PRODUCT INFORMATION AS APPROVED BY THE CHMP ON 21 JUNE 2012, PENDING ENDORSEMENT BY THE EUROPEAN COMMISSION

SUMMARY OF PRODUCT CHARACTERISTICS (TOLPERISONE-CONTAINING ORAL FORMULATIONS)

4.1 Therapeutic indications

[the currently approved indications should be deleted and replaced by the following]

- Symptomatic treatment of post-stroke spasticity in adults.

4.2 Posology and method of administration

[the wording below should be inserted]

…
Paediatric population
The safety and efficacy of tolperisone in children have not been established.

Patients with renal impairment
Experience in patients with renal impairment is limited and a higher frequency of adverse events has been observed in this patient group. Therefore, individual titration with close monitoring of the patient's condition and renal function is recommended in patients with moderate renal impairment. Use of tolperisone is not recommended in patients with severe renal impairment.

Patients with hepatic impairment
Experience in patients with hepatic impairment is limited and a higher frequency of adverse events has been observed in this patient group. Therefore, individual titration with close monitoring of the patient's condition and hepatic function is recommended in patients with moderate hepatic impairment. Use of tolperisone is not recommended in patients with severe hepatic impairment.

Method of administration
The medicine should be taken after meals with a glass of water.
Insufficient food intake may decrease the bioavailability of tolperisone.

4.3 Contraindications

[the wording below should be inserted]

Hypersensitivity to the active substance tolperisone or to the chemically similar eperisone or to any of the excipients listed in section 6.1.
…

4.4 Special warnings and precautions for use

[the wording below should be inserted]

Hypersensitivity reactions

During post marketing experience with tolperisone the most frequently reported adverse reactions were hypersensitivity reactions. Hypersensitivity reactions ranged from mild skin reactions to severe systemic reactions including anaphylactic shock. Symptoms may include erythema, rash, urticaria, pruritus, angioedema, tachycardia, hypotension or dyspnoea.

Females, patients with hypersensitivity to other drugs or with a history of allergy may be at a higher risk.

In case of a known hypersensitivity to lidocaine increased caution during the administration of tolperisone because of possible cross-reactions is warranted.

Patients should be advised to remain vigilant for any symptoms compatible with hypersensitivity and to stop tolperisone and seek medical advice immediately if such symptoms occur.

Tolperisone must not be re-administered after an episode of hypersensitivity to tolperisone.
…

4.5 Interaction with other medicinal products and other forms of interaction

[the wording below should be inserted]

Pharmacokinetic drug interaction studies with the CYP2D6 substrate dextromethorphan indicate that tolperisone co-administration may increase the blood levels of drugs which are metabolised dominantly by CYP2D6 such as thioridazine, tolterodine, venlafaxine, atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine.

In vitro experiments in human liver microsomes and human hepatocytes did not suggest significant inhibition or induction of other CYP isoenzymes (CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP1A2, CYP3A4).

Increase in tolperisone exposure is not expected after concomitant administration of CYP2D6 substrates and/or other drugs due to the diversity of the metabolic pathways of tolperisone.

The bioavailability of tolperisone is decreased when taken without food, therefore consistent administration in relation to meals is recommended (see also sections 4.2 and 5.2).

Although tolperisone is a centrally acting compound, its potential to cause sedation is low.
In the case of co-administration with other centrally acting muscle relaxants, the dose reduction of tolperisone should be considered.

Tolperisone potentiates the effect of niflumic acid, therefore reduction of the dose of niflumic acid or other NSAID should be considered in case of co-administration.

[the wording below should be deleted, as relevant]

~~Tolperisone does not influence the CNS effects of alcohol.~~

4.7 Effects on ability to drive and use machines

[the wording below should be inserted]
…
Patients who experience dizziness, somnolence, disturbance in attention, epilepsy, blurred vision or muscular weakness while taking tolperisone should consult his/her doctor.

4.8 Undesirable effects

[the wording below should be inserted]

The safety profile of tolperisone containing tablets is supported by data on more than 12,000 patients.
According to these data, the most frequently concerned system organ classes are skin and subcutaneous tissue disorders, general disorders, neurological disorders and gastrointestinal disorders.

In post-marketing data, hypersensitivity reactions associated with tolperisone administration account for about 50-60% of the reported cases. The majority of the cases express non-serious and self-limiting conditions. Life-threatening hypersensitivity reactions are reported very rarely.
…
confusion (very rare),

hyperhidrosis (rare)
…

[the wording below should be deleted, as relevant]

~~No hypersensitivity case with fatal outcome after tolperisone treatment has been registered.~~

~~Although tolperisone is a centrally acting compound, it does not induce sedation. Therefore the preparation can be combined with sedatives, hypnotics and tranquillisers.~~

5.2 Pharmacokinetic properties

[the wording below should be inserted]
…
High-fat meal increases the bioavailability of orally administered tolperisone by approx. 100% and increases the peak plasma concentration by approx. 45% as compared with fasting condition, delaying time to peak by approx. 30 minutes.

PACKAGE LEAFLET
(TOLPERISONE-CONTAINING ORAL FORMULATIONS)

[the wording below should be inserted in the relevant sections]

1. What *{invented name}* is and what it is used for

Tolperisone is a medication that acts on the central nervous system. It is for the treatment of the pathologically elevated skeletal muscle tone after a stroke in adults.

2. What you need to know before you take *{invented name}*

Do not take *{invented name}*

If you are allergic to the active substance (tolperisone hydrochloride) or to medicines containing eperisone or any of the other ingredients of this medicine (listed in section 6).
…

Warnings and precautions
…
Hypersensitivity reactions:
During post marketing experience with medicinal products containing tolperisone (the active substance of *{invented name}*) the most frequently reported side effects were hypersensitivity reactions. Hypersensitivity reactions ranged from mild skin reactions to severe systemic reactions (e.g. allergic shock).

Females, patients in older age, or treated with concomitant medications (mainly with NSAIDs) seem to be at a higher risk to experience hypersensitivity reactions. Also, patients with drug allergy or allergic diseases or conditions (such as atopy: hay fever, asthma, atopic dermatitis with high serum IgE, urticaria) in the past history or who suffer from viral infections at the same time appear to be at a higher risk to have allergic reaction against this medicine.

Early signs of hypersensitivity are: flushing, rash, severe itching of the skin (with raised lumps), wheezing, difficulty in breathing with or without swelling of the face, lips, tongue and/or throat, difficulty in swallowing, fast heart beat, low blood pressure, fast decrease in blood pressure.
If you feel these symptoms stop taking this medicine immediately and contact your doctor or the nearest emergency department.
If you have ever had allergic reaction to tolperisone you must not use this medicine.

If you have a known allergy for lidocaine you have a higher risk to be allergic to tolperisone. In this case talk to your doctor before starting the treatment.

Children and adolescents
The safety and efficacy of tolperisone in children have not been established.
…

Driving and using machines
…
If you experience dizziness, somnolence, disturbance in attention, epilepsy, blurred vision or muscular weakness while taking *{invented name}* consult your doctor.

3. How to take Tolperisone film-coated tablet

…
The medicine should be taken after meals with a glass of water.
…
Use in children and adolescents
The safety and efficacy of Tolperisone in children have not been established.

Patients with kidney impairment
Your regular medical follow-up will include frequent monitoring of kidney function and your condition during therapy with *{invented name}* because a higher frequency of adverse events has been observed in this patient group. If you have severe kidney problems you should not take this medicine.

Patients with liver impairment
Your regular medical follow-up will include frequent monitoring of liver function and your condition during therapy with Tolperisone because a higher frequency of adverse events has been observed in this patient group. If you have severe liver problems you should not take this medicine.
…

4. Possible side effects

…
Rare side effects
…increased sweating
…
Very rare side effects
…confusion, severe allergic reaction (allergic shock)
…