NOTIFICATION OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC
FAX NUMBER – 44 20 75237051

This notification is an official referral under Article 107i of Directive 2001/83/EC as amended to the PRAC made by Germany – Federal Institute for Drugs and Medicinal Devices/BfArM

Medicinal Product(s), Active Substance(s) Strength(s) and Pharmaceutical Form(s) Therapeutic class	Flupirtine containing medicinal products All strengths and pharmaceutical forms N02BG07
Marketing Authorisation Holder(s) in the Referring Member State	TEVA GmbH and others

Background

Flupirtine containing products in Germany are currently authorised via the national and decentralised procedure 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 formulation 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.
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.

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-mediaction was noted in 25 cases
- Causality according to the RUCAM score: 1 highly probable, 9 probable, 17 possible, 6 unlikely, 2 excluded, 14 insufficiently documented
- Severity according to the DILIN 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, 1male, 1 unknown
- Mean age: 57 (24-81)
- 4 Patients with BMI ≥ 30
- Mean duration of flupirtine use was 67 days (21-180)
- Hepatotoxic co-mediaction 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: 9 possible, 1unlikely (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 3, 31 and 58,6 % of the patients treated with flupirtine (Li et al. 2008, Michel et al. 2011, Ueberall et al. 2012).
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 (Puls et al. 2011) 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 critera. 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

Based on the above Germany considers that the benefit-risk ratio of flupirtine in the indication treatment of acute pain may be 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.

Furthermore a dear-healthcare-professional-communication should be distributed in order to inform 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.

In view of the above Germany requests the PRAC to give a recommendation under the urgent union procedure, article 107i of the Directive 2001/83/EC as amended for flupirtine containing products.

A draft List of Questions to be submitted to the MAHs is annexed (see Annex I).

[redacted]

Prof. Dr. Walter Schwerdtfeger
President
Federal Institute for Drugs and Medical Devices (BfArM)
Bonn, February 28th, 2013

Annex I

Flupirtine

Notification of a referral under article 107i of Directive 2001/83/EC

Draft List of Questions

To be addressed by the marketing authorisation holders for flupirtine containing medicinal products

1. Please provide information on the current authorisations and marketing status of your flupirtine containing products in the different member states and non EU-countries, data on sales figures and estimates of patient exposure.
2. Please provide information on the indications, doses, treatment duration, contraindications, warnings and precautions and undesirable effects included in the SmPCs and PLs of your flupirtine containing products. Please tabulate the main differences between the SmPCs of the different member states.
3. Please provide an analysis of all individual cases you are aware of reporting liver failure or liver transplantation and of all cases with a fatal outcome from the SOC hepatic and biliary disorders for flupirtine containing products including a causality assessment based on the RUCAM score and on the WHO-UMC system.
4. Please provide an aggregate analysis of all individual cases from the SOC hepatic and biliary disorders for flupirtine containing products not covered by the previous question.
5. Please provide information on and analysis of all data that you are aware of that could be relevant to evaluate the risk of hepatotoxicity associated with flupirtine, including data from pre-clinical and clinical studies as well as from published literature.
6. Please provide data on the efficacy of flupirtine containing products. Data should be organised by type of pain (acute/chronic), intensity of pain and indication (cause of pain).
7. Please provide a benefit-risk assessment for flupirtine containing products for both the acute and the chronic pain indication. Please make proposals for risk minimization measures which could improve the benefit-risk ratio of flupirtine, e.g. limiting the duration of use or deletion of indications.