test will be applied if required.

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 proportion of patients with pre-existing liver disease or alcohol abuse problems or 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 each database separately.

9.7.2 IMS® Disease Analyzer

9.7.2.1 Prescriber characteristics

Characteristics of flupirtine prescribing physicians

- Region (East or West Germany)
- Number of patients at practices

9.7.2.2 Patient characteristics

Demographic characteristics

The demographic characteristics of flupirtine patients will be described as follows:

- **Age:**
  - Mean, SD, median, range
  - Percentage of patients with age
    - < 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
  - Additionally these age groups will be displayed:
    - < 9 years
    - 10-19 years
    - 20-29 years

- **Gender:**
  - Percentage of male patients
  - Percentage of female patients
- **Insurance status**
  - Percentage of patients with statutory health insurance (SHI)
  - Percentage of patients with private insurance

Medical history – co-morbidities

The following co-morbidities will be analysed for two different time periods before exposure start. The first time period covers 12 months before exposure start, the second time period covers the complete history available for the individual patients (at least 12 months before exposure start). Only patients with a history of at least 12 months will be included in this analysis.

Co-morbidities will be presented as diagnosis coded by ICD-10 codes. The following co-morbidities will be considered:

- Liver diseases
- Alcohol dependence
- Diseases leading to contraindications for NSAIDs or weak opioids (such as myocardial infarction or stroke)

The following analyses will be conducted:

- Percentage of patients with liver diseases
- Percentage of patients with alcohol abuse
- Percentage of patients with any of both contraindications
- Percentage of patients with any diagnosis of disease contraindicated for NSAIDs and weak opioids

Medical history - treatment with NSAIDs and weak opioids before flupirtine exposure start

The proportion of patients with pre-treatment with at least one NSAID and/or weak opioid will be analysed considering:

- NSAIDs (list in the Annex 3)
- Weak opioids such as codeine phosphate, dextropropoxyphene, dihydrocodeine or tramadol

The pre-treatments will be analyzed for the time period 12 months before exposure start. Only patients with a follow-up of at least 12 months will be included in this analysis.

The following analyses will be conducted:

- Percentage of patients with at least one prescription of NSAID
- Percentage of patients with at least one prescription of weak opioids
- Percentage of patients with at least one prescription of NSAID or weak opioids

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-b) 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-b) 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.

The following analysis will be performed:

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

9.7.2.3 Exposure

Exposure will be defined as one or more prescriptions for flupirtine. These prescriptions will be identified using the ATC code for flupirtine or INN. The 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 in the respective selection window.

The **duration of exposure** will be calculated as follows:

- **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 the recommendation by the physician will be determined.

- **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 pack size and the recommended daily dose
  - For all prescriptions: from the prescription date plus the expected number of days of drug supply based on the pack size and the DDD (400 mg / day)

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

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.

In order to allow the comparability of number of prescriptions or episodes during the follow-up period, the patients will be subdivided in the follow-up periods presented below:

- patients with a follow-up of at least 3 months after the first flupirtine prescription
- patients with a follow-up of at least 6 months after the first flupirtine prescription
- patients with a follow-up of at least 9 months after the first flupirtine prescription

It has to be considered, that the patient groups defined above will not be mutually exclusive. Patients with a follow-up period of at least 9 months will be included in all three defined groups. Patients with a follow-up period of at least 6 months will be part of the groups with a follow-up of at least 6 and of at least 3 months.

The analyses concerning number of prescriptions or episodes will be performed for each of the 3 follow-up periods.

The following parameters will be considered in the analysis:

- Number of packages
- Size of packages
- Strength of packages
- Recommended daily dose
- Recommended treatment duration
- Prescription length
- Single use and repeated use

The following analyses will be performed:

- Number of prescriptions per patient per month
- Percentage of prescriptions with different formulations
- Length of treatment episodes
- Percentage of patients with single flupirtine prescription during defined follow-up periods

- Percentage of patients with repeated flupirtine prescriptions during defined follow-up periods
- Percentage of patients with single treatment episode (based on DDD) during defined follow-up periods
- Percentage of patients with more than one treatment episode (based on DDD) during defined follow-up periods
- Percentage of patients with information concerning recommended treatment dose by the physician
- Percentage of patients with information concerning recommended treatment duration by the physician
- Percentage of prescriptions with information for treatment longer than 14 days (based on the recommendation by the physician)
- Percentage of prescriptions with information for treatment up to 14 days (based on the recommendation by the physician)
- Percentage of patients with treatment episodes up to 14 days for all episodes (based on DDD)
- Percentage of patients with at least one treatment episode longer than 14 days (based on DDD)
- Percentage of patients with repeated flupirtine prescriptions during one month follow-up period

9.7.2.4 Concomitant prescriptions

Concomitant use of drugs known to have potential hepatotoxic effect will be evaluated. A list of substances known to have potential hepatotoxic effect is presented in Annex 3.

Two approaches will be used to define concomitant prescription:

- Every prescription of a drug with known hepatotoxic effect performed at the same day as the flupirtine prescription
- Every prescription of a drug with known hepatotoxic effect performed during the recommended treatment duration (only for prescriptions with recommended treatment duration)

The following analysis will be performed:

- Percentage of flupirtine prescriptions with concomitant prescription of drugs known to have potential hepatotoxic effect during flupirtine treatment

9.7.2.5 Monitoring of liver function

The percentage of prescriptions with following liver function tests (laboratory tests for ASAT, ALAT, AP, GGT) will be analysed in patients of 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.

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

9.7.2.6 Statistical comparison

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:

- Proportion of patients with pre-existing liver disease or alcohol abuse problems
- Proportion of patients with pre-treatment with NSAIDs and weak opioids
- Proportion of patients with any diagnosis of disease contraindicated for NSAIDs or weak opioids
- Distribution of principal diagnoses
- Proportion of patients with single and repeated flupirtine prescriptions within a defined time period
- Proportion of prescriptions with concomitant use of drugs known to have potential hepatotoxic effect
- Proportion of prescriptions with LFT monitoring during flupirtine treatment
- Length of treatment episodes
- Proportion of patients with at least one treatment episode longer than 14 days (based on DDD)

9.7.3 IMS® LRx

9.7.3.1 Prescriber characteristics

Characteristics of flupirtine prescribing physicians

- Specialty
- Region

9.7.3.2 Patient characteristics

Demographic characteristics

The demographic characteristics (age, gender) of flupirtine patients will be described.

- **Age:**
  - Mean, SD, median, range
  - Percentage of patients with age
    - o < 18 years
    - o 18 to 29 years
    - o 30 to 39 years
    - o 40 to 49 years
    - o 50 to 59 years
    - o 60 to 69 years
    - o 70 years and older
  - Additionally these age-groups will be displayed:
    - o < 9 years
    - o 10-19 years
    - o 20-29 years
- **Gender:**
  - Percentage of male patients
  - Percentage of female patients

Medical history - treatment with NSAIDs and weak opioids before flupirtine exposure start

The proportion of patients with pre-treatment with at least one NSAID and/or weak opiod will be analysed considering:

- NSAIDs (list in the Annex 3)
- Weak opioids such as codeine phosphate, dextropropoxyphene, dihydrocodeine or tramadol

The pre-treatments will be analyzed for the time period 12 months before exposure start. Only patients with a follow-up of at least 12 months will be included in this analysis.

The following analyses will be conducted:

- Percentage of patients with at least one prescription of NSAID
- Percentage of patients with at least one prescription of weak opioids
- Percentage of patients with at least one prescription of NSAID or weak opioids

9.7.3.3 Exposure

Exposure will be defined as one or more prescriptions for flupirtine. These prescriptions will be identified using the ATC code for flupirtine or INN. The 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 in the respective selection window.

Prescription length (in days) will be calculated as the prescription fill date plus the number of days determined from the expected duration 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.

A **treatment episode** will be defined as one or more prescriptions (repeated prescriptions) of flupirtine with gaps between prescription lengths 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.

In order to allow the comparability of number of prescriptions or episodes during the follow-up period, the patients will be subdivided in the follow-up periods listed below:

- patients with a follow-up of at least 3 months after the first flupirtine prescription
- patients with a follow-up of at least 6 months after the first flupirtine prescription
- patients with a follow-up of at least 9 months after the first flupirtine prescription

The patient groups defined above will not be mutually exclusive. Patients with a follow-up period of at least 9 months will be included in all three defined groups. Patients with a follow-up period of at least 6 months will be part of the groups with a follow-up of at least 6 and of at least 3 months.

The analyses concerning number of prescriptions or episodes will be performed for each of the 3 follow-up periods.

The following parameters will be considered in the analysis:

- Number of packages
- Size of packages
- Strength of packages
- Prescription length
- Single use and repeated use

The following analyses will be performed:

- Number of prescriptions per patient per month
- Percentage of prescriptions with different formulations
- Length of treatment episodes
- Percentage of patients with single flupirtine prescription during defined follow-up periods
- Percentage of patients with repeated flupirtine prescriptions during defined follow-up periods
- Percentage of patients with single treatment episode during defined follow-up periods
- Percentage of patients with more than one treatment episode during defined follow-up periods
- Percentage of patients with repeated flupirtine prescriptions during one month follow-up period
- Percentage of patients with treatment episodes up to 14 days for all episodes
- Percentage of patients with at least one treatment episode longer than 14 days

9.7.3.4 Concomitant prescriptions

Concomitant use of drugs known to have potential hepatotoxic effect will be evaluated. A list of substances known to have potential hepatotoxic effect is presented in Annex 3. Every prescription of a drug with known hepatotoxic effect performed at the same day as the flupirtine prescription will be considered as concomitant prescription.

The following analysis will be performed:

- Percentage of flupirtine prescriptions with concomitant prescription of drugs known to have potential hepatotoxic effect

9.7.3.5 Statistical comparison

The comparison of patients/prescriptions of the two observational periods (assessment period and reference period) based on IMS® LRx data will consider the following outcome parameters and will be stratified by incident and prevalent users:

- Proportion of patients with pre-treatment with NSAIDs and weak opioids
- Proportion of patients with single and repeated flupirtine prescriptions within a defined time period
- Proportion of prescriptions with concomitant use of drugs known to have potential hepatotoxic effect
- Length of treatment episodes
- Proportion 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 Health.

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 specialities in the IMS® Disease Analyzer does not, however, exactly reflect the balance in Germany. In order to overcome this limitation the use of IMS® LRx is considered for the PASS flupirtine. This database provides 60% of all SHI prescriptions in Germany.

Data collection

IMS® DA:

- The IMS® Disease Analyzer has limitations consistent with a provider-sourced EMR database. Patients who seek care outside the EMR practice setting will not have that utilisation recorded in the database.
- Patients cannot be tracked across panel. Therefore, double counting of patients cannot be completely neglected when analysing more than one panel, for this study the PCP and orthopaedist panel.
- Another consequence is that prescriptions one patient has received from different specialties cannot be followed up. In order to overcome this limitation LRx data will be analysed in addition to provide information on drug utilisation per patient across specialties.
- Limited information is available on OTC products. Some information can be retrieved from the analysis of ‘Green Prescriptions’. Green prescriptions are used in Germany for drugs for which a prescription by a physician is not required and can be considered as recommendation. The patient has to pay for such a drug completely by himself as these drugs are not covered by the SHI. This will limit the information available on the pre-treatment with NSAIDs as substances like for example ibuprofen can be taken by self-medication.
- Information on alcohol abuse will be obtained by using ICD-10 codes “Mental and behavioural disorders due to use of alcohol” (F10). This can only be evaluated in the study if the flupirtine prescribing physician has documented the diagnosis of alcohol abuse. Therefore, an underestimation of alcohol abuse is likely.

IMS® LRx:

- The IMS® LRx provides information on dispensed drugs and might therefore not completely reflect the prescribing behaviour of the physicians. Due to the broad coverage of LRx this can be neglected.

- Information on prescriptions is only available if the patient fills the prescription in a pharmacy covered by the IMS® LRx database. If the patient switches to a pharmacy outside this panel the information of the follow-up prescription is missing.

Missing information

IMS® DA:

- Laboratory values are not available for all patients. Results will be provided for the subsample with available information and the significance of findings with respect to study objective will be addressed.
- 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 cannot be exactly determined. The dose recommendation “on demand (pro re nata)” is very often given in the therapy of acute pain which occur repeatedly. Therefore, the actual treatment duration is often shorter compared to the length of the prescription.

IMS® LRx:

- Information on diagnosis is not provided. Therefore, no information on indication and medical history is available from this data source.
- No information is available on NSAIDs purchased OTC.
- No information is available on recommended daily dose and treatment duration. It is possible to analyse the prescription length which is often longer than the actual treatment duration.

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 / adverse reactions

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

According to the current guidelines of the ISPE (2007) and the EMA Guideline on GVP: Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA 2012, 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, 18].

12. Plans for disseminating and communicating study results

The study will be registered in 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) and following the STROBE checklist[19, 20].

The final study report will be submitted to the 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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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]
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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

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	February 2014	Summary of Product Characteristics Flupirtinmaleat-Hormosan 100mg Hartkapseln, Dated February 2014

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:
Post-Authorisation Safety Study (PASS) for Flupirtine – Effect of Risk Minimisation Measures in Germany

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]	☒	☐	☐	13,14
1.1.2 End of data collection[2]	☒	☐	☐	13,14
1.1.3 Study progress report(s)	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	13,14
1.1.6 Final report of study results.	☒	☐	☐	13,14

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why 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)	☒	☐	☐	11,17
2.1.2 The objective(s) of the study?	☒	☐	☐	11,17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12,18
2.1.4 Which 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)	☒	☐	☐	11,18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	11,17
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	12,18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12,19
4.2.2 Age and sex?	☒	☐	☐	12,19
4.2.3 Country of origin?	☒	☐	☐	12,18
4.2.4 Disease/indication?	☒	☐	☐	12,19
4.2.5 Co-morbidity?	☒	☐	☐	20
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19

Comments:

The intention is to include all patients with flupirtine prescriptions in a defined time period; no selection with respect to age, sex or indication

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)	☒	☐	☐	26,30
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)	☒	☐	☐	26,30
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	18,19
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
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:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	21,22
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.)	☐	☐	☒	
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)	☒	☐	☐	19,20,24-32
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug	☒	☐	☐	19,20,24-32

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
use history, co-morbidity, co-medications, life style, etc.)				
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	21
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	21
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:

The intention is to include all patients of the selected physician panels of IMS® DA and IMS® LRx during the defined time periods in the analysis. A preliminary check of patient counts has shown that for the smallest patient group about 2200 patients can be expected.

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?	☒	☐	☐	23
10.3 Are descriptive analyses included?	☒	☐	☐	23
10.4 Are stratified analyses included?	☒	☐	☐	23
10.5 Does the plan describe methods for adjusting 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?	☒	☐	☐	23
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	23
11.3 Are methods of quality assurance described?	☒	☐	☐	32
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?	☒	☐	☐	33,34
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)	☒	☐	☐	33,34
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	22,23
12.3 Does the protocol address other limitations?	☒	☐	☐	33,34

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?	☒	☐	☐	34
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	34

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?	☒	☐	☐	13

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)?	☒	☐	☐	35
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	35

Comments:

Name of the main author of the protocol: Birgit Ehlken

Date: 24/09/2015

Signature: _____

Annex 3. Additional information

a. List of flupirtine-containing medicinal products marketed 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

b. Selection of diseases associated with acute pain

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/

Source: http://apps.who.int/classifications/icd10/browse/2010/en

c. Chronic pain

F45.4 Persistent somatoform pain disorder
F62.8 Other enduring personality changes - Chronic pain personality syndrome
R52.1 Chronic intractable pain
R52.2 Other chronic pain

d. Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

The table below provides a list of NSAIDs; the list will be reviewed before the statistical analysis, completed in the case substances are missing and included in the statistical analysis plan.

ATC code	Substance class	Substances
M01A	NSAIDs	
M01AB	Acetic acid derivatives	Indomethacin Diclofenac Acetmetacin Proglumetacin Aceclofenac
M01AC	Oxicams	Piroxicam Meloxicam
M01AE	Propionic acids	Ibuprofen Dexibuprofen Naproxen
M01AH	Coxibe	Celecoxib Etiricoxib Parecoxib
M01AX	Other nonsteroidal antiphlogistics and antirheumatics	Nabumeton Glucosamin
N02B	Other analgesics and antipyretics	
N02BA	Salicylates	Acetylsalicylic acid
N02BB	Pyrazolones	Phenazone Metamizole
N02BE	Anilide	Paracetamol

e. Drugs know to have a potential hepatotoxic effect

The figure below provides drugs know to have a potential hepatotoxic effects according to Navarro 2006; the list will be reviewed before the statistical analysis, completed in the case substances are missing and included in the statistical analysis plan.

Source: Navarro VJ, Senior JR. Drug-Related Hepatotoxicity. N Engl J Med 2006; 354:731-9.

Hepatocellular (Elevated ALT)	Mixed (Elevated ALP + Elevated ALT)	Cholestatic (Elevated ALP + TBL)
Acarbose	Amitriptyline	Amoxicillin–clavulanic acid
Acetaminophen	Azathioprine	Anabolic steroids
Allopurinol	Captopril	Chlorpromazine
Amiodarone	Carbamazepine	Clopidogrel
Baclofen	Clindamycin	Oral contraceptives
Buproprion	Cyproheptadine	Erythromycins
Fluoxetine	Enalapril	Estrogens
HAART drugs	Flutamide	Irbesartan
Herbals: kava kava and germander	Nitrofurantoin	Mirtazapine
Isoniazid	Phenobarbital	Phenothiazines
Ketoconazole	Phenytoin	Terbinafine
Lisinopril	Sulfonamides	Tricyclics
Losartan	Trazodone	
Methotrexate	Trimethoprim–sulfamethoxazole	
NSAIDs	Verapamil	
Omeprazole		
Paroxetine		
Pyrazinamide		
Rifampin		
Risperidone		
Sertraline		
Statins		
Tetracyclines		
Trazodone		
Trovafloxacin		
Valproic acid		

Figure 1. Liver Injury and Its Patterns.

Liver injury is defined as an alanine aminotransferase (ALT) level of more than three times the upper limit of the normal range, an alkaline phosphatase (ALP) level of more than twice the upper limit of normal, or a total bilirubin (TBL) level of more than twice the upper limit of normal if associated with any elevation of the alanine aminotransferase or alkaline phosphatase level. Liver injury is further characterized as hepatocellular when there is a predominant initial elevation of the alanine aminotransferase level or as cholestatic when there is a predominant initial elevation of the alkaline phosphatase level; a mixed pattern comprises elevations of both the alanine aminotransferase and alkaline phosphatase levels. Recognizing the pattern of liver injury helps to categorize it, since drugs tend to create injury predominantly in one or another pattern. The injury patterns are not mutually exclusive, and a mixed pattern of injury may occur in many instances of drug-related hepatotoxicity. HAART denotes highly active antiretroviral therapy, and NSAIDs nonsteroidal antiinflammatory drugs.

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

Weak Opioids:

- Postoperative pain management of children undergoing tonsillectomy and/or adenoidectomy
- Hypersensitivity to codeine sulfate or any component of the product
- Respiratory depression in the absence of resuscitative equipment
- Acute or severe bronchial asthma or hypercarbia
- Paralytic Ileus
- Meperidine and tramadol are contraindicated along with MAO inhibitors
- Raised Intracranial tension

NSAIDs:

- Allergy to aspirin or any NSAID
- Bleeding peptic ulcer
- Kidney disease
- Past transient ischemic attack (excluding aspirin)
- Past stroke (excluding aspirin)
- Past myocardial infarction (excluding aspirin)
- Coronary artery disease (excluding aspirin)
- Undergoing coronary artery bypass surgery
- In third trimester of pregnancy/Breast feeding