

Appendix to CMDh position

Divergent positions to CMDh position

Article 107i of Directive 2001/83/EC

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

Tetrazepam

Divergent statement

The following member of CMDh did not agree with the CMDh's Position on the Article 107i referral for tetrazepam containing medicinal products based on the following reasons:

-Muscle relaxants including tetrazepam represent a recognized and widely used therapeutic option for short term pain relief of muscular contractures in 12 Member States. The availability of alternative muscle relaxants may vary across countries, a circumstance that was not taken into account by the PRAC recommendation. Failure to take it into considerations may cause undesirable shifts to other alternatives with uncertain safety consequences. The alternative treatments have their own limitations and safety issues. The evidence of occurrence of cutaneous adverse reactions with tetrazepam in a greater frequency than other products of the same pharmacological class is based in data coming from spontaneous reports, with the inherent limitations of this source of information, in particular for comparing risks. The majority of these cases came from one Member State. Other national databases and national and/or European registries have failed to demonstrate a higher reporting rate of skin reactions. Scientific recommendation of PRAC failed to explain such an unexpected disparity of data among EU countries.

-In the large majority of the serious cases reported, tetrazepam was co-administered with other medicines that could have contributed to the reactions. This is not the case with other benzodiazepines that are compared with tetrazepam regarding reported skin reactions.

- The number of reported cases of cutaneous reactions is very low compared to the patient exposure (estimated in 153 million of patient exposed in the last ten years). The rarity of these serious adverse reactions has been also suggested by data from population-based registries in member states.

- 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. These data suggest that the incidence rate of Steven-Johnson syndrome and Toxic Epidermal Necrolysis in tetrazepam users is not significantly different to the incidence obtained for other benzodiazepine users and compatible with that reported in the general population in Europe.

-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.

- It should also be recognized the fact that both the PRAC recommendation and the CMDh position regarding this recommendation has been adopted with the majority support of Member states that have not a MA for tetrazepam while most Member states with a MA for tetrazepam supported their maintenance with risk minimizing measures, reinforcing the idea that no major concerns exists that recommend the suspension of the product in the European market. The consequences of the suspension of the marketing of tetrazepam in the 12 Member States where the product is currently available for more than 20 years have not been carefully addressed. It may lead to substitution by other medicines not approved as muscle relaxants

Due to the above mentioned arguments the below mentioned CMDh Member considers 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.

CMDh member expressing a divergent position:

Sophie Colyn (BE)	24 April 2013	Signature:
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Article 107i of Directive 2001/83/EC

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

Tetrazepam

The following CMDh Members support the divergent position appended to the PRAC recommendation on tetrazepam containing medicinal products dated 11 April 2013, as stated below:

CMDh members expressing a divergent position:

Petya Grueva (BG)	24 April 2013	Signature:
Jitka Vokrouhlická (CZ)	24 April 2013	Signature:
Susanne Winterscheid (DE)	24 April 2013	Signature:
Chrysoula Ntaousani (EL)	24 April 2013	Signature:
Monta Emersone (LV)	24 April 2013	Signature:
Žydrūnas Martinėnas (LT)	24 April 2013	Signature:
Jacqueline Genoux-Hames (LU)	24 April 2013	Signature:
Helen Vella (MT)	24 April 2013	Signature:
Ada Georgescu (RO)	24 April 2013	Signature:
Mária Polláková (SK)	24 April 2013	Signature:

Divergent statement from PRAC Members

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.

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Divergent statement

The following member of CMDh did not agree with the CMDh's Position on the Article 107i referral for tetrazepam containing medicinal products based on the following reasons:

-Muscle relaxants including tetrazepam represent a recognized and widely used therapeutic option for short term pain relief of muscular contractures in 12 Member States. The availability of alternative muscle relaxants may vary across countries, a circumstance that was not taken into account by the CMDh recommendation. Failure to take it into considerations may cause undesirable shifts to other alternatives with uncertain safety consequences. The alternative treatments have their own limitations and safety issues. The evidence of occurrence of cutaneous adverse reactions with tetrazepam in a greater frequency than other products of the same pharmacological class is based in data coming from spontaneous reports, with the inherent limitations of this source of information, in particular for comparing risks. The majority of these cases came from one Member State. Other national databases and national and/or European registries have failed to demonstrate a higher reporting rate of skin reactions. Scientific recommendation of CMDh failed to explain such an unexpected disparity of data among EU countries.

-In the large majority of the serious cases reported, tetrazepam was co-administered with other medicines that could have contributed to the reactions. This is not the case with other benzodiazepines that are compared with tetrazepam regarding reported skin reactions.

- The number of reported cases of cutaneous reactions is very low compared to the patient exposure (estimated in 153 million of patient exposed in the last ten years). The rarity of these serious adverse reactions has been also suggested by data from population-based registries in member states.

- 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. These data suggest that the incidence rate of Steven-Johnson syndrome and Toxic Epidermal Necrolysis in tetrazepam users is not significantly different to the incidence obtained for other benzodiazepine users and compatible with that reported in the general population in Europe.

-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.

- It should also be recognized the fact that both the PRAC recommendation and the CMDh position regarding this recommendation has been adopted with the majority support of Member states that have not a MA for tetrazepam while most Member states with a MA for tetrazepam supported their maintenance with risk minimizing measures, reinforcing the idea that no major concerns exists that recommend the suspension of the product in the European market.

Due to the above mentioned arguments the below mentioned CMDh Member considers 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.

CMDH member expressing a divergent position:

Luisa Garcia-Vaquero (ES)	24 April 2013	Signature:
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