

08 March 2013

**Rationale for the triggering of procedure  
under Article 107i of Directive 2001/83/EC  
on flupirtine**

**presented by the Federal Institute for Drugs and Medicinal  
Devices/BfArM, Germany**

**Disclaimer :**

This assessment report was provided by the German Competent Authority at the time of the initiation of the procedure. It provides background scientific information which complements the final notification request sent by the German Competent Authority for an EU review.

It should be understood that this assessment report reflects the position of the German Competent Authority at the time of the initiation of the referral procedure and is without prejudice to any future position to be established on the matter by the European Medicines Agency through its Scientific Committees.

## Background

In Germany there are currently 42 authorised flupirtine containing medicinal products, including 13 products authorised via the decentralised and 29 products authorised via the national procedure. While the originator's product was already authorised in 1984 the majority of products has been authorised since 2011.

Concerned member states of the decentralised procedures with Germany as reference member state were Luxembourg, Portugal, Bulgaria, Czech Republic, Estonia, Hungary, Lithuania, Latvia, Poland, Romania and Slovakia.

Flupirtine containing products in Germany are currently authorised as prescription-only drugs for the treatment of acute and chronic pain such as painful muscle tenseness, tension headache, cancer pain, dysmenorrhoea and pain following trauma or orthopaedic surgery or injuries. Extended release formulations are authorised for the treatment of acute and chronic pain such as painful muscle tenseness only and i.v. formulations are only indicated for short-term treatment (single application) of post-operative pain, in particular associated with muscle tenseness.

Patient exposure to flupirtine in Germany has increased steadily from 7,9 million DDD in 2001 to 28,1 million DDD in 2011.

Regarding the mechanism of action flupirtine is claimed to be a selective neuronal potassium channel opener (SNEPCO). It has also been shown to act as functional NMDA receptor antagonist<sup>1</sup>.

## Safety

Against the background of a steadily increasing patient exposure Germany has observed a growing number of reports of probably idiosyncratic liver toxicity associated with flupirtine. Reactions ranged from asymptomatic liver enzyme elevation to fatal liver failure or liver transplantation.

The German database of adverse drug reactions has recorded a total of 954 reports for flupirtine including 330 reports from the SOC hepatic and biliary disorders. 49 cases from this SOC reported liver failure and 15 cases had a fatal outcome or resulted in liver transplantation.

The 49 cases of liver failure are characterized as follows:

- 41 female, 7 male, 1 unknown
- Mean age was 51 years (range 24-81)
- 12 reports had a fatal outcome, 3 resulted in liver transplantation.
- Mean duration of flupirtine use was 60 days
- Hepatotoxic co-medication was noted in 25 cases
- Causality according to the RUCAM score (Roussel Uclaf Causality Assessment Method<sup>2</sup>): 1 highly probable, 9 probable, 17 possible, 6 unlikely, 2 excluded, 14 insufficiently documented
- Severity according to the DILIN (Drug Induced Liver Network, Fontana et al. 2010) severity scale: 1 mild, 7 moderate to severe, 18 severe, 13 fatal (including 3 liver transplantation), 8 unassessable

The 15 cases with a fatal outcome or resulting in liver transplantation are characterized as follows:

- 13 female, 1 male, 1 unknown
- Mean age: 57 (24-81)
- 4 Patients with BMI  $\geq$  30
- Mean duration of flupirtine use was 67 days (21-180)
- Hepatotoxic co-mediation was noted in 9 cases
- Causality according to the RUCAM score: 1 probable, 3 possible, 3 unlikely, 3 excluded, 5 insufficiently documented
- Causality according to WHO-UMC<sup>3</sup>: 9 possible, 1 unlikely (for death), 5 unassessable
- Severity according to the DILIN severity scale: 14 fatal (including 3 liver transplantation), 1 severe (death not caused by liver failure)

There are no reports of liver failure from published clinical trials. However, there are three more recent clinical trials reporting elevated transaminases in patients treated with flupirtine:

- The German multicentre double-blind randomized controlled SUPREME study<sup>4</sup> investigated the efficacy of flupirtine 400 mg modified release (MR) compared with tramadol 200 mg extended release (ER) and placebo for the management of moderate to severe chronic low back pain with a treatment duration of 4 weeks. Efficacy of flupirtine was non-inferior. It should be noted that in this study efficacy of tramadol was not significantly different from placebo and doses were chosen without titration. 71,2 % of patients received diclofenac as rescue medication. AST and ALT elevations were noted in 51 % and 58,6 % of the patients treated with flupirtine. It should be noted that similar rates of liver enzyme elevations were noted in the placebo group.
- An international double blind study<sup>5</sup> investigating off-label use in patients with overactive bladder-syndrome comparing flupirtine 400 mg ER, tolterodine 4 mg ER and placebo was prematurely discontinued when major elevations of liver enzymes (> 3 times the upper normal limit) were noted in several flupirtine-exposed patients. ALT values more than 3 times the upper normal limit were observed in 14 of 84 flupirtine exposed patients, 0 of 41 tolterodine-treated patients and in 1 of 82 placebo exposed patients. Liver enzyme elevations were noted in 31 % of patients receiving flupirtine for  $\geq$  6 weeks. Liver enzyme elevation usually occurred after 4-6 weeks. All patients recovered.
- A study<sup>6</sup> in Chinese patients with subacute low back pain compared Flupirtine 100 mg TID with tramadol 50 mg TID for 5-7 days. Liver enzyme or bilirubin elevations were noted in 3 of 105 flupirtine-treated patients and 1 of 104 tramadol-treated patients.

A hospital based case control study from Germany (in publication) investigating 198 patients with transaminases >3x ULN found a significantly increased odds ratio of 29,2 (4,3-594,0) for flupirtine but not for diclofenac, ibuprofen or paracetamol.

Another publication<sup>7</sup> described a series of 6 cases of flupirtine-induced liver injury, including 1 patient requiring liver transplantation. The time to onset of liver injury following initiation of flupirtine ranged from 3 weeks to 24 months (median 4 months). The likelihood of flupirtine as the cause of liver injury was assessed as probable in 4 cases and as highly probably in 2 cases according to the RUCAM criteria. Histologically extensive perivenular necrosis with

associated ceroid pigment-laden macrophages and a mild to moderate lymphocytic infiltrate was common in all cases. Accidental re-exposure of one patient resulted in a plasma cell rich hepatitis with perivenular necrosis.

### **Efficacy**

Following evaluation of all efficacy studies available to BfArM it appears that these studies mainly support the indication for the treatment of acute pain but that there is insufficient data supporting the treatment of chronic pain. Thus, the requirements of the “Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain” for a general pain indication are not fulfilled.

### **Benefit-risk evaluation and recommendations**

Germany has received several reports of severe liver toxicity including cases with a fatal outcome or leading to liver transplantation. Causality has been assessed as at least possible in part of these cases. Additional cases have been described in the literature. The majority of these cases seem to occur after a treatment duration of several weeks. While no cases of severe liver toxicity were observed in published clinical trials liver enzyme elevations in up to 58,6 % of patients were noted.

Furthermore efficacy data available to Germany seem to be insufficient to support the indication chronic pain or long term treatment regimes.

Based on the above Germany considers that the benefit-risk ratio of flupirtine in the indication treatment of acute pain may remain favourable provided that the duration of use is limited to short-term treatment (exact duration to be defined) and that the product information is updated to include adequate warnings and precautions, in particular precise recommendations for controlling liver enzymes before and during therapy and to stop treatment when liver enzyme elevations occur.

At the same time Germany considers that the benefit-risk ratio of flupirtine in the indication treatment of chronic pain appears to be unfavourable considering the aforementioned risks and the absence of efficacy data in this indication.

It should be noted that the authorisation of extended release formulations of flupirtine is called into question in case the chronic pain indication is revoked.

In order to further mitigate the risk of hepatotoxicity a dear-healthcare-professional-communication should be distributed with the aim of informing healthcare professionals on the risk of liver toxicity with flupirtine, the necessity of controlling liver enzymes, stopping treatment in case of liver enzyme elevations, the maximum treatment duration, indications and other recommendations resulting from this referral procedure if applicable.

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3. The Uppsala monitoring center. The use of the WHO-UMC system for standardised case causality assessment.
4. 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.
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