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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

INN: flupirtine

Procedure number: EMEA/H/A-31/1458

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Information on the procedure

In 2013, as a result of an urgent Union procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1363), the marketing authorisations (MAs) for flupirtine-containing medicinal products were varied to impose restrictions and risk minimisations measures implemented in view of the risk of liver injury. In 2017, results of observational studies imposed as an outcome of this urgent union procedure indicated a low degree of compliance with the authorised terms of use of flupirtine-containing medicinal products and more specifically, with the above-mentioned restrictions and risk minimisations measures. In addition, cases of drug induced liver injury (DILI), including serious cases, continued to be received in EudraVigilance (EV) with flupirtine-containing medicinal products reported as suspected or interacting products.

In view of the recent study results and as cases of liver injury continue to be reported, the German national competent authority (BfArM) considered that the impact of the risk of liver injury on the benefit-risk balance of these medicinal products and the adequacy of the related risk minimisation measures, should be reviewed.

On 19 October 2017, the BfArM therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of flupirtine-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Flupirtine is a 'selective neuronal potassium channel opener' that acts by opening Kv7 potassium channels leading to functional N-methyl-D-aspartate receptor antagonism. Additionally, a facilitating effect on gamma-aminobutyric acid A receptors has been described.

It was first authorised in the European Union (EU) in 1984 as an alternative analgesic to opioids and non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment pain. It is currently authorised for the treatment of acute pain in adults, for whom treatment with other analgesics (e.g. NSAIDs, weak opioids) is contraindicated.

Flupirtine-containing medicinal products are currently approved in 8 Member States (MSs) of the European Union: Estonia, Germany, Latvia, Lithuania, Luxembourg, Poland, Portugal and Slovakia. It is available on prescription only in the EU for oral use as 100 mg capsules and 400 mg prolonged-release tablets and for rectal use as 150 mg suppositories. Over the last years exposure to flupirtine has continually decreased in the EU; from approximately 20,640,000 defined daily dose (DDD) in 2013, to around 6,570,000 DDD in 2017. Usage is the highest in Germany.

In 2013, having identified a growing number of hepatotoxicity reactions reported in association with flupirtine and considering the available evidence of efficacy in the treatment of acute and chronic pain (authorised indications at the time), the BfArM initiated a urgent union procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1363) requesting the PRAC to make a recommendation on whether the MAs for these medicinal products should be maintained, varied, suspended or withdrawn.

Based on the review of all data available at the time, the PRAC concluded that the use of flupirtine-containing medicinal products is associated with an increased risk of hepatotoxicity. The PRAC also concluded that the efficacy in the management of chronic pain was very limited and that in view of the risk of hepatotoxicity, the benefit-risk balance was no longer favourable in that indication. The PRAC considered that the benefit-risk balance remained favourable in the management of acute pain when treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated, provided the below measures to minimise the risk of hepatotoxicity were implemented. Since no cases of hepatotoxicity including cases with fatal outcome or which resulted in liver transplantation had been identified 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, acknowledging that the majority of cases included concomitant medication known to have potential for hepatic adverse drug reactions and that the combination of COX-2 inhibitors or NSAIDs with flupirtine may significantly increase the severity of the hepato-biliary reactions, a contraindication was added for patients with pre-existing liver disease or taking concomitantly other medication known to cause DILI. It was also recommended that liver function should be kept under close monitoring i.e. after each week of treatment with flupirtine, which should be discontinued upon signs of liver disorders. These measures were communicated to the relevant healthcare professional (HCP) in a letter in July 2013. In addition, conditions were imposed on the MAs, namely that the marketing authorisation holders (MAHs) develop educational materials to inform prescribers and patients of the hepatotoxicity risk associated with flupirtine and on the measures necessary to minimise the risk and that the MAHs conduct a drug utilisation study (DUS) to characterise prescribing practices during typical clinical use in representative groups of prescribers and a post-authorisation safety study (PASS) to evaluate the effectiveness of the risk minimisation activities. The procedure concluded in September 2013 with the adoption of a European Commission decision.

Results of these DUS and PASS studies have recently become available and showed a very limited compliance with the above mentioned changes to the terms of the MAs for flupirtine-containing medicinal products[1]. In addition cases of DILI, including serious events continued to be received in EV after the additional risk minimisation measures were fully implemented (in 2015).

Therefore, the BfArM triggered a referral under Article 31 of Directive 2001/83/EC requesting the PRAC to assess the impact of the risk of liver injury on the benefit-risk balance of these medicinal products and the adequacy of the related risk minimisation measures, and to issue a recommendation on whether the relevant MAs should be maintained, varied, suspended or revoked.

2.2. Data on safety

The PRAC considered all data submitted from different sources. This included submitted results from searches in the safety databases of the MAHs, in EV, published literature and results from the PASS and DUS imposed as conditions to the MAs. A summary of the most relevant data is presented below.

2.2.1. Spontaneous reporting

2.2.1.1. Marketing authorisation holders databases

Four MAHs have presented analyses of all events of DILI, hepatic/liver failure, and alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 3x ULN, fatal cases and cases reporting liver transplant based on the results of a search in their safety database for case reports where flupirtine-

[1] MEDA Pharma GmbH & Co. KG: PASS procedure EMEA/H/N/PSR/J/0007, national DUS procedure;
Ratiopharm GmbH/TEVA GmbH group: national PASS and DUS procedure;
Hormosan Pharma GmbH and Aristo Pharma GmbH: national PASS and DUS procedure, identical study reports.

containing medicinal products are a suspected or interacting medicinal product. The analyses were based on a search for preferred terms (PTs) within the standard MedDRA query (SMQ) “hepatic disorders” (broad), SMQ “biliary disorders” (broad) and system organ class (SOC) “hepatobiliary disorders”. Cases presented by one MAH were poorly documented and will not be presented here. The three other MAHs provided results of searches covering cases received between 29 March 2013 and 7 November 2017 (dataset 1) or 1 April 2013 and 31 August 2017 (dataset 2 and 3), whilst they could have occurred earlier. The most relevant data is presented below, jointly or, when not feasible due to insufficient data to identify duplicates, individually. Causality assessment was performed both with the World Health Organisation – Uppsala Monitoring Centre (WHO-UMC) and the Roussel Uclaf Causality Assessment Method (RUCAM) system.

2.2.1.1.1. Reports of drug induced liver injury

One hundred twenty seven (127) cases were identified in the safety database of the originator (dataset 1), followed by 12 (dataset 2) and 22 (dataset 3). In the three datasets, the majority of cases involved women (52 %-95.5 %) and the mean age was about 54 years (54.6-56.6 years) with a range from 28 to 87 years. Most of the reports were classified as serious (76.4 %-100 %) and indication for use, i.e. acute or chronic pain was unknown in most cases (72.7 %-90.55 %). Most reports originated from Germany (137) followed by Israel (7), Portugal (3), Russia (1) and India (1). A fatal outcome was noted in 3 cases.

Considering cases in the dataset 1, the strength and formulation most frequently reported was 400 mg extended release (63 %) followed by 100mg immediate release (8.7 %). Time to onset ranged from 1 day to 4 years with a mean ranging from 48 days to 109.2 days. More cases reported a time-to-onset (TTO) > 14 days (33 %-72.7 %) than ≤ 14 days (4.5 %-25 %) but proportions of cases with unknown TTO were high (22.7 %-51.2 %). Concomitant medication known to cause DILI was observed in ≤ 50 % of patients (17.3 %-50 %) but proportions of reports lacking this information were high (50 %-63 %). Pre-existing liver disease was seldom reported (3.9 %-9.1 %) but information was unavailable in a substantial proportion of cases (30.7 %-83 %). Weekly liver function tests (LFT) were identified in less than 8.7 % of reports but information on LFT was also lacking in a substantial proportion of cases (49.6 %-100 %). Based on the WHO criteria, causality was assessed as possible (22.9 %), probable (20.5 %) or certain (6.3 %) in the majority of cases while only 3.9 % were assessed as unlikely. Similarly, using the RUCAM score causality was assessed as possible (43.3 %) or probable (14.2 %) in the majority of cases while 37.8 % were assessed as unlikely and 4.7 % as excluded.

2.2.1.1.2. Reports of hepatic/liver failure

Nineteen (19) reports of hepatic/liver failure were identified in the dataset 1, 3 in the dataset 2 and 5 in the dataset 3.

Considering the cases in the dataset 1, characteristics were similar to the overall group of cases of hepatobiliary toxicity. Differences included a higher proportion of female patients (73.7%) and concomitant medication known to cause DILI was observed more frequently (26.3 % vs 17.3 %, concomitant medication with NSAIDS, COX-2 inhibitors, morphine or paracetamol in 5/19 cases and unknown in 14/19 cases). A shorter mean TTO (75.2 vs 109.2 days) and higher proportion (15.8 % vs. 7.1 %) of patients with a TTO ≤ 14 days (11 days in 2 cases and 13 days in 1 case) was also observed in these cases. The TTO ranged from 11 days to 1 year. In the cases reported in the other datasets, TTO was either longer than two weeks or not assessable. In 3/19 cases, liver failure occurred 1 week, 46 days and over 3 weeks after discontinuation of flupirtine treatment. In the 3 cases which occurred within 14 days of treatment initiation, an NSAID, cyclo-oxygenase (COX-2) inhibitors, or paracetamol were taken concomitantly in 2/3 cases (celecoxib and paracetamol in 1 case, ibuprofen in the other).

In all 3 cases, the outcome was recovered/ resolved. Based on the WHO criteria 11/19 cases were assessed as at least possibly related to flupirtine and 2 cases as unlikely. Using the RUCAM score 10 cases were rated as possible or probable and 9 cases as excluded or unlikely. One patient showed a positive rechallenge.

2.2.1.1.3. Reports of ALT or AST ≥ 3x ULN

Nineteen (19) reports of ALT or AST ≥ 3 x ULN were identified in the dataset 1. Characteristics of these cases were similar to the overall group of cases of hepatobiliary toxicity. The TTO ranged from 21 to 363 days. Based on the WHO criteria 13/19 cases were assessed as at least possibly related to flupirtine and 1 case as unlikely. Using the RUCAM score 15 cases were rated as possible or probable and 4 cases as unlikely. No additional relevant information was identified in the other datasets, apart from 2 cases with a TTO ≤ 14 days.

2.2.1.1.4. Reports of fatal cases

Considering the three datasets, 3 cases with a fatal outcome were identified. One of these occurred in December 2012 further to acute hepatic failure, hepatotoxicity and icterus, in a patient treated concomitantly with medications known to cause liver injury. The two other cases occurred after completion of the previous review, including one in the EU. This case concerns a 78-year-old female patient treated with flupirtine (200 mg/day) for over 6 months (152 days) for chronic pain due to lumbar and gluteal pain. Flupirtine-induced liver failure has been reported, however the cause of death is confounded with cholangitis. No details have been provided regarding investigations for other causes of liver failure or potentially hepatotoxic concomitant medications. The patient died in August 2013. The causality is assessed as possible with both WHO-UMC and RUCAM.

The second case which occurred after 2013, originates from the literature (Philips, 2017 [2]). A first LFT after over 5 weeks of treatment flupirtine 300 mg/day showed elevated results and treatment was discontinued. The patient developed worsening jaundice over 5 days and encephalopathy 3 days later. No transplant could be performed. The patient was kept under supportive care including therapeutic plasma exchange and died 8 days after hospital admission. Liver biopsy was performed post mortem that revealed features of pan acinar necrosis and total collapse of hepatic angioarchitecture with the loss of reticulin framework; extensive bile ductular reaction with an abundance of mixed inflammatory cells, predominantly neutrophils and macrophages with diffuse ceroid inclusions. Causality is considered possible with WHO-UMC and probable with RUCAM.

2.2.1.1.5. Reports of cases with liver transplant

Considering the three datasets, 4 cases of liver transplant were identified. All reports included only minimal information. All occurred in 2013, two before July, one in September and one at an unknown date. TTO was only available in one case only (122 days). Information on concomitant medication known to cause DILI was lacking in all cases. The dosage form was 400 mg ER in 2 cases, 100mg IR in one case and unknown in the fourth case. The outcome was unavailable in all cases. Based on the WHO criteria, causality was assessed as probable (2), possible (1) and unassessable (1). With the RUCAM criteria it was assessed as probable (2), possible (1) and unlikely (1).

[2] Philips CA, Paramaguru R, Kumar L, Augustine P. Flupirtine associated acute liver failure- case from India and review of literature. Indian Journal of Medical Specialities. 2017;8(2):95-98.

2.2.1.2. EudraVigilance database

A search in EV was conducted by EMA with the SMQ 'hepatic disorders' broad, SMQ 'biliary disorders' broad under the SOC 'hepatobiliary disorders' for cases reported up to the 7 December 2017 with flupirtine as suspect or interacting medicinal product.

In total 666 cases were reported to EV (hepatic PTs from the SOC Hepatobiliary disorders combined with the relevant SMQs 'Hepatic disorders' Broad and SMQ 'Biliary disorders' Broad), 52 cases of acute hepatic failure were reported, and in 23 cases the outcome was fatal due to liver toxicity. Of the 635 cases that include a time-to-onset analysis with cut off ≤ 14 days versus > 14 days, in 71 cases (7 non-serious), the hepatotoxicity occurred in the first 14 days after flupirtine onset, and in 35 cases the time to onset was < 7 days. Following high reporting frequency between 2007 and 2013, a decrease was noted with the lowest frequency in 2015, followed by a new elevation in frequency in 2016 and 2017 (2014: 35 cases, 2015: 16 cases, 2016: 21 cases, 2017 up to 7 December: 32 cases).

Between 3 April 2013 and 7 December 2017, 84 cases of DILI, 15 cases of hepatic failure, 23 cases of acute liver failure and 3 cases of liver transplant were reported to EV. In addition, 2 fatal cases were reported as having occurred during this period, one of which in the EU. In addition, between October 2013 and 7 December 2017, of the evaluable cases, 25 serious hepatic cases occurred within the first two weeks of treatment; including 15 cases in which the time to onset was < 7 days. Among these 25 cases, events reported included acute hepatic failure (5), drug induced hepatitis (1) and elevated liver enzymes (1). Some cases showed progression to liver failure, despite treatment discontinuation further to detection of elevated liver enzymes in the first two weeks. Finally, between 1 April 2015 and 7 December 2017, a total of 5 serious cases were reported, including 2 with a TTO shorter than a week.

2.2.2. Literature

A review of the literature was conducted with a particular focus on articles that became available since the previous procedure. Seven articles were identified and are summarised below.

A hospital-based case-control surveillance study was the subject of two publications (Douros, 2014 [3]; Douros, 2015 [4]). In this study patient data were collected from 2002 until 2011 in 51 hospitals in Berlin, Germany, in order to examine hepatotoxicity of medicinal products (hepatotoxicity defined as elevation of ALT or AST ≥ 3x ULN or a total bilirubin level higher than 34.2 µmol/l [= 2 mg/dl] without underlying liver disease). In total 198 patients with acute idiopathic hepatitis, 377 inpatient controls and 708 outpatient controls were ascertained. The study identified a large number of medicinal products as possible causes of hepatotoxicity, including phenprocoumon (OR 3.3, 95 % CI 1.5, 6.7), amiodarone (OR 5.5, 95 % CI 1.3, 21.2), clozapine (OR 34.6, 95 % CI 2.8, 824.9) and flupirtine (OR 40.2, 95 % CI 5.5, 856.9). Seven cases of DILI with flupirtine association leading to hospitalisation were identified with causality assessed as highly probable (2/7) or probable (5/7) based on the RUCAM scale. Three of the patients developed acute liver failure. The time to onset of symptoms varied from 11 days to 8 months. Discontinuation of flupirtine led to clinical and laboratory improvement in all patients. One of these two articles also included a review of all cases of "drug related hepatic disorders - severe case only" (Standardized MedDRA Query) included in the ADR database of the BfArM. In total 248 reports of severe flupirtine-associated hepatotoxicity from 1991 until March 2012 were identified, showing female sex predominance (80.2 %) and high prevalence of acute liver failure (15.3 %). Complete data regarding the time elapsing from the beginning of medication until the onset of

[3] Douros A, Bronder E, Andersohn F, et al. Flupirtine-induced liver injury-seven cases from the Berlin Case-control Surveillance Study and review of the German spontaneous adverse drug reaction reporting database. Eur J Clin Pharmacol. 2014;70(4):453-459.
[4] Douros A, Bronder E, Andersohn F, et al. Drug-induced liver injury: results from the hospital-based Berlin Case-Control Surveillance Study. Br J Clin Pharmacol. 2015;79(6):988-999.

symptoms were available in 60 % of the reports (n=148). Of those, 9 % (13/148) had a time to onset of less than 1 week. Death was reported in eight cases.

An abstract reported the results of a retrospective analysis of all patients from one German centre who were hospitalised between 2010 and 2013 for DILI (Ziagaki, 2013 [5]). DILI was very likely associated with flupirtine in 18 patients (38 %) and with other medicinal products in 29 patients (62 %). The mean time between onset of symptoms and admission to hospital was 10±7 [0-30] and 6±8 [0-30] days in the two groups, respectively (p = n.s). Patients in the flupirtine group were mostly female (17/1 vs. 16/13, p=0.01). Two patients in the flupirtine group underwent liver transplantation. No patient died from DILI. Mean ALT levels were similar in both groups at days 0, 3, 7 and 14 of hospitalisation (p = n.s.).

Another article reported the first case of fatality due to flupirtine-induced acute liver failure from India, which is already described above (Philips, 2017).

Two articles discussed possible genetic risk factors for hepatotoxicity of flupirtine. One study investigating the influence of genetic polymorphisms of N-acetyltransferases (NAT2), UDP-glucuronosyltransferase 1A1 (UGT1A1) and glutathione–S-transferase P1 (GSTP1) found that approximately 12 % of bioavailable flupirtine immediate release and 8 % of bioavailable flupirtine modified release was eliminated as mercapturic acid derivatives into the urine independent of these genotype (Siegmund, 2015 [6]). The second article reviewed the cases of 10 patients with suspected flupirtine-related DILI, with recovery following flupirtine withdrawal (Nicoletti, 2016 [7]). In the 6 flupirtine DILI cases included in a genome-wide association study (GWAS), the authors found a significant enrichment of the DRB1*16:01-DQB1*05:02 haplotype (minor allele frequency 0.25) as compared to the controls (minor allele frequency 0.013). The odds ratio for haplotype carriers was 18.7 (95 % CI 2.5–140.5, P=0.002) using population-specific HLA control data. The same frequency was observed for the 4 cases genotyped by direct HLA typing. The authors also found a significant association in the combined cohort (10 cases) (odds ratio 18.7, 95 % CI 4.31–81.42, P=6.7×10–5) and concluded that a strong association exists between flupirtine DILI and the DRB1*16:01-DQB1*05:02 haplotype, adding further evidence to the involvement of the adaptive immune system in the pathogenesis of DILI.

An article reported the results of a study investigating the effect of N-acetylcysteine (NAC) and glucocorticoid therapy (prednisolone) on the management of 21 cases of severe flupirtine-induced liver injury, compared to 30 other cases of patients that did not received these treatments, between June 2010 and July 2014 (Borlak, 2017 [8]). The study found that based on serum biochemistries (AST, ALT bilirubin) the cases treated with NAC/prednisolone resolved more rapidly (p<0.01) when compared to untreated cases.

2.2.3. Observational studies (imposed PASS and DUS)

Results of three imposed PASS and three DUS available were considered by PRAC.

[5] Ziagaki A, Boehm S, Felkel C, et al. The analgesic flupirtine may induce severe hepatocellular liver injury in women. Hepatology. 2013;58(4):384A.
[6] Siegmund W, Modess C, Scheuch E, et al. Metabolic activation and analgesic effect of flupirtine in healthy subjects, influence of the polymorphic NAT2, UGT1A1 and GSTP1. Br J Clin Pharmacol. 2015;79(3):501-513.
[7] Nicoletti P, Werk AN, Sawle A, et al. HLA-DRB1*16: 01-DQB1*05: 02 is a novel genetic risk factor for flupirtine-induced liver injury. Pharmacogenet Genomics. 2016;26(5):218-224.
[8] Borlak J, van Bommel F, Berg T. N-acetylcysteine and prednisolone treatment improved serum biochemistries in suspected flupirtine cases of severe idiosyncratic liver injury. Liver Int. 2017.

2.2.3.1. Methods

To evaluate the effectiveness of the risk minimisation measures, two MAHs conducted retrospective chart reviews to investigate compliance to the terms of the MAs as amended as an outcome of the Article 107i procedure in 2013. To this end, compliance was compared over different 6-months periods, before the Article 107i procedure, after the procedure but before the dissemination of the educational materials and after its dissemination. One MAH (TEVA) recruited 165 centres in Germany including around 1,100 patients, while the other one (MEDA) included 27 private practices physicians issuing 588 prescriptions to 429 patients in Germany and 14 prescribers mainly in hospitals or primary healthcare centres issuing 315 prescriptions to 264 patients in Portugal.

Two other MAHs (Hormosan Pharma and Aristo Pharma) submitted joint results of a retrospective cohort study conducted in an outpatient setting in Germany using two longitudinal patient-level databases, an electronic medical record database (IMS Disease Analyzer) and a prescription database (IMS LRx) comparing to one-year periods, one before and one after the implementation of the measures of the Article 107i procedure. The data from the two databases were analysed separately. In IMS Disease Analyzer 22,467 and 14,703 flupirtine users were included in the study for the reference and the assessment period, respectively, while 377,345 and 164,669 flupirtine users in the reference and in the assessment period, respectively, were included in the analysis using the IMS LRx database.

Regarding the characterisation of prescribing practices during typical clinical use in representative groups of prescribers, the same four MAHs conducted three retrospective drug utilisation studies in an outpatient setting in Germany using one (IMS Disease Analyzer – MEDA, Hormosan Pharma and Aristo Pharma) or two (IMS Disease Analyzer and IMS LRx – TEVA) longitudinal patient-level electronic medical record database, either over four calendar year starting in 2012 or over 2012, 2014 and on also included the 12 month-period following the dissemination of the educational materials (April 2015).

2.2.3.2. Results

Usage data

Overall, a decrease in number of patients with a flupirtine prescription was documented in Germany in the time periods after implementation of the RMMs as compared to before (2012), ranging from a decrease by 9.4 % to a decrease by 63.3 %, depending on the study. It is noted that in contrast in Portugal the number of both patients and prescriptions increased over time (2012: 71 patients, 75 prescriptions; 2014: 89 patients, 97 prescriptions; 2015: 132 patients, 143 prescriptions).

The majority of patients in Germany received only one single prescription in each study period as shown in all PASS and DUS (ranging from 59.9 % in 2012 identified in the IMS LRx database to 93.0 % in 2015) and were incident users. Most studies showed slight increases in the numbers of single and incident users in the study periods after implementation of the RMMs, except for one of the PASS showing a very slight decrease in percentage of patients with a single flupirtine prescription from 2014 (90.0 %) to 2015 (86.9 %).

Indication

One of the PASS and of the DUS, showed a slight decrease in the proportion of prescriptions issued for “acute pain” or “acute exacerbation of chronic pain” from 2012 to 2015 (67.4 % to 53.2 % and 59.7 % to 56.8 %, in Germany respectively in both studies; 77.3 % to 73.4 % in Portugal), while an increase of prescriptions for chronic pain was observed (32.2 % to 46.8 % in Germany and 17.3 % to 23.8 % in Portugal). In contrast, in all other studies the percentage of patients with a diagnosis associated with “acute pain” increased slightly following the implementation of the risk minimisation measures

(83.32 % to 85.94 %; 72.3 % to 75.1 %; 95.9 % to 96.7 % (out of the 50 % where information was available); 92.5 % (out of the 57.8 % where information was available) to 94.1 % (out of the 52.8 % where information was available), respectively in the studies), while the one for patients with a diagnosis linked to chronic pain slightly decreased.

The percentage of patients in whom at least one contraindication for other analgesics was present decreased slightly according to two of the PASS (60.2 % (no data for 4.46 %) to 55.8 % (no data for 4.16 %); 45.0 % to 42.4 %), increased slightly according to a DUS (69.4 % to 71.4 % in IMS Disease Analyzer and 57.1 to 52.3% in IMS LRx) and remained unchanged according to another DUS (39.7 % to 39.9 %). In the third PASS, a contraindication for other pain therapies was reported as a reason to prescribe flupirtine at a decreasing frequency in Germany (7.7 % to 5.4 %) and increasing frequency in Portugal (0.0 % to 2.8 %). This aspect was not directly measured in the third DUS.

Maximum treatment length

In all but one study, the percentage of patients treated with flupirtine up to a maximum of 14 days (or percentage of prescriptions for up to a maximum of 14 days) increased significantly from the time period before to the ones after implementation of the RMMs (60.75 % to 82.33 %; 51.6 % to 75.4 % in IMS disease analyzer and 71.1 % to 91.8% IMS LRx; 66.9 % to 81.6 %: 75.1 % to 90.6 % in IMS disease analyzer; 68.3 % to 90.3 % in IMS LRx; 51.7 % (out of 28.8 % for which the information was available) to 70 (out of 24.8 % for which the information was available)) and the mean duration of treatment decreased (67 days to 39 days; 24.4 days to 15.6 days in IMS disease analyzer);28.5 days to 16.1 day in IMS LRx; 29.9 days to 20.2 days; 75.1 % to 90.6 % IMSs disease analyser and 68.3 % to 90.3 % in IMS LRx; 24.4 days to 18.3). However in another PASS the percentage of patients treated for more than 14 days increase from 36.5 % to 48.4 % and the mean duration of treatment increased from 19.8 days to 22.1 days. The mean duration of treatment prescribed by physician remained higher than the maximum recommended duration of 14 days in all studies in Germany. In Portugal, in the PASS where this data was available, the mean recommended duration of medication intake was lower compared to Germany and below 14 days in all study periods (ranging between 12.8 and 13.3 days).

Contraindication

In all studies the proportion of patients without pre-existing liver diseases or alcohol abuse ranged from 82 % to 99.2 % and remained unchanged or increased across study periods. Regarding concomitant treatment with other medications known to cause DILI, the proportion of prescriptions recording such medication decreased in a PASS (47.2 % to 46.8 %) and was relatively constant in another PASS (45.1 % to 43.9 % in IMS disease analyzer; 29.3 % to 30.5 % in IMS LRx). In the third PASS measuring the proportion of patients not taking such medication, an increase was observed (69.40 % to 73.82 %). Relatively similar results were observed in a DUS 71.8 % to 71.8 % IMS disease analyzer; from 63.4 % to 65.8 % in IMS LRx). Regarding prescribers in Portugal, in the PASS which collected data there, the already high proportion of prescriptions showing non-compliance through concomitant medication known to cause DILI further increased from 74.7 % in 2012 to 76.3 % in 2014 and 83.9 % in 2015. Information on pre-existing liver diseases or alcohol abuse was not given in one of the DUS while information on concomitant medication was not given in two of the DUS.

Liver function tests

Despite a slight increase over time (around 0.5-3 %) in all studies, in 2015 still only a minority of between 4.4 % and 18.8 % of patients had LFTs during/following treatment (within 1 week or 1 month of flupirtine prescription, depending on the study). In addition, in one PASS the percentage of patients for whom treatment was not discontinued although LFTs showed abnormal results increased from 0.4 % to 1.6 %.

Overall non-compliance

Overall, in the two PASS where this was analysed, using combined primary endpoint consisting of six predefined criteria based on the liver-related safety restrictions (discussed above individually), the non-compliance was > 95 % in any of the study periods, meaning that almost all prescriptions fulfilled one or more criteria of non-compliance. Study results indicate that the prescribers with almost all prescriptions willingly or unknowingly did not adhere to the safety restrictions introduced to minimise the risk of hepatotoxicity associated with flupirtine.

2.2.4. Discussion on safety

The increased risk of hepatotoxicity associated with flupirtine treatment was demonstrated previously and concluded upon by PRAC in 2013. The reporting rate for hepatic cases with flupirtine (regardless of causality) was 15.2 cases/100,000 patients-years (based on a patient exposure of 893,000 patient-years). The PRAC had 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 (idiosyncratic) adverse drug reaction.

Analysis of the individual case reports identified from the safety databases of the MAHs and in EudraVigilance demonstrated that cases of DILI, including cases of acute liver failure, cases necessitating a liver transplant and cases with a fatal outcome continue to be received. Information from the new cases and from published articles including results of cohort studies, confirm the hepatotoxic effect of flupirtine. Events have also been reported in patients without concomitant risk factors and in patients receiving treatment of ≤ 14 days. Whilst no fatal case or case necessitating liver transplant have occurred during the first two weeks of treatment, serious cases have been reported with shorter TTO, including in a few cases TTO < 7 days. Newly available data did not provide significant relevant information on risk factors, predictability or preventability of hepatotoxicity and uncertainty remains about a specific pattern of flupirtine-related hepatotoxicity.

Additionally, uncertainties remain regarding the pathomechanism of flupirtine-induced liver injury. Some research groups (Siegmund, 2015; Borlak, 2017) suggest that DILI could be caused by reactive quinone diimines produced from flupirtine, based on earlier studies on the in vitro metabolism of flupirtine (Methling, 2009 [9]). However, detailed investigations about the influence of genetic polymorphisms of potentially involved enzymes, such as N-acetyltransferases (NAT), glucuronosyltransferases (UGT) and glutathione S-transferases (GST) could not confirm associations with flupirtine-induced DILI (Siegmund, 2015). Results of a published study of approximately 20 cases and 30 control cases, suggested that treatment of severe flupirtine DILI with NAC/prednisolone can lead to a more rapid normalisation of levels of liver enzyme compared to no treatment, however 2 patients with late start of NAC/prednisolone treatment developed hepatic encephalopathy and required liver transplant (Borlak, 2017). The results of this study would need confirmation by further prospective studies. Although HLA-DRB1*16: 01-DQB1*0502 haplotype could be considered as a risk factor (Nicoletti, 2106), the sensitivity (thereby predictive value) of this biomarker is relatively low (50 %, 3 of the 6 cases in the GWAS and 2 of the 4 replication cases as heterozygous for the haplotype), hence patients that do not carry this haplotype, may still be at risk for developing DILI. Furthermore, only a small proportion of the total risk of DILI will relate to the identified HLA genotype (frequency of DRB1*16:01 DILI haplotype in the largest European group, USA NMDP European Caucasian cohort, n= 1,242,890 individuals, was estimated to be 0.014).

[9] Methling K, Reszka P, Lalk M, et al. Investigation of the in vitro metabolism of the analgesic flupirtine. Drug Metab Dispos. 2009;37(3):479-493.

Acknowledging the methodological limitations of the different PASS and DUS studies, including in term of sample size, representativeness and missing information, PRAC noted that overall they consistently reflected an important lack of compliance with the required measures to minimise the risk of hepatotoxicity. The studies showed a significant decrease in the number of patients and prescriptions. However a clear impact on the use of the products was only seen for the proportion of patients treated for a maximum of 14 days which increased significantly, while only minor or no effect was observed on other parameters related to measures aimed to minimise the risk of hepatotoxicity. Constant but low rates of patients with liver diseases or alcohol dependence in the medical history were noted. On the other hand rates of patients with concomitant use of medicinal products known to have a potential hepatotoxic effect or without known contraindications for the treatment with other analgesics are still high and no relevant decrease was observed over time. Additionally, the extremely low rate of adherence to weekly LFTs is of concern. The combined primary endpoint consisting of six predefined criteria based on the liver-related safety restrictions was fulfilled in less than 5 % of the patients after complete implementation of the risk minimisation measures. The PRAC considered that the observational studies showed a lack of physician's overall compliance with the safety restrictions introduced during the previous EU review. In addition, the individual case reports of hepatobiliary toxicity show a substantial proportion of cases with non-compliance with the safety restrictions introduced following the previous review, in particular with regard to concomitant medication known to cause DILI, therapy duration and LFT. The PRAC concluded that the measures implemented as an outcome of the previous review had failed in adequately minimising the risk of liver injury associated to the use of flupirtine-containing medicinal products.

The PRAC considered if any further measures could efficiently minimise the risk of hepatotoxicity, including additional materials to communicate on the previous measures and on the risk of hepatotoxicity, reduction of the pack size, and introduction of a new warning regarding genetic risk factors proposed by the MAHs. As observed in the above studies, the DHPC and educational materials for healthcare professional and patients disseminated to inform on the hepatotoxicity risk, and the necessary measures to reduce it, have been ineffective in ensuring compliance with the terms of the MAs. Therefore, the PRAC raised serious doubts as to the possible additional impact of further communication through a second DHPC, additional amendments to the information in the PI and the packaging or the setting up of an informative website and of further educational materials such as prescriber checklist and a patient alert card. PRAC considered that reductions of the pack size could ensure that patients visits their doctors at more frequent intervals, however this would not ensure that LFTs are carried out at weekly intervals, nor would it impact adherence to the other required measures. Regarding the proposed inclusion of a warning that "*patients with the genetic haplotype DRB1*16:01-DQB1*05:02 could have an up to 19-fold higher risk of developing a clinically significant Drug-induced Liver Injury (DILI) and should not receive flupirtine-containing products*", as discussed above this genetic biomarker would not allow to reliably identify or predict the patients at risk for flupirtine induced liver injury. In addition, genotyping prior to initiation of treatment is not feasible at present nor a proportionate measure in this clinical setting. Therefore, PRAC considered that the inclusion of such warning would not have an impact on minimising the risk of hepatotoxicity. Several MAHs also proposed to set up a joint patient registry to collect information on the genetic haplotype of the patients that experienced a flupirtine-related DILI, however this proposed additional pharmacovigilance activity, whilst potentially allowing further characterisation of this biomarker would not be relevant considering the difficulties detailed above.

In conclusion, the PRAC could not identify further measures that would ensure effective minimisation of the risk of hepatotoxicity associated to the use of flupirtine-containing medicinal products.

2.3. Data on efficacy

Clinical data on the efficacy of flupirtine in acute pain (single doses or as-needed treatment) was thoroughly assessed within the 2013 Article 107i procedure. The efficacy of flupirtine in the treatment of acute pain was shown in several short-term treatment randomised clinical trials (treatment durations ranging from single dose, up to 5 days, up to 1 week and up to 3 weeks) performed mainly in the 1970s and 1980s. The efficacy of flupirtine in the treatment of acute pain was shown in several short-term treatment randomised clinical trials (treatment durations ranging from single dose, up to 5 days, up to 1 week and up to 3 weeks) performed mainly in the 1970s and 1980s. 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 was sufficient evidence on efficacy in the acute (nociceptive) pain indication (mild, moderate and severe).

Eight further studies, published after the 107i procedure, were review by PRAC. Seven of these investigated flupirtine in the treatment of acute pain in post-surgery conditions and are summarised below (Jain, 2013 [10]; Yadav, 2014 [11]; Attri, 2015 [12]; Yadav, 2015 [13]; Ahuja, 2015 [14]; Thapa, 2016 [15]; Chinnaiyan, 2017 [16]). The last study investigated the influence of flupirtine on the preoperative anxiety of patients undergoing craniotomy procedure (Yadav 2017 [17]). This is not an authorised indication and the results are therefore not further discussed here.

Table 1. Flupirtine efficacy in the treatment of acute pain; overview of data which became available since the previous review

Study author/study ID and design	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Jain, 2013. Placebo-controlled, double-blinded, randomized N=50 [47 completed]	Primary objective: reducing morphine requirements during the 48 h after surgery. Secondary: pain scores (at rest and on movement)	Patients undergoing breast surgery	Female patients, ASA physical status I-III, aged 18-70 years	Flupirtine (100 mg) or placebo administered orally 2 hrs before surgery and on the morning of the first postoperative day. Patient controlled analgesia (PCA) with IV morphine (1 mg bolus, 5 min lockout time, and a maximum hourly limit of 8 mg).	Morphine requirements during the 48 h after surgery were significantly lower in the flupirtine group [19.5 mg, standard deviation (SD) 14.5 mg] compared with the placebo group (30.3 mg, SD 18.1 mg) (P¼0.017). There were no statistically significant differences between the groups in pain scores (at rest and on movement)

[10] Jain R, Ratre BK. Flupirtine reduces morphine requirements after carcinoma breast surgery: a randomised double blind controlled trial. International Journal of Pharma and Bio Sciences. 2013;4(4):B98-B104.
[11] Yadav G, Choupoo S, Das SK, et al. Evaluating the role of flupirtine for postcraniotomy pain and compare it with diclofenac sodium: a prospective, randomized, double blind, placebo-controlled study. J Neurosurg Anesthesiol. 2014;26(1):32-36.
[12] Attri JP, Sandhu GK, Khichy S, Singh H, Singh K, Sharan R. Comparative evaluation of oral flupirtine and oral diclofenac sodium for analgesia and adverse effects in elective abdominal surgeries. Anesth Essays Res. 2015;9(1):72-78.
[13] Yadav G, Behera SS, Das SK, Jain G, Choupoo S, Raj J. Role of flupirtine as a preemptive analgesic in patients undergoing laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol. 2015;31(2):169-173.
[14] Ahuja V, Mitra S, Kazal S, Huria A. Comparison of analgesic efficacy of flupirtine maleate and ibuprofen in gynaecological ambulatory surgeries: A randomized controlled trial. Indian Journal of Anaesthesia. 2015;59(7):411-415.
[15] Thapa D, Ahuja V, Dass C, Gombar S, Huria A. Effect of preoperative flupirtine on postoperative morphine sparing in patients undergoing total abdominal hysterectomy. Saudi J Anaesth. 2016;10(1):58-63.
[16] Chinnaiyan S, Sarala N, Arun HS. A comparative study of efficacy and safety of flupirtine versus piroxicam in postoperative pain in patients undergoing lower limb surgery. Journal of Pain Research. 2017;10:2471-2477.
[17] Yadav G, Jain G, Singh M. Role of flupirtine in reducing preoperative anxiety of patients undergoing craniotomy procedure. Saudi J Anaesth. 2017;11(2):158-162.

Study author/study ID and design	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
				All patients were also given acetaminophen 1 g 6 hourly	
Yadav, 2014 Placebo- and Active controlled, double-blinded, randomized N=390 [371 completed]	Primary outcome: reduction of Visual Analogue Scale (VAS) score at 0, 1, 2, 4, 6, 8, 12, 16 and 24 h following study start.	Patients undergoing craniotomy procedure	Patients of either sex, ASA physical status I-II, aged 18-70 years	Flupirtine (100 mg) or diclofenac (50mg) or placebo administered orally. All medications were given 8 hourly on second postoperative day for 48 hours. Tramadol 50 mg IV was given as rescue analgesia	There was significant reduction of Visual Analogue Scale score in flupirtine and diclofenac group when compared to control (P<0.0001). Pain relief observed in control, flupirtine, and diclofenac group was 69.8 %, 90.2 %, and 90.5 %, respectively. Need of rescue analgesia was significantly less in flupirtine and diclofenac group as compared to control (P<0.0001)
Attri, 2015 Active controlled, double-blinded, randomized N=100 [371 completed]	Reduction of VAS score postoperativ ely	Patients undergoing abdominal surgery	Patients of either sex, ASA physical status I-II, aged 18-65 years	Flupirtine (100 mg) or diclofenac (50mg) administered orally. Study started after 12 h of surgery, study drugs were then repeated every 6 hourly for 5 days postoperatively. Tramadol 50 mg IM was given as rescue analgesia	Visual analogue scores decreased more rapidly in diclofenac group during 1st h, hence there was rapid onset of analgesia in this group as compared to flupirtine group but later on VAS was comparable in both groups at all measured intervals (P > 0.05)
Yadav, 2015 Placebo-controlled, double-blinded, randomized N=66 [55 completed]	Time to first analgesic requirement, assessment of postoperativ e pain in terms of VAS, and analgesic requirement postoperativ ely	Patients undergoing laparoscopic cholecystecto my	Patients of either sex, ASA physical status I-II, aged 18-70 years	Flupirtine (200 mg) or placebo administered orally, 2 h before the surgery. For any pain complaints (VAS > 3), a dose of 1 g paracetamol IV was given on the first postoperative day, at intervals of 4 h or more. If the patients complained of pain in between paracetamol doses, injection tramadol 50 mg diluted with 4 ml normal saline and was given over a 2 min period as rescue analgesia.	Time to first analgesic requirement was significantly prolonged in the flupirtine group as compared with the placebo group. There was significant pain reduction in early postoperative period (up to 4 h), but no changes occurred thereafter. Total analgesic requirement (including rescue analgesia) and side-effects were comparable between the groups except for higher sedation in flupirtine group

Study author/study ID and design	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Ahuja, 2015 N=60 [60 completed] Active-controlled, patient/nurse-blinded, randomized	Verbal Numerical Rating Scale (VNRS) on movement at 0, 2, 4, 6 and 8 h following surgery	Patients undergoing gynaecological ambulatory surgeries	Female patients of ASA physical status I-II, aged between 18 and 70 years	Flupirtine (100 mg) or ibuprofen (800mg) administered orally, 1 h prior to surgery and then every 8 h for 48 h. Tramadol 100 mg IV was administered as rescue analgesic in 100 ml normal saline over 30 min if the VNRS on movement was >3 during the study period	VNRS on movement was statistically reduced at 2 h after surgery (P = 0.04) in group flupirtine as compared to group ibuprofen. The analgesic efficacy was similar in both the groups at 4, 6, 8, 12, 24 and 48 h after surgery. The satisfaction scores at 24 and 48 h post-operatively were superior in group flupirtine as compared to group ibuprofen (P < 0.001)
Thapa, 2016 Placebo-controlled, double-blinded, randomized N=50 [50 completed]	Primary outcome: cumulative morphine consumption at 48 h postoperatively. Secondary outcomes: haemodynamics, VAS at rest, VAS on cough	Patients undergoing total abdominal hysterectomy	Female patients of ASA physical status I-II, aged between 30 and 60 years	Flupirtine 100 mg or placebo administered orally, 1 h prior to surgery. Postoperatively, a titrated loading dose of IV morphine 0.1 mg/kg was followed with patient-controlled analgesia with morphine (bolus of 0.01 mg/kg with a lockout time of 7 min)	The cumulative mean morphine consumption (standard deviation [SD]) at 48 h (40.4 [6.0] vs. 47 [6.6] mg, P = 0.001) was reduced in-group flupirtine as compared with placebo. The cumulative mean VAS at rest (SD) (3 [0.7] vs. 3.7 [0.7], P = 0.001) and on cough (3 [0.9] vs. 3.8 [0.5], P = 0.002) were reduced in-group flupirtine as compared with placebo at 48 h postoperatively
Chinnaiyan, 2017 Open-label, randomized N=76 [71 completed]	VAS at 2, 4, 8, 12, 24, 48, 72, 96, and 120 hours, Behavioral Pain Assessment Scale (BPAS) and functional activity score (FAS) at 12, 24, 48, 72, 96, and 120 hours, Total pain relief (TOTPAR24) score for first 24	Patients undergoing lower limb surgery	Patients of either sex, ASA physical status I-II, aged 18-50 years	Flupirtine 100 mg or piroxicam 20 mg orally 6 hours after surgery and then twice daily orally for 5 days. Patients were administered tramadol 100 mg injection intravenously as rescue medication if VAS score was >3 during the postoperative period.	Flupirtine and piroxicam reduced VAS score 48 hours postoperatively compared to baseline (p=0.006 and 0.001) and piroxicam produced significant reduction in pain at 8, 12, and 120 hours compared to flupirtine (p=0.028, 0.032, 0.021). TOTPAR24 and PSS at 24 hours were comparable between the treatments. BPAS scores at 24 hours were reduced significantly in patients receiving either drug (p=0.001). FAS improved at 72 hours in patients receiving piroxicam.

Study author/study ID and design	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
	hours, patient satisfaction score (PSS), need for rescue analgesia				

2.3.1. Discussion on efficacy

The PRAC considered all newly available efficacy data available in the context of all the data reviewed in the Article 107i procedure.

Post-surgical pain conditions are well-established and understood models for acute pain, which is commonly used for analgesics that are intended to be used in (moderate to severe) acute pain conditions. In four studies, treatment with flupirtine was initiated before the surgical procedure with the intent to show a reduction in postoperative pain and/or consumption of analgesics, which was achieved in the four studies. However the sample size of the studies was small and the clinical relevance of a reduction in postoperative opioids consumption is not established. The other three studies support the efficacy of flupirtine in acute (nociceptive) pain indication (mild, moderate and severe) previously shown in clinical trials.

An online search on 17 January 2018 for medical guidelines on pain therapy mentioning flupirtine online retrieved eight German guidelines and one Cochrane review. Two guidelines, respectively on nuchal pain (Scheurer, 2016 [18]) and on cervical radiculopathy (Pohl, 2017 [19]), list flupirtine as a muscle relaxants and advise not to use muscle relaxants for these conditions. A guideline on lumbar radiculopathy states that it was updated to delete flupirtine from the section on therapies (Glocker, 2012 [20]). Two guidelines on treatment of disc prolapse with radicular symptoms (Bauer, 2014 [21]) and on non-specific lower back pain state (Bundesärztekammer, 2107 [22]) that there is insufficient data with regard to the benefit of flupirtine in the treatment of back pain and that flupirtine should not be used for the treatment of non-specific lower back pain. The Cochrane review does not make recommendations with regard to flupirtine, but states that comparisons with flupirtine are not relevant as flupirtine is no longer available (Wiffen, 2017 [23]). Finally a guideline on therapy of episodic or chronic tension type headache and other chronic daily headache (Straube, 2014 [24]) states that efficacy of flupirtine has been reported for acute treatment in children based on an earlier publication

[18] Scheurer MCJ-F. DEGAM (German College of General Practitioners and Family Physicians) S1 Handlungsempfehlung Nackenschmerzen June 2016.
[19] Pohl M. S2k-Leitlinie Zervikale Radikulopathie. Leitlinien für Diagnostik und Therapie in der Neurologie 2017; AWMF-Registernummer: 030/082.
[20] Glocker FX. Lumbale Radikulopathie. Leitlinien für Diagnostik und Therapie in der Neurologie 2012; AWMF-Registernummer: 030/058.
[21] Bauer J, Böhle, E.; Bork, H. Leitlinie zur konservativen und rehabilitativen Versorgung bei Bandscheibenvorfällen mit radikulärer Symptomatik. Deutsche Gesellschaft für Orthopädie und Orthopädische Chirurgie (DGOOC) 2014; AWMF-Register Nr. 033/048.
[22] Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Nicht-spezifischer Kreuz-schmerz – Langfassung, 2. Auflage. Version 1. 2017.
[23] Wiffen PJ, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. Cochrane Database of Systematic Reviews. 2017(5).
[24] Straube A. Therapie des episodischen und chronischen Kopfschmerzes vom Spannungstyp und anderer chronischer täglicher Kopfschmerzen. Leitlinien für Diagnostik und Therapie in der Neurologie 2014; AWMF-Registernummer: 030/077.

(Evers, 2008 [25]); of note flupirtine-containing medicinal products are not authorised for use in children in the EU.

The PRAC considered that the results of the newly available studies do not constitute new relevant information on efficacy. These support the efficacy of flupirtine in acute (nociceptive) pain indication (mild, moderate and severe) previously demonstrated in clinical trials. It is noted that no medical guidelines recommending the use of flupirtine in any pain indication could be identified, and that other therapeutic options are available.

3. Benefit-risk balance

Flupirtine is a 'selective neuronal potassium channel opener' that acts by opening Kv7 potassium channels leading to functional N-methyl-D-aspartate receptor antagonism. Additionally a facilitatory effect on gamma-aminobutyric acid A receptors has been described.

In 2013, an urgent union procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1363) was initiated further to the increased reporting of hepatotoxicity reactions in association with flupirtine. Based on the review of all data available at the time, the PRAC concluded that flupirtine is associated with an increased risk of hepatotoxicity. At the time, the PRAC considered that the benefit-risk balance would remain favourable in the management of acute pain when treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated provided that a number of risk minimisation measures were implemented. These included the restriction of the maximum treatment duration to two weeks, a contraindication in patients with pre-existing liver disease or taking concomitantly other medication known to cause drug liver injury and weekly monitoring of liver functions. These measures were communicated to the relevant healthcare professional (HCP) in a letter and educational materials was implemented to inform prescribers and patients of the risk and associated measures to minimise it. The MAHs were required to conduct a drug utilisation study (DUS) to characterise prescribing practices and a post-authorisation safety study (PASS) to evaluate the effectiveness of the risk minimisation activities.

The PRAC considered all newly available safety and efficacy data, including information provided by the marketing authorisation holders on cases of liver injury, results of the above mentioned observational studies (DUS and PASS), data available in EudraVigilance and the scientific literature, in the context of the data reviewed in the previous Article 107i procedure.

The PRAC is of the opinion that the results of the newly available studies support the efficacy of flupirtine in the management of acute (nociceptive) pain (mild, moderate and severe) previously demonstrated in clinical trials. It was noted that no medical guidelines recommending the use of flupirtine in any pain indication could be identified.

Data from spontaneous reports and the literature confirm the risk of unpredictable and potentially fatal liver injury associated to the use of flupirtine-containing medicinal products. Cases of drug induced liver injury (DILI), including cases of acute liver failure, cases necessitating a liver transplant and cases with a fatal outcome have been received since the previous review. Serious cases have also been received following the implementation of the related risk minimisation measures. PRAC considered that the newly available safety data, confirmed the known risk of unpredictable and potentially fatal liver injury.

[25] Evers SK, P.; Pothmann, R.; Heinen, F.; Ebinger, F. Therapie idiopathischer Kopfschmerzen im Kindes- und Jugendalter. Nervenheilkunde. 2008;27:1127–1137.

Despite their limitations, the six observational studies conducted consistently showed a substantial lack of compliance with the measures required to minimise the risk of hepatotoxicity. Furthermore, the individual case reports of hepatobiliary toxicity show a substantial proportion of cases with non-compliance with the safety restrictions.

The PRAC concluded that while the use of flupirtine-containing products has decreased, the measures implemented have been ineffective to minimise the hepatotoxicity risk to an acceptable level.

The PRAC discussed whether further risk minimisation would sufficiently minimise the risk of hepatotoxicity. This included additional materials to communicate on the previous measures, reduction of the pack size, and introduction of a new warning regarding genetic risk factors. However, considering the failure of the previous measures, the absence of risk factors sensitive enough to predict the risk of hepatotoxicity, the clinical setting where these medicinal products are used, the PRAC could not identify further measures that would ensure effective minimisation of the risk of hepatotoxicity associated to the use of flupirtine-containing medicinal products. Therefore, in view of the impossibility to minimise sufficiently the risk of hepatotoxicity, the PRAC concluded that this risk outweighs the benefits of flupirtine in the treatment of acute pain, when treatment with other analgesics is contraindicated. Further, the PRAC could not identify conditions which if fulfilled in the future would demonstrate a positive benefit-risk balance for these products in their current indication. Consequently, the PRAC recommend the revocation of the marketing authorisations for flupirtine-containing medicinal products.

4. Risk management

The Committee, having considered the data submitted in the procedure was of the opinion that no feasible risk minimisation measures would be able to reduce the risks to an acceptable level.

5. Direct Healthcare Professional Communications and Communication plan

The PRAC adopted the wording of a direct healthcare professional communication (DHPC) to inform healthcare professionals of the conclusions of the review and therefore the upcoming unavailability of flupirtine-containing medical products. The PRAC also agreed on a communication plan.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for flupirtine-containing medicinal products (see Annex I).
- The PRAC reviewed all newly available safety and efficacy data, including information provided by the marketing authorisation holders on cases of liver injury, results of observational studies, data available in EudraVigilance and the scientific literature, in the context of the data reviewed in the previous procedure EMEA/H/A-107i/1363 and in relation to the risk of hepatotoxicity associated to flupirtine-containing medicinal products.

- The PRAC considered that there is no new significant information on the demonstrated efficacy of flupirtine in the management of acute (nociceptive) pain (mild, moderate and severe).
- The PRAC concluded that the safety data confirm that the use of flupirtine-containing medicinal products is associated with a risk of unpredictable and potentially fatal liver injury.
- Considering the new reports of liver injury, together with the results of observational studies, indicating a very low compliance to the measures recommended in 2013 to minimise the risk of hepatotoxicity, the PRAC concluded that these measures have not been effective in adequately minimising the risk of hepatotoxicity.
- The PRAC discussed further risk minimisation proposals and concluded that no feasible measures would ensure effective minimisation of the hepatotoxicity risk to an acceptable level and that therefore this risk outweighs the benefits of flupirtine in the treatment of acute pain, when treatment with other analgesics is contraindicated.
- Furthermore, the PRAC could not identify any condition, the fulfilment of which would demonstrate a positive benefit-risk balance for flupirtine-containing medicinal products in their current indication.

The Committee, as a consequence, considers that the benefit-risk balance of flupirtine-containing medicinal products is no longer favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisations for flupirtine-containing medicinal products.