



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 January 2013
EMA/PRAC/15160/2013

PRAC List of questions to be addressed by the marketing authorisation holders

For tetrazepam containing medicinal products

Article 107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1352

INN/active substance: Tetrazepam



The marketing authorisation holders MAH(s) for tetrazepam containing medicinal products are requested to provide the following:

Question 1

- a. Please provide information on the currently authorised tetrazepam-containing products in the different member states and their current marketing status, including information about the indication(s), doses, 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. The specific information about treatment duration and duration restriction present in the SmPC should be specified.
- b. Please also provide information on sales figures and estimated patient exposure by country for the last thirty years and by country and by year for the last ten years (method used for estimation should be explained and detailed).
- c. Please provide all available information on mean treatment duration observed with tetrazepam.

Question 2

- a. Please provide a detailed cumulative review of cases reporting cutaneous reactions since marketing authorisations: all cases retrieved using the Standardised MedDRA Queries (SMQ) broad "Severe cutaneous adverse reactions" and other serious cases belonging to the System Organ Class (SOC) "Skin and subcutaneous tissue disorders" with your tetrazepam-containing medicinal product. The MAH should also provide a detailed review of cases reporting hypersensitivity reactions (SMQ broad "Anaphylactic reaction").

In both, following cases should be particularly detailed and discussed:

- i. Cases in which tetrazepam is the only drug administered or the only suspected,
- ii. Cases in which an allergic work-up with tetrazepam was performed.

These reviews should include information on age and gender of patients, indication of use, duration of treatment and dose, time to onset since treatment initiation, information on rechallenge and on dechallenge, outcome, seriousness, concomitant medications, relevant medical history.

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

- b. Please provide a cumulative comprehensive analysis from non-clinical studies, clinical trials (including both MAHs sponsored and non-sponsored studies), pharmaco-epidemiological studies, published literature), that are relevant to evaluate the risk of cutaneous reactions with tetrazepam.

Question 3

A separate estimation of the notification rate for all cutaneous reactions and for hypersensitivity reactions (including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) symptom), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) retrieved as mentioned in Q.2-a. in patients treated with medicinal products containing tetrazepam should be provided since marketing authorisation, by country and by year for the last ten years. The MAHs should present the method used for the calculation of the notification rate.

Question 4

Please, provide details on the possible mechanism of cutaneous reactions induced by tetrazepam, on the basis of non-clinical, clinical, epidemiological, published data and all other available data. The relationship between chemical structure of tetrazepam and the cutaneous reactions observed should be discussed in comparison with the other benzodiazepine molecules.

Question 5

Please provide an analysis of the balance of risks and benefit of tetrazepam containing medicinal products particularly taking into account the cutaneous reactions, in the currently approved indication(s) in the EU. Based on European or international recommendations, the place of tetrazepam among the currently available therapeutic armamentarium for the authorized indications should be discussed.

Question 6

- a. Please provide details of any specific measures that have already been taken in order to minimise the risk of cutaneous reactions in patients using tetrazepam and comment on the impact of such measures.
- b. Please provide proposals and justification with supportive evidence for any risk minimisation measures to address the risk of cutaneous reactions in patients using tetrazepam, including changes to the Summary of Product Characteristics, Labelling and Package Leaflet, which could be taken in order to improve the benefit/risk of tetrazepam containing medicinal products for oral use. Please also comment on how the impact of such measures should be monitored and assessed.