Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations subject to conditions and detailed explanation for the differences from the PRAC recommendation

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations subject to conditions and detailed explanation for the differences from the PRAC recommendation

The CMDh considered the below PRAC recommendation dated 13 June 2013 with regards to the flupirtine containing medicinal products.

1. Overall summary of the scientific evaluation of flupirtine containing medicinal products by PRAC

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[1,2,3] reported elevated transaminases in 3%, 31% and 58.6% respectively, of the patients treated with flupirtine. Another publication[4] described six cases of flupirtine-induced liver injury, including one requiring liver transplantation.

[1] 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;

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

[3] 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;

[4] 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;

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.

The PRAC reviewed the data submitted by the marketing authorisation holders and other stakeholders from clinical and non-clinical studies, epidemiological studies, spontaneous reports and published literature.

Overall, 11.8 million patients have been treated with flupirtine containing medicinal products since 1999.

Clinical 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[iii] 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.

Clinical 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[5] and a one-year[6,7].

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.

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).

Risk minimisation measures

As part of the risk minimisation measures the PRAC recommended amendments to the product information for all flupirtine containing medicinal products. The amendments aim to reflect the restricted use of maximum of two weeks of treatment, consequently only for use 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 increase in hepato-biliary 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.

The exact wording recommended by the PRAC to relevant sections of the Summary of Product Characteristics (SmPC) and Package Leaflet (PIL) are found in Annex III of this recommendation.

In view of the risks of hepatotoxicity the PRAC considered there was a need to recommend further risk minimisation measures to ensure the safety and effective use in acute pain.

The PRAC also recommended that Periodic Safety Update Reports should be submitted yearly.

[5] 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

[6] 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)

[7] 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 endorsed a Direct Healthcare Professional Communication (DHPC), to communicate the outcome of the present review to the healthcare professionals, in particular, the restricted indication and maximum duration of use and to highlight the risk of hepatotoxicity and the necessary measures needed to minimise this risk.

The PRAC also agreed on the need of a risk management plan to be submitted together with a protocol for a drug utilisation study aiming to characterise prescribing practices during typical clinical use in representative groups of prescribers.

Furthermore the PRAC requested that the protocol of a Post Authorisation Safety Study (PASS) should be submitted within the risk management plan submission, to evaluate the effectiveness of the risk minimisation activities.

Finally educational materials 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.

Benefit-risk balance

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.

Overall conclusion and conditions to the Marketing Authorisations

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.

Grounds for PRAC 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.

The PRAC in accordance with Article 107j(3) of Directive 2001/83/EC, recommended by a majority 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, as well as a drug utilisation study (see Annex IV – Conditions of marketing Authorisations);

b. the marketing authorisation holders should implement risk minimisation measures;

c. the marketing authorisations of flupirtine containing medicinal products (see Annex I) should be varied (in accordance with changes to the product information as set out in Annex III).

2. Detailed explanation for the differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation. However, the CMDh considered that changes were necessary to the wording proposed in section 2 of the PL, in order to accurately reflect the PRAC recommended amendments to the SmPC section 4.3 “contraindications”.

The CMDh therefore reworded this section, as follows:

2. What you need to know before you use < product name >
[The wording below should be inserted in the relevant sections]

[Oral pharmaceutical forms and suppositories]
Do not <take><use><Product name> if you:
- suffer from pre-existing liver disease
- suffer from alcoholism
- concomitantly use other medicinal products known to cause drug induced liver injury.

[Solution for injection (i.m.)]
Do not use <Product name> if you:
- suffer from pre-existing liver disease
- suffer from alcoholism
- concomitantly use other medicinal products known to cause drug induced liver injury.

[…]

Warnings and precautions

[All pharmaceutical forms]
Your doctor will test liver function every week during treatment with <Product Name> because increased liver enzyme levels, hepatitis and liver failure have been reported in association with flupirtine therapy. If liver function tests show pathological results your doctor will ask you to discontinue intake/use of <Product Name> immediately.

If you observe any symptoms that may indicate hepatic damage during treatment with <Product Name> (e.g. loss of appetite, nausea, vomiting, abdominal discomfort, fatigue, dark urine, jaundice,

pruritus) you have to discontinue intake/use of <Product Name> and to seek medical advice immediately if any such symptoms occur.
[...]

CMDh position

The CMDh having considered the PRAC recommendation dated 13 June 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC reached a position on the variation to the terms of the marketing authorisations of flupirtine containing medicinal products for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III and subject to the conditions set out in Annex IV.