EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 April 2013
EMA/279100/2013

Assessment report for tetrazepam containing medicinal products

Procedure under Article 107i of Directive 2001/83/EC

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

INN: Tetrazepam

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Background information on the procedure

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 authorisation for tetrazepam containing medicines further to evaluation of data resulting from pharmacovigilance activities in France.

2. Scientific discussion

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.

2.1. Clinical aspects

Tetrazepam is indicated for painful contractures in rheumatology or spasticity in the EU. Some Member States have both indications, when other Member States have only one of the above mentioned indications.

Benzodiazepines facilitate the inhibitory activity of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter found in the central nervous system, spinal cord, as well as many areas of the brain. They do this by interacting with a macromolecular membrane complex (BZP receptor), which is functionally coupled to GABA receptor and chloride ion channel. A synergism occurs between GABA and BZPs, resulting in an increased affinity of the receptor for the drug, probably due to the increased GABA binding to its receptor. This interaction promotes the opening of the chloride channel and leads to hyperpolarization of the cell membrane. The resulting negatively charged, hyperpolarized membrane can no longer be depolarized/stimulated by excitatory neurotransmitters. This is the mechanism felt to

mediate the sedative, hypnotic, anticonvulsant and muscle relaxant properties of tetrazepam (Drugdex 2012).

It should be noted though that tetrazepam has a unique profile, having a cyclophene ring instead of the phenyl ring common to benzodiazepines.

Prescribed by oral route under the formulation of a 50 mg tablet, the recommended dose range is from 25 mg (initial dose for elderly patients and patients with renal or hepatic insufficiency) to 150 mg daily depending on the clinical context. Average duration of treatment varies across the Member States.

2.1.1. Safety

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

Data provided by Member States

French pharmacovigilance review

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 up to 30 June 2012.

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 81 cases of SJS, TEN or DRESS.

Cases of anaphylaxis were also reported (97 cases of urticaria with or without concomitant palpebral or facial oedema, 21 cases of Quincke's Oedema and 10 cases of angioedema) and there were two additional cases of anaphylactic shock (System Organ Class, or SOC, "Immune System Disorders").

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.

The non-skin related serious adverse events were mainly neurological events, psychiatric events and general disorders.

Data provided by the Spanish Agency on Medicines and Medical Devices

The Spanish Agency on Medicines and Medical Devices provided an analysis of data from a registry on severe cutaneous reactions in the Madrid area (PIELen Red) that did not receive any report of SJS/TEN within the period of 2011-12. Data from BIFAP, an electronic database of medical records of primary healthcare for pharmacoepidemiological studies, was also presented but did not identify a higher incidence of SJS/TEN with tetrazepam when compared with the other benzodiazepine users.

Data submitted by the European registry of severe cutaneous adverse reactions to drugs (RegiSCAR database)

The European registry of severe cutaneous adverse reactions to drugs had in its records 721 validated cases of SJS/TEN, recorded between 2003 and 2010. In 15 cases (2%) there was exposure to tetrazepam, and causality was determined as follows:
- 2 with probable causality (1 in association with 2 other probable causes)
- 1 with possible causality and no other suspect
- 2 with possible causality in association with medications of equal possible causality
- 10 with medications for which causality was assessed to be superior

RegiSCAR therefore considers tetrazepam to be a 'drug under surveillance'.

Data submitted by MAHs (originator)

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 as follows:

- 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 (n = 31),
- erythema (28 cases),
- toxic skin eruption (19 cases),
- skin exfoliation (16 cases),
- dermatitis bullous
- Not Otherwise Specified (NOS) (16 cases),
- DRESS syndrom (7 cases).

In addition, 37 respiratory reactions, as usually reported in context of anaphylactic reactions, were also reported; they referred to different degrees of respiratory impairment, ranging from dyspnea/tachypnea to respiratory failure or distress. Moreover, 18 vascular reactions reported within context of anaphylactic reactions were identified; they referred to hypotension, circulatory collapse or shock.

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.

Stevens-Johnson and Lyell's Syndrome:

Sixty-five (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. Among these 65 cases, 3 cases of TEN and 3 cases of SJS were identified from the scientific literature. They were reported in 37 women and 27 men; gender was unknown in 1 case. All referred to adults, aged from 19 to 87 years with mean age: 55 years; it is noteworthy that 25 (38%) cases were reported in elderly patients.

For the 38 cases for which indication for tetrazepam was reported, in 35 cases, tetrazepam was given as a muscle relaxant, in 1 case tetrazepam was given within indication of spastic syndrome.

In 10 cases, the diagnosis was confirmed by skin biopsy and in an additional case the result of the skin biopsy was compatible either with lupus (in a patient with no identified history of lupus disorder according to our knowledge) or toxidermia.

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) (Table 1).

Table 1: Time to onset, daily doses and duration of the tetrazepam treatment for both SJS and TEN.

SJS/TEN: Time to onset		SJS - TEN: Treatment duration		SJS - TEN: Daily dose	
[0 - 3 days]	6	[0 - 4 days[	9	< 100 mg	19
]3 - 6 days]	3	[4 - 8 days[	10	[100 - 200 mg[	8
]6 - 21 days]	14	[8 - 15 days[	12	[200 - 300 mg[	1
]21 days - 1 month]	6	[15 days - 1 month]	14	[400 - 500 mg[	1
]1 - 6 months]	4	]1 month - 3 months]	2	≥ 500 mg	1
Unknown [a]	32	Unknown	20	Unknown	35
Total	65	Total	65	Total	65

Allergic tests were performed in 9 cases, 7 of which the patch test was only positive for tetrazepam.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Seven (7) cases of drug rash with eosinophilia and systemic symptoms (DRESS) were reported with no fatal outcome. No case was reported with tetrazepam in monotherapy and no patient had a history of previous DRESS. Allergic tests were performed in 4 cases. Patch tests were positive only for

tetrazepam. In two cases, a causal role of tetrazepam was considered to be probable as hypersensivity tests were positive, in 5 cases, the causal relation was considered as possible.

Erythema Multiforme (EM)

Fourty-eight (48) medically confirmed unsolicited cases of EM with no fatal outcome. No case was reported with tetrazepam in monotherapy. 14 patients had a medical history: 3 had a previous EM, 8 patients had various type of allergy, 1 patient suffered from a lupus and 2 patients had herpes infection. Allergy tests were performed in 13 cases and at least one was positive for tetrazepam. In 6 cases, the causal relationship with tetrazepam was assessed as probable and in 38 cases the causal role was considered as compatible.

Acute Generalized Exanthematous Pustulosis (AGEP)

Seventeen (17) cases of acute generalized exanthematous pustulosis were reported with no fatal outcome. No case was reported with tetrazepam in monotherapy. Three patients had a medical history of AGEP, two patients of psoriasis, and 6 of allergy. Allergy tests were performed in 2 cases and were positive for tetrazepam. In one case the causal role was assessed as probable, in 13 cases the causal role was assessed as possible and in 3 cases no conclusion could be drawn.

Angioedema

A total of 34 cases of angioedema were reported with no fatal outcome. No case was reported with tetrazepam in monotherapy. Ten patients had a medical history of allergy. In 4 cases, tetrazepam was the only administered or suspected drug (one case was assessed as probable, two as possible and one as not assessed). In general, two cases were reported as probable, 28 cases as possible and coadministered drugs could have also contributed in 21 cases, 1 case as unrelated and 3 cases as not assessed.

Anaphylactic or anaphylactoid shock

Four (4) cases of anaphylactic or anaphylactoid shocks were detected, they contained limited information. The causal role of tetrazepam was assessed as possible in all cases.

Urticaria

A total of 47 cases of urticaria were confirmed with no fatal outcome. A medical history of the patient was provided in 8 cases (7 allergy, 1 respiratory disorder). In 8 out of 47 cases, allergic tests were performed, and in 7 cases they were positive for tetrazepam. In 5 cases, the causal role of tetrazepam were considered as probable, in 36 cases as possible, in two cases as unrelated and in four cases as unassessable.

Dermatitis exfoliative

Thirty-three (33) cases of dermatitis exfoliative were identified with no fatal outcome. No cases were reported with tetrazepam in monotherapy. 4 patients had a history of allergy, another patient has a history of allergy and psoriasis; moreover, 1 patient had a history of asthma NOS, psoriasis in 3 additional cases, and 2 patients had a history of unspecified rash.

Allergic tests were performed in 9 cases of which 3 were positive only for tetrazepam, suggesting a causal role for tetrazepam.

Overall assessment of the MAH's data:

Five hundred and thirteen (513) distinct cases referring to 748 reactions were identified by MAH involving cutaneous reactions.

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). Treatment duration as well as daily dose do not seem to correlate with the emergence of SCARs and SCARs mainly occurred at the recommended dose.

PRAC acknowledged that majority of cases reported involved the use of multiple medicinal products. However the imputability of tetrazepam is strong in 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.

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.

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.

Conclusion on safety

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.

[1] Sanchez I et al. Stevens-Johnson syndrome from tetrazepam. Allergol Immunopathol 1998;26:55-57
[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] Bachmeyter 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 la. 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 la. Delayed hypersensitivity to tetrazepam. Allergy 1997;52(11):1145-6
[10] LagnouiR et al. Fatal toxic epidemal 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

2.1.2 Efficacy

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

1. Painful Muscular Contractures

Antispasmodics are used to decrease muscle spasm associated with painful condition such as low back pain which is the most common musculoskeletal condition, affecting 84% of the general adult population.

Since the initial marketing authorisations the efficacy of tetrazepam was assessed in several published controlled double blind studies versus placebo (Table 2) and versus comparators (Table 3).

Efficacy versus placebo

Overall, the efficacy of tetrazepam in the painful contractures indication is supported mainly by two small double blind placebo-controlled clinical trials (Arbus 1987 and Salzmann 1993) involving 70 patients in total (50 patients and 20 patients respectively). In these studies only limited efficacy was shown for the treatment of painful restriction mobility of the spinal cord. In a further study of 65 patients no statistically significance between groups was found.

Table 2: controlled double blind studies with tetrazepam versus placebo in painful muscular contractures

Study	Patients	Intervention	Efficacy results
Arbus 1987 Study C 222 A Report 119.6.051 (16)(17)	50 patients with acute or chronic lumbago of definite lesional origin.	T or P for 12 days. T dosage increased from 50 mg/day to 150 mg/day from the 1st to the 3rd day, then 150 mg/day up to 12 days	T > P for overall efficacy by physician, pain by patient and physician, contracture, finger to ground distance, Schober's index, spontaneous potentials at electromyography. Most of comparisons are significant on the 5th day of treatment.
Dienel 1987 Report 119.0.027 (18) *	65 patients with pain and muscular tension in the low back region resulting from degenerative changes in the corresponding intervertebral disc.	T 150 mg/day or tizanidine 12 mg/day or P, for 21 days.	No statistically significant difference between the groups.
Pförringer 1989 Study P 1106 Report 119.6.026 (19)(20)	152 patients with chronic low back pain.	T 150 mg/day or P, for 14 days.	T > P for daytime pain, and for 2 items of the Clinical Global Impression (severity of illness, impression of change), on the 7th day of treatment).
Salzmann 1993 (21)	20 patients with acute painful restriction of mobility of the cervical spine and overall marked impairment.	T 150 mg/day or P, for 7 days.	T > P for the summed score of pain, restriction of mobility, and general impairment, and for paracetamol consumption, both assessed during the whole study duration.

T:=Tetrazepam, P=Placebo

Efficacy versus comparators

The efficacy of tetrazepam was compared to other active drugs in several double blind studies. Kountouri study in 1985 showed no statistically significant difference between tetrazepam and chlormezanone treatment of cervical syndrome. Also, in Dienel 1987 and Bröse 1996 studies, no

statistically significant difference between tetrazepam group and, tizanidine or methocarbamol group were detected.

Table 3: Controlled double-blind studies with tetrazepam versus active drug in painful muscular contractures

Study	Patients	Intervention	Efficacy results
Kountouris 1985 Report 119.6.025 (22)	30 patients with cervical syndrome.	T 50 to 150 mg/day, or chlormezanone 200 to 600 mg/day, for 20 days.	No statistically significant difference between the groups, except sleep quality better with tetrazepam.
Dienel 1987 Report 119.0.027 (18) *	65 patients with pain and musculat tension in the low back region resulting from degenerative changes in the corresponding intervertebral disc.	T 150 mg/day or tizanidine 12 mg/day or P, for 21 days.	No statistically significant difference between the groups.
Lebaux 1996 (23)	63 patients with postoperative contracture of the knee	T 100 mg/day or thiocolchicoside 16 mg/day, for 10 days	T < thiocolchicoside for pain relief from the 2nd day of treatment, and for contracture measured on the 11th day.
Bröse 1996 (24)	48 patients with painful skeletal muscle disorders.	T or methocarbamol for 14 days. T dosage increased from 50 mg to 150 mg from the 1st day to the 4th day, then 150 mg/day. Methocarbamol 8 tablets/day from the 1st dat to the 3rd day, then 6 tablets/day.	No statistically significant difference between the groups.

T:=Tetrazepam, P=Placebo
* Placebo- and active-controlled study

2. Spasticity

Spasticity is a predominant clinical sign of pyramidal and parapyramidal syndromes which appears in many different neurological disorders. Antispasticity medications include benzodiazepines and non-benzodiazepines.

Efficacy versus comparators

Efficacy of tetrazepam was compared to four active drugs in double blind controlled studies in spasticity indication (table 4), but no statistically significant difference between the groups was detected.

Table 4: Controlled double-blind studies with tetrazepam versus comparators in spasticity indication

Study	Patients	Intervention	Efficacy results
Rimpel 1988 Report 119.6.030 (27)	22 patients with disseminating encephalomyelitis (multiple sclerosis), spastic paraplegia or tetraplegia suffering from chronic residual urine problems.	T 100 to 200 mg/day, or baclofen 20 to 40 mg/day (individual dose adjustment), for 28 days.	No statistically significant difference between the groups.
Pellkofer 1988 Report 119.6.008 (28,29)	47 patients with multiple sclerosis and spastic motor disturbances of the lower extremities.	T 25 to 250 mg/day, or tizanidine 2 to 16 mg/day, or baclofen 5 to 60 mg/day (individual dose adjustment), for 35 days.	No statistically significant difference between the groups.
Schlickenrieder 1988 Report 119.6.009 (30,31)	30 patients with multiple sclerosis, spastic motor disturbances and disturbed micturition.	T 25-50 mg unit doses or baclofen 2.5-5 mg unit doses, (individual dose adjustment), for 35 days	No statistically significant difference between the groups.
Delwaide 1997 (32)	14 patients with spasticity.	T single dose of 50 mg, or diazepam single dose of 10 mg	No statistically significant difference between the groups.

T:=Tetrazepam

Conclusion on efficacy

The efficacy of tetrazepam in the painful contractures indication is supported mainly by two small double blind placebo-controlled clinical trial showing limited efficacy.

The PRAC noted that current clinical 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.

3. Overall discussion and benefit / risk assessment

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.

The PRAC considered risk minimisations 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.

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.

4. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the review of tetrazepam and the resulting regulatory measures.

Relevant European healthcare professional organisations were consulted and provided input on the draft DHPC. The final version of this DHPC agreed by the PRAC is provided together with the communication plan (see attachments to this report).

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent to physicians who treat patients with painful contractures and spastic syndromes (e.g. general practitioners, rheumatologists) and pharmacists.

5. Conclusion and grounds for the recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC, for tetrazepam containing products (see Annex I).
- 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 tetrazepam containing medicinal products.

For the suspension to be lifted, the National competent authorities of Member States shall verify that the following conditions are fulfilled by the MAHs:

the MAHs should identify a patient population for which the benefit risk ratio of tetrazepam containing medicines is positive on the basis of scientifically relevant supportive data.

Appendix 1

Listing of submissions of all data received by the Agency by 04 February 2013

Listing of submissions of all data received by the Agency (i.e. from MAHs and other stakeholders)

Tetrazepam containing medicinal product(s)

Submission by:
Stakeholders
RegiSCAR
Patient
Patient
MAHs
Biogaran
Infarama bvba (Representative for Will-Pharma)
MIP Pharma GmbH
Sanofi-Aventis recherche & developpement
Stada Arzneimittel AG
Terapia S.A. (Representative for Ranbaxy)
Zydus France
Daiichi Sankyo France SAS
KSK-Pharma AG
Heumann Pharma GmbH and Co. Generica KG**

** *Marketing Authorisation of Tetrazepam 50 Heumann withdrawn on 4 February 2013*

Appendix 2

Divergent positions to PRAC recommendation

Article 107i of Directive 2001/83/EC

Procedure No: EMEA/H/A-107i/1352

Tetrazepam

Divergent statement

The following members of PRAC did not agree with the PRAC's Recommendation on the Article 107i referral for tetrazepam containing medicinal products based on the following reasons:

-Muscle relaxants including tetrazepam represent a recognized therapeutic option for short term pain relief of muscular contractures.

-The risk of developing a serious skin reaction is very low compared to the patient exposure. The rarity of these serious adverse reactions has been suggested by data from population-based registries in member states.

-Beyond data from spontaneous reports, epidemiological studies in member states have not confirmed an increased risk of serious cutaneous adverse reactions (SCAR) of tetrazepam compared to active substances of the same pharmacological class.

-In the large majority of the serious cases reported, tetrazepam was co-administered with other medicines that could have contributed to the reactions.

-The limitation of the treatment duration to a maximum of 6 days minimizes the risk of developing serious skin reactions with no evidence of impairment of the benefits.

-Additional measures could further minimize the risk of skin reactions including: An update of the product information including contra-indication in patients with a medical history of severe cutaneous adverse reactions such as Steven-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme or drug reaction with eosinophilia and systemic symptoms; contra-indication in children and adolescents up to age 18; contra-indication during pregnancy; warning on the skin reactions and on the drug interactions with substance known to be related to these cutaneous reactions; the limitation of the pack size; a patient card delivered by the health care professionals explaining the risk; a dear Health Care Professional Letter informing about these changes.

-The listing of tetrazepam containing products as subject to additional monitoring in the European Union.

-The measurement of the proposed risk minimization measures focused on specific indicators through a Drug Utilization Study could provide further information on the effectiveness of the proposed strategy.

-The alternative treatments have their own limitations and safety issues.

Due to the above mentioned arguments the below mentioned PRAC Members consider the benefit/risk balance of tetrazepam positive justifying the maintenance of the marketing authorisations of all tetrazepam-containing medicinal products subject to variation and conditions to the marketing authorisations.

PRAC members expressing a divergent position:

Jean-Michel Dogné (BE)	11 April 2013	Signature: ……...
Daniela Pomponiu (RO)	11 April 2013	Signature: ……...
George Aislaitner (EL)	11 April 2013	Signature: ……...
Jana Mladá (CZ)	11 April 2013	Signature: ……...
Jacqueline Genoux-Hames (LU)	11 April 2013	Signature: ……...
Jolanta Gulbinovic (LT)	11 April 2013	Signature: ……...
Amy Tanti (MT)	11 April 2013	Signature: ……...
Martin Huber (DE)	11 April 2013	Signature: ……...
Maria Popova-Kiradjieva (BG)	11 April 2013	Signature: ……...
Anna Mareková (SK)	11 April 2013	Signature: ……...
Miguel-Angel Macia (ES)	11 April 2013	Signature: ……...
Andis Lacis (LV)	11 April 2013	Signature: ……...
Filip Babylon (Representative of healthcare professionals)	11 April 2013	Signature: ……...