Package Insert
Myo – MR®

Product Summary

1. Name of the medicinal product
Myo – MR®

2. Qualitative and quantitative composition
Each film coated tablet contains:
Tolperisone Hydrochloride 150 mg
Excipients q.s

3. Pharmaceutical form
Film coated tablet

4. Clinical particulars
4.1 Therapeutic indications
Spasticity of the skeletal muscles.

4.2 Posology and method of administration
Myo – MR® should be used as prescribed by the physician. General recommendations are:
Adults and adolescents from age 15: daily dose is 150 mg – 450 mg per os divided into 3 doses, according to the individual requirements and tolerance of the patients. This dosage can also be applied for long-term treatment (several months or years) without dose reduction. In the elderly dose modification or reduction is not necessary; the doses recommended are well tolerated.

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

- Hypersensitivity to the active substance tolperisone or to the chemically similar eperisone or to any of the excipients listed in section 6.1.
- Myasthenia gravis.
- Lactation.

4.4 Special warnings and precautions for use

Special attention is required in treatment of patients who already receiving antihypertensive therapy, since according preliminary clinical observations tolperisone may cause decreased blood pressure of approximately 10 to 30 mm Hg in transient after a single dose or in case of long-term therapy as well.

There is no need of reduction or modification of dosages in special treatment groups such as elderly people, however as it is known that inter-individual variations may require attention and the oral doses of tolperisone might need to be individualized.

Inter-individual differences may be observed in all treatment groups, based on the
metabolism, which takes place primarily in the liver. Tolperisone undergoes an extensive first pass effect, and only 20% of an administered dose appear unchanged in the blood. The metabolism is NADPH-dependent, since the omission of this coenzyme completely abolished the consumption of tolperisone. It has been demonstrated that both P450-dependent and P450-independent microsomal biotransformations are involved in tolperisone metabolism, in vitro. Hydroxymethyl metabolite formation revealed to be the main P450-mediated metabolic pathway. CYP2D6 was identified as the key enzyme in metabolism, however involvement of CYP2C19 and CYP1A2 were also shown in lesser extent. It was evidenced that P450-independent metabolism was mediated to a small extent by FMO3. Metabolites detected and indirect evidences from inhibition studies pointed toward the substantial involvement of presumable microsomal carbonyl reductase in the metabolism of tolperisone.

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
No interaction between tolperisone and medications prescribed for concomitant diseases has been observed that would restrict the administration of tolperisone. However, tolperisone is metabolised by the cytochrome P450 system, in particular CYP2D6. Therefore, interactions with drugs that are metabolised by the same system cannot be excluded. Tolperisone does not affect cortical functions and the arousal level; therefore, it can be given together with hypnotics, sedatives and
trianquillizers. However, dose reduction may be considered when tolperisone tablets are administered concomitantly with other centrally acting muscle relaxants. On the basis of clinical trials, it can be concluded that tolperisone potentiates the effect of NSAIDs.

Additional that has described in 4.4, in treatment of patients who already receiving antihypertensive therapy, possible interactions may be considered, however there is no direct evidences of clinical observations reported. Based on the current data tolperisone inhibits reflexes by two main mechanisms: on the one hand by influencing the inhibition of voltage-dependent sodium channels, and on the other hand by influencing synaptic transmission through inhibiting sodium and calcium channels. However, additional mechanisms can not be completely excluded (e.g. effects through alpha receptors). A theoretical sites of interference can not be ruled out due the direct inhibition of tolperisone, on the Na\(^+\) and in lesser extent on the Ca\(^+\) channels in experimental conditions. However, reports showed that the Ca\(^+\) antagonistic action occurring generally in higher concentrations, compared to the action on Na\(^+\) channels. The sites and extent of possible interactions need to be elucidated.

Tolperisone tablets do not cause either somatic or psychical dependency.

According to present data tolperisone tablets do not have any influence on the results of clinical laboratory examinations.

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.

4.6 Pregnancy and lactation

Pregnancy

No teratogenic effect of tolperisone was noted in any animal studies. Since there are no human study results available, tolperisone should only be used in pregnancy (especially in the first trimester), if the expected therapeutic benefits are unambiguously higher than the foetal risk.

Lactation

Since there are no data available whether tolperisone is excreted into breast milk, it must not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. 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

Undesirable effects of Tolperisone are transient, and decrease or even stop by reducing the dose.

Adverse events are listed below by frequency as follows.

very common: ≥1/10, common ≥1/100 to <1/10, uncommon ≥1/1,000 to < 1/100, rare ≥1/10,000 to < 1/1,000, very rare < 1/10,000, not known: cannot be estimated from the available data.

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 cases of any hypersensitivity reaction, the administration of tolperisone should be discontinued.

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.

**4.9 Overdose**

There are limited data available on the overdose of tolperisone. The therapeutic index of tolperisone is wide and there are literature reports of oral administration of 600mg tolperisone in children without any severe toxic symptom. In some children 300–600mg/day tolperisone administered orally was associated with irritability. Tolperisone has no specific antidote. In tolperisone overdose general symptomatic and supportive measures should be taken.

**5. Pharmacological properties**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: other centrally acting agents

Tolperisone is a centrally acting muscle relaxant with properties similar to local anaesthetics. The precise mechanism of action of tolperisone is not fully known. It
possesses high affinity for nervous tissue, reaching the highest concentration 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** - Tolperisone stabilises the cell 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.

The blood flow enhancing effect of tolperisone is still not understood. Involvement of calcium-antagonistic, slight spasmolytic or slight anti-adrenergic effects have been proposed.

5.2 Pharmacokinetic properties

**Absorption**

The absorption of orally administered tolperisone from the small intestine is good. Peak plasma concentration is observed 0.5 – 1 hour after the oral intake. Bioavailability is about 20% due to significant first-pass metabolism.

**Biotransformation**

Tolperisone is extensively metabolised in the liver and kidneys. There are no
observations that suggest a pharmacological activity of the metabolites. In animal studies on distribution, relative accumulation of tolperisone was observed in the diencephalon, pons and medulla oblongata, as well as in the main organs of elimination such as liver and kidney.

**Elimination**

Tolperisone and its metabolites are excreted almost entirely through the kidneys. 98% of the administered dose is excreted with the urine within 24 hours. Less than 0.1% of the dose is eliminated in the intact form. When administered orally, the elimination half-life of tolperisone in men was calculated to be approximately 2-4 hours with a large inter-individual variation.

Tolperisone is reported to have a relatively high volume of distribution (5l/kg b.w.); the total plasma clearance is $1.9\pm0.4$ l/h/kg. The overall binding rate of tolperisone racemate to human plasma proteins is 95%.

**Food increases the bioavailability.**

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. Therefore, it is recommended to take Tolperisone tablets after meals.

**5.3 Preclinical safety data**

In acute animal toxicity studies large doses of tolperisone caused ataxia, tonic-clonic seizures, dysnpoea and respiratory failure were reported. Based on animal studies tolperisone is not teratogenic. Embryotoxic variations were observed in rats at 500 mg/kg and in rabbits at 250 mg/kg oral doses. These doses were multiple times higher than the doses applied in humans.

**6. Pharmaceutical particulars**

**6.1 List of excipients**

Titanium dioxide IP

**6.2 Incompatibilities**

None known.
6.3 Shelf life
24 months

6.4 Special precautions for storage
Store between 15°C – 30°C. Protect from light and moisture.

Administrative data
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9. Date of text
16th May 2016