Annex II

Scientific conclusions and grounds for

Variation to the terms of the Marketing Authorisations *(oral formulations)*

and

Revocation of the Marketing Authorisations *(parenteral formulations)*

Scientific conclusions

Overall summary of the scientific evaluation of tolperisone-containing products (see Annex I)

Tolperisone is a centrally acting muscle relaxant first synthesized in 1956, and used in clinical practice since the 1960's. The precise mechanism of action is not fully known. It possesses high affinity for nervous tissue, reaching the highest concentrations in the brain stem, spinal cord and peripheral nerve tissue. The chemical structure of tolperisone is similar to that of lidocaine and, similarly to lidocaine, tolperisone has membrane stabilising effects. Tolperisone reduces the sodium influx through the isolated nerve membrane in a dose dependent way, thus amplitude and frequency of action potentials are reduced. Furthermore, inhibitory effects on voltage dependent Ca^{2+} channels have been demonstrated, suggesting that tolperisone might also reduce the transmitter release in addition to its membrane stabilising effect. Tolperisone exerts its action at 3 levels:

- Peripheral level – stabilises the membrane of neurons, and consequently supresses the amplitude and frequency of the action potentials. It is capable of inhibiting the pathological peripheral impulse condition induced by pain, which could start various motoric or vegetative reflexes that would lead to increased muscular tone.
- Central-spinal level – tolperisone reduces the increased mono- and polysynaptic reflex activity in a dose-dependent manner to the physiological level. This effect is well demonstrated in several animal models.
- Central-reticular level – An imbalance between supraspinal facilitatory and inhibitory control can also lead to an enhanced reflex activity and an increased muscle tone. Tolperisone reduces the reticulo-spinal facilitation in the brainstem and has been shown to be effective in alleviating experimental gamma-rigor of reticular origin.

Tolperisone-containing products are currently approved in the following EU countries: Bulgaria, Cyprus, Czech Republic, Germany, Hungary, Latvia, Lithuania, Poland, Romania and Slovak Republic.

The following indications have been approved in at least one Member State (specific wording of the indication may vary from product to product):

- Acute or chronic treatment of pathologically elevated skeletal muscle tone in organic neurological disorders
- Treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases (e.g. spondylosis, spondylarthrosis, cervical and lumbar syndromes, arthrosis of large joints)
- Rehabilitation after orthopaedic and trauma surgery
- Treatment of obliterative vascular diseases as well as syndromes due to impaired vascular innervation (e.g. acrocyanosis, dysbasia angioneurotica intermittens)
- Little's disease (infantile diplegia spastica) and other encephalopaties accompanied by dystonia

On 15 July 2011, Germany triggered a referral under Article 31 of Directive 2001/83/EC. Germany considered that the numerous reports of hypersensitivity reactions received in the post authorisation phase are indicative of a safety concern which is not balanced by the limited evidence of efficacy. The CHMP was therefore requested to give its opinion on whether the marketing authorisations for medicinal products containing tolperisone, and associated names should be maintained, varied, suspended or withdrawn.

Clinical Efficacy

Treatment of pathologically elevated skeletal muscle tone in organic neurological disorders

This indication is mainly supported by the Stamenova (2005) study, which is of acceptable quality. In this randomised, double-blind, placebo controlled, multicentre study efficacy of tolperisone has been shown in the symptomatic treatment of patients with spasticity following cerebral stroke.

The Ashworth scale used in this study is a validated instrument generally accepted for the clinical evaluation of degree of spasticity. The mean improvement in the Ashworth score found in the Stamenova study was 32% in the overall ITT (intention-to-treat) population and 42% in the subgroup of patients receiving 300-450 mg/day). Van Denburg et al. (2008) have found a 33% change in the Ashworth Scale to correlate with a 1-point change in the Physician's global assessment score in patients with post-stroke spasticity, indicating clinical relevance. The improvement in Ashworth scale was accompanied by a statistically significant difference in the investigator's overall assessment of efficacy in favour of tolperisone. Further functional secondary parameters (i.e. the modified Barthel Index (assessing activities of daily living), capacity to perform routine activities and walking endurance) consistently favoured tolperisone over placebo. Mean maximum walking distance per 2 minutes at final visit was approx. 70 meters in the tolperisone and 40 meters in the placebo group.

In the Stamenova study, patients could be titrated up to 900 mg per day, thus only a subgroup (35%) of tolperisone patients was treated within the dose range currently approved in the SPC (150-450 mg). However, efficacy results of the subgroup treated with a daily tolperisone dose of up to 450 mg/day were consistent with the results of the whole ITT population. In conclusion the Stamenova study can be regarded as a positive study, the results of which are indicative of a clinically relevant effect of tolperisone in the treatment of patients with post-stroke spasticity.

In contrast, the prematurely terminated Avigen study AV650-018 (2007) failed to demonstrate any effect in the multiple sclerosis population. The interim analysis results indicated that it failed to achieve statistical significance in any evaluated efficacy endpoint.

The Feher study (1985) used the Rivermead scale, which has shown high validity and reliability in assessment of motor function in stroke patients. While the results are difficult to interpret due to the lack of a placebo control group to verify assay integrity, this randomised, double-blind actively controlled study provides supporting evidence of efficacy of tolperisone in terms of improvement of mobility in patients with spasticity caused by neurological disorders.

In the Melka study (1997), the reduction in muscle tone (as measured by the Ashworth scale) was accompanied by a consistent improvement in functional parameters indicative of clinical relevance. However, it only included patients with spasticity caused by neurolathyrism. Neurolahyrism affects predominantly young adult males at time of famine and generally does not occur in European countries, therefore generalisation of the study results to the existing indication is questionable. The Melka study can only be considered as providing supportive evidence of efficacy in the treatment of spasticity caused by neurological diseases.

Taken together, the existing dataset is indicative of a modest effect of tolperisone in the treatment of spasticity caused by neurological disorders. It is important to note that the evidence of efficacy is mainly based on the results of the Stamenova study, which only included patients with post-stroke spasticity.

Treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases

In the only study in this indication where superiority of tolperisone over placebo in the primary outcome was shown (Pratzel 1995), this was achieved using a new parameter in the formula for calculation which was not pre-determined but rather introduced in post-hoc efficacy analysis. Validation of new parameters needs to be done beforehand if proof of efficacy is to be derived from a study. In addition, the improvement in PPT was not accompanied by a corresponding improvement in

the mobility of patients. It is therefore not plausible how the reduction of a triggered PPT could have been translated into a clinically relevant effect in patients with painful reflex muscle spasm.

The Struck 2002 study failed to demonstrate a significant improvement in the primary endpoint, and the two secondary parameters for which a statistically significant improvement could be seen are subjective, and not considered clinically meaningful given that they were not accompanied by commensurate improvements in clinically relevant parameters such as pain intensity, pain at movement and motility. The Struck 2004 study also failed to demonstrate a significant improvement in the primary endpoint. In addition, all patients started by receiving doses above the approved dose. Finally, the Hodinka 2001 study also failed to demonstrate a relevant difference in the primary endpoint, and the only transient significant difference observed was in the Roland-Morris Disability Scale at day 7, having disappeared at day 14.

It can therefore be concluded that of the four main studies in this indication, which became available after the initial marketing authorisation was granted, one suffers from substantial deficiencies and the remaining 3 failed to demonstrate an effect on the efficacy outcome.

Rehabilitation after orthopaedic and trauma surgery

The data available on this indication comes from two observational studies (1986 and 1989) with a total of 166 patients, where 450 mg tolperisone were given daily for a few weeks. In both studies, tolperisone is given to a very heterogeneous population as part of a rehabilitation program, so it is not possible to isolate the effect of tolperisone from the effect of other interventions and therefore this data does not support the evidence of efficacy in this particular indication.

Treatment of obliterative vascular diseases as well as syndromes due to impaired vascular innervation

Very limited information exists on the efficacy of tolperisone in this indication. There are no GCP-compliant studies, there is 1 actively-controlled trial and a few observational studies. The actively controlled study was open label, used pentoxyphyllin as control and involved a total of 70 patients.

Little's disease and other encephalopaties accompanied by dystonia

Very limited information exists on the efficacy of tolperisone in this indication. The only studies that exist are of observational nature, were conducted in a heterogeneous population and contain extremely limited information.

Parenteral formulation

There are a few studies where a parenteral formulation was used. These are mostly observational and extremely limited documentation is available. The only double-blind, placebo-controlled studies identified where parenteral tolperisone was used and that have acceptable methodological standards were conducted in indications where efficacy has not been demonstrated, that have never been approved for the product or included only a very small number of patients in the indication of interest.. No data was submitted in support of the dosing recommendations.

Clinical safety

While no fatal case of hypersensitivity was reported, around 10% of all cases reported with tolperisone were considered to be life-threatening. Hypersensitivity reactions account for more than half of the spontaneous reports in the originators database, followed by adverse events (AEs) from the SOCs (System Organ Class) Gastrointestinal disorders, General disorders and administration site conditions and Nervous system disorders. Analysis of spontaneous reports suggests that hypersensitivity reactions are more frequent in women, patients with previous or current allergic disease or those using NSAIDs or other analgesics concomitantly. A causal relationship with tolperisone was assessed as at least possible in 90% of all hypersensitivity reactions.

There is a discrepancy between the patterns of spontaneous reports and the reports from studies. While only a small number of reports of hypersensitivity reactions were observed in the studies submitted, they represent more than half of all spontaneous reports. Hypersensitivity can be a significant event and cases of anaphylactic reactions/anaphylactic shock have been reported. The currently approved product information does not seem to adequately reflect the risk or communicate it to patients in order to allow early identification of signs of hypersensitivity. It is also noted that the reporting rates in Germany appear to be significantly higher than those calculated through the MAH's database.

The mechanism of tolperisone-related hypersensitivity is unknown. Hypotheses include tolperisone metabolites as hapten formations activating the patient's immune system through covalent modification of proteins, or structural similarity to the local anaesthetic lidocaine.

Due to lack of adequate data, no firm conclusions on the influence of renal or hepatic function can be drawn, although the existing data does not raise cause for concern.

It was noted that information in the Summary of Product Characteristics regarding interactions, effects on ability to drive and use machines and effect of food on pharmacokinetic parameters was not reflecting the latest available data. It was also noted that not all products mentioned the adverse events confusion and hyperhidrosis in the product information and that this should be harmonised.

It is well known that the safety profile of a product may vary depending on the formulation. However, as hypersensitivity is a characteristic of the active substance rather than of the formulation, the concerns identified with the oral formulations are also relevant for the parenteral formulation. The company that holds these marketing authorisations was asked to submit any existing data in support of its safety and dosing recommendations, but no relevant data was submitted for assessment as the marketing authorisation holder concluded itself that the data is insufficient to conclude that the benefits outweigh the risks and proposed that the marketing authorisations for the parenteral formulations be revoked.

Overall conclusion

The CHMP has considered the totality of the available data on the safety and efficacy of tolperisone.

While no fatal case of hypersensitivity was reported, around 10% of all cases reported with tolperisone were considered to be life-threatening. Hypersensitivity reactions account for more than half of the spontaneous reports in the originators database, followed by adverse events (AEs) from the SOCs Gastrointestinal disorders, General disorders and administration site conditions and Nervous system disorders. Analysis of spontaneous reports suggests that hypersensitivity reactions are more frequent in women, patients with previous or current allergic disease or those using NSAIDs or other analgesics concomitantly. A causal relationship with tolperisone was assessed as at least possible in 90% of all hypersensitivity reactions.

There is a discrepancy between the patterns of spontaneous reports and the reports from studies. While only a small number of reports of hypersensitivity reactions were observed in the studies submitted, they represent more than half of all spontaneous reports. Hypersensitivity can be a significant event and cases of anaphylactic reactions/anaphylactic shock have been reported. The currently approved product information does not seem to adequately reflect the risk or communicate it to patients in order to allow early identification of signs of hypersensitivity. It is also noted that the reporting rates in Germany appear to be significantly higher than those calculated through the MAH's database.

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The mechanism of tolperisone-related hypersensitivity is unknown. Hypotheses include structural similarity to the local anaesthetic lidocaine, so the risk for cross-reactions needs to be consistently described in the product information. The product information should also be updated so that all products contain consistent and updated information on interactions, effects on ability to drive and use

machines, the effect of food on bioavailability, influence of renal or hepatic function and adverse reactions.

On the efficacy side, the existing dataset is indicative of a modest effect of tolperisone in the treatment of spasticity caused by neurological disorders, but it is important to note that the evidence is mainly based on the results of the Stamenova study - which only included patients with post-stroke spasticity.

Relevant studies also exist in the locomotor indication, the majority of which failed to demonstrate the efficacy of the product. The only study in this indication with a positive outcome contains significant methodological deficiencies which preclude any conclusion on the efficacy of the product.

For the remaining indications (rehabilitation after orthopaedic and trauma surgery, treatment of obliterative vascular diseases as well as syndromes due to impaired vascular innervation, and Little's disease and other encephalopaties accompanied by dystonia) there is extremely limited evidence of efficacy, mainly based on small studies with inadequate design and including a heterogeneous population. It is therefore considered that efficacy in these indications has not been demonstrated. In this respect, the CHMP took note of the fact that the marketing authorisation holder of the products for which these indications are approved concluded that the evidence of efficacy is insufficient to balance the risks associated to the product and proposed that the indications be deleted.

Based on the totality of the data made available on the safety and the efficacy of tolperisone, the CHMP considered that the risk of hypersensitivity is more significant than previously identified, and that as a consequence the demonstrated clinical benefits only outweigh the risks in the restricted indication *symptomatic treatment of post-stroke spasticity in adults*.

It is well known that the safety profile of a product may vary depending on the formulation. However, as hypersensitivity is a characteristic of the active substance rather than of the formulation, the concerns identified with the oral formulations are also relevant for the parenteral formulation. The company that holds these marketing authorisations was asked to submit any existing data in support of its safety and dosing recommendations, but no relevant data was submitted for assessment as the marketing authorisation holder concluded itself that the data is insufficient to conclude that the benefits outweigh the risks and proposed that the marketing authorisations for the parenteral formulations be revoked.

The CHMP endorsed a communication i.e. 'Dear Healthcare Professional Communication (DHPC)' to communicate the outcome of the present review.

Benefit–risk balance

The Committee concluded that the benefit-risk balance of tolperisone-containing oral formulations is positive under normal conditions of use only in the symptomatic treatment of post-stroke spasticity in adults, subject to the changes to the product information agreed.

The Committee also concluded that the benefit-risk balance of tolperisone-containing parenteral formulations is not positive, and recommends the revocation of the corresponding marketing authorisations.

Re-examination procedure

Following the adoption of the CHMP opinion and recommendations during the June 2012 CHMP meeting, re-examination requests were received from Gedeon Richter PLC and PP Nature Balance Lizenz GmbH, as they considered that there is adequate data supporting the efficacy of tolperisone in the "*treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases*" indication. The MAHs also disagreed with the CHMP assessment of the safety profile of tolperisone. Gedeon Richter PLC proposed to restrict the indication to "*Short-term treatment of muscle spasms in adult patients with acute non-specific low back pain*", with a maximum duration of treatment of 7 days.

The CHMP therefore carried out a new assessment of the available efficacy data in the concerned indication. In particular, the CHMP re-assessed 4 pooled analyses (Alken-2005, Farkas-2011, Varga-2011a and Varga-2011b) of randomised clinical trials (Pratzel 1995, Struck 2002 and Struck 2004) and requested the Biostatistics Working Party (BSWP) to give its view on the pooled analyses data. Having noted the BSWP assessment, the CHMP concluded that there are serious concerns regarding the appropriateness of the statistical methodology used for the pooled analyses, mainly because they have been based on fixed effects models in the presence of evident heterogeneity but in particular because the main grounds for the refusal of the evidence relate to the lack of compliance with the key criteria detailed in *the CHMP Points to consider* document (CPMP/EWP/2330/99). As a result, the CHMP considered that none of the provided pooled analyses could be considered as supportive to demonstrate the efficacy of tolperisone in the "*treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases"* indication, nor in the proposed restricted indication.

The CHMP also consulted its Neurology Scientific Advisory Group (SAG). The SAG stated that it did not consider the results of the 4 pooled analyses to be supportive of the efficacy of tolperisone. Overall, the SAG considered that the analyses has not been performed appropriately and that the provided data did not allow an assessment of how the various population and treatment characteristics were taken into account for the analyses. The SAG was also of the opinion that it is not possible to derive any conclusion regarding the efficacy of tolperisone, nor was it possible to identify any specific patient subgroups that could benefit from treatment with tolperisone compared to other treatments.

The CHMP also considered a recently conducted meta-analysis presented during the October 2012 oral explanation but raised concerns with regard to the methodology of the analysis and the quality of the included individual studies and therefore concluded that this meta-analysis did provide any additional support of the efficacy of tolperisone. The CHMP also noted the MAH proposal to conduct a clinical study to collect additional evidence of the efficacy of tolperisone in the proposed restricted low back pain indication, as a post-referral commitment, as well as the related draft study synopsis. However, the Committee considered the proposed study to be inadequate to provide conclusive evidence regarding the potential efficacy of tolperisone in the proposed indication, in particular due to the short treatment duration proposed.

With regard to the safety of tolperisone, the CHMP reviewed the available safety data and retained its previous conclusions that there is a risk of hypersensitivity reactions associated with tolperisone, with data showing that 10% of all reported cases of hypersensitivity were considered to be life-threatening. A causal relationship with tolperisone was assessed as at least possible in 90% of all hypersensitivity reactions.

Based on the totality of the data available on the safety and the efficacy of tolperisone and having noted the opinions of the BSWP and the SAG, the CHMP confirmed its initial conclusion that the risk of hypersensitivity is more significant than previously identified at the time of the initial marketing authorisation, and that as a consequence the benefits of tolperisone are outweighed by the risks in the indication *"treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases" as well as in the proposed restricted indication "short-term treatment of muscle spasms in adult patients with acute non-specific low back pain*".

The Committee therefore concluded that the benefit-risk balance of tolperisone-containing oral formulations is positive under normal conditions of use only in the symptomatic treatment of post-stroke spasticity in adults, subject to the changes to the product information agreed.

Grounds for the variation/revocation to the terms of the marketing authorisation

Whereas

- The Committee considered that the risk of hypersensitivity reactions is more significant than previously identified.

- The Committee is of the opinion that the evidence for clinically significant efficacy of tolperisone in the currently approved indications is extremely limited, and therefore the potential benefit for patients in these indications is outweighed by the identified risk.
- The Committee is also of the opinion that there is evidence of clinically significant efficacy of tolperisone in the symptomatic treatment of post-stroke spasticity in adults.
- The Committee therefore considered that the benefit-risk balance of tolperisone-containing oral formulations under normal conditions of use:
    - Is positive for symptomatic treatment of post-stroke spasticity in adults.
    - Is not positive for treatment of muscular hypertonicity and muscle spasms associated with locomotor disease.
    - Is not positive for rehabilitation after orthopaedic and trauma surgery.
    - Is not positive for treatment of obliterative vascular diseases as well as syndromes due to impaired vascular innervation.
    - Is not positive for Little's disease and other encephalopaties accompanied by dystonia.
- The Committee also concluded that, in the absence of relevant data to support the efficacy in the dosing recommendations approved, the potential benefit of tolperisone-containing parenteral formulations is outweighed by the identified risk of hypersensitivity.

The Committee, as a consequence, concluded that the benefit-risk balance of tolperisone-containing oral formulations is positive under normal conditions of use only in the symptomatic treatment of post-stroke spasticity in adults, taking into account the changes to the product information agreed.

The Committee also concluded that the benefit-risk balance of tolperisone-containing parenteral formulations is not positive, and recommends the revocation of the corresponding marketing authorisations.

Therefore, in accordance with Article 32(4)(d) of Directive 2001/83/EC, the CHMP recommended:

- The variation to the terms of the marketing authorisation for the oral formulations of medicinal products referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion.
- The revocation of the marketing authorisation for the parenteral formulations of medicinal products referred to in annex I.

The conditions affecting the marketing authorisations are set out in Annex IV.

The divergent positions are appended to this opinion.