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

## Statistical Analysis Plan

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## 2. List of abbreviations

| | |
|---|---|
| ATC | Anatomical Therapeutic Chemical Classification |
| BfArM | Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) |
| DA | IMS® Disease Analyzer |
| DDD | Daily Defined Dose |
| DUS | Drug Utilization Study |
| EMA | European Medicines Agency |
| EMR | Electronic Medical Record |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| GP | General Practitioner |
| GVP | Good Pharmacovigilance Practices |
| 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 |
| MAH | Marketing Authorization Holder |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| PCP | Primary Care Physician |
| SAS | Statistical Analysis Systems |
| SmPC | Summary of Product Characteristics |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| WHO | World Health Organization |

## 3. Signature page

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## 4. 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 (indications) explicitly associated with Flupirtine prescriptions
    - Co-diagnoses associated with Flupirtine prescriptions
- Therapies, related to Flupirtine patients
    - Co-prescriptions received by Flupirtine patients (analysis period)
    - Further therapies received by Flupirtine patients (patient's history)
- 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 (>14days) leading to contraindications for the use of Flupirtine
- Liver functions test, if available within 1 week after exposure to Flupirtine

# 5. Research methods

## 5.1. 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).

## 5.2. 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.

## 5.3. Study time period

The selection of patients from the IMS® Disease Analyzer will be carried out in two defined 12-month periods from January 1, 2012 to 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.

## 5.4. 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.

## 5.5. 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.

Detailed prescriptions of the databases were performed in the underlying protocol version 3.0 from 25.09.2015.

## 5.6. Variables

The following variables will be considered in the DUS flupirtine.

<u>IMS® Disease Analyzer (PCP and orthopaedist panel)</u>

- Number of prescribing physicians
- Region of office (East/West Germany)
- Number of overall patients in the office

- Number of patients with at least one prescription of flupirtine-containing medicinal product
- Patient characteristics
  - Age
  - Gender
  - Insurance status (private or SHI insured)
  - Indication for Flupirtine exposure
- Flupirtine exposure
  - Number of Flupirtine prescriptions per patients during the 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 (>14days) leading to contraindication for Flupirtine
- Diseases contraindicated for NSAIDs and weak opioids
- Liver function tests - as far as available within 1 week after Flupirtine exposure

## 6. Data analysis

### 6.1. General remarks

Data from IMS® Disease Analyzer will be analysed as follows:

- by physician panels (PCP and orthopaedist panel) and
- by study cohorts of patients (patients with flupirtine prescriptions before the review of SmPC (reference period) and patients with flupirtine prescriptions after the review of SmPC (assessment period))

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 ICD-10 classification will be used to identify relevant diagnoses from data sources.

The WHO ATC classification will be used to select drugs of special interest (for example NSAIDs (Annex B-IV), weak opioids (Annex B-V) from the data sources.

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. Examples of corresponding table shells are presented in Annex A of this SAP. 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 review of SmPC will be calculated. For comparison of patients initiating on flupirtine since the review of SmPC with patients treated with flupirtine before the review 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.

The following patient groups will be used to perform statistical analysis comparing data before (reference period) and after (assessment period) the review of SmPC:

- **Reference period**: all patients with at least one prescription of flupirtine in the reference period
- **Assessment period**: all patients with at least one prescription of flupirtine in the assessment period

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 will be presented graphically for the following parameters:

- Proportion of patients with contraindications for NSAIDs and weak opioids
- Flupirtine treatment duration
- Proportion of patients with single and repeated flupirtine prescriptions within a defined time period
- Proportion of prescriptions with liver function test (LFT) monitoring during flupirtine treatment

## 6.2. Definitions

The table below includes definitions used for the analysis of the study variables:

| | |
|---|---|
| Exposure start date of flupirtine | The date of the patient's first record of flupirtine prescription during the reference or assessment period |
| Follow-up | Observation time after exposure start during reference or assessment period |
| Medical History | Patient's individual observational time before flupirtine exposure start date |
| Prevalent user | Patient 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 exposure start |
| 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 exposure start |
| Treatment gap | Time period (in days) between the start date of a prescription and the end date of the preceding prescription (according to expected number of days of drug supply based on the package size and the DDD) |
| Treatment episode | Single prescription or series of consecutive prescriptions with a treatment gap between two consecutive prescriptions of ≤ 7 days |

## 6.3. Stratification

The analysis will be stratified by incident and prevalent users.

## 6.4. IMS® Disease Analyzer

### 6.4.1. Prescriber characteristics

The analyses will be conducted on patient level.
The following parameters will be analyzed:

- **Region of practice:**
  - Number and percentage of Flupirtine patients in East Germany
  - Number and percentage of Flupirtine patients in West Germany
- **Number of all patients at practices:**
  - Mean, SD, median, range

### 6.4.2 Patient characteristics

**Demographic characteristics**

The demographic characteristics will be analyzed on patient level.

The following parameters will be analyzed:

- **Age:**
  - Mean, SD, median, range
  - Number and 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
- **Gender:**
  - Number and percentage of male patients
  - Number and percentage of female patients
- **Insurance status**
  - Number and percentage of patients with statutory health insurance (SHI)
  - Number and percentage of patients with private insurance

**Diseases leading to contraindications for NSAIDs or weak opioids**

A list of ICD-10 codes with diseases contraindicated for NSAIDs or weak opioids is displayed in ANNEX B-V.

The following analysis will be conducted:

- Number and percentage of patients with any diagnosis of disease contraindicated for NSAIDs or weak opioids 12 months prior to first prescription of Flupirtine (patient's history).

**Long-term medications leading to contraindications for Flupirtin**

A therapy duration exceeding 90 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 patients with at least one long-term therapy leading to contraindication of Flupirtine 12 months prior to first prescription of Flupirtine (patient's history).

**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

**Indication for flupirtine prescription**

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

- 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 B-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 B-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 analyzed separately.

The findings of principal diagnoses will be grouped by diagnosis according to ICD-10 codes including diseases associated with acute pain (selection of codes see Annex B-II). The analysis will be conducted on prescription level.

The following analysis will be performed:

- Number and percentage of prescriptions, stratified by diagnosis (ICD-10 code) (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)

**Therapies related to Flupirtine treatment**

Patients treated with Flupirtine will be monitored by analyzing all co-prescriptions within the 12 months history 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)].

### 6.4.3 Exposure

Exposure to flupirtine will be defined as one or more prescriptions for flupirtine. These prescriptions will be identified using the WHO 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 period.

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 recommendation by the physician will be determined.

- **Prescription length** (in days) will be determined as follows:

  - 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: from the prescription date plus the expected number of days of drug supply based on the package size and the defined daily dose (DDD) (400 mg / day)

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

**Treatment episode**

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 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.

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

### 6.4.5 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[3]

The laboratory tests listed below will be considered:

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

The analysis will be conducted on prescription level.

The following analysis will be performed:

- Number and percentage of flupirtine prescriptions with at least one liver function tests within 1 week after the prescription date of flupirtine.

### 6.4.6 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)

## 6.5. Methods for handling missing data

The data will be analyzed as reported. Missing values will not be replaced.
In case of a high percentage of missing values, it may be decided to exclude variables from analysis.

## 6.6 Levels of statistical significance

Planned exploratory analyses will be performed at 5% significance level. Confirmatory analyses are not planned.

## 6.7. Deviations from analyses intended in the protocol

No deviations of analyses from the protocol were planned.

## 6.8. Data management

IMS® Disease Analyzer Version 6.6 Build 3 or future updates will be used to select and retrieve data from IMS® Disease Analyzer. The data extraction will be performed by a programmer with extensive programming and analysis experience with the

LifeLink EMR-EU data. The extraction will be conducted according to IMS internal Standard Operation Procedures (SOPs).
All datasets extracted from the databases will be saved at IMS files.

### 6.9. Safety assessment

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

### 6.10. Statistical software used for analysis

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

### 6.11. 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)[1]. When reporting results of this study, the appropriate STROBE checklist (von Elm, 2007) will be followed[2].

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.

# 7. References

1. 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.
2. 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
3. Fachinformation MEDA Pharma GmbH & Co. KG, Product Flupigil® 100 mg Hartkapseln, Status as of October 2013

# Annex A. Examples of table shells

### I. IMS® Disease Analyzer

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

**Table 1: Prescriber characteristics (Source: IMS® DA, panel)**

| Parameter | | Reference period | Assessment period |
|---|---|---|---|
| **Number of physicians** | N | | |
| **Number of practices** | N | | |
| **Region of practice** | | | |
| West Germany | n (%*) | | |
| Ost Germany | n (%*) | | |
| **Number of patients at practice** | n<br>mean (SD)<br>median<br>min-max | | |

*% based on total number of practices

**Table 2: Demographic characteristics (Source: IMS® DA, panel)**

| Parameter | | | Reference period | | | Assessment period | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total N = | Incident N = | Prevalent N = | Total N = | Incident N = | Prevalent N = |
| **Age** | | mean (SD) | | | | | | |
| | | median | | | | | | |
| | | min-max | | | | | | |
| **Age, grouped** | | | | | | | | |
| | < 18 years | n (%) | | | | | | |
| | 18-29 years | n (%) | | | | | | |
| | 30-39 years | n (%) | | | | | | |
| | 40-49 years | n (%) | | | | | | |
| | 50-59 years | n (%) | | | | | | |
| | 60-69 years | n (%) | | | | | | |
| | ≥ 70 years | n (%) | | | | | | |
| **Gender** | | | | | | | | |
| | Male | n (%) | | | | | | |
| | Female | n (%) | | | | | | |
| **Insurance status** | | | | | | | | |
| | SHI | n (%) | | | | | | |
| | Private insurance | n (%) | | | | | | |

N=total number of patients

**Table 3: Medical history – co-morbidities (Source: IMS® DA, panel)**

| Parameter | | Reference period | | | Assessment period | | |
|---|---|---|---|---|---|---|---|
| | | Total | Incident | Prevalent | Total | Incident | Prevalent |
| | | N = | N = | N = | N = | N = | N = |
| **Patients with a 12 months history** | | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** |
| Number and percentage of patients identified as contraindicated of NSAIDs/weak opioid treatment | n (%[2]) | | | | | | |
| Number and percentage of long-term therapies leading to contraindication of Flupirtine | n (%[2]) | | | | | | |
| Number and percentage of patients with concomitant diseases during observation period, grouped by ICD codes | n (%[2]) | | | | | | |

N=total number of patients
[1] : total number of patients with available history
[2] : % based on total number of patients within available history

**Table 4: Medical history – treatment with NSAIDs and weak opioids before flupirtine (Source: IMS® DA, panel)**

| Parameter | | Reference period | | | Assessment period | | |
|---|---|---|---|---|---|---|---|
| | | Total | Incident | Prevalent | Total | Incident | Prevalent |
| | | N = | N = | N = | N = | N = | N = |
| **Patients with a 12 months history** | | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** |
| At least one prescription of NSAID[3] | n (%[2]) | | | | | | |
| At least one prescription of weak opioids[3] | n (%[2]) | | | | | | |
| At least one prescription of NSAIDs or weak opioids[3] | n (%[2]) | | | | | | |

N=total number of patients
[1] : total number of patients with available history
[2] : % based on total number of patients within available history

**Table 5: Medical history – indication for flupirtine prescription (Source: IMS® DA, panel)**

| Parameter | | Reference period | | | Assessment period | | |
|---|---|---|---|---|---|---|---|
| | | Total | Incident | Prevalent | Total | Incident | Prevalent |
| | | N = | N = | N = | N = | N = | N = |
| **Principal diagnosis[3]** | | | | | | | |
| Diagnosis #1 – ICD-10 code | n (%) | | | | | | |
| Diagnosis #2 – ICD-10 code | n (%) | | | | | | |
| Diagnosis #3 – ICD-10 code | n (%) | | | | | | |
| Diagnosis ## - ICD-10 code … | n (%) | | | | | | |
| | | | | | | | |
| Associated with acute pain | n (%) | | | | | | |
| Associated with chronic pain | n (%) | | | | | | |

N=total number of patients

**Table 6: Exposure to flupirtine – general data (Source: IMS® DA, panel)**

| Parameter | | Reference period | | | Assessment period | | |
|---|---|---|---|---|---|---|---|
| | | Total N = | Incident N = | Prevalent N = | Total N = | Incident N = | Prevalent N = |
| **Number of prescriptions per patient per month** | mean (SD)<br>median<br>min-max | | | | | | |

N=total number of patients

**Table 7: Exposure to flupirtine – formulation and length of episodes (Source: IMS® DA, panel)**

| Parameter | | Reference period | | | Assessment period | | |
|---|---|---|---|---|---|---|---|
| | | Total N = | Incident N = | Prevalent N = | Total N = | Incident N = | Prevalent N = |
| **Length of treatment episodes** | mean (SD)<br>median<br>min-max | | | | | | |

N=total number of patients

**Table 8: Exposure to flupirtine – treatment duration (Source: IMS® DA, panel)**

| Parameter | | | Reference period | | | Assessment period | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total N = | Incident N = | Prevalent N = | Total N = | Incident N = | Prevalent N = |
| **Information concerning recommended treatment dose available** | | | | | | | | |
| | yes | n (%) | | | | | | |
| | no | n (%) | | | | | | |
| **Information concerning recommended treatment duration available** | | | | | | | | |
| | yes | n (%) | | | | | | |
| | no | n (%) | | | | | | |
| **Recommended treatment duration** | | | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** | **N[1] =** |
| | ≤ 14 days | n (%[2]) | | | | | | |
| | > 14 days | n (%[2]) | | | | | | |

N=total number of prescriptions
[1] : total number of prescriptions with recommended treatment duration
[2] : % based on total number of prescriptions with recommended treatment duration

**Table 9: Concomitant prescriptions (Source: IMS® DA, panel)**

| Parameter | | Reference period | | | Assessment period | | |
|---|---|---|---|---|---|---|---|
| | | Total N = | Incident N = | Prevalent N = | Total N = | Incident N = | Prevalent N = |
| **Prescriptions with at least one liver function test within 1 week after flupirtine prescription** | n (%) | | | | | | |

N=total number of prescriptions

# Annex B. Further information

## I. 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

## II. 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 Other spondylopathies
M49 Spondylopathies in diseases classified elsewhere

M50-M54 Other dorsopathies
M50 Cervical disc disorders
M51 Other intervertebral disc disorders
M53 Other dorsopathies, 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 (excluded R52.1 and R52.2) Pain, not elsewhere classified

Source:

- http://apps.who.int/classifications/icd10/browse/2015/en
- ICD-10-GM Version 2015, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-2015-WHO Version for; 2015. [Access 12/06/2015]

## III. 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.

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

## IV. Weak opioids

The table below lists a selection of opioid substances step II of grade-scheme of World Health Organisation (WHO).

| **WHO ATC code** | **Substances** |
|---|---|
| N02AA08 | Dihydrocodeine |
| N02AX01 | Tilidine (Naloxon) |
| N02AX02 | Tramadol |
| R05DA04 | Codeine |

Source:
Grundlagen der Speziellen Schmerztherapie. Hrsg. Junker, U., Nolte, T. Urban & Vogel GmbH, München 2005

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

**Weak Opioids:**

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

**NSAIDs:**

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