

Rationale for triggering of the Article 107i procedure on Tetrazepam containing medicines

Minutes of the French survey concerning Tetrazepam

Rapporteur: Regional Center of Pharmacovigilance (CRPV) of Bordeaux

Trade name	Myolastan [®] and generics
INN	Tetrazepam
Pharmaceutical form	50 mg tablet
Pharmacological class	Benzodiazepine – Centrally-acting muscle relaxants
Registration procedure	National
MA date	3 May 1967
Commercialisation date	19 January 1969
MA Holders	Sanofi, Daiichi Sankyo, Arrow, Biogaran, Cristers, EG Labo, Mylan, Qualimed, Ranbaxy, Ratiopharm, Sandoz, Teva Santé, Zydus
Added medical value	Insufficient (opinion issued in December 2005)

1. Introduction

Tetrazepam is a benzodiazepine with a MA granted in 1967 for the “treatment of painful muscle spasms in rheumatology (in combination with other specific treatments)”.

During the French Pharmacovigilance working party (*Comité Technique de Pharmacovigilance*, CTPV) meeting held on 28 June 2011, a noteworthy case of eczema following occupational exposure while crushing tablets was presented. This was the opportunity to report the significant number of tetrazepam-related adverse cutaneous reactions in the French national pharmacovigilance database (*Base Nationale de Pharmacovigilance*, BNPV); it was then decided to initiate an official survey on tetrazepam-related adverse reactions, particularly those of the cutaneous.

The investigation report was presented at the French Pharmacovigilance working party on the 6th of November 2012. Given these results, the the French Pharmacovigilance working party raised the matter to the National Pharmacovigilance Committee (*Commission Nationale de Pharmacovigilance*).

In December 2005, tetrazepam’s *Added Medical Value* (ASMR, Amélioration du Service Médical Rendu) was deemed as insufficient in its indication, by the HAS¹; hence, tetrazepam containing products are no more reimbursed in Franc since December 2011.

2. Méthodology:

The survey concerned all cases of the French national database until 30 June 2012, and the serious cases of MAH. Duplicates have been identified.

The survey was supplemented with a text search in the national database for serious cases and cutaneous reactions.

A monitoring of the literature was also performed to complete these data.

3. Results:

National pharmacovigilance database data

A total of 1,616 adverse event cases, of which 648 (40%) were serious, were analysed. Patients were mainly female (61.5%) with a mean age of 50 years.

Skin reactions (805, of which 305 were serious) represented half of the reported cases. Of these, 59 were cases of erythema multiform (1 of these was fatal), 33 were cases of Stevens-Johnson Syndrome (1 of these was fatal), 33 were cases of Lyell’s Syndrome (9 of these were fatal), 15 were

¹ HAS: Haute Autorité de Santé: [French agency in charge of recommendation on reimbursement of medicines in France.](#)

cases of DRESS Syndrome or Drug hypersensitivity, plus 3 possible such cases, 5 were cases of Acute generalized exanthematous pustulosis (with a possible 6th case), 67 were cases of drug eruption, 118 were cases of urticaria (21 of these were severe cases) and there were many cases of Type IV delayed hypersensitivity. Six cases were described following occupational exposure. Of these cases, 37.7% had a causality at least plausible and 14% a likely or very likely causality.

The mean time to onset for the Lyell's syndrome cases was 12 days (median time to onset 13 days), for the Stevens-Johnson syndrome cases the mean time to onset was 11 days (median time to onset 9 days) and for the DRESS cases it was 22 days (median time to onset 12 days).

Tetrazepam was the only suspected medicinal product or had a causality score that was higher than those of concomitant treatments in 5 Lyell's cases, 4 Stevens-Johnson cases and 9 DRESS cases.

Of the 115 cases having had an allergy test (tetrazepam was tested 105 times), there were 79 cases with a positive tetrazepam patch test, and 67 of these cases had negative patch tests for the concomitant medicinal products. Therefore, the proportion of positive tetrazepam tests was high (75%) and 64% of the cases were positive for tetrazepam only.

Cases of anaphylactic shock were also reported (21 cases of Quincke's Oedema, 10 cases of angioedema and 2 cases of anaphylactic shock).

Compared with the 5 other most frequently-used benzodiazepines (alprazolam, bromazepam, lorazepam, oxazepam and diazepam), tetrazepam stands out for the high number of related skin adverse reactions (ADR).

The estimated reporting rate confirms that serious skin reactions are very rare. By comparing the number of serious skin ADRs to the number of people treated, an estimated reporting rate of 1 case per 350,528 patients was found for 2009 and 1 case per 149,850 patients for 2010. If only new patients are considered, the estimated reporting rate is 1 case per 197,823 new patients in 2009 and 1 case per 74,384 new patients in 2010. For the most serious skin adverse reactions (Stevens-Johnson, Lyell's and DRESS), the estimated reporting rate was 1 case per 650,980 patients treated in 2009 and 1 case per 598,400 patients treated in 2010. If only new patients are considered the rates were 1 per 367,385 in 2009 and 1 per 793,433 in 2010.

The non-skin related serious adverse reactions were mainly neurological (133 serious cases, including 11 cases of coma, 13 cases of drowsiness, 7 cases of convulsions, 5 cases of consciousness disorders and 2 cases of loss of consciousness leading to a car accident), psychiatric (38 serious cases, including 14 cases of confusion, 2 cases of disorientation, 2 cases of stupor, 2 suicide attempts and 5 cases of abuse or addiction) and general. The majority of the reported cases involved the use of multiple medicinal products (e.g., combinations including analgesics, non-steroidal anti-inflammatory drugs or muscle relaxants).

Pharmaceutical company data

Of the 72 serious MAH cases (cases that were also found in the national database were excluded to avoid duplicates), there were 7 cases of Lyell's Syndrome (2 of which were fatal), 4 cases of DRESS Syndrome, 4 cases of erythema multiforme, 1 case of Stevens-Johnson Syndrome, 1 case of leucocytoclastic vasculitis, 1 case of bullous dermatitis, and 8 cases of various rashes. It should be noted that there were also 5 suicides and 5 suicide attempts.

These data were supported by the literature, where publications of cutaneous reactions or series of such cases were predominant among articles on the adverse reactions of the product.

Exposure data

Tetrazepam is one of the most frequently used benzodiazepines in France (and the one most frequently used in terms of prevalent cases in 2009 and 2010 according to the data of the French national health insurance fund) and its use rose from 2005 to 2010. Since the decision of stopping reimbursement of the product in 2011, the number of boxes sold in French retail pharmacies from January 2012 to May 2012 decreased by 36% compared with the same period of the previous year.

Over a 5-year period (2006-2011), 36.2% of patients treated with a benzodiazepine were treated with tetrazepam, with an exposure prevalence that increased up to 30-40 years of age and decreased starting at 50-60 years of age. In 76% of the cases, patients complied with the dosage.

Tetrazepam is launched in at least 6 countries of the European Union. Based on MAH data, tetrazepam exposure is particularly high in Spain, and elevated but to a lesser extent in France and Germany.

The duration of treatment is recommended to be "as short as possible" in the SPC of other European countries available during the survey (treatment duration recommendations were only present in Austria – 3 months maximum - and Belgium – 3 weeks maximum), but these are recommendations for

preventing addiction and not for preventing cutaneous adverse reactions. France has no recommended treatment duration limit.

In addition to the data presented to the Pharmacovigilance Technical Committee, an analysis of the data from the general sample of subjects affiliated (SSA) to the general health insurance scheme was performed by the ANSM's health product epidemiology department.

Reimbursement data up to 30 November 2011 (the date of de-reimbursement) on SSA subjects were analysed.

The number of subjects beginning a treatment in France was estimated at 3.2 million in 2010 and 2.6 million in 2011. Of the 43,607 analysed SSA subjects (mean age 45.6 years, 57.8% women), 90.3% received 1 dispensation of the product over the entire study period and therefore had a treatment of less than 1 month for which the daily dose could not be estimated. In contrast: 9.4% of the subjects received 2 to 5 dispensations with a median treatment duration of 1 month, 0.3% received 6 to 12 dispensations with a median treatment duration of 5 months and 0.3% received more than 12 dispensations with a median treatment duration of 14.4 months.

Of the 4,241 subjects who received more than 2 dispensations, 67.9% received a mean daily dose of less than 150 mg/d, 22.9% received 150 to 300 mg/d, 4.8% received 300 to 450 mg/d and 4.5% received over 450 mg/d. The daily dosage depends on how many times the medicinal product had been dispensed: subjects who took more than 300 mg all belonged to the category of subjects who received 2 to 5 dispensations. Subjects who received more than 5 dispensations mainly took doses of less than 150 mg/d.

4. Discussion and conclusion of the rapporteur from the French Regional safety center

The rapporteur concluded that the utilisation of tetrazepam is associated to a significant rate of often-serious cutaneous adverse reactions with a plausible causality due to the high frequency of positive allergy tests, which is uncommon for a benzodiazepine. There does not seem to be a cross-reaction with other benzodiazepines.

Furthermore, the rapporteur emphasises the presence of typical pharmacological benzodiazepine reactions, the high exposure in France (approximately 3.5 million of patients treated in 2009 and 2010) and the frequent multiple drug exposure (e.g. with NSAIDs, analgesics, thiocolchicoside) for pain that is usually benign. It was also reiterated that there is probably a significant under-reporting due to how long tetrazepam has been on the market.

Finally, the rapporteur highlighted that, tetrazepam is currently the only benzodiazepine on the French market with an unlimited prescription duration, but the risk of addiction with tetrazepam has not been proven. Furthermore, de-reimbursement reduced the level of exposure, but only partially given tetrazepam's low price.

A relationship between the chemical structure of tetrazepam and of the chlormezanone (a muscle relaxant withdrawn from the market for severe cutaneous reactions) has been discussed. According to the opinion of a chemist expert, because of the different molecular structures and the lack of common metabolites, no clear mechanistic explanation can be provided to these tetrazepam-related cutaneous reactions.

At the end of this survey, the rapporteur concluded that the risk appears unacceptable and suggested the suspension of the MA. In case not, he suggested the limitation of the treatment duration to 3 days, with a reduction of the number of tablets per box, a prohibition of the prescription renewal and restriction of tetrazepam treatment for bedridden patients.

5. Discussion and conclusion of the National Pharmacovigilance Commission

The pharmaceutical companies reported that there was compliance with the recommended dosage in the majority of the cases and that, according to EPPM (IMS) data, the treatment duration was less than 15 days in 70% of the prescriptions (8% of the prescriptions were for less than 5 days, 20% were for less than a week, 28% were for 8 to 10 days and 13% were for 11 to 15 days).

The companies emphasised that the cutaneous risk was identified in the SPC and that a request to modify the information to add DRESS syndromes had been submitted by the innovator. Nevertheless, it was highlighted that the leaflet most likely had poor information about cutaneous risk and the need to discontinue tetrazepam in case of cutaneous symptoms occurring;

It was also reiterated that the tetrazepam MA is old with limited efficacy data.

The members of the National Pharmacovigilance Committee underlined the existence of severe cutaneous adverse reactions that are specific to tetrazepam and the risk within the scope of occupational exposure (heightened by crushing practices in particular). They also pointed out that 92% of patients are treated for more than 5 days, which increases the risk of tetrazepam sensitisation. They discussed the risk of prescribing other muscle relaxants: other benzodiazepines, even though tetrazepam is the only benzodiazepine with an MA as a muscle relaxant, or other available muscle relaxants (thiocolchicoside, methocarbamol, mephenesine), whose safety profiles seem to be better in terms of cutaneous risk. The report of prescription is a major issue given the high number of tetrazepam prescriptions and so, should be closely monitored by ANSM in case of MA of tetrazepam containing products suspended. The risk of a tetrazepam cross reaction with other benzodiazepines seems limited due to tetrazepam's tertiary structure, which is different from of other benzodiazepines.

Based on the rapporteur's proposals and due to the very rare but severe cutaneous adverse reactions that may be life-threatening, suspension of the MA of tetrazepam containing products and the initiation of a European referral procedure was voted: 7 members against, 3 members abstained, and 15 members were in favour of this measure.

Post -NC note:

Further to the opinion of the National Pharmacovigilance committee to suspend the MA of tetrazepam-containing products, the ANSM initiated on 20 December 2012, a referral procedure with the new European Pharmacovigilance Committee, the PRAC. This Urgent Union procedure will allow to issue a recommendation for all tetrazepam-containing products (oral forms) authorised in Europe.