EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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PRAC List of questions

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

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

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

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1. Background

In March 2013 an Article 107i referral for flupirtine-containing medicines was triggered by Germany following an increasing number of reports of drug-induced liver injury (DILI) ranging from asymptomatic increase in liver enzymes to liver failure, including a number of fatal cases and liver transplants. The referral (EMEA/H/A-107i/1363) concluded with major restrictions in the use of flupirtine. Furthermore, risk minimisation measures (RMM), a post-authorisation safety study (PASS) and a drug utilisation study (DUS) were imposed.

Assessment of the PASS and the DUS submitted by the MAHs as well as of individual case reports provide evidence of the failure of the RMM and the persistence of cases of hepatic failure.

2. Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

Question 1

Please provide an overview of the status of marketing authorisation of flupirtine-containing products in different EU countries and worldwide. Please use a table for EU countries and a separate table for non-EU countries to provide relevant information as follows:

Product name	Country	Strength	Dosage Form	Pack sizes authorised (marketed)	Date of launch	Marketing status

Question 2

Please provide an overview of estimated overall and monthly exposure to flupirtine-containing products as defined daily dose (DDD) sold per licensed dosage and application form.

Question 3

Please provide all data with a focus on new evidence, including a review of all case reports (serious and non-serious), since the last referral procedure relevant to evaluate the risk of drug induced liver injury with flupirtine-containing medicinal product(s) and an analysis of this data.

The search for case reports should be based on the MedDRA Preferred Terms (PTs) within the SMQ “Hepatic disorders” (broad), SMQ “Biliary disorders” (broad) and SOC “Hepatobiliary disorders” and cases where flupirtine- containing medicinal products are a suspected or interacting medicinal product.

This review should also include a causality analysis based on the Roussel Uclaf Causality Assessment Method (RUCAM).

A **summary tabulation of all reports** should be provided, see **Table 1 in the annex**. A separate summary tabulation should be presented for reports of

a) hepatic/liver failure (any type)

b) ALT or AST ≥ 3 x ULN

c) fatal outcome

d) liver transplant

Additionally a **tabulation of all individual reports** as shown in **Table 2 in the annex** should be presented separately for each of the groups a)-d).

Furthermore, a **summary tabulation of all MedDRA reaction preferred terms (PT)** in alphabetical order reported within the above mentioned SMQs and SOC should be presented, see **Table 3 in the annex**.

Finally, a **count of reported indications for use (MedDRA PT)** by frequency should be provided, see **Table 4 in the annex**.

CIOMS forms for all individual case reports and sorted by the MAHs' individual case numbers should be included as an annex.

Excel tables of all of the above tabulations should be provided as an annex.

Question 4

Provide a full benefit/risk assessment of your flupirtine-containing medicinal product(s) in the currently approved indication in the EU. This should include an assessment of the impact of the occurrence of the risk of drug induced liver injury. The assessment should also include a critical review of the effectiveness of the current safety restrictions and RMM considering the outcomes of the DUS and the PASS.

Question 5

In light of available data on the effectiveness of risk minimisation including the results of the DUS and the PASS please provide proposals and justifications with supportive evidence for any further risk minimisation measures (including changes to the SmPC/PL) which may effectively minimise the risk of hepatotoxicity and improve the benefit/risk balance of flupirtine-containing medicinal products. The feasibility of these measures should be properly discussed, taking into account the therapeutic setting in which flupirtine-containing products are used. The MAHs should also make proposals to monitor the effectiveness of these RMM, as applicable.

Table 1

Reporting period:		
Search strategy:		
Total number of reports for flupirtine containing products during reporting period:		
Total number of reports for flupirtine containing products and above search strategy during reporting period:		
Characteristic	Category	Result/Number of reports (% if applicable)
Patient gender	Male	
	Female	
	Not specified /Unassessable	
Patient age	Range	
	Mean	
	Median	
	Child (<18 years)	
	Adult (18-64 years)	
	Elderly (>65 years)	
	Not specified /Unassessable	
Seriousness	Serious	
	Non-serious	
	Not specified /Unassessable	
Primary source country	*Country 1*	
	Country 2	
	etc.	
Strength and formulation of product used	*100 mg IR*	
	400 mg IR	
	150 mg sup	
Indication for use	Acute pain	
	Chronic pain	
	Not specified /Unassessable	
Time to onset of DILI	Range	
	Mean	
	Median	
	≤ 14 days	
	>14 days	
	Not specified /Unassessable	
Concomitant medication known to cause DILI	Yes	
	No	
	Not specified /Unassessable	
Pre-existing liver disease or alcohol abuse	Yes	
	No	
	Not specified /Unassessable	
Weekly liver function test	Yes	
	No	
	Not specified /Unassessable	
Causality assessment (WHO UMC)	Unlikely	
	Possible	
	Probable/Likely	
	Certain	
	Unassessable/Unclassifiable	
Causality assessment (RUCAM score)	excluded (≤0)	

	unlikely (1-2)	
	possible (3-5)	
	probable (6-8)	
	highly probable (>8)	
	not assessable	
Outcome	Resolved	
	Not resolved at time of reporting	
	Fatal outcome	
	Outcome not reported	

Table 2

Case 1	***MAHs individual case number***	
Source	Study/literature/HCP/consumer	
Receive date	*e.g. 11/07/2013;*	
Therapy dates	*e.g. 10/06/2013-24/06/2013*	
Patient sex	*e.g. female*	
Patient age	*e.g. 45 years*	
Seriousness	serious/non-serious/not specified	
Liver Reactions reported	*e.g. icterus, liver failure*	
Liver Reactions of special interest	hepatic/liver failure (any type)/ ALT or AST ⩾ 3 x ULN/ fatal outcome / liver transplant/ none	
Strength and formulation of product used	e.g. 100 mg IR	
Daily dose used (mg)		
Indication for use	*e.g. back pain*	acute pain/chronic pain/type of pain unassessable
Time to onset of DILI (days)	*e.g. 15 days*	≤ 14 days, >14 days, TTO unassessable
Concomitant medication known to cause DILI	*e.g. paracetamol*	
Pre-existing liver disease or alcohol abuse	*e.g. history of hepatitis B*	
Weekly liver function test	yes/no/ unassessable	
Causality assessment (WHO-UMC)	certain/probable/possible/unlikely/unassessable	
Causality assessment (RUCAM)	highly probable/probable/possible/unlikely/excluded/not assessable	
Outcome	Resolved/ Not resolved at time of reporting/ Fatal outcome/ Outcome not reported	
Other comments	*e.g. positive rechallenge, patient recovered*	
Case 2	***MAHs individual case number***	
…	…	

Table 3

Reaction MedDRA PT	Number of reports per reaction PT		
	Non-serious	Serious	Total
e.g. Acute hepatic failure	*e.g. 25*		

Total number of case reports	e.g. 165		

Table 4

Indication MedDRA PT	Number of reports per indication PT
e.g. Back pain	*e.g. 65*