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Assessment report for tolperisone-containing medicinal products

Procedure number: EMEA/H/A-31/1311

Referral under Article 31 of Directive 2001/83/EC

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



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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

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for medicinal products containing tolperisone, and associated names should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

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 of tolperisone is not fully known. The most prominent effect of tolperisone is its inhibitory action on pathways of spinal reflexes. It suppresses the mono and polysynaptic reflex transmission by both pre-synaptic and post-synaptic mechanisms.

Tolperisone 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 suppresses 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 encephalopathies accompanied by dystonia

On the basis of the information submitted by the different marketing authorisation holders, the posology for tolperisone was found to be the same in all Member States.

Film coated tablets 50 mg and 150 mg: the daily dose for adults is 150-450 mg, divided in 3 doses according to the individual needs and tolerance of the patient. Children: Under the age of 6 years: daily 5 mg/kg body mass, divided in three doses. Between the age of 6 to 14 years: daily 2-4 mg/kg body mass, divided in three doses.

Solution for injection (100 mg + 2.5 mg)/ml solution for injection can be given intramuscularly in 100 mg doses twice daily, or as a single 100 mg daily dose in slow intravenous injection. In children: solution for injection is contra-indicated.

Also based on the information submitted by the individual MAHs, the worldwide exposure to tolperisone between 1995 and 2010 was calculated to be approximately 6 260 957 patient-treatment years.

2.2. Clinical efficacy

The CHMP considered all available data submitted by the MAHs from clinical trials and observational studies, including data that became available since the granting of the initial marketing authorisation.

More than 80 clinical trials and observational studies have been conducted with tolperisone since its introduction into clinical practice in the 1960's. Very few of these studies were conducted according to the current medical standards and Good Clinical Practices (GCPs).

2.2.1. Results

Treatment of pathologically elevated skeletal muscle tone in organic neurological disorders

Pathologically elevated skeletal muscle tone, also referred to as spasticity, has been defined as an increase in muscle tone due to hyperexcitability of the stretch reflex and is characterised by a velocity-dependent increase in tonic stretch reflexes. The mechanisms underlying spasticity appear to involve not only the stretch reflex arc itself but also higher centres in the central nervous system with damage to descending pathways in the spinal cord resulting in hyperexcitability of alpha motoneurons in the cord. Spasticity is associated with some very common neurological disorders: multiple sclerosis, stroke, cerebral palsy, spinal cord and brain injuries, and neurodegenerative diseases affecting the upper motor neuron, pyramidal and extrapyramidal pathways. The degree of spasticity may vary from mild muscle stiffness to severe, painful, uncontrollable muscle spasms which may lead to permanent contractures that eventually result in posture and joint deformities. Spasticity can also result from a rare but intractable complication of the overconsumption of the seeds and foliage of *Lathyrus sativus*, a plant grown in Asia and Africa (neurolathyrism).

There are three GCP compliant controlled clinical trials with acceptable methodological standards that became available since the initial marketing was granted:

Pongratz & Stamenova (2000) / Stamenova et al. (2005) [Stamenova P.; Koytchev R.; Kuhn, K. et al.: *A randomized, double-blind, placebo-controlled study of the efficacy and safety of tolperisone in spasticity following cerebral stroke*. *Eur J Neurol* 12 (6), 453-461 (2005)]: This placebo-controlled, randomised clinical trial included a total of 120 patients (18-75 years) with central muscular spasticity due to cerebral stroke¹. Patients were randomly allocated to receive tolperisone 50 mg TID PO (60 patients) up-titrated up to 900 mg daily if necessary (titration period of 4 to 20 days) or placebo (60 patients) for a treatment duration of 12 weeks. Primary endpoint was the change in spasticity scores (Ashworth scale) at end of treatment versus baseline. The capacity to perform routine movements, the modified Barthel index, and the overall assessment of efficacy served as secondary endpoints.

In this trial 3 patients in the tolperisone group finished the study with 3x2 tablets (300 mg), 16 patients with 3x3 tablets (450 mg which is according to the currently approved posology), 27 with 3x4 tablets (600mg), 1 with 3x5 tablets (750 mg) and 9 with 3x6 tablets (900 mg). Correspondingly, 600

¹ Cerebral stroke more than 2 months prior to study inclusion; degree of spasticity of at least 2 on Ashworth scale in at least one joint region.

mg tolperisone daily was the most common dose, while 15% of the patients were treated even with 900 mg/day. Dose-effect correlation analyses failed to establish a clear relationship between titrated final dose and clinical response, and between final dose and baseline symptom intensity. Tolperisone was significantly superior to placebo in alleviating post-stroke spasticity ($p < 0.0001$; PP and ITT population). Forty-seven patients in the tolperisone group (78.3%) experienced a clinically relevant improvement (at least 1-point reduction in spasticity degree) compared to only 27 patients (45%) on placebo.

The most important finding of this study was the statistically highly significant improvement in spasticity (as measured by the Ashworth scale) after tolperisone compared to placebo. These results were found both in the ITT and the PP population. Moreover, all secondary parameters revealed the same tendency for superior efficacy of tolperisone over placebo.

Table 1: Percent changes on the Ashworth Scale at 4-6 weeks in the Pongratz study. Note that the clinical relevance threshold is at about 33 % (VanDenburgh 2008).

Population	Percent improvement from baseline in the Ashworth score (Pongratz study)				Statistical comparison between groups
	tolperisone		placebo		
	mean	95% CI	mean	95% CI	
ITT	31,66%	26,4 – 36,93%	14,35%	9,81- 18,88%	p < 0.001
PP	30,94%	25,33- 36,55%	13,76%	9,18- 18,35%	p < 0.001
ITT, patients on 150-450 mg/day (3x1 – 3x3 tablets daily)	41,66%	32,96- 50,36%	18,42%	10,89- 25,94%	p < 0.001
PP, patients on 150-450 mg/day (3x1 – 3x3 tablets daily)	41,14%	31,90- 50,38%	19,11%	10,99- 27,24%	p < 0.001

Fehér et al. (1985) This actively-controlled, randomised clinical trial included a total of 48 patients with spastic hemiparesis and fully developed spasticity due to cerebral lesions. 24 Patients received 150 mg tolperisone TID PO, 20 of which were included in the efficacy analysis, and 24 patients received 25 mg baclofen TID PO for 6 weeks, 18 of which were included in the efficacy analysis. Efficacy endpoints were changes in the Rivermead Motor Assessment Scale for the evaluation of global functions and mobility and the Barthel index for determination of self-reliance in daily living activities. Improvement observed on the Rivermead and the Barthel scales was higher in the tolperisone (3 x 150 mg) group compared to the baclofen (3 x 25 mg) group, the difference being statistically significant for the Rivermead scale.

Melka et al. (1997) this double-blind, placebo controlled, monocenter study included 72 patients with spasticity caused by neurolathyrism. Several efficacy parameters were assessed by the physician and the patients, none of which is specified as primary efficacy parameter in the publication. After 12 weeks of treatment with 300 mg tolperisone daily (divided in two single doses) and placebo, respectively, efficacy results showed significant reduction of spastic muscle tone in the adductors ($p = 0.001$) and achilles ($p = 0.004$) in the tolperisone treatment group as measured by the Ashworth Scale. These were accompanied by significant improvements in walking ability (physician's and patients' assessments with $p = 0.000001$ and $p = 0.001$, respectively), walking speed, power in the legs, ankle clonus, flexor spasms and significant overall subjective improvement. Patients in the active treatment group reported significantly less falls compared to the placebo group. Patients with severe symptoms at baseline had only modest improvement which was not statistically significant.

A further study was conducted with the primary objective of showing the safety of tolperisone in patients with spasticity caused by multiple sclerosis:

Avigen Study AV650-018 (2007) (A two-part (double-blind followed by open-label), placebo-controlled, randomized trial to assess the safety, tolerability (primary objectives), and preliminary efficacy (secondary objective) of AV650 (tolperisone hcl) in subjects with spasticity associated with multiple sclerosis) was prematurely terminated after results of an interim analysis became available. The primary objective of this study was to assess the long-term safety and tolerability of daily doses of 450 and 900mg Tolperisone HCl, respectively.

During the first part patients had been randomized into one of three treatment groups (placebo, tolperisone 450 mg, tolperisone 900 mg). Patients were dose titrated within 7 days and then kept on that dose level for further 4 weeks. Thereafter a second open label treatment phase was planned,

during which all patients would have been treated with tolperisone. 165 patients were randomized into the study (placebo = 55, tolperisone 450 mg = 58, tolperisone 900 mg = 52). 150 patients (ITT population) completed Visit DB 3 (end of double blind treatment phase, placebo = 48, tolperisone 450 mg = 54, tolperisone 900 mg = 48).

According to the abbreviated study report the main secondary efficacy endpoint, change from baseline in Ashworth score at Week-5, failed to achieve statistical significance (p values >0.6) for AV650 450 mg (-0.7 ± 0.83 , Mean $\pm$ SD) or 900 mg (-0.7 ± 0.93) as compared to placebo (-0.6 ± 0.79). Further efficacy endpoints also failed to show efficacy of tolperisone on spasticity or pain in multiple sclerosis patients.

Treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases

This indication covers muscle spasms that occur in response to local trauma or musculoskeletal and joint disorders such as spondylosis, spondylarthrosis, cervical and lumbar syndromes and arthrosis. Reflex muscle spasms produces muscular rigidity and acts as a protective mechanism to prevent movement of an inflamed or damaged joint. Increased spinal reflex activities lead to painful muscle contraction, which can result in reduced blood flow, further contributing to pain, movement limitation and intensified muscle tension.

There are four placebo-controlled clinical trials that followed GCP requirements and which became available after the initial marketing authorisation was.

Pratzel et al. (1995) [Pratzel, H. G.; Alken, R. G.; Ramm, S.: *Efficacy and tolerance of repeated oral doses of tolperisone hydrochloride in the treatment of painful reflex muscle spasm: results of a prospective placebo-controlled double blind trial. Pain* 67, 417-425 (1996)]: This placebo-controlled, randomised clinical trial involved a total of 137 patients with painful reflex muscle spasm associated with diseases of the spinal column or the proximal joints. Patients received tolperisone 100 mg TID PO or placebo for 21 days. The majority of patients (34 patients on tolperisone and 31 patients on placebo) were also treated with standardised physiotherapy. Primary endpoint was calculated from the change in pressure pain threshold (PPT) at point of maximum pain, complemented by 16 standard pressure points. Secondary parameters were Clinical Global Impression (CGI), patients' symptoms assessment (pain, restriction of mobility, muscle tension), joint mobility, manual palpation findings, and global efficacy assessment by patient and investigator. During the 3-week rehabilitation programme, both treatment groups recovered. The average PPT increase at day 21 was 74.3% in the tolperisone arm and 48.5% in the placebo arm, with a between group difference of 25.8%. No significant differences were seen in the evaluation of the secondary parameters, with CGI showing a non-significant trend in favour of the active substance (mean placebo-corrected CGI-S score change at the final visit was -0.21).

Struck (2002) This randomised, double-blind, placebo controlled study included 194 patients with high or low back pain due to painful reflex muscle spasm of different origins (degenerative, traumatic, inflammatory). Patients received tolperisone 150 mg TID PO titrated up to 900 mg daily if necessary, or placebo for 10 to 12 days after titration. Concomitant NSAIDs needed to remain constant and physiotherapy was standardised. The primary efficacy endpoint was PPT at the maximum pain point. Secondary endpoints were mean pressure pain threshold, pain intensity, pain at movement and reduced motility, muscle spasm at palpation, the Hannover Questionnaire, CGI, and rating of efficacy by patient and investigator (Likert scale). Superiority of tolperisone regarding the primary efficacy parameter in the ITT population was not demonstrated ($p=0.27$). The only efficacy parameters for which statistical significance was reached were the 'global improvement' ($p=0.03$) and the 'therapeutic effect' ($p=0.01$) components of the CGI.

Struck (2004) This placebo-controlled, randomised clinical trial included a total of 248 patients with high or low back pain due to painful reflex muscle spasm of different origins (degenerative, traumatic, inflammatory). Patients received tolperisone 600 mg daily (TID) PO (starting dose for 4-5 days), up- or down titrated up to 900 mg or 450 mg daily, if necessary, or placebo for 3 weeks, subsequent to titration. Concomitant NSAIDs were not allowed, and physiotherapy required standardisation. Primary efficacy endpoint was PPT at the maximum pain point. Secondary endpoints were pain intensity, pain at movement and reduced motility, muscle spasm at palpation, the Oswestry functional questionnaire, grip strength, and rating of overall efficacy by patient. In the majority of patients, pain was localised in the low back region. Both treatment groups showed improvement at the end of the study. Superiority of tolperisone regarding the primary efficacy parameter in the ITT population could not be

demonstrated. A post-hoc subgroup analysis markedly/severely ill patients indicated that tolperisone was superior to placebo in PPT enhancement.

Hodinka (2001) This placebo-controlled, randomised clinical trial included 279 patients with acute uncomplicated low back pain. Patients received tolperisone 150 mg TID PO or placebo over 14 days. Non-study interventions to alleviate low back pain were not allowed, including non-pharmacological interventions. The primary efficacy endpoint was change in pain (visual analogue scale [VAS]). Secondary endpoints were functional status (Roland-Morris Disability Scale), number of days of work absenteeism, global rating of efficacy by patient, global assessment of patients' condition by investigator, range of motion, and quantity of rescue analgesic (paracetamol) consumption. No relevant difference was seen between tolperisone and placebo treated patients with respect to the primary efficacy parameter. A transient significant difference was seen in the Roland-Morris Disability Scale at day 7 ($p=0.034$), which disappeared at day 14.

Rehabilitation after orthopaedic and trauma surgery

Muscular tension, muscular hypertonia, contracture and spasticity are the most commonly occurring postoperative symptoms after trauma operations, partly due to the restored or altered anatomy of the operated region, and partly due to long immobilization. The basic components of postoperative therapy include physiotherapy, curative gymnastics and drug therapy.

The data available on this indication comes from two observational studies with a total of 166 patients, where 450 mg tolperisone were given daily for a few weeks.

Huber 1986 An observational study was performed with tolperisone 450 mg daily dose. Although the conditions in which tolperisone therapy were indicated are quite heterogeneous, 29 patients from the 93 patients enrolled to the study took the medicine as postoperative treatment of traumatologic and orthopaedic operations on the extremities. The other indications were arteriosclerosis obliterans, leg ulcer, and functional myogenic spasm after thermal trauma. Due to the heterogeneity of conditions in many cases, tolperisone was not used in monotherapy although other muscle relaxant agents had not been prescribed to these patients. Efficacy evaluation was based on the following clinical parameters: improvement of muscular function, relaxation of tense musculature and reconstitution of limited articular motion as well as subjective judgements of symptoms. The author concluded that tolperisone treatment given during the 1-6 weeks rehabilitation program could result in a reduction of muscle spasm and rigidity, improvement of articular function and function of the extremities.

Dömötör 1989 A study was performed to evaluate the effectiveness of tolperisone in postoperative rehabilitation. During a two year period, patients who had developed immobility after a variety of diagnoses were recruited into the study and relief of postoperative muscular hypertension, contracture, spasticity and improvement of limited motion were analyzed. A total of 73 patients were treated with the drug on 3x150 mg average daily dose, used for several weeks according to requirements. The majority of the pathological alterations was localized in the lower extremities. Oral tolperisone therapy was used as postoperative treatment in parallel with gymnastics, in the majority of cases following the neurosurgical operation of genicular alterations. A high number coxarthrosis patients (orthopaedic surgery) were also treated, especially those with prolonged and eventful postoperative period. In the course of examinations, the parameters of locomotor functions were recorded and tolerance of the drug was observed. Changes of the most important parameters were scored, such as improvement of articular movement measured in degrees, decrease of articular volume, changes of intensity of pain, performance of curative physical exercise and shortening of postoperative therapeutic period compared to the average (not treated with tolperisone) duration.

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

Vascular indications include peripheral arterial disease, diabetic angiopathy, thrombangiitis obliterans, Raynaud's disease as well as syndromes developing on the basis of impaired vascular innervation (acrocyanosis, dysbasia angioneurotica intermittent).

Very limited information exists on the efficacy of tolperisone in this indication. There are no GCP-compliant studies, there is 1 actively-controlled trial (using pentoxifyllin as control) and a few observational studies. The actively-controlled trial is briefly discussed below.

Hoffmann 1980 In this study, Hoffmann et al evaluated the effect of 100 mg oral tolperisone (Mydocalm) t.i.d. versus 200 mg pentoxifylline t.i.d. in a prospective, open-label, parallel-group, randomized study. The recommended dose of tolperisone was 3x100 mg daily, although it could be

varied between 2x100 mg to 3x200 mg daily, depending on the severity of the condition. This study involved 70 patients suffering from obliterative peripheral arterial diseases (mainly Fontaine's stages I and II). The duration of the treatment was 6 weeks. In the tolperisone group the increase of claudication distance was greater than that of pentoxifylline group as evaluated by a standardized walking test.

Clinical symptoms were also recorded: cold sensation, paraesthesias, acrocyanosis and cutis marmorata tended to improve similarly in both treatment groups. However, pain at rest responded better to tolperisone than to pentoxifylline. The investigators concluded that Doppler measurements on the arteria tibialis posterior and arteria dorsalis pedis demonstrated an unequivocal improvement of the blood flow in both groups, both before and after loading; with no difference between the tolperisone and pentoxifylline group.

Little's disease and other encephalopathies accompanied by dystonia

Very limited information exists on the efficacy of tolperisone in this indication. There are only 3 observational studies which are briefly described below.

Kiss et al. 1967 An observational study conducted by in 1967 involved 120 children with organic cerebral damage and cerebral dysfunction of different aetiology, exhibiting no severe neurological findings. Inclusion criteria were head injury with or without loss of consciousness, cerebral atrophy, organic cerebral lesion, cerebral hypoxia, prematurity/small birth weight, dystrophy, meningitis, infectious disease, epilepsy (tolperisone as adjuvant), paroxysmal atypical attacks without loss of consciousness, nocturnal enuresis, neurotic reaction, behavioural disorder, irritability / hypermotility, learning difficulties, impaired memory and attention, speech disorder, headache, vertigo, and sleep disorder. 72 boys and 48 girls aged 2-17 years were treated with orally administered tolperisone. The duration of treatment varied between 360 days and less than 30 days. 2 patients received tolperisone for 360 days, 10 patients for 200-300 days, 31 patients for 100-199 days, 68 patients for 30-39 days and 9 patients for less than 30 days. The daily dosage ranged between 150 mg and 600 mg. The most frequent dose was 3x100 mg/day. 1 patient received 600 mg/day, 21 patients received 450 mg/day, 92 patients received 300 mg/day and 5 patients received 150 mg/day. Although the patient population was rather heterogenous, in 21 patients (18%) freedom of symptoms or very marked improvement could be achieved, 87 patients (72%) symptoms improved while for 12 patients (10%) symptoms remained unchanged.

Blazsó 1962 Blazsó et al performed an observational study on 72 paediatric patients (from 6 months to 15 years) with different neurological diagnosis accompanied by disturbance of motor function (due to dystonic or hypotonic musculature). 40 patients had cerebral palsy and 16 patients had central nervous impairment following meningo-encephalitis and 30 of all these patients had dystonia and partly spastic musculature. They received 5-15 mg/kg/day doses of tolperisone as well as physiotherapy. Even though the population of the study was not homogenous with different diseases involved with variable impact of tolperisone on muscular tonicity, the authors concluded that tolperisone exercised a beneficial influence of tolperisone on encephalopathies of various origin accompanied by dystonia, rigidity and spasms.

Peja 1998 Peja et al presents the data of a total of 50 children with infantile cerebral palsy receiving complex rehabilitation treatment in a department for paediatric rehabilitation. Thirty-five patients had spastic tetraparesis, 9 had spastic hemiparesis and 6 had paraparesis (mean age 8 years old). The dose of tolperisone was gradually increased; the average starting dose was 4.9 mg/kg/day, while the average maintenance dose amounted to 6.0 mg/kg/day. The clinical improvement, changes of muscle spasticity accompanied to cerebral palsy was evaluated with a modified Ashworth's scale (The Modified Ashworth Scale is considered the primary clinical measure of muscle spasticity in patients with neurological conditions.)

The motility of children showed significant, moderate, or slight improvement in 30, 24 and 32% of the cases, respectively, and remained unchanged in 14%. The Ashworth score had a tendency to decrease and the changes became significant ($p < 0.001$) by the 3rd week. The effect was more pronounced on the side of worst spasticity. Adverse reactions were reported as not severe, the most frequent being sleepiness, tiredness, muscular weakness and dizziness. The intensity of these adverse reactions decreased as the treatment proceeded or they disappeared, thus there was no need to interrupt the treatment for any child.

2.2.2. Discussion on 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 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 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 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, 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. Neurolathyrism 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), 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 as per the specified analysis plan. 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 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.

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 pentoxifyllin as control and involved a total of 70 patients.

Little's disease and other encephalopathies 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.

2.3. Clinical safety

The MAHs submitted their own overviews and critical summaries of all spontaneous adverse events observed with tolperisone-containing products. Information from clinical trials was also analysed.

2.3.1. Results

Post marketing spontaneous data

Hypersensitivity reactions account for more than half of the spontaneous reports in the originators database, followed by adverse drug reactions (ADRs) from the SOC Gastrointestinal disorders, General disorders and administration site conditions and Nervous system disorders.

The most frequently reported hypersensitivity related ADRs were hypersensitivity (6.3% of all reports), urticaria (5.1%), pruritus (4.8%), dyspnoea (4.2%), angioedema (3%), erythema (2.6%), rash (1.8%) and anaphylactic reaction / anaphylactic shock (1.6%/1.2%).

About 10% of all cases were considered life-threatening and the majority of these cases concern hypersensitivity. No fatal reports related to hypersensitivity reactions were observed. There was a single case with a fatal outcome following a suicidal overdose of tolperisone and concomitant alcohol consumption.

Causal relationship with tolperisone was assessed as at least possible in 90% of all hypersensitivity reactions. Positive dechallenge was noted in 23.2% of all hypersensitivity cases, positive rechallenge in 5.6% and both in 3%.

77% of patients experiencing hypersensitivity were between 18 and 65 years of age, 7% were > 65, 1% < 18 and in 15% age was not reported. The data show a significant predominance of female patients for the hypersensitivity reactions. This could either be attributed to the pattern of usage, or could reflect an increased risk for hypersensitivity in female patients.

Approximately 15% of patients experiencing hypersensitivity to tolperisone had at least one allergic episode in the medical history, or had an allergy at the time of the drug intake. In approximately 24% of patients with life-threatening hypersensitivity reactions, drug-induced hypersensitivity or allergic reaction was described in the medical history. This is suggestive of an increased risk for hypersensitivity in patients with a history of drug hypersensitivity to other substances.

Time to onset was within one day or less in about 50% of the hypersensitivity cases where time to onset was reported.

A third of the hypersensitivity reactions were confounded by the presence of a relevant concomitant agent frequently causing hypersensitivity reactions (mostly NSAIDs).

The spontaneous reporting rate since 1995 for the originator product was calculated as 0.02/100.000 patient days for all ADRs and as 0.01/100 000 patient days for hypersensitivity reactions. The reporting rates were significantly higher in Germany (0.14 and 0.08/100 000).

The pattern of non-hypersensitivity ADRs was in line with the known safety profile of tolperisone. No new safety signals could be detected. As in most cases the indication was either unknown or locomotor diseases, no conclusions can be drawn on the frequencies of ADRs in relation to the different indications.

WHO Vigibase reports

A total of 1714 cases involving tolperisone with a total of 3354 reported AEs were analysed (clinical trial data excluded).

The majority of ADR were reported from Thailand (68.4%) and Germany (14%).

The most frequently reported SOC is Skin and subcutaneous tissue disorders (50.2 % of all AEs) followed by Gastrointestinal disorders, General disorders and administration site conditions and respiratory, thoracic and mediastinal disorders. The most frequently reported reactions are pruritus (13.1 %), rash (11.7 %) and urticaria (7.7%). There were 58 reports of anaphylactic shock (1.7 %).

Hypersensitivity reactions represent 65.1% of all the reports based on the relevant MedDRA SMQs.

There were 3 fatal and 17 life-threatening cases. None of the 3 fatal cases were related to hypersensitivity reactions. Fourteen (14) of the 17 life threatening cases were associated with hypersensitivity.

Clinical trial data

In the five most recent placebo-controlled phase III studies (Pratzel 1995, Truck 2002, Struck 2004, Hodinka 2001, Pongratz/Stamenova 1999-2001) conducted in the locomotor and neurologic indications, 479 patients were exposed to tolperisone, 227 of which received 600 mg or higher doses (up to 900 mg) daily. There were 105 tolperisone-related adverse drug reactions reported, of which 7 serious, and no life-threatening or fatal reports.

Two SOC's covered about two-thirds of the total number of ADRs: Gastrointestinal disorders (48 non-serious and 2 serious ADRs) and Nervous system disorders (20 non-serious and 2 serious ADRs).

No significant difference was found between the two major indications (locomotor diseases (4 studies) / neurological spasticity (1 study) with regard to safety. No serious hypersensitivity concern was raised. Hypersensitivity was observed in 4 patients (0.8 %). All reactions were allergic skin reactions, and one was rated as serious.

A systematic literature analysis of 111 relevant publications (including controlled and uncontrolled/observational studies but excluding case reports which are processed as spontaneous reports in the MAHs' safety databases) evaluated adverse event data from 12 008 exposed patients, and 1280 ADR were identified.

The five most affected SOCs (81% of reports) and ten most frequently experienced reactions with tolperisone were: General disorders and administration site conditions (fatigue, injection site warmth, asthenia, injection site joint redness), Nervous system disorders (dizziness, somnolence, headache), Gastrointestinal disorders, Skin and subcutaneous system disorders (hyperhidrosis, skin reaction), Musculoskeletal and connective tissue disorders (myalgia).

In total 82 ADRs which could be associated with hypersensitivity reactions were identified: skin reactions (39), dyspnoea (3), dermatitis allergic (8), generalized erythema (1), prurigo/pruritus (6), rash (13), urticaria (4) and flushing (6).

Of the 12008 patients, 5130 were included in a single prospective, observational, open-label study (MD 35.22, Germany, 1999, 150-450 mg per day, recommended treatment duration: 3 weeks). One hundred and thirty-nine (139) non-serious adverse reactions were reported, but there was no serious adverse reaction. A total of 11 non-serious hypersensitivity-related adverse reactions were observed (allergic dermatitis (7), pruritus (2), eye swelling (1), flushing (1)). A slightly higher rate of reactions was noted in patients with renal or hepatic disease.

Interactions

An *in vitro* CYP inhibition study in human liver microsomes was conducted recently and found that the *in vitro* inhibitory potential of tolperisone on CYP2B6, CYP2C8 and CYP2C19 was either not detectable or negligible. Accordingly, the possibility of drug-drug interaction on these CYP isoenzymes is considered highly unlikely. The lack of inhibition of CYP2C9, CYP1A2 and CYP3A4 has been previously published (Dalmadi 2003).

Similarly, the potential of tolperisone to induce the CYP1A2, CYP3A4 or CYP2B6 isoforms was also tested *in vitro* on human hepatocytes. Based on the results, tolperisone is not considered to be an inducer of the CYP1A2, CYP3A4 and CYP2B6 enzymes *in vitro*. Moreover, based on our knowledge of cellular mechanisms leading to CYP enzyme induction, as tolperisone is not an inducer of CYP3A4 it also can be concluded that it is not an inducer of CYP2C8, 2C9 and 2C19 either.

Effects on ability to drive and use machines

Tolperisone is a centrally-acting compound, and data from both spontaneous reports and clinical studies indicates that adverse events in the Nervous System disorders SOC have been consistently reported, amongst which somnolence/dizziness. Therefore it is possible that tolperisone influences the ability to drive and use machines, and it cannot be excluded that it potentiates the effects of alcohol and other centrally-acting medicinal products.

Safety in patients with renal and/or hepatic impairment

Tolperisone is metabolised extensively, and both drug and its metabolites are excreted almost entirely (approx. 98%) through the kidneys. Such properties indicate that in case of renal impairment the elimination of tolperisone metabolites may be limited, and consequently exposure may be increased in case of renal impairment.

No studies were ever performed aimed at investigating the pharmacokinetics and safety of tolperisone specifically in patients with impaired renal or liver function. In the observational study from Strathmann AG (1999), 110 patients (2.1%) were documented as having had renal disease, and 218 (4.2%) were documented as having had hepatic disease. In this study, the most common adverse reactions were fatigue (n=46) and gastrointestinal complaints (n=37). Patients suffering from renal or hepatic disease with pathological laboratory value deviations (creatinine, creatinine clearance, transaminases, GGT) showed a 2-3 times higher incidence of adverse events than patients with normal laboratory values (6.4% vs. 2.6%).

The number of spontaneous reports of adverse reactions in patients where renal or hepatic impairment is mentioned is very low, and although it does not raise cause for concern, it also does not allow drawing firm conclusions on the safety of tolperisone in this patient population.

Effect of food on pharmacokinetic parameters

At the time tolperisone was first developed, no recommendations regarding the influence of food were available.

Later studies conducted by two different MAHs demonstrated that, compared to the fasting state, fat-rich food increases the bioavailability of tolperisone by about 100%. As this conclusion is based upon results of two well-designed studies conducted with different formulations of tablets, it seems to be a characteristic of the active substance rather than the formulation.

The extent of the food effect is not a serious concern because clinical data are available from at least seven clinical studies where patients were instructed to take tolperisone after food. Based on general biopharmaceutical principles, it might be presumed that the effect of a light meal is somehow less than the effect of standard fat-rich breakfast used in the comparative kinetic trials. Thus, the 100 % figure can be considered as an upper limit. Another important observation is that food increases C_{max} only to a minimal extent. This might be explained by a higher extent of absorption associated with a lower absorption rate and these two effects partly or fully compensating each other. Overall, taking tolperisone tablets with food is appropriate because tolperisone has a very short half-life (1.5h) and fat-rich food seems to prolong the absorption with minimal impact on C_{max}.

Other adverse events

During the review of the product information approved for the different products, it was noted that some products fail to reflect the possibility of occurrence of confusion (very rare) and hyperhidrosis (rare).

Parenteral formulations

Medicinal products containing tolperisone as solution for injection are currently authorised in the following Member States: Hungary, Latvia, Lithuania, Poland, Romania and Slovak Republic. It is well known that the safety profile of a product may vary depending on the formulation, and therefore the company that holds these marketing authorisations was asked to submit any existing data in support of its safety and dosing recommendations. In the response, the marketing authorisation holder of the parenteral formulations concluded itself that the data is insufficient to conclude that the benefits outweigh the risks and that the marketing authorisations for the parenteral formulations should be revoked. No relevant data was submitted for assessment. 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.

2.3.2. Discussion on clinical safety

While no fatal cases of hypersensitivity reactions were 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.

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.

Parenteral formulation

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.

2.4. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

The CHMP, having considered the data submitted, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.5. Overall benefit/risk assessment

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

While no fatal cases of hypersensitivity reactions were 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.

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.

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.

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 encephalopathies 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 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.

Due to lack of adequate data on the safety of tolperisone in patients with renal impairment and patients with hepatic impairment, no conclusions on the influence of renal or hepatic function can be drawn. In order to improve knowledge of the product in these patient populations, the CHMP considered that it can be of interest that the MAHs conduct appropriate studies to further investigate the safety of tolperisone in these patient populations.

2.6. Re-examination procedure

Following the adoption of the CHMP opinion and recommendations during the June 2012 CHMP meeting, re-examination requests were received from two of the MAHs involved in the procedure, Gedeon Richter PLC and PP Nature Balance Lizenz GmbH, on 13th and 12th of July, respectively. The scope of the re-examination was limited to the benefit-risk of tolperisone in the deleted indication *"treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases"*.

It is noted that the CHMP is a scientific committee and that while it operates within the legal framework, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the CHMP, and therefore the re-examination of the referral procedure under Article 31 of Directive 2001/83/EC focused only on the scientific grounds for re-examination.

Detailed grounds for re-examination submitted by the MAH

The MAHs considered that there is adequate data supporting the efficacy of tolperisone in less-chronic patients and in low back pain. In particular, Gedeon Richter PLC stated that 4 pooled analyses (Alken-2005, Farkas-2011, Varga-2011a and Varga-2011b) – hereinafter referred to as 'the 4 pooled analyses' - of three positive and negative randomised, placebo-controlled, GCP-compliant studies conducted in the "painful muscle spasm with locomotor disease in adults" indication (Pratzel 1995, Struck 2002 and Struck 2004) were not taken into account when the CHMP initially assessed the indication. The MAH considered that pooled analyses can be of great importance when multiple studies are available with negative results, which is the typical case with centrally acting muscle relaxants, including tolperisone.

The MAHs also disagreed with the CHMP assessment of the safety profile of tolperisone and the conclusion that the risk of hypersensitivity reactions is more significant than previously identified. The MAHs argued that the concern about the hypersensitivity signal was assessed in 2004, resulting in the update of the Product Information of tolperisone-containing medicinal products and that since then, no increased frequency or severity of hypersensitivity reactions have been observed. The MAHs were of the opinion that the risk of hypersensitivity is not more significant than previously identified, and that serious hypersensitivity reactions are very rare with tolperisone. The MAHs also considered that tolperisone has several safety advantages over other muscle relaxants.

The MAHs therefore considered that the benefit-risk balance of oral tolperisone in the indication *"treatment of muscular hypertonicity and muscle spasms associated with locomotor disease"* is

positive. Gedeon Richter PLC also 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.

CHMP conclusion on grounds for re-examination

The CHMP confirmed that it had considered the totality of the data submitted by the MAHs in the context of the initial referral procedure, including non-controlled studies and bibliographic data, including the 4 pooled analyses referred to in the grounds for re-examination. However, the majority of this data was considered to be inadequate from a scientific point of view and was therefore not considered to be critical to the assessment of the efficacy of tolperisone. The CHMP assessment focused mainly on the four randomised placebo-controlled studies (Pratzel 1995, Hodinka 2001, Struck 2002 and Struck 2004) which complied with GCP requirements. In the context of the re-examination, the CHMP carried out a new assessment of the available data on the efficacy of tolperisone in the concerned indication. In particular, the CHMP addressed the point of the 4 pooled analyses, which had been submitted as part of the MAH responses during the referral procedure and assessed by the CHMP. However, the CHMP considered them to be of inadequate quality and therefore not supportive of the efficacy of tolperisone in the indication “*treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases*”. In the context of the re-examination procedure, the CHMP carried out a new assessment of the available efficacy data, in accordance with the procedural advice on the re-examination of CHMP opinions. In particular, the CHMP requested the Biostatistics Working Party (BSWP) to give its view on the methodology and the results of the 4 pooled analyses.

The BSWP assessed the 4 pooled analyses and noted that they covered two endpoints: Pressure Pain Threshold (PPT), which was the primary parameter of the studies and the Clinical Global Impression (CGI), a secondary parameter which appears to be preferred by a recent Cochrane review. They also covered both full analysis (FAS) and per protocol (PP) subsets and analysed the overall population as well as the subgroup of patients with high baseline CGI (“markedly ill” or “worse”). The PPT variable was analysed using different approaches in the individual clinical trials (i.e. absolute difference, relative change and AUC) and the pooled analyses considered all of them.

The BSWP noted the key requirements described in the *CHMP Points to Consider document on Application with 1.) Meta-analyses and 2.) One Pivotal study* (CPMP/EWP/2330/99) and reviewed the methodology used for the four analyses. Alken (2005) used an analysis of covariance (ANCOVA) model to analyse PPTDiff and AUC values with the factors treatment group, study, the treatment group by study interaction term and, the baseline value of PPT. Varga (2011a) analysed the same studies included in Alken (2005) but used the PPTPCT (absolute change) variable. Varga (2011b) used the same methodology as the two previous pooled analyses (Alken 2005 & Varga 2011a), but conducted on the subgroup of patients with high baseline CGI (“markedly ill” or “worse”). Farkas (2011) assessed CGI with component of “severity of illness” between the first and last visits as main outcome, using a Mantel-Haenszel random effects model to estimate the pooled risk ratio (RR) and the 95% confidence interval.

Assessing the methodology, the BSWP considered that there were serious concerns regarding the appropriateness of the statistical methodology used for the analysis of the main outcome: PPT baseline difference, (PPTDiff), relative change of PPT (PPTPCT) and AUC of PPT (AUC). In the ANCOVA model (Alken 2005), there was evidence of heterogeneity (i.e. statistical significance of the treatment-by-study interaction term at the 10% level) for the main time point at 21 days with the main population set (FAS). The main issue was the use of fixed effects models, which is not acceptable in the current scenario with heterogeneity, instead a random effects model should have been used. Although the analysis conducted in the more severe subset of patients (Varga, 2011b) did not show evidence of heterogeneity for the 3 variables on the PPT (PPTDiff, PPTPCT & AUC), this may be due to the lack of power of the heterogeneity test or because only two of the three trials were included. In addition, the use of 3 different approaches (PPTDiff, PPTPCT & AUC) to analyse the same variable (PPT) leads to an issue of multiplicity, particularly given the *post hoc* setting.

Assessing the results, the BSWP noted that the forest plot confirmed a potential heterogeneity problem but a quantification of the heterogeneity was only possible through the review of the individual pooled reports. For PPTDiff, PPTPCT & AUC, an inverse correlation of the effect size with the sample size was also identified. Only the Pratzel (1995) study (the oldest one with the smallest sample size) is positive. Of note, the other two are negative, and particularly, the newest trial with the larger sample size is the most negative suggesting a detrimental effect (although non-significant). The correlation of the effect size with the study size and age of the study might be related to changes in either the type of patients or the study quality. None of these points appear to be identified or discussed by the MAH. Regarding

the CGI responder analysis, the BSWP noted that although the statistical method used to estimate the pooled risk was considered adequate, there was a serious concern of bias given that 20 patients in the tolperisone group and 18 patients on placebo from the FAS population (Tolperisone: n=282; Placebo: n=288) were excluded, without justification or detailed description on the handling of missing data. The results can therefore not be considered valid. All primary trials were negative for this *post hoc* endpoint. Finally, and more importantly, the criteria describing the prerequisites for a retrospective meta-analysis to provide sufficient evidence for a claim were not met: (a) some studies clearly positive, (b) no statistically significant heterogeneity, (c) inconclusive studies showing positive trends in the primary variable and (d) pooled 95% confidence interval well away from the null. In particular, the lack of fulfilment of points (a) and (d) is obvious and critical.

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 of the main outcome, mainly because they have been based on fixed effects models in the presence of evident heterogeneity which prevents to draw conclusions on the efficacy of tolperisone in the indication "*treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases*". However, the main grounds for the refusal of the evidence from these retrospective analyses for a regulatory claim 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), to receive advice on a number of questions. In particular, the adequacy of the 4 pooled analyses of the placebo-controlled randomized clinical trials was discussed. The SAG acknowledged that PPT is a validated tool for measuring chronic pain and suggested that it could also be used in acute pain, if used together with a pain intensity scale or a numerical rating scale 0-10 and a functional or disability scale. The use of the S-score in acute pain was not endorsed. However, the SAG stated that it did not consider the results of the pooled analyses to be supportive of the efficacy of tolperisone. Overall, the SAG considered that the pooled analyses had not been performed appropriately. There were many other tolperisone-studies which were not included in the analyses and other data from studies investigating other patient population than stroke patients are not available. In addition, only one of the included studies was considered to be contributing as the other studies were not supportive. The SAG also noted that out of the included studies, the more recent study by Struck 2004, which included a larger number of patients, was negative, which is of concern. Finally, the provided data did not allow an assessment of how the various population and treatment characteristics were taken into account for the analyses (underlying pathology, treatment dosage, length of treatment...). The SAG was also of the opinion that it is not possible to derive any conclusion regarding the efficacy of tolperisone in the proposed restricted indication based on data from studies in CNS conditions, nor was it possible to identify any specific patient subgroups that could benefit from treatment with tolperisone compared to other treatments.

Finally, the CHMP considered the data presented by the MAHs during the oral explanations held on 17 October 2012. In particular, the MAH presented results from a recently conducted meta-analysis using studies conducted by Avar (1967), Ammer (1980), Pratzel (1995), Hodinka (2001) and Rao (2011). The CHMP raised concerns with regard to the methodology of this meta-analysis, including the weighting of the individual studies, and with regard to the quality of the included studies and therefore concluded that it did not provide any additional support of the efficacy of tolperisone.

The CHMP also noted the MAH proposal to conduct a further clinical study with a suitable design, to collect additional evidence of the efficacy of tolperisone in the proposed restricted 'low back pain' indication, as a post-referral commitment. The MAH provided a draft study synopsis describing a randomised, multicentre, double-blind, placebo-controlled post-authorisation efficacy and safety study, comparing tolperisone with tizanidine. 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 because of the short treatment duration proposed.

In conclusion, having assessed the available data, including new data obtained since the initial marketing authorisation and noted the opinions of the BSWP and the SAG, the CHMP retained its conclusion that the evidence of clinically significant efficacy of tolperisone in the "*treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases*" indication or in the proposed restricted indication is not sufficient.

Safety

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 were considered to be life-threatening. A causal relationship with tolperisone was assessed as at least possible in 90% of all hypersensitivity reactions. The CHMP therefore confirmed its opinion that the risk of hypersensitivity reactions is more significant than previously identified at the time of the initial marketing authorisation.

Overall benefit-risk assessment

In view of the grounds submitted by the MAHs, it should be noted that in examining the *“treatment of muscular hypertonicity and muscle spasms associated with locomotor diseases”* indication and the proposed restricted indication, the CHMP took into consideration the grounds of Article 116 Directive 2001/83/EC. According to Recital 7 of Directive 2001/83/EC, *“the concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.”* The CHMP therefore assessed the safety and efficacy of tolperisone in order to conclude on the benefit-risk balance of the product. If the efficacy is insufficient to outweigh the risks, the benefit-risk balance must be considered to be negative.

Based on the totality of the data available on the safety and the efficacy of tolperisone, 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”*.

2.7. Communication plan

As part of this referral procedure, the MAHs and the CHMP agreed the wording of a ‘Dear healthcare professional’ communication designed to inform prescribers of the risk of hypersensitivity reactions in association with tolperisone-containing products, the revised therapeutic indications and the withdrawal of the parenteral formulations (see enclosure 9), to be sent to relevant health care professionals within 25 days of the EC decision being issued.

2.8. Changes to the product information

The CHMP recommended that amendments be introduced in the Summary of product Characteristics of all tolperisone-containing products changes, affecting the following sections: 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8 and 5.2. Similarly, amendments should be introduced to sections 1, 2, 3, and 4 of the Package Leaflet (see enclosure 8).

3. Overall conclusion

Having considered all the data provided by the MAHs in writing and in the oral explanations, the report from the Biostatistics Working Party and the outcome of the neurology scientific advisory group in accordance with Article 32 of Directive 2001/83/EC:

- 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:
 - o Is positive for symptomatic treatment of post-stroke spasticity in adults.
 - o Is not positive for treatment of muscular hypertonicity and muscle spasms associated with locomotor disease.
 - o Is not positive for rehabilitation after orthopaedic and trauma surgery.
 - o Is not positive for treatment of obliterative vascular diseases as well as syndromes due to impaired vascular innervation.
 - o Is not positive for Little's disease and other encephalopathies 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 report and to the opinion.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.

Appendix

Divergent positions

The undersigned members of CHMP did not agree with the Committee's opinion recommending the restriction of the therapeutic indication for tolperisone-containing products, in particular with regard to the negative opinion for the indication "*Short-term treatment of muscle spasms in adult patients with acute non-specific low back pain*". The reasons for divergent opinion were the following:

- The safety profile of tolperisone-containing products is considered acceptable. The analysis of the available safety data did not reveal that the risk of the hypersensitivity reactions is higher than previously identified. The relative risk of the life threatening cases can also be assessed as very low. Observed higher reporting rate of the adverse events of tolperisone in Germany in comparison to other European countries seems to be country specific and may reflect improved reporting rates. In the opinion of the SAG Neurology, based on the data provided by the MAH, there appears to be no demonstrated increase in safety concerns regarding the use of tolperisone but safety monitoring of tolperisone should continue.
- Regarding efficacy, the restriction of the tolperisone indication to only post-stroke conditions cannot be entirely justified. Spasticity is a velocity dependent increased resistance to tonic stretch and it is part of the Upper Neuron Syndrome. The clinical syndrome resulting from an Upper Motor Neuron lesion depends more on the location, extent and the time since it occurred than on the pathology of the lesion. Spasticity can result from injury to cortex, basal ganglia, thalamus, brain stem, cerebellum, spinal cord etc. The injury can be: stroke, cerebral palsy, but also hypoxic or traumatic brain or spinal cord injury, encephalitis, hereditary spastic paraplegia, various myelopathies etc. The aetiology has little influence on the spasticity, which may develop as a consequence of various neurological disorders and the necessity to treat spasticity depends on individual patient need, rather than the underlying disease. The SAG Neurology acknowledged that there may be overlaps between the pathways involved in spasticity and in muscular spasms related to acute back pain.

The results of placebo controlled, randomized clinical studies with tolperisone in the "*Short-term treatment of muscle spasms in adult patients with acute non-specific low back pain*" indication possess some deficiencies which raise doubts regarding the quality of the proof of efficacy. However, some of the outcomes of these studies did not allow for an unambiguous statement that tolperisone is surely an ineffective drug. In addition many published studies (although some of lower quality) and extensive clinical experience with tolperisone (>50 years) in the clinical practice, support the opinion that tolperisone may be an effective drug also in this indication.

In addition, the place of muscle relaxants in the treatment of muscle spasm in the course of low back pain is stable. Many clinical guidelines (Austria, Canada, Europe (acute), Finland, France, Germany, the Netherlands and the United States) recommend their use in the treatment of this condition (Koes et al. 2010; Cochrane review – van Tulder et al. 2003). Moreover, several guidelines, recommendations and reviews support the clinical use of tolperisone in the treatment of painful muscle spasms (Strohmeier, 2010; Budai, 2011; Koó, 2011).

- The position of the SAG neurology was that based on the safety profile of tolperisone and the available data, there may be a place for tolperisone in the proposed restricted therapeutic indication. The MAH proposal to conduct a study with a suitable design according to the current scientific standards is welcome and could provide more evidence of the clinical efficacy of tolperisone.

We therefore consider that the scientific evaluation has revealed no new emerging safety issues and confirmed the safety of tolperisone. With regard to efficacy, the evidence from the literature, although limited by the fact that many studies are old and may not meet the standards required nowadays, together with the extensive clinical experience, support that tolperisone is an effective treatment option in the proposed indication.

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