

Annex II

Scientific conclusions and grounds for suspension of the marketing authorisations

Scientific conclusions and grounds for suspension of the marketing authorisations (see Annex I)

The CMDh, having considered the PRAC recommendation dated 11 April 2013 with regards to the tetrazepam containing medicinal products, agrees with the recommendation therein as stated below:

Overall summary of the scientific evaluation of Tetrazepam containing medicinal products by PRAC

Tetrazepam is a benzodiazepine indicated for painful contractures in rheumatology or spasticity. Benzodiazepines (BZP) facilitate the inhibitory activity of gamma-aminobutyric acid (GABA) leading to sedative, hypnotic, anticonvulsant and muscle relaxant properties.

Tetrazepam containing medicinal products are authorised in Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Latvia, Lithuania, Luxembourg, Poland, Romania, Slovakia and Spain (see Annex I for the list of tetrazepam containing medicinal products authorised in the EU).

On 20 December 2012 France informed the European Medicines Agency, pursuant to Article 107i of Directive 2001/83/EC, of their consideration to revoke the marketing authorisations for Tetrazepam containing medicines further to the evaluation of data resulting from pharmacovigilance activities.

Following reporting of new serious cutaneous reactions with the use of tetrazepam, the French National Competent Authority reviewed in November 2012 the cutaneous risk associated with tetrazepam based on results of a national pharmacovigilance survey. This review of pharmacovigilance concerned skin adverse drug reactions (ADRs) recorded in the French National Pharmacovigilance database since the granting of the first marketing authorisations of tetrazepam in 1967 in that Member State. This evaluation highlighted an increased cutaneous risk of tetrazepam in addition to the pharmacological expected ADRs of benzodiazepines: half of the ADRs reported with tetrazepam were cutaneous and amongst the 648 serious cases reported, 305 cases were reported under the System Organ Class (SOC) "Skin and subcutaneous disorders": 33 cases of Stevens - Johnson syndrome (SJS), 33 of Toxic Epidermal Necrolysis (TEN), 59 Erythema Multiforme (EM) and 15 cases of Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms (DRESS Syndrome) were detected with fatal outcome in 11 cases.

The PRAC considered available data including data from the French pharmacovigilance survey, data provided by other Member States, stakeholder's submissions and data submitted by MAHs, as well as published data.

Safety

During the French national pharmacovigilance survey an analysis of cutaneous cases reported in the national pharmacovigilance database since the initial Marketing Authorisation up to 30 June 2012 was performed.

At the date of 30 June 2012, 2382 cases with tetrazepam were registered in the French national database. Of these, 1617 had a "suspected" or "interaction" WHO code. After excluding one double entry, 1616 cases were considered for the analysis. Within these 1616 cases, 805 (49.80 %) ADRs involved "skin and subcutaneous tissue disorders" SOC, of which 305 (37.9%) were serious cases including life threatening and fatal cases. These included 33 cases of SJS (including 1 fatal case), 33 cases of Lyell's Syndrome (TEN) (including 9 fatal cases), 59 cases of EM (including 1 fatal case), 15 cases of DRESS Syndrome, 3 possible cases of DRESS Syndrome and 5 cases of acute generalised

exanthematous pustulosis. Tetrazepam was the only suspected drug or had a causality score higher than the concomitant treatments in 18 out of 81 cases of SJS, TEN or DRESS.

Cases of anaphylaxis were also reported. In addition, 10 cases of angioedema evoking an immediate hypersensitivity mechanism and 67 cases of drug eruption, in addition to the previous cases, with or without the involvement of at least one organ were described.

Many of the skin adverse events were maculopapular, but they were also vesicular, pustular, purpuric or bullous at times. This is indicative that serious cutaneous reactions with tetrazepam are probably linked to a type IV delayed hypersensitivity mechanism, as supported by positive patch tests in 79 out of 115 cases having had an allergy test.

As provided by the Marketing Authorisation Holder of the originator medicinal product in their written response to the PRAC list of questions, according to the MAH's pharmacovigilance database since the product launch in 1969 up to the 31 of May 2012 (Data Lock Point), 513 cutaneous or allergic distinct cases referring to 748 reactions were reported with tetrazepam. Thirty-eight (38) cases were non medically-confirmed cases and 475 cases were medically-confirmed; among them, 180 cases were directly reported to the Company, 245 cases were reported by Health Authorities, and 50 cases were identified in the scientific worldwide literature. Overall, the most frequently reported skin reactions are by decreasing order various types of rashes without any specificity (162 cases), pruritus (94 cases), Erythema Multiforme (48 cases), urticaria (47 cases), Toxic Epidermal Necrolysis (35 cases), angioedema (34 cases), Stevens-Johnson Syndrome (31 cases), erythema (28 cases), toxic skin eruption (19 cases), skin exfoliation (16 cases), dermatitis bullous, Not Otherwise Specified (NOS) (16 cases) and DRESS Syndrome (7 cases).

A specific analysis about the most relevant serious adverse cutaneous reactions reported by the MAH in relationship of their nature and severity was made in the MAH's response to the PRAC list of questions. Overall, more than 40% of the reported cases are related to the skin disorder SOC; severe Cutaneous Adverse Reactions to Drugs (SCARs), such as SJS, TEN, DRESS Syndrome and EM were diagnosed upon tetrazepam treatment and 11 fatal cases were reported; in 8 cases, it was reported as the result of the skin reaction and in 3 cases, it was related to an associated reaction. Allergic tests were performed in several cases. Overall, an estimated 70%-80% of the allergy tests performed were positive. In most of the cases, the causal relationship of tetrazepam was reported as possible (86% of the cases) and in some cases as probable (11% of the cases).

PRAC acknowledged that majority of cases reported involved the use of multiple medicinal products. However the imputability of tetrazepam is strong in a high number of cases. This is confirmed by the results of the allergic tests for which in a number of cases only tetrazepam had positive results. In addition, cases of rechallenge with new skin disorders episodes were reported.

Concerning the SJS/TEN cases described by the MAH 65 medically-confirmed serious cases of SJS/TEN were reported. These cases concerned 31 cases of SJS and 35 cases of TEN, including one case with both reactions. In 10 cases, the diagnosis was confirmed by skin biopsy. Time to onset ranged from 1 to 3 weeks in 14 patients, while 9 cases were reported with a shorter time to onset (< 7 days) including 6 cases with a very short time to onset between 1- 3 days. Almost all cases with information about duration of treatment with tetrazepam, a duration of up to one month treatment was observed in most cases; in 9 cases, the duration was very short (less than 4 days).

Severe cutaneous adverse reactions with tetrazepam are also described in published literature^{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11}. Skin adverse events were also submitted in responses from other MAHs and the Stakeholders submissions.

¹ Sanchez I et al. Stevens-Johnson syndrome from tetrazepam. *Allergol Immunopathol* 1998; 26: 55-57

The MAH presented its views on the possible mechanism of cutaneous reactions induced by tetrazepam: a structural difference between tetrazepam and other benzodiazepines (i.e. the substituted cyclohexenyl ring of tetrazepam) may be linked to the various cutaneous hypersensitivity reactions observed for tetrazepam. The potential for nucleophilic attack proposed in the literature (by *Barbaud et al, 2009*) is consistent with the mechanism proposed by in silico analysis, and may explain the reported lack of cross-reactivity between tetrazepam and other benzodiazepines in patients with cutaneous hypersensitivity reactions. Tetrazepam affinity for skin could explain the localization of the hypersensitivity reaction.

The PRAC considered risk minimisation measures, including reduction of duration of treatment to 6 days and a restricted indication, to mitigate the risk of serious cutaneous adverse reactions. Further risk minimisation measures such as additional amendments to the product information (contraindications, warnings), communication material (patient alert card, dear Health Care Professional Letter) and reduction of pack size were also considered during the discussions.

Taking into account the indications of tetrazepam, the effectiveness of a reduction of duration of treatment was questioned by the PRAC in view of the potential for repeated use. In addition the PRAC considered that the clinical data supporting the 6-day duration treatment benefit were insufficiently robust.

In view of the unpredictability of this type of adverse reactions, a restricted indication would not be an effective risk minimisation measure.

The option of a patient alert card was also discussed but this was not considered effective in preventing these types of SCARs.

Having assessed the totality of the risk minimisation measures proposed, the PRAC concluded that given the risk and the unpredictability of serious cutaneous adverse reactions with tetrazepam the proposed measures were not sufficient to reduce the risk to a clinically acceptable level.

In view of the above, the PRAC considered that tetrazepam, compared to the medicines of the same pharmacological class, is associated with an increased risk of serious cutaneous adverse reactions including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Erythema Multiform and DRESS syndrome which can be life threatening and fatal.

Efficacy

Tetrazepam is a benzodiazepine indicated for painful contractures in rheumatology and in spastic syndromes across the Member States. Some Member States have both indications.

Results of clinical studies with the use of tetrazepam in both indications have been published since the marketing authorisations of tetrazepam. Overall, the efficacy of tetrazepam in the painful contractures indication is supported mainly by two small double blind placebo-controlled clinical trial (*Arbus 1987*

² Camarasa JG et al. Tetrazepam allergy detected by patch test. *Contact Dermatitis* 1990;22:246

³ Quinones D et al. Photodermatitis from tetrazepam. *Contact Dermatitis* 1998 ;39(2):84

⁴ Bachmeyer C. Probable drug rash with eosinophilia and systemic symptoms syndrome related to tetrazepam. *J Eur Acad Dermatol Venereol* 2008;22(7):887-8

⁵ Cabreizo Ballesteros et al. Erythema multiforme to tetrazepam. *J Investig Allergol Clin Immunol* 2007;17(3):205-6

⁶ Delesalle F et al. Toxic epidermal necrolysis caused by tetrazepam. *International Journal of Dermatology* 2006;45(4):480

⁷ Del Pozo MD et al. Tetrazepam Allergy. *Allergy* 1999;54(11):1226-27

⁸ Sanchez-Morillas L et al. Systemic dermatitis due to tetrazepam. *J Investig Allergol Clin Immunol* 2008;18(5):404-406

⁹ Blanco R et al. Delayed hypersensitivity to tetrazepam. *Allergy* 1997;52(11):1145-6

¹⁰ Lagnouir et al. Fatal toxic epidermal necrolysis associated with tetrazepam. *Therapie* 2001;56(2):187-96

¹¹ Thomas E et al. Acute generalised exanthematous pustulosis due to tetrazepam. *J Investig Allergol Clin Immunol* 2008;18(2):119-122

and *Salzmann 1993*) involving 70 patients in total (50 patients and 20 patients respectively). In these studies only limited efficacy was shown.

The PRAC also noted that current guidelines do not refer to the use of tetrazepam in the spasticity indication.

The efficacy of tetrazepam was also compared to other active drugs in controlled double blind studies: these studies did not show statistically significant difference between the groups in both indications.

The PRAC considered that the available efficacy data, including data which became available since the initial marketing authorisation, showed only very limited clinical efficacy of tetrazepam in its approved indications.

Overall conclusion

Based on the above, the PRAC concluded that tetrazepam is associated with safety concerns in relation to serious, potentially fatal, skin reactions and shows limited clinical efficacy.

The PRAC considered that the risk minimisations measures discussed during the assessment, including reduction of duration of treatment and restricted indication, were not sufficient to reduce the risk.

The PRAC therefore concluded that the benefit-risk balance of tetrazepam containing medicinal products is not favourable.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC, for tetrazepam containing products.
- The PRAC considered the totality of the data available for tetrazepam containing products in relation to the risk of cutaneous adverse reactions. This included data from the Member States and published literature data which became available since the original marketing authorisations, as well as the MAH responses and the Stakeholders submissions.
- The PRAC noted that serious adverse cutaneous reactions have been reported with tetrazepam, including fatal cases.
- The PRAC considered, after having reviewed the available data that tetrazepam, compared to the medicines of the same pharmacological class, is associated with an increased risk of serious cutaneous adverse reactions including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Erythema Multiform and Drug Reaction of Eosinophilia Systemic Symptoms (DRESS) which can be life threatening and fatal.
- The PRAC considered that the available efficacy data, including data which became available since the initial marketing authorisation, showed only very limited clinical efficacy of tetrazepam in its approved indications.
- The PRAC considered that the risk minimisations measures discussed during the assessment, including reduction of duration of treatment and restricted indication, were not sufficient to reduce the risk of serious cutaneous reactions.

In view of the safety concerns in relation to serious, potentially fatal, skin reactions and the limited efficacy of tetrazepam, the PRAC concluded that pursuant to Article 116 of Directive 2001/83/EC the benefit-risk balance of tetrazepam containing medicines is considered no longer favourable.

Therefore, following the provisions under Article 107i of Directive 2001/83/EC, the PRAC recommends the suspension of the marketing authorisations for all medicinal products referred to in Annex I.

The conditions for lifting the suspension of the marketing authorisations are set out in Annex III.

CMDh position

The CMDh, having considered the PRAC recommendation dated 11 April 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC and the oral explanation attended by a Marketing Authorisation Holder on 22 April 2013, reached a position on the suspension of the marketing authorisations of tetrazepam containing medicinal products.

The conditions for lifting the suspension of the marketing authorisations are set out in Annex III.