



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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PRAC List of questions

To be addressed by the marketing authorisation holder(s) for
diacerein-containing medicinal products

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

Procedure number: EMEA/H/A-31/1349

INN/active substance: Diacerein



The marketing authorisation holders MAH(s) for diacerein-containing medicinal products for oral use are requested to provide the following:

Question 1

- a) Please provide information on the currently authorised oral diacerein-containing products in the different member states and their current marketing status, including information about the indication(s), doses, treatment duration, contraindications, warnings and precautions, and undesirable effects included in the Summary of Product Characteristics and the package leaflet. Please tabulate the main differences between the SmPCs/package leaflets in the different EU Member States.
- b) Please also provide information on sales figures and estimated patient exposure by country and by year since the marketing (method used for estimation should be explained and detailed).
- c) Demographic data about patients treated with oral diacerein should also be provided.

Question 2

Based on the available clinical data (trials and bibliographic references), the efficacy of diacerein in the currently approved indications should be assessed on the following criteria:

- Pain: the clinical relevance of the effect should be discussed, particularly taking the placebo effect into consideration;
- NSAIDs sparing effect: based on the delayed effect and aim of this kind of product, the NSAIDs sparing effect should be characterised;
- Impact on radiologic signs and evolution towards surgery: if any, clinical data should be provided and discussed.

Question 3

For potential hepatotoxicity,

- a) Please provide a cumulative detailed analysis of all cases of post-marketing spontaneous reports with diacerein-containing medicinal products (using the SMQ broad: Hepatic disorders). Cases in which diacerein is the only drug administered or the only suspected drug should be particularly discussed. These analysis should include information on age and gender of patient, indication of use, duration and dose, time to onset, rechallenge, nature of liver toxicity (cholestatic, cytolytic, mixed), dechallenge, outcome, seriousness, concomitant medications, relevant medical history. An assessment of causality should also be provided and possible risk factors discussed.
- b) Please provide a comprehensive analysis of data from pre-clinical studies, clinical trials (including both MAHs sponsored and non-sponsored studies), pharmaco-epidemiological studies, published literature with diacerein-containing medicinal products.
- c) Please provide a review of all other available data (i.e. pre-clinical data and other clinical data including epidemiological studies, and review of published data) in particular data regarding other compounds with a chemical structure of anthraquinone, that are relevant to evaluate the risk of hepatotoxicity with oral medicinal products containing diacerein.
- d) Cases of hepatic disorders with others anthraquinone-derivates should be compared to those reported with diacerein.
- e) On the basis of pre-clinical, clinical, epidemiological and published data, the mechanism of liver toxicity of diacerein should be discussed.

Question 4

For cutaneous reactions,

- a) Please provide a cumulative detailed analysis of cases of post-marketing spontaneous reports, (all cases extracted using the SMQ broad "Severe cutaneous adverse reactions" and serious cases belonging to the SOC "Skin and subcutaneous tissue disorders") and hypersensitivity

reactions (SMO broad "Anaphylactic reaction") with your diacerein-containing medicinal product. Cases in which diacerein is the only drug administered or the only suspected drug should be particularly discussed.

These analyses should include information on age and gender of patient, indication of use, duration and dose, time to onset, rechallenge, dechallenge, outcome, seriousness, concomitant medications, relevant medical history.

An assessment of causality should also be provided and possible risk factors discussed.

- b) Please provide a comprehensive analysis from pre-clinical studies, clinical trials (including both MAHs sponsored and non-sponsored studies), pharmaco-epidemiological studies, published literature) with your diacerein-containing medicinal product.¹

Question 5

Anthraquinone derivatives have laxative properties.

- a) Please provide a cumulative safety review of serious reports of gastrointestinal disorders reported with diacerein post-marketing spontaneous reports. The MAHs should separately assess cases reporting these ADRs isolated (diarrhoea only) and cases reporting a combination of them, i.e. any combination of diarrhoea with or without any others ADRs. Cases in which diacerein is the only drug administered or the only suspected drug should be particularly discussed.
- b) This review should include information on age and gender of patients, indication of use, duration and dose, time to onset, rechallenge, dechallenge, outcome, seriousness, concomitant medications, relevant medical history. An assessment of causality should also be provided and possible risk factors discussed.
- c) Please provide a comprehensive analysis of data from pre-clinical studies, clinical trials (including both MAHs sponsored and non-sponsored studies), pharmaco-epidemiological studies, published literature) with diacerein containing products.
- d) Please provide an estimation of the notification rate of all cases (serious and non-serious) of diarrhoea in patients treated with oral medicinal products containing diacerein. The MAHs should present the number of cases and the method used for the calculation of the notification rate.
- e) An analysis of the incidence of diarrhoea reported in the literature with diacerein containing products should also be presented.

Question 6

- a) Please provide a description and analysis of all serious ADRs other than those mentioned in questions 3, 4 and 5, reported with oral diacerein and discuss the emergence of any potential signals.
- b) On the basis of all available data, please provide and discuss the impact of adverse drug reactions reported with diacerein-containing product on the patient compliance.

Question 7

Please provide a full benefit-risk assessment of diacerein containing medicinal products for oral use in the currently approved indication(s) in the EU. Based on European or international recommendations, the place of oral diacerein among the currently available therapeutic armamentarium for patients with osteoarthritis should be discussed.

¹ For studies published in the literature, the response should include also studies at the active substance level (i.e. not specifically with your own medicinal product), following the same criteria used for assessing the results of published literature in PSURs (cf. Guideline on good pharmacovigilance practices (GVP) – Module VII PSUR section "Literature" EMA/816292/2011 Page 20/65).

Question 8

- a) Please provide details of any specific measures that have already been taken in order to minimise the hepatic, gastro-intestinal and cutaneous risks in patient using oral diacerein and comment on the impact of such measures.
- b) In addition, where appropriate, please provide proposals and justification with supportive evidence for any measures to further minimise the hepatic, gastro-intestinal and cutaneous risks including changes to the Summary of Product Characteristics, Labelling and Package Leaflet which could be taken in order to improve the benefit/risk of diacerein containing medicinal products for oral use. Please also comment on how the impact of such measures should be monitored and assessed.