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SCIENCE MEDICINES HEALTH

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## Assessment report for flupirtine containing medicinal products

Procedure under Article 107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1363

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.



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## 1. Background information on the procedure

On 28 February 2013, the German Federal Institute for Drugs and Medical Devices (BfArM) notified the Member States, European Medicines Agency and the European Commission in accordance with article 107i of Directive 2001/83/EC, of its intention to vary the marketing authorisation of all strengths and pharmaceutical forms of flupirtine containing medicinal products to remove the indication in chronic pain and to restrict the use to a short-term treatment in acute pain.

The decision of the BfArM was based on a recent evaluation of pharmacovigilance data namely an increased number of adverse drug reaction reports of severe liver toxicity associated with flupirtine, (including cases with fatal outcome or leading to liver transplantation) and the subsequent risk/benefit evaluation performed.

The PRAC was requested to assess the matter and to make a recommendation under the provisions of article 107i of Directive 2001/83/EC to the Human Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) on any measures necessary to ensure the safe and effective use, and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.

After reviewing all the available data submitted by the Marketing Authorisation Holders (MAHs) and by others Stakeholders, the PRAC adopted a recommendation on 13 June 2013.

## 2. Scientific discussion

Flupirtine is a 'selective neuronal potassium channel opener' (SNEPCO) that acts by reducing the excessive electrical activity that leads to many pain states. It also acts as functional N-methyl-D-aspartate (NMDA) receptor antagonist.

It is authorised in the European Union since 1984 as an alternative analgesic to opioids and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for the treatment of acute and chronic pain (such as painful muscle tenseness, tension headaches, cancer pain, dysmenorrhoea and pain following trauma or orthopaedic surgery or injuries).

Flupirtine is available as 100 mg immediate release capsules, 400 mg modified release tablet, 75 mg and 150 mg suppositories and as solution for injection (100 mg). Overall, the oral and suppositories formulations are indicated for the treatment of acute and chronic pain while the injectable is indicated for short-term use for acute pain such as post-operative pain. The WHO defined daily dose (DDD) for flupirtine oral is 400 mg. The maximum daily dose should not exceed 600 mg. Overall, the duration of treatment is recommended to be established individually by the prescriber.

Flupirtine-containing medicinal products are currently approved in 11 Member States (MSs) of the Union on prescription only: Bulgaria, Estonia, Germany, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Romania and Slovak Republic. The 100 mg immediate release capsules are available in all MSs. Other dosages and pharmaceutical forms are available in Germany only.

Patient exposure to flupirtine was greater in Germany and has increased steadily from 7,9 million DDD in 2001 to 28,1 million DDD in 2011. The 400 mg modified release tablets, although only authorised in Germany, is the most prescribed formulation in the Union since 2007.

The German National Competent Authority (BfArM) identified a growing number of hepatotoxicity reactions (probably idiosyncratic) reported in association with flupirtine. A total of 330 hepatic and biliary disorders were reported post-marketing, of which 49 involved liver failure and 15 had a fatal outcome or resulted in liver transplantation. There were no reports of liver failure from published

clinical trials. However, three published studies<sup>1,2,3</sup> reported elevated transaminases in 3%, 31% and 58.6% respectively, of the patients treated with flupirtine. Another publication<sup>4</sup> described six cases of flupirtine-induced liver injury, including one requiring liver transplantation.

Based on the above safety concerns and further to consideration of the current evidence of efficacy of flupirtine in the treatment of chronic and acute pain, the BfArM considered the benefit-risk not to be favourable in the treatment of chronic pain and potential favourable in acute pain subject to effective implementation of risk minimisation measures (e.g. limited duration of treatment, closely liver monitoring) and therefore on 28 February 2013 initiated an urgent union procedure under Article 107i of Directive 2001/83/EC.

## 2.1. Clinical safety

Overall, the safety data submitted and reviewed were spontaneous reports, several publications, clinical and non-clinical data, and a meta-analysis. These data are hereafter presented and discussed.

### Hepatotoxicity

- *Post marketing data*

A total of 570 serious and non-serious flupirtine hepatic case reports have been reported up to 28 March 2013, accordingly to the market leader MAH's safety database. Most cases were reports of increased liver enzymes, jaundice, hepatitis or hepatic failure.

Of the 570 hepatic cases (421 serious and 149 non-serious), 341 were from the hepatobiliary system organ class (SOC) of which 299 were serious (88%) and 42 non-serious (12%). Forty six reports are related to (acute) liver failure, liver transplantation and cases with fatal outcome. The following discussion excludes cases with fatal outcome which are discussed separately later on in this report.

The majority of cases (405 out of a total 570) were in female patients (71%) whereas 144 cases (25%) are in men and the remaining are of unknown **gender**. The distribution of **age of patients** shows some differences with, in both genders, a maximum between 50 – 59 years of age. The second highest in women is between 60-69 years while for men is between 40-49 years of age.

The mean **duration of treatment** was 94 days (1 to 1,308 days) for patients taking flupirtine. Treatment duration was unknown in 32.54% of the cases. Twenty-three percent of patients experienced hepatobiliary adverse events during treatment lasting up to 28 days, 13% were in the range of 29 to 42 days of treatment and 64% of patients experienced an adverse event after 42 days of treatment.

About 50 % of the **adverse events** (AEs) relate to elevated hepatic enzymes, including increases in liver transaminases and blood bilirubin. In 285 case reports out of 570, at least an increase of hepatic

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<sup>1</sup> Li C, Ni J, Wang Z et al. *Analgesic efficacy and tolerability of flupirtine vs. tramadol in patients with subacute low back pain: a double-blind multicentre trial.* Curr Med Res Opin 2008; 24(12):3523-3530;

<sup>2</sup> Michel MC, Radziszewski P, Falconer C, Marschall-Kehrel D, Blot K. *Unexpected frequent hepatotoxicity of a prescription drug, flupirtine, marketed for about 30 years.* British Journal of Clinical Pharmacology 2012; 73(5):821-825;

<sup>3</sup> Uberall MA, Mueller-Schwefe GH, Terhaag B. *Efficacy and safety of flupirtine modified release for the management of moderate to severe chronic low back pain: results of SUPREME, a prospective randomized, double-blind, placebo- and active-controlled parallel-group phase IV study.* Curr Med Res Opin 2012; 28(10):1617-1634;

<sup>4</sup> Puls F, Agne C, Klein F et al. *Pathology of flupirtine-induced liver injury: a histological and clinical study of six cases.* Virchows Arch 2011; 458(6):709-16;

enzymes was reported. Hepatitis, including acute, toxic or cholestatic hepatitis was reported in 129 and jaundice in 79 of all 570 analysed case reports.

Concomitant medication was present in 220 cases (of the total 341 cases) from the hepatobiliary SOC.

Overall, during the period 1999 to 28 March 2013 a total of 136 reports of liver injury (DILI, hepatic necrosis, (acute) liver failure, including fatal cases), including 15 fatal reports were identified. These cases come from spontaneous reporting and literature. Based on a patient exposure of 893,000 patient years, the **reporting rate** is of 15,2 cases/100 000 patient years, regardless of causality. The reporting rate for fatal cases of liver injury is estimated at 1,68 cases/100 000 patient years.

Cases of hepatobiliary disorders with fatal outcome, liver transplantation and liver failure were presented by the MAHs separately and are hereafter summarised:

#### Cases with fatal outcome

There were 16 cases reported with fatal outcome: females only, with mean age of 58 years (range 21-81 years), with an average of 8 weeks on treatment with flupirtine (range from 4-12 weeks). The daily dose in most of the cases was 300 mg (3x100 mg) immediate release formulation or 400 mg modified release formulation.

Co-medication was reported in 7 patients (54%) and unknown in the remaining cases. The co-medications were analgesics (such as ibuprofen, paracetamol, naproxen) and other substances (such as alendronic acid, ramipril, levothyroxine). In accordance with WHO causality assessment: 3 cases were considered "possible" related with flupirtine (all cases of reported co-medication), 3 considered "unlikely" and in 10 cases "no clear assessment" could be performed. It should be noted that one fatal report was excluded from the total number of 16 because the patient died due to the underlying cancer disease.

#### Cases of liver transplantation

There were 6 cases of liver transplantation following treatment with flupirtine reported in 4 females and 2 males patients with mean age of 44 years (range 33 - 53 years), with an average of 5.4 weeks on treatment (range from 2 - 10 weeks). The daily dose in most of the cases was 300 mg immediate release formulation or 400 mg modified release formulation.

Co-medication was reported in 5 patients (83%) and unknown in the remaining case. The co-medications were analgesics (such as ibuprofen, ibuprofen + tramadol in 3 cases, tramadol) and other substances (such as metamizol, amitriptyline). In accordance with WHO causality assessment all 6 cases were considered "possible" related with flupirtine (5 cases with co-medication and a mono-therapy case).

#### Cases of liver failure

There were 25 cases of liver failure following treatment with flupirtine reported in 22 females and 3 males patients with mean age of 49 years (range 28 - 68 years), with an average of 17 weeks of treatment duration (range from 2 - 65 weeks). The daily dose in most of the cases was 300 mg immediate release formulation or 400 mg modified release formulation.

Co-medication was reported in 20 patients (80 %) and unknown in the remaining 5 cases. The co-medications were analgesics (such as NSAIDs, ibuprofen + tramadol, tramadol) and other substances (such as metamizol, amitriptyline). In accordance with WHO causality assessment: 21 cases were considered "possible" related with flupirtine (11 cases with co-medication, 5 cases in mono-therapy

and 5 cases with co-medication not relevant for Drug Induced Liver Injury - DILI) and in 4 cases "no clear assessment" could be performed.

These 25 cases were also assessed by the Roussel Uclaf Causality Assessment Method (RUCAM): 1 case was "probable" related to flupirtine, 10 cases "possible" (2 cases in mono-therapy and 8 with co-medication), 7 cases "unlikely" and remaining 7 cases not assessable.

The PRAC noted the differences in cases of **hepatobiliary disorders SOC with fatal outcome, liver transplantation and liver failure** reported by the MAHs (47) and the cases identified by the German National Competent Authority, BfArM (49).

The 49 cases identified by the BfArM were reported in 41 females, 7 males and 1 unknown gender, mean age was 51 years (range 24 – 81 years), mean time to onset was 78 days (median 55, range 14 - 365 days) and hepatotoxic co-medication was noted in 25 cases. These cases were assessed by RUCAM: 1 case considered "highly probable", 9 "probable", 17 "possible", 6 "unlikely", 2 "excluded", 14 "insufficiently documented". The **time to onset** of liver failure was observed in 25 % of the cases for each of the following periods after 2-3 weeks, 3-8 weeks, 8-13 weeks and >13 weeks, respectively (information on time to onset was available in 35 cases only).

The 15 cases with a **fatal outcome** or resulting in liver transplantation identified by BfArM were reported in 13 females, 1 male, 1 unknown gender, mean age of 57 years (range 24 - 81 years), the mean time to onset was 70 days (median 63,5, range 21 - 140 days) and hepatotoxic co-medication was present in 9 cases. Causality assessed by RUCAM showed: 1 "probable", 3 "possible", 3 "unlikely", 3 "excluded", 5 "insufficiently documented". The **time of onset** of liver failure resulting in death or transplantation was observed in 2 of the cases (25 %) after approximately 3 - 5 weeks. The remaining 6 cases occurred after 60 days of treatment (information on time to onset was available in 8 cases only).

Overall the conclusions of the analyses of both set of cases are largely the same regardless of the differences in reported number of cases. This is also further confirmed by the retrospective analysis performed by Anderson and Borek<sup>5</sup> on 226 suspected cases of DILI with flupirtine, which is presented below.

- *Clinical and epidemiological studies*

Anderson and Borlak<sup>5</sup> (2011) performed a retrospective evaluation of all reported cases (n=226) to BfArM and AkdÄ of drug induced liver injury (DILI) in association with the use of flupirtine over a period of 17-years (1993 to 2009). About 76% were female, age between 40 to 60 years (56%) or older (35%). A total of 84,5 % were serious reports. A total of 6 cases with a fatal outcome were identified. The median daily dose of flupirtine was reported with 300 mg and the median duration of exposure was 56 days.

All cases were re-assessed for plausibility and causality of flupirtine associated DILI. Based on WHO-UMC scale: 6,2 % were "certain", 8,4 % "probable", 54,9 % "possible", 14,6 % "unlikely" and 15,9 % "unclassified/unclassifiable". Thus 69,5 % of the reports were rated as at least possible. In 14 (6,2 %) of the cases outcome of re-challenge was reported. In 13 of these cases (93 %) rechallenge resulted in reoccurrence or worsening of the symptoms. In 59 of the 226 cases no concomitant medication was reported. In 32 of these cases, positive dechallenge was observed. In 167 (73,9 %) concomitant

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<sup>5</sup> Anderson N and Borek J, *Correlation versus causation? Pharmacovigilance of the analgesic flupirtine exemplifies the need for refined spontaneous ADR reporting*. Public Library of Science (PLoS) One 2011; 6(10):e25221

medication was reported of which 151 reported concomitant medication with known liver related side effects. The average number of concomitant drugs with labeled liver related side effects was 3.

Statistical analysis has not shown any significant relationship between markers of hepato-biliary impairment (i.e. AST, ALT, bilirubin) and daily dose or cumulative dose nor with duration of treatment nor time to onset. These findings are suggestive of a type B or idiosyncratic adverse drug reaction in these patients.

Histology reports of **liver biopsies** were available in 49 patients and identified 36 cases showing features of toxic liver damage (29 of which were cases with concomitant medication with labeled hepatic ADR). A total of 19 cases were considered as possible/probable idiosyncratic type B reactions (lack of a dose-relationship but close temporal relation to flupirtine exposure, no concurrent infections, co-medication with known hepatobiliary ADR profile or other co-medication, autoimmune antibodies and alcohol abuse, time to onset < 90 days of treatment).

The authors postulate a relationship between the number of drugs given and the severity of liver impairment (level of ALT or AST) suggesting that a combination of COX-2 inhibitors or NSAIDs or with flupirtine may significantly aggravate and/or increase the incidence of hepatobiliary ADRs. However no clear relationship between the number of concomitant potentially hepatotoxic drugs and ALT or AST blood levels can be concluded.

*Klein et al. (2011)*<sup>6</sup> concluded that clinicians should be aware of the potential hepatotoxicity with flupirtine treatment in adults with no underlying liver disease, and that liver enzymes should be monitored carefully with initiation of chronic flupirtine treatment. The authors also emphasized that Flupirtine therapy should be discontinued without undue delay, in case that elevated serum liver enzymes are observed.

*Pulls et al. (2011)*<sup>4</sup> published a case series of 6 patients with liver injury (including one patient requiring liver transplantation). The causal relationship with flupirtine according to RUCAM was: 4 cases "probable" (including the patient requiring transplantation) and 2 cases "highly probably" (despite the presence of concomitant medication with labelled hepatic ADR in 5 patients). Time to onset was 3 months in 3 patients, 1 month, 4 months and 7 months. Apart from elevated transaminases 4 patients also presented with jaundice and elevated INR. All patients not requiring (i.e. 5 patients) transplantation recovered after discontinuation of flupirtine and showed normalization of ALT levels. Accidental re-exposure in one patient caused another strong elevation of liver parameters and liver biopsy showed an acute hepatitis with an infiltration by plasma cells and eosinophils.

The authors conclude that clinical and histological features raise the possibility of an immune-mediated toxicity and that flupirtine-mediated liver injury has to be classified as idiosyncratic or type B reaction but acknowledged the difficulty in assessing cause-and-effect relationship in idiosyncratic hepatotoxic reactions. The authors further concluded that flupirtine should be included in the list of drugs capable of causing severe liver injury in rare instances, and that the monitoring of liver enzymes in patients taking flupirtine is warranted.

*The SUPREME study (2012)*<sup>3</sup> was a multicentre, double-blind, randomised controlled study in 363 patients for the management of moderate to severe lower back pain aiming to demonstrate non-

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<sup>6</sup> Klein F, Glanemann M, Rudolph B, Seehofer D, Neuhaus P. *Flupirtine-induced hepatic failure requiring orthotopic liver transplant*. *Exp Clin Transplant* 2011;9(4):270-272.

inferior /superiority of flupirtine 400 mg modified release (MR) compared with tramadol 200 mg extended release (ER) and placebo with a treatment duration of 4 weeks.

This study showed elevations of liver enzymes in patients randomised to flupirtine comparable to placebo patients. Increases in liver enzyme scores (defined as any increase at the end of the 4-week treatment cycle vs. those values obtained at baseline) were a common occurrence in all three study groups: placebo group for AST/ALT/GGT in 47.6/49.5/52.9%; flupirtine group in 51.0/58.6/69.0% and in the tramadol group in 39.6/33.0/21.1%. Changes in liver parameters (defined as those twice above the upper reference range) were found in 5 patients of the placebo group (5/120, 4,2%), 6 patients of the flupirtine (6/119, 5,0%) group and in 1 patient of the tramadol group (1/116, 0,9%).

Michel *et al* (2012)<sup>2</sup> published results of a double-blind, double-dummy, three-armed comparison of flupirtine modified release (400 mg/day titrated to 600 mg/day after 8 weeks), tolterodine ER (4 mg/day) and placebo for 12 weeks investigating the efficacy of flupirtine in the treatment of overactive bladder syndrome. The study was discontinued prematurely when major elevations of liver enzymes were observed in several flupirtine exposed patients: ALT elevations of > 3 times the ULN were seen in 14/84 (16,7 %) patients on flupirtine, in 0/41 (0 %) patients on tolterodine and in 1/82 (1,2 %) patients on placebo. In the group of patients receiving flupirtine for  $\geq$  6 weeks elevations of ALT or AST were noticed in 31 % of the patients. It remains unclear why substantial liver enzyme elevations were seen more frequently in this study (> 3 x ULN: 16,7 %) than in other trials (e.g. SUPREME: > 2 x ULN: 5 %).

Li *et al.* (2008)<sup>1</sup> conducted a randomised, double-blind, parallel-group trial comparing flupirtine 100 mg (n = 105) vs. tramadol 50 mg (n = 104), both three times daily for 5-7 days to investigate efficacy and tolerability in Chinese patients with moderate to severe low back pain.

Although adverse effects occurred significantly less often in patients in the flupirtine than in the tramadol group, it was noted that 6 patients in both groups showed abnormal laboratory results at the end of a one week treatment course. Most abnormalities affected the white blood cell-count (4 on tramadol and 2 on flupirtine) and liver enzymes/bilirubin (1 vs. 3 cases, respectively). In all cases, the deviations returned to the normal range after the treatment ended.

- Possible mechanisms of hepatotoxicity of flupirtine

The clinical and histological features of flupirtine-induced liver injury is likely the result of a combination of hepatocellular damage caused by reactive oxygen species (ROS) and glutathione depletion as well as an immune mediated toxicity whereby Kupffer cells and other immune competent cells play a key role. This hypothesis requires further investigation since it is not supported by the available non-clinical data.

In a one-year study in rats, the cytoplasm of hepatic parenchymal cells appeared condensed and eosinophilic (only at doses of 90 mg/kg or higher). In a two-year mouse study, slight to moderate hepatocellular hypertrophy, increased incidence of single-cell necrosis and increased pigment deposition in macrophages were observed in males and increased incidence of single-cell necrosis was observed in females at 100 mg/kg. At 300 (450) mg/kg, the incidence and degree of these changes increased along with a higher deposition of pigment in hepatic macrophages of females. In addition, altered cell foci and nodular hepatocellular hyperplasia were increased. However, overall the available preclinical data do not support a dose-dependent adverse effect of flupirtine on the liver.

The PRAC took note of the MAH suggestion of an apparent over representation of modified release formulation associated hepatic cases compared to immediate release formulation cases to be due to properties of the modified formulation or to issues related to the CMC or API supplier. The data provided in this regard is not enough for an evaluation to be performed.

- *Analysis of case reports in EudraVigilance*

An analysis of EudraVigilance data in line with the scope of this referral and with focus on MedDRA hepatic SMQs was considered for the assessment. In total 800 individual case safety reports (ICSR) with flupirtine as suspected or interacting medicinal products were identified. The majority of the cases were received from Germany (773 reports, including 23 fatal reports), Portugal (11 reports) and only 1 to 3 reports each from the remaining countries.

While only few reports have been noted until 2004 the number of ICSR has risen steadily since 2005. The majority of reports were spontaneous reports (752) followed by 32 reports from studies and 16 from other sources. A total of 553 (69%) ICSR concerned females and 225 (28 %) concerned males, gender unknown in 22 cases. The total number of cases reporting reactions from the SOC "hepatobiliary disorders", the SMQ "hepatic disorders" and the SMQ "biliary disorders" is 482.

A total of twenty four (24) cases were reported with fatal outcome. Seventeen (17) of reported in the context of liver toxicity including sixteen (16) from Germany (15 fatal cases at the time of the notification of this referral), and one (1) from Switzerland.

### ***Other risks***

Although no specific data was provided in this regard it is noted that the most commonly reported adverse reactions for flupirtine include neurological disorders (e.g. fatigue, dizziness, insomnia, loss of appetite, headache, increased sweating) and gastrointestinal disorders (e.g. nausea, abdominal pain/discomfort, diarrhea). Although these adverse drug reactions may result in discontinuation of treatment in part of the patients there is no evidence that they may progress to life threatening situations outside the context of cases of overdose. These are reflected in the product information for flupirtine-containing products.

### ***Discussion and conclusion on safety***

A total of 570 serious (421) and non-serious (149) flupirtine hepatic case reports have been reported up to 28 March 2013, accordingly to the market leader MAH's safety database. Most cases were reports of increased liver enzymes, jaundice, hepatitis or hepatic failure.

The reporting rate for hepatic cases with flupirtine (regardless of causality) is of 15,2 cases/100 000 patients years (based on a patient exposure of 893, 000 patients year).

During the period of 1999 to March 2013 a total of 136 reports of flupirtine drug induced liver injury (DILI, hepatic necrosis, liver failure including fatal cases) have been identified in spontaneous reporting and literature including 15 cases with fatal outcome.

The time to onset of liver failure observed in spontaneous reporting was 25 % for each of the cases after 2-3 weeks, after 3-8 weeks, after 8-13 weeks and after >13 weeks (information on time to onset was available in 35 cases of the total 49 cases). Liver transplantation or fatal cases resulting from liver failure were seen after 3-5 weeks of treatment in 25% of the cases and the remaining after 60 days of treatment (information is only available from 8 cases of the total of 15 fatal cases).

Data from the literature as well as data from randomised clinical trials<sup>1,2,3,4</sup> showed an increment of markers for hepato-biliary impairment associated with the treatment of flupirtine. Cases possible related to flupirtine treatment, and with re-challenge reported, had reoccurrence or worsening of the symptoms in 93% of the cases. It is acknowledged that the majority of cases included concomitant medication known to have potential for hepatic adverse reactions and that the combination of COX-2

inhibitors or NSAIDs with flupirtine may significantly increase the severity of the hepato-biliary reactions.

The PRAC noted that based on clinical and histological features, the hepatotoxicity of flupirtine may be immune-mediated and that hepatotoxicity associated with flupirtine treatment may be type B or idiosyncratic adverse drug reaction.

Based on the current available data as described above, the PRAC concluded that flupirtine is associated with an increased risk of hepatotoxicity. Since no cases of hepatotoxicity including cases with fatal outcome or which resulted in liver transplantation have been identified so far in the first two weeks of treatment, PRAC concluded that flupirtine use should be restricted to a maximum of two weeks of treatment.

In addition, treatment with flupirtine is not recommended in patients with pre-existing liver disease or taken concomitantly other medication known to cause drug liver injury. Moreover, liver function should be kept under closely monitoring i.e. weekly during the treatment with flupirtine which should be discontinued upon symptoms and signals of liver disorders.

## 2.2. Clinical efficacy

Clinical data on the use of flupirtine in acute pain (single doses or as-needed treatment), in chronic pain (during 5 days to 2 weeks of treatment and during 4 to 8 weeks of treatment) and in cancer pain was submitted. These data are summarised hereafter.

### Treatment of acute pain

The efficacy of flupirtine in the treatment of acute pain was shown in several short-term treatment (ranging from single dose, up to 5 days, up to 1 week and up to 3 weeks) randomised clinical trials performed mainly in the 1970s and 1980s. The studies were performed against several active controls (Pentazocine/naloxone, paracetamol, codeine and placebo) and are hereafter summarised:

Table 1. Overview of the studies performed in acute pain

Study name /study author	Study Design	Indication (type of pain)	Duration of treatment	Total number of patients (F/M)	Flupirtine dose	Comparators and doses	Efficacy conclusions
Bikhazi et al	Randomised, Double-blind	Postsurgical pain (acute pain)	Single dose	222 (138/84)	IR 200 mg IR 300 mg	Placebo Pentazocine/naloxone 50/05 mg Codeine 60 mg	With exception of the pentazocin/naloxen on variable SPID no significant differences to placebo were seen
Bloomfield et al [n.75075]	Randomised, Double-blind	Pain after episiotomy (acute pain)	Single dose	249 (249/0)	IR 100 mg IR 200 mg	Placebo Paracetamol 650 mg	All active treatments were significantly superior to placebo, based on total pain relief score and the patient's global assessment only flupirtine 200 mg and paracetamol were superior
Bloomfield et al [n.75084]	Randomised, Double-blind	Pain after episiotomy (acute pain)	Single dose	166 (166/0)	IR 200 mg IR 200 mg plus paracetamol 650mg	Placebo Paracetamol 650mg Codeine 60 mg	Significant superiority over placebo was shown only for the group receiving flupirtine plus paracetamol
Borgognone et al	Randomised, Double-blind	Postsurgical pain (acute pain)	Every 8 hours or as needed	30 (16/14)	IR 200 mg IR 150 mg suppositories	Placebo	Pain reduction was significant in comparison to placebo after 3 and 6 hours post administration

Eisenberger	Randomised, Double-blind	Posttraumatic or postsurgical pain (acute pain)	Up to 3 days	90 (41/49)	IR 100 mg	Placebo	Efficacy in terms of pain relief when compared with placebo
Fanitini	Randomised, Double-blind	Traumatic pain (acute pain)	Single dose	50 (14/36)	IR 100 mg	Placebo	Efficacy was significantly superior to placebo
Galasko	Randomised, Double-blind	Traumatic pain (acute pain)	Single dose	60 (21/39)	IR 200 mg	Placebo	Trend like effect within the first 2 hours, significant at 3 and 4 hours after administration
Galasko	Randomised, Double-blind	Posttraumatic or postsurgical pain (acute pain)	Single dose	60 (31/29)	IR 200 mg	Placebo	No significant difference observed between active and placebo possibly because of the too long latency phase
Mehlisch	Randomised, Double-blind	Postsurgical pain (acute pain)	Single dose	142 (61/81)	IR 100 mg IR 200 mg	Placebo Paracetamol 650 mg Codeine 60 mg	Paracetamol was found to be superior to placebo
Singleton	Randomised, Double-blind	Postsurgical pain (acute pain)	Single dose	160 (113/47)	IR 100 mg IR 200 mg	Placebo Paracetamol 650 mg Codeine 60 mg	All active groups except 100 mg were found to be superior to placebo
Niland et al	Randomised, Double-blind	Postsurgical pain ( dental surgery) (acute pain)	Single dose	251 (6/245)	IR 100 mg IR 200 mg	Placebo Paracetamol 650 mg Paracetamol 650 mg plus oxycodone 10 mg	SPID indicated efficacy of both doses but not TOTPAR
Studd	Randomised, Double-blind	Pain after hysterectomy (acute pain)	Single dose	62 (62/0)	IR 50 mg IR 100 mg IR 200 mg	Placebo	Efficacy of 200 mg, although this could not be confirmed statistically
Venhaus	Randomised, Double-blind	Migraine, vasomotoric, other types of headache (acute pain)	Up to three days	174 (136/37)	IR 200 mg	Placebo Paracetamol 1000 mg	Efficacy superior to placebo, and in some cases to paracetamol
Breuel [n. 75036]	Randomised, Double-blind	Pain after injuries (acute pain)	Up to 2 weeks	115 (50/65)	IR 100 mg	Pentazocine 50 mg	Exhibited analgesic effects similar to that of pentazocine but with better tolerability
Breuel [n. 75041]	Randomised, Double-blind	Dysmenorrhoeic complaints (acute pain)	Up to 2 weeks	126 (126/0)	IR 100 mg	Pentazocine 50 mg	Flupirtine tended to provide more analgesia than pentazocine
Mohing	Randomised, Double-blind	Pain following bone surgery (acute pain)	Up to 1 week	30 (21/9)	IR 100 mg	Naproxen 250 mg	Similar analgesic effect
Riethmuller-Winzen [n. 75099]	Randomised, Double-blind	Dysmenorrhoea (acute pain)	Up to 1 week	162 (162/0)	IR 100 mg	Indomethacin 25 mg	Similar analgesic effect, indomethacin tended to provide better pain relief
Naser et al 2012	Randomised, Double-blind	Postoperative pain	Up to 5 days	114 (47/57)	IR 100 mg	Tramadol 50 mg	Delivers the same analgesic efficacy as oral tramadol, but exhibits less adverse effects

Most of the studies were placebo-controlled and used appropriate pain intensity scales. Different pain models (visceral and somatic) for different severity of pain were evaluated.

## Treatment of chronic pain

Data on efficacy of flupirtine in the use of chronic pain is very limited. Most studies presented are in management of pain in short term use only and management of chronic pain is intended for long term use in most cases.

Table 2. Overview of the studies performed in chronic pain

Study name /study author	Study Design	Indication (type of pain)	Duration of treatment	Total number of patients (F/M)	Flupirtine dose	Comparators and doses	Efficacy conclusions
Worz, Bolten et al 1996	Randomised, Double-blind	Chronic myofascial low back pain	7 days	166 (95/71)	IR 100 mg Day 1+2, 2 x 100 mg Day 3+4, 3 x 100 mg Then 4 x 100 mg	Placebo Chlomezanone 200 mg	Chlomezanone was considered effective for myosasms however its efficacy was not found different from placebo. The global assessment indicated significant superiority of flupirtine over placebo, but not of chlomezanone.
Schilling	Randomised, Double-blind	Different forms of rheumatic diseases (chronic pain)	Up to 7 days	25 (14/11)	IR 50 mg	Indomethacin 25 mg	Similar analgesic effect
Weigmann et al	Randomised, Double-blind	Low back pain (chronic pain)	7 days	269 (178/88)	MR 400 mg	Flupirtine 100 mg	The study demonstrated the therapeutic equivalence of OD administration of the 400 mg containing MR formulation with the q.i.d. administration of the daily dose of 400 mg of the IR formulation.
Li et al 2008	Randomised, Double-blind	Subacute low back pain (chronic pain)	7 days	220 (135/85)	IR 100 mg	Tramadol 50 mg	Flupirtine 100 mg three times daily was associated with a reduction in pain and improvements in functional capacity equivalent to that observed with tramadol 50 mg three times daily, and was better tolerated
Fernandez 1982	Randomised, Double-blind	Osteoarthritis (chronic pain)	4 weeks	90 (68/22)	IR 100 mg IR 200mg	Placebo	In particular, 200 mg TID, but to some extent also 100 mg TID, showed significant improvement for indices reflecting analgesic activity, but was not active in indices reflecting inflammatory components
Worz, Lobisch et al 1996	Randomised, Double-blind	Chronic tension-type headache (Chronic pain)	2 week	53 (32/21)	IR 100 mg	Placebo	It was significantly more effective than placebo
SUPREME Study 2012	Randomised, Double-blind	Chronic low back pain (chronic pain)	4 weeks	355 (220/135)	MR 400 mg	Placebo Tramadol 200 mg	The analgesic efficacy of flupirtine MR 400mg OD was at least comparable of that of tramadol ER 200 mg OD and superior to that of placebo, also when considering the higher usage of rescue medication in the placebo and the tramadol groups

Breuel [ No 75042]	Randomised, Double-blind	Neuralgia/ neuritis	4 weeks	122 (64/58)	IR 100 mg	Pentazocine 50 mg	Similar analgesic effect
Breuel [ No 75043]	Randomised, Double-blind	Various manifestations of non-articular rheumatism	8 weeks	121 (69/52)	IR 100 mg	Pentazocine 50 mg	Similar analgesic effect

In addition, published studies on the use of flupirtine in cancer pain were provided. Five studies with a total of 376 treated patients were performed for the indication of cancer pain. The efficacy of flupirtine was compared to the opioids pentazocine (3 studies: study of Breuel n. 75062, study by Scheef and study by Morl both with duration of 4 weeks) and tramadol (2 studies: Study of Riethmuller-winzen and study of Luben et al). Flupirtine shows at least similar analgesic efficacy as opioids such as pentazocine and tramadol for cancer pain (compared doses of both flupirtine and control treatment within approved recommendations). The planned treatment duration was no longer than 4 weeks.

### **Studies in long term treatment**

Two prospective, uncontrolled clinical studies<sup>7,8</sup> on the use of flupirtine in cases of chronic pain over a period of 6 months up to one year were submitted.

Table 3. Outline and conclusions of the study by Herrmann<sup>7</sup> investigating the use of flupirtine over a period of 2 – 6 months

<b>Indication as outlined</b>	<b>Chronic pain due to rheumatic diseases, arthritis, or degenerative disease of spine</b>
<b>Type of pain (classified)</b>	<b>Chronic pain</b>
<b>Planned treatment duration</b>	<b>One part 2 months, another part 6 months</b>
<b>Design</b>	<b>Uncontrolled</b>
<b>Total / M / F // % female (overall)</b>	<b>263 / 63 / 200 // 76.4% female</b>
<b>Drug, dose</b>	<b>Flupirtine (IR) capsules 100 mg, maximum of 400 mg/day</b>
<b>Comparator</b>	<b>None</b>
<b>Efficacy conclusions</b>	<b>No evidence for development of tolerance to the analgesic effect.</b>

In this study, the long-term tolerability (particularly regarding liver enzymes) and the analgesic efficacy were investigated in two groups of patients (n = 263) with chronic pain. Flupirtine was used over 2 months (158 patients) and in the 2nd group over 6 months (105 patients).

76.4% of the 263 patients were women and 237 patients were still in the study after 2 months (11 and 15 dropouts of the 2 and 6 month group, respectively). The tolerance analysis was performed with data of 251 patients and with 104 patients after two and 6 month, respectively.

There was no evidence for decreasing efficacy over time during this uncontrolled study.

In the other (below presented) study patients with simultaneous treatment with other analgesics of strong effect, high-risk outpatients (decomposed cardiac, circulatory, hepatic and renal diseases, severe cerebro-organic diseases) pregnant women and women capable of bearing children and not doing anything for contraception or nursing mothers, carcinomas, abuse of or dependence on alcohol and drugs were excluded. Over a period of 52 weeks the patients were recommended to take 3 x daily 100 mg of flupirtine, where the patient could vary the daily dose as required. The minimum dose was 100 mg flupirtine, the permitted maximum dose 600 mg/day.

Table 4. Outline and results of the study by Herrmann<sup>8</sup> investigating the use of flupirtine over a period of 12 months

<b>Indication as outlined</b>	<b>Chronic pain due to rheumatic diseases, arthritis, or degenerative disease of spine</b>
<b>Type of pain (classified)</b>	<b>Chronic pain</b>
<b>Planned treatment duration</b>	<b>One year</b>
<b>Design</b>	<b>Uncontrolled, followed by a single-blind placebo wash-out phase</b>
<b>Total / M / F // % female (overall)</b>	<b>214 / 53 / 161 // 84.3% female</b>
<b>Drug, dose</b>	<b>Flupirtine (IR) capsules 100 mg, maximum of 600 mg/day</b>
<b>Comparator</b>	<b>None</b>
<b>Efficacy conclusions</b>	<b>No evidence for development of tolerance to the analgesic effect. No evidence for withdrawal symptoms.</b>

Only 119 out of 191 included in the study completed the 52-week planned treatment. 17% of patients discontinued treatment due to lack of efficacy. The high dropout rate (38%) of this uncontrolled trial raises concerns about the adverse drug reactions that may lead patients to discontinue the treatment and doubts about its conclusions.

No controlled trials were presented for planned treatment durations longer than 8 weeks, and only one was prolonged longer than 4 weeks (Study by Breuel No.75043).

### **Discussion and conclusion on efficacy**

Data on efficacy of flupirtine in the use of chronic pain is very limited. Most studies presented are in management of pain in short term use only and management of chronic pain is intended for long term use in most cases. The two long term clinical studies presented (which became available since the granting of the initial Marketing Authorisation) were uncontrolled and regarded the use of flupirtine over a period of 2 - 6 months study<sup>7</sup> and a one-year<sup>8,9</sup>.

In fact, available efficacy designed studies are for periods no longer than 8 weeks.

The PRAC also noted that according to the current scientific knowledge including the Note for Guidance on clinical investigation of medicinal products for treatment of nociceptive pain (CPMP/EWP/612/00) clinical data of at least 3 months for the treatment of mild to moderately severe chronic back pain is required. This is particularly important with regards back pain model due to the expected high rate of spontaneous remission.

Therefore, the PRAC considered that flupirtine containing medicinal products only show very limited efficacy in the management of chronic pain. In view of the hepatotoxicity and very limited efficacy PRAC concluded that the benefit/risk for flupirtine containing medicinal products in the management of chronic pain is no longer favourable.

<sup>7</sup> Herrmann WM: *Investigation of the long-term tolerability of the analgesic flupirtine in patients who require analgesics regularly over a long period of time. – Open trial over 6 months or 8 weeks.* Degussa-Report No. D-09998 / 75 101

<sup>8</sup> Herrmann WM: *Final report: Investigation of the long-term tolerability of the analgesic flupirtine in patients who require analgesics regularly over long periods of time. Open study over 12 months, single blind subsequent observation period of 14 days (including an „Additional evaluation about a group of very old patients > 80 years“)* Degussa-Report No. D-09998 / 75 057 C, (for publication see also below)

<sup>9</sup> Herrmann WM, Hiersemenzel R, Aigner M et al.: *Die Langzeitverträglichkeit von Flupirtin. Offene multizentrische Studie über ein Jahr.* Fortschr. Med. 111 (1993) 46-50

The PRAC considered that in the short term use studies, the efficacy of flupirtine in acute pain was at least comparable to the comparators. The PRAC considers that there is sufficient evidence on efficacy in the acute (nociceptive) pain indication (mild, moderate and severe).

### **2.3. Risk minimisation activities**

#### ***Risk management plan***

Routine pharmacovigilance has been conducted since first marketing authorisation and safety information summarised in the core company data sheet (CCDS). The PRAC recommended that a core RMP should be submitted to the national competent authorities for assessment reflecting the following risk minimisation measures agreed within the PRAC recommendation.

#### ***Changes to the Product Information***

Based on above assessment, the PRAC recommended amendments to the product information for flupirtine containing medicinal products. The amendments aim to reflect the restricted use of maximum of two weeks of treatment, consequently only in acute pain and when other analgesics are contraindicated. Also aiming minimisation of the hepatotoxicity risk associated with flupirtine, close monitoring of the liver function during treatment should be performed and its use contraindicated in patients with pre-existing liver disease. In addition, the frequency of the observed increased in hepatobiliary markers in clinical studies lead to a higher frequency of occurrence of these adverse drug reactions and consequently amendments to the products information in this regard.

Furthermore, the PRAC decided that flupirtine-containing medicinal products should be included in the additional monitoring list. Therefore, further amendments have been included in the product information as per published templates by the "Quality Review Documents" group.

The exact wording recommended by the PRAC to relevant sections of the SmPC and PI are found further below in the corresponding section of this report.

#### ***Information and awareness of the Healthcare professionals and Patients***

Educational measures are necessary in order to clearly inform prescribers and patients on the hepatotoxicity risk associated with flupirtine and on the measures necessary to minimise the risk.

##### *i. DHPC and Communication action plan*

A direct healthcare professional communication (DHPC) has been discussed and agreed during the assessment of these medicinal products to inform the healthcare professionals on the changes to the use of flupirtine-containing medicinal products.

##### *ii. Educational Material*

PRAC also recommended that educational material are necessary in order to clearly inform prescribers and patients on the hepatotoxicity risk associated with flupirtine and on the measures necessary to minimise the risk. These have been requested by PRAC for submission within the risk management plan.

## **Future Monitoring**

### *i. Drug utilisation study (DUS)*

In order to better understand the potential extent of inappropriate prescribing of flupirtine containing medicinal products, the MAH should conduct a drug utilization study (DUS). This drug utilization study should aim to characterise prescribing practices during typical clinical use in representative groups of prescribers. The protocol of this study should be submitted within the risk management plan for agreement with the national competent authorities of the Member States.

### *ii. Post-authorisation safety study (PASS)*

A post-authorisation I safety study to evaluate the effectiveness of the risk minimisation activities was recommended by the PRAC. The protocol of this study should be submitted within the risk management plan for agreement with the national competent authorities of the Member States.

The PRAC also recommended that flupirtine-containing medicinal products should be included in the additional monitoring list and that PSURs should be submitted yearly.

## **2.4. Product information**

The PRAC recommended the amendments to be introduced in the summary of product characteristics (SmPC) and package leaflet (PL).

### **Summary of Product Characteristics**

[For medicinal products subject to additional monitoring ONLY:

The black symbol and the statements should only appear preceding section 1 "Name of the Medicinal Product". The black symbol shall be a black inverted equilateral triangle: the symbol shall be proportional to the font size of the subsequent standardised text and in any case each side of the triangle shall have a minimum length of 5 mm. For the purpose of preparing the product information annexes please use the black triangle as presented in this template (see below).]

< ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions. >

### **Section 4.1 Therapeutic indications**

#### **[Oral pharmaceutical forms and suppositories]**

Treatment of acute pain in adults.

< Product Name > must only be used if treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated.

#### **[Solution for injection (i.m.)]**

For single dose application in adults with postoperative pain. If a longer duration of use is required, other pharmaceutical forms are available.

< Product Name > must only be used if treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated.

### **Section 4.2 Posology and method of administration**

#### **[100 mg IR pharmaceutical form, suppositories]**

Flupirtine should be administered at the lowest effective dose for the shortest duration necessary to achieve adequate analgesia.

The duration of treatment must not exceed 2 weeks.

#### Paediatric population

The safety and efficacy of flupirtine in children and adolescents have not been established. <Product Name> should not be used in children and adolescents under the age of 18 years.

#### **[400 mg MR pharmaceutical form]**

Flupirtine should be administered for the shortest duration necessary to achieve adequate analgesia.

The duration of treatment must not exceed 2 weeks.

#### Paediatric population

The safety and efficacy of flupirtine in children and adolescents have not been established. <Product Name> should not be used in children and adolescents under the age of 18 years.

#### **[Solution for injection (i.m.)]**

#### Paediatric population

The safety and efficacy of flupirtine in children and adolescents have not been established. <Product Name> should not be used in children and adolescents under the age of 18 years.

### **Section 4.3 Contraindications**

#### **[Oral pharmaceutical forms and suppositories]**

Patients with pre-existing liver disease or alcohol abuse must not take <Product Name>. Concomitant use of flupirtine with other drugs known to cause drug induced liver injury must be avoided (see Section 4.5).

#### **[Solution for injection (i.m.)]**

<Product Name> should not be used in patients with pre-existing liver disease or alcohol abuse. Concomitant use of flupirtine with other drugs known to cause drug induced liver injury must be avoided (see Section 4.5).

### **Section 4.4 Special warnings and precautions for use**

#### **[All pharmaceutical forms]**

Liver function tests must be performed at weekly intervals during treatment with <Product Name> because increased liver enzyme levels, hepatitis and liver failure have been reported in association with flupirtine therapy.

If abnormal liver function tests or clinical symptoms consistent with liver disease occur, treatment with <Product Name> must be discontinued.

Patients should be advised to remain vigilant for any symptoms compatible with hepatic damage during treatment with <Product Name> (e.g. loss of appetite, nausea, vomiting, abdominal pain, fatigue, dark urine, jaundice, pruritus) and to discontinue intake of <Product Name> and to seek medical advice immediately if any such symptoms occur.

### **Section 4.5 Interaction with other medicinal products and other forms of interaction**

#### **[All pharmaceutical forms]**

Concomitant use of flupirtine with other drugs known to cause drug induced liver injury must be avoided (see Section 4.3).

### **Section 4.8 Undesirable effects**

#### **[All pharmaceutical forms]**

Hepatobiliary disorders:

Very common: Transaminases increased.

Not known: Hepatitis, liver failure.

*[The wording below should be inserted at the end of this section]*

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via **the national reporting system listed in Appendix V\***.

*[\*For the printed materials: No reference to the Appendix V should be included in the printed materials. The above grey-shaded terms will only appear in the published version of the approved product information annexes on EMA's website. The actual details of the national reporting system (as listed within the Appendix V) of the concerned Member State(s) shall be displayed on the printed version. Linguistic adjustments may also be necessary depending on the grammatical rules of the languages used.]*

## **Package Leaflet**

The package leaflet was aligned to the SmPC proposals.

## **3. Benefit-risk assessment**

Based on the current available data as described above, the PRAC concluded that flupirtine is associated with an increased risk of hepatotoxicity. Since no cases of hepatotoxicity including cases with fatal outcome or which resulted in liver transplantation have been identified so far in the first two weeks of treatment, PRAC concluded that flupirtine use should be restricted to a maximum of two weeks. In view of this and of the very limited efficacy of flupirtine in the management of chronic pain, PRAC concluded that the benefit-risk balance of flupirtine containing medicinal products in the management of chronic pain was no longer favourable.

For the treatment of acute pain, the PRAC recommended that the benefit still outweighs the hepatotoxicity risk when treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated. In order to ensure a favourable benefit/risk in this indication, PRAC concluded that treatment should be restricted to a maximum of 2 weeks.

In addition, treatment with flupirtine is contraindicated in patients with pre-existing liver disease or taken concomitantly other medication known to cause drug liver injury. Moreover, liver function should be kept under closely monitoring i.e. weekly during the treatment with flupirtine which should be discontinued upon symptoms and signals of liver disorders. Furthermore the PRAC agreed on additional pharmacovigilance activities and risk minimisation measures.

## **4. Overall conclusion**

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanation, the PRAC concluded that:

- a. the marketing authorisation holders should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;
- b. the marketing authorisation holders should implement risk minimisation measures;
- c. the marketing authorisations should be varied.

The PRAC considered that a Direct healthcare professional communication (DHPC) was needed to communicate the outcome of the present review.

The PRAC also recommended that the MAH should submit a full risk management plan (RMP) within a certain timeframe. The protocol of drug utilisation study in order to characterise prescribing practices

for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription should be also be submitted as part of the RMP.

The PRAC concluded that the risk-benefit balance of flupirtine containing medicinal product(s) in the treatment of acute pain remains favourable subject to the restrictions, warnings, other changes to the product information, additional pharmacovigilance activities and additional risk minimisation measures agreed.

With regards to the management of chronic pain PRAC concluded that the benefit-risk in this indication is no longer favourable.

## 5. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the measures taken for the safe use of these medicinal products. The final version of this DHPC agreed by the PRAC is provided together with the communication plan (see attachments to this report).

The MAH should agree the translations and local specificities of the DHPC with national competent authorities as the prescribing physicians vary from country to country and they must be adapted accordingly. Differences in target populations by Member State need to be discussed and aligned with the National Competent Authorities.

## 6. Conclusion and grounds for the recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC, for flupirtine containing medicinal products.
- The PRAC reviewed all available data from clinical and non-clinical studies, epidemiological studies, spontaneous reports and published literature on the safety and efficacy of flupirtine containing medicinal products, as well as stakeholders' submissions in particular with regards to the risk of hepatotoxicity.
- The PRAC is of the opinion that data from safety provide evidence for an increased risk of hepatotoxicity including cases with fatal outcome or resulted in liver transplantation when duration of treatment is longer than 2 weeks.
- The PRAC considered that flupirtine containing medicinal products only show very limited efficacy in the management of chronic pain. In view of the hepatotoxicity and very limited efficacy PRAC concluded that the benefit/risk for flupirtine containing medicinal products in the management of chronic pain is no longer favourable.
- The PRAC concluded that in view of the currently available safety data in order to maintain a favourable benefit/risk in the management of acute pain, flupirtine containing medicinal products should have treatment duration restricted to 2 weeks, contraindicated in patients with pre-existing liver disease. In addition, patients should have their liver function monitored after each full week of treatment and treatment should be stopped if there are signs of liver problems.
- The PRAC also concluded that there was need for further risk minimisation measures such as information to patients and healthcare professionals. Direct healthcare professional

communication were agreed, together with the timelines for distribution and that a post-authorisation safety study as well as a drug utilisation study should be conducted.

The PRAC, as a consequence, concluded that pursuant to Article 116 of Directive 2001/83/EC the risk-benefit balance for flupirtine containing medicinal products in the management of chronic pain is not favourable.

The PRAC concluded that the benefit-risk balance for flupirtine containing medicinal products remains favourable in the treatment of acute pain subject to the agreed restrictions, contraindications, warnings, other changes to the product information and additional risk minimisation measures.

## **Appendix 1**

*Listing of submissions of all data received by the Agency*

Listing of submissions of all data received by the Agency (i.e. from MAHs and other stakeholders) for Flupirtine-containing medicinal product(s)

<b>Submission</b>
<b>MAHs</b>
Teva Europe
Vitapharma Generics GmbH
Meda Pharma
ZeNTIVA (Sanofi)
<b>Stakeholders</b>
Healthcare professionals' organisation - Pain Association
Healthcare professional – Psychiatry
Research Institute
Healthcare professional
Healthcare professionals' organisation
Healthcare professional - pain therapist
Patients' organisation
Healthcare professionals' organisation - Pain Society
Healthcare professional - Neurologist

## Appendix 2

### *Divergent positions to PRAC recommendation*

## Article 107i of Directive 2001/83/EC

Procedure No: EMEA/H/A-107i/1363 for Flupirtine containing medicinal products

### Divergent statement

The following members of PRAC did not agree with the PRAC's Recommendation on the Article 107i referral for flupirtine containing medicinal products based on the following reasons:

- Uncertainties about the benefits in the proposed indications

From an efficacy point of view, both the data provided by the marketing authorisation holders and the published studies show very limited evidence of the efficacy of flupirtine in the proposed indications of acute pain. The few published studies on acute, mild-moderate pain have a number of deficiencies including small number of patients, lack of statistical analysis of outcomes, or lack of a placebo group. A single study with an acceptable design and well described (Überall 2012) which seems to show an equivalent efficacy with regard to tramadol, cannot be deemed as proof of efficacy since in the same study, tramadol was not superior to placebo. This suggests some deficiencies in the study and questions data reliability. Some of the problems above described for mild-moderate acute pain, are also identified in the studies for moderate-severe acute pain.

Overall, there is an absence of well designed randomised, double blind, placebo controlled studies with clinical meaningful results to support the efficacy of flupirtine in short term (< 2 weeks) analgesic treatment.

- Uncertainties about the hepatotoxicity and the risk minimiation strategy proposed

The lack of clarity on the mechanism by which flupirtine causes hepatotoxicity is of real concern and the data indicate it is most likely idiosyncratic, and not due to accumulation, since there is no dose dependency and no clear time-relationship. This is further supported by pre-clinical experiments and liver biopsy data suggesting it is idiosyncratic in nature. Consequently the risk of hepatotoxicity with flupirtine is unpredictable, and hence cannot be excluded in short term use (up to 2 weeks).

Any risk mitigation strategy needs to be sufficiently robust and evidence driven to prevent unnecessary harm in the context of a treatment for which there are therapeutic alternatives. Given that the hepatotoxic effect of flupirtine is most likely idiosyncratic this calls in to question the ability to introduce appropriate risk minimisation measures. Inclusion of a requirement for weekly liver function monitoring is considered to add an additional unnecessary burden to patients with no clear benefit in terms of risk minimisation. Furthermore they are not considered clinically feasible and hence are unlikely to be adhered to in routine clinical practice.

### **PRAC member expressing a divergent position:**

Herve Le Louet	13 June 2013	Signature: .....
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**PRAC member expressing a divergent position:**

Lennart Waldenlind	13 June 2013	Signature: .....
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**PRAC member expressing a divergent position:**

Isabelle Robine ( FR)	13 June 2013	Signature: .....
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**Divergent statement**

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**PRAC member expressing a divergent position:**

Julie Williams (UK)	13 June 2013	Signature: .....
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**Divergent statement**

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- Uncertainties about the benefits in the proposed indications

From an efficacy point of view, both the data provided by the marketing authorisation holders and the published studies show very limited evidence of the efficacy of flupirtine in the proposed indications of acute pain. The few published studies on acute, mild-moderate pain have a number of deficiencies including small number of patients, lack of statistical analysis of outcomes, or lack of a placebo group. A single study with an acceptable design and well described (Überall 2012) which seems to show an equivalent efficacy with regard to tramadol, cannot be deemed as proof of efficacy since in the same study, tramadol was not superior to placebo. This suggests some deficiencies in the study and questions data reliability. Some of the problems above described for mild-moderate acute pain, are also identified in the studies for moderate-severe acute pain.

Overall, there is an absence of well designed randomised, double blind, placebo controlled studies with clinical meaningful results to support the efficacy of flupirtine in short term (< 2 weeks) analgesic treatment.

- Uncertainties about the hepatotoxicity and the risk minimiation strategy proposed

The lack of clarity on the mechanism by which flupirtine causes hepatotoxicity is of real concern and the data indicate it is most likely idiosyncratic, and not due to accumulation, since there is no dose dependency and no clear time-relationship. This is further supported by pre-clinical experiments and liver biopsy data suggesting it is idiosyncratic in nature. Consequently the risk of hepatotoxicity with flupirtine is unpredictable, and hence cannot be excluded in short term use (up to 2 weeks).

Any risk mitigation strategy needs to be sufficiently robust and evidence driven to prevent unnecessary harm in the context of a treatment for which there are therapeutic alternatives. Given that the hepatotoxic effect of flupirtine is most likely idiosyncratic this calls in to question the ability to introduce appropriate risk minimisation measures. Inclusion of a requirement for weekly liver function monitoring is considered to add an additional unnecessary burden to patients with no clear benefit in terms of risk minimisation. Furthermore they are not considered clinically feasible and hence are unlikely to be adhered to in routine clinical practice.

**PRAC member expressing a divergent position:**

Dolores Montero (ES)	13 June 2013	Signature: .....
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**Divergent statement**

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Sabine Straus (NL)	13 June 2013	Signature: .....
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Almath Spooner (IE)	13 June 2013	Signature: .....
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Jean-Michel Dogné (BE)	13 June 2013	Signature: .....
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Marieke De Bruin	13 June 2013	Signature: .....
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Kamila Czajkowska (PL)	13 June 2013	Signature: .....
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**PRAC member expressing a divergent position:**

Kirsten Myhr	13 June 2013	Signature: .....
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