22 May 2025
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CHMP List of questions

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

Referral under Article 31 of Directive 2001/83/EC

Procedure number: EMA/REF/0000271842

INN/active substance: ipidacrine

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

Question 1 (information on the products)

Concerning your ipidacrine-containing medicinal product(s) please provide in the annexed table:

a) Data on overall patient exposure by therapeutic indication, pharmaceutical form, daily dose and duration of treatment.

b) Information included in the summary of product characteristics (SmPC) and package leaflet (PL) on therapeutic indications and posology, and, regarding the risks of hepatotoxicity and high doses, on warnings and precautions, and undesirable effects.

Question 2 (efficacy)

c) Please provide and critically discuss the evidence of the therapeutic efficacy of ipidacrine-containing medicinal products for each authorised indication in the EU at the authorised posologies, outlining the specific treatment objective for each of them. This should include all clinical trial data (including both MAH-sponsored and non-MAH sponsored studies), pharmaco-epidemiological studies (including observational studies), and published literature.

d) Please provide a thorough discussion on the evidence supporting the posologies of the tablet formulations exceeding 80 mg daily in the authorised indications.

e) Please provide and discuss the evidence supporting the authorised posology of the solutions for injection in each indication. This should include how this evidence supports the existing recommendations for prescribers on transitioning patients from parenteral to oral formulations.

f) Please provide and discuss a summary of clinical guidelines and supportive publications on the current approach to management of the conditions in relation to ipidacrine use.

Question 3 (non-clinical safety)

Please provide all available non-clinical data relevant to evaluate the hepatic safety profile of ipidacrine-containing medicinal products (including e.g. MAH-sponsored studies and published literature). The MAH is requested to discuss any hepatotoxicity findings from MAH-sponsored studies and published literature, and conduct an "integrated risk assessment" based on the 'Reflection paper on non-clinical evaluation of drug-induced liver injury (DILI)' (EMEA/CHMP/SWP/150115/2006).

Question 4 (clinical safety)

Please provide all available safety data relevant to evaluate the hepatic safety profile of ipidacrine-containing medicinal products, accompanied by an analysis and critical discussion of such data. This should include:

a) Clinical trial data (including both MAH-sponsored and non-sponsored studies), pharmaco-epidemiological studies (including observational studies) and published literature.

b) A cumulative review of all case reports (serious and non-serious) since authorisation of the originator. For this purpose, all the hepatobiliary disorders MedDRA Preferred Terms (PTs) reported where an ipidacrine-containing medicinal product is a suspected or interacting medicinal product should be provided. Causality assessment should be performed for the serious cases using the WHO-UMC scoring system and possible risk factors should be discussed. These analyses should include analyses on age and sex of patient, indication of use, duration and dose, time to onset, outcome, seriousness, concomitant medications and illnesses, relevant medical history or any other factors.

Question 5 (safety)

Given the structural similarity between ipidacrine and tacrine, and considering the known hepatotoxicity of tacrine, which mechanism remains to be fully elucidated, please provide a detailed justification why concerns relating to tacrine hepatotoxicity may not be applicable to ipidacrine.

Question 6 (safety)

Please provide and discuss all available safety data relevant to evaluate the safety profile of ipidacrine if taken at higher doses (>80 mg).

Question 7 (benefit-risk)

Based on the above, please provide a full benefit-risk balance assessment of ipidacrine-containing medicinal product(s) in each of the currently approved indication(s). The MAH(s) should provide justified proposals for any measures (including changes to the product information, such as but not limited to proposals to revise the therapeutic indication(s) in line with applicable guidance) which could be implemented to improve the benefit-risk balance of ipidacrine-containing medicinal product(s).

Annex

Question 1

a)

INN	Product name	Type of marketing authorisation	Marketing and legal status	Indications[1]	Pharmaceutical forms and strengths	Estimated patient exposure[2]	Doses (as approved and used in clinical practice)	Treatment duration (as approved and used in clinical practice)

[1]. The MAH(s) should clearly indicate for which country a specifically dedicated presentation has been granted for a particular indication.
[2]. Expressed in patient years and stratified by Member State, by indication, pharmaceutical form, daily dose, and duration of treatment. Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

b)

PI	SmPC	PL
Indications		
Posology (incl. max. daily dose)		
Warnings and precautions		
Undesirable effects		