



Public Assessment Report

Name of the Product:

Merisone

50 mg, 150 mg film-coated tablets

(tolperisone hydrochloride)

Procedure number: HU/H/373/001-003/MRP

Marketing authorisation holder: Meditop Pharmaceutical Co. Ltd.

Date: 9 December 2015

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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE
ON THE PUBLIC ASSESSMENT REPORT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Merisone (in Germany: Tolperison-HCl neurax-pharm) 50 mg and 150 mg film-coated tablets. The holder of the marketing authorisation is Meditop Pharmaceutical Co. Ltd. in the RMS.

The active substance is 50 mg or 150 mg tolperisone hydrochloride in each film-coated tablet, respectively.

The other ingredients are:

- tablet core: betaine hydrochloride, microcrystalline cellulose, mannitol, crospovidone, stearic acid and talc;
- tablet coating: Opadry II white (lactose monohydrate, hypromellose, titanium dioxide and Macrogol 4000).

Merisone 50 mg and 150 mg film-coated tablets are white, round film-coated tablet with a “50” or “150” mark on one side, respectively, and a special code sign on the other side. The breaking surface is white. They are packed in PVC/Alu blister and carton.

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

Before taking Merisone film-coated tablets

Should not take Merisone film-coated tablet those, who

- are allergic to the active substance (tolperisone hydrochloride) or to medicines containing eperisone or any of the other ingredients of this medicine;
- suffer in myasthenia gravis (an immunological disease associated with muscle weakness);
- breastfeed their baby.

Warnings and precautions

Hypersensitivity reactions: during post-marketing experience with medicinal products containing tolperisone (the active substance of Merisone film-coated tablets) the most frequently reported side effects were hypersensitivity reactions. They ranged from mild skin reactions to severe systemic reactions (e.g. allergic shock).

Females, elderly patients, or patients treated with concomitant medications (mainly with non-steroid anti-inflammatory drugs 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 heartbeat, low blood pressure, fast decrease in blood pressure. Feeling these symptoms taking this medicine should be stopped immediately and the doctor or the nearest emergency department contacted immediately. Those who ever had allergic reaction to tolperisone must not use this medicine.

Those who have a known allergy for lidocaine have a higher risk to be allergic to tolperisone. In this case the doctor must be consulted before starting the treatment

Children and adolescents

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

Other medicines and Merisone

There are no data on dose-limiting interactions of Merisone film-coated tablets. Although tolperisone is a centrally acting drug, it does not cause sedation (does not reduce the ability to concentrate). Therefore, it can simultaneously be taken with hypnotic or sedative medicines. However, dose adjustment should be considered when used concomitantly with other centrally acting skeletal muscle relaxants.

Tolperisone potentiates the effects of niflumic acid. Therefore, in case of concomitant administration a reduction of the dose of niflumic acid or other NSAID should be considered.

Taking Merisone film-coated tablet with food and drink

Food and liquid consumption do not influence the absorption of the preparation. However, it is important that this medicine is taken after having a sufficient meal.

Pregnancy, breast-feeding and fertility

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby should consult their doctor for advice before taking this medicine.

Although, there is no evidence that Merisone film-coated tablets would have harmful effect on the foetus, after careful evaluation of the risk/benefit ratio the doctor should decide whether to take this medicine or not, particularly in the first three months of pregnancy.

Merisone film-coated tablet must not be used during breastfeeding.

Driving and using machines

This medicine has no influence on the ability to drive or use machines. However, those who experience dizziness, somnolence, and disturbance in attention, epilepsy, blurred vision or muscular weakness while taking Merisone film-coated tablet must consult their doctor.

Merisone film-coated tablets contain lactose monohydrate

Merisone 50 mg and 150 mg film-coated tablets contain lactose monohydrate (1.44 mg or 5.4 mg in each tablet, respectively) as well as titanium dioxide (E 171) as excipient.

Those who have been told by their doctor that they have an intolerance to some sugars, contact the doctor before taking this medicinal product.

How to take Merisone film-coated tablets?

The recommended dose is

- three times 1 – 3 Merisone 50 mg film-coated tablets daily.
- three times 1 Merisone 150 mg film-coated tablets daily.

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

The patient's regular medical follow-up will include frequent monitoring of kidney function and the condition during therapy with Merisone film-coated tablets because a higher frequency of adverse events has been observed in this patient group. Those who have severe kidney problems should not take this medicine.

Patients with liver impairment

The patient's regular medical follow-up will include frequent monitoring of liver function and the condition during therapy with Merisone film-coated tablets because a higher frequency of adverse events has been observed in this patient group. Those who have severe liver problems should not take this medicine.

What to do if take more Merisone film-coated tablet have been taken than it should be?

If the patient has taken more tablets than the doctor prescribed, the doctor must be contacted immediately or the emergency unit of the nearest hospital must be visited.

What to do if taking Merisone film-coated tablet was forgotten?

No double dose to make up for a forgotten tablet should be taken.

May taking Merisone film-coated tablet be discontinued?

Taking this medicine should not be discontinued prematurely even if the patient feels the effect of Merisone film-coated tablet too strong or weak. In such cases the doctor should be contacted.

Possible side effects

Like all medicines, Merisone film-coated tablets can cause side effects, although not everybody experiences them.

The side effects are usually mild and disappear upon discontinuation of taking the preparation.

Uncommon side effects (from 100 patients less than 1, but from 1000 patients more than 1 is affected): loss of appetite, insomnia, sleep disturbance, headache, dizziness, somnolence, low blood pressure, abdominal discomfort, diarrhea, dry mouth, indigestion, nausea, muscle weakness, muscle aches, pain in the extremities, weakness, malaise, fatigue.

Rare side effects (from 1000 patients less than 1, but from 10,000 patients more than 1 is affected): hypersensitivity (allergic) reaction, serious allergic reaction (anaphylactic reaction), reduced activity, depression, disturbance of attention, tremor of the hand, convulsion, sensory defect, sensory disturbance, lethargia, visual disturbance, dizziness, tinnitus, chest tightness, tachycardia, palpitation, hypotension, flushing, breathing difficulty, bleeding of the nose, panting, epigastric pain, constipation, flatulence, vomiting, mild liver impairment, allergic skin symptoms, increased sweating, itching (pruritus), urticaria, rash, urinary incontinence, protein in the urine, discomfort of the extremities, feeling of drunkenness, feeling of warmth, thirst, irritability, elevation of bilirubin levels, abnormal liver enzyme levels, reduction of platelet count, elevation of white blood cell count.

Very rare side effects (from 10,000 patients less than 1 is affected, including the isolated cases): anaemia, swelling of the lymph nodes, severe allergic reactions (allergic shock), abnormal thirst (polydipsia), confusion, bradycardia, osteoporosis, chest discomfort, elevation of creatinine levels.

After marketing authorization a new adverse event were reported (the frequency is unknown): angioedema (including face oedema and lip swelling).

How to store Merisone film-coated tablets?

Store it below 30 °C. Keep it out of the sight and reach of children.

Scientific discussion

This module reflects the scientific discussion for the MRP approval of Merisone 50 mg and 150 mg film-coated tablets. The procedure was finalised at 3 July 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member States concerned.

This Mutual Recognition Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: Germany) concerned the generic version of tolperisone 50 mg and 150 mg film-coated tablets (Merisone, named Tolperison-HCl neuraxpharm filmtabletten in Germany).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary.

The original marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC (generic application). The applicant has adequately demonstrated bioequivalence between the product and reference products. The originator (and reference) products were Mydeton film-coated tablets (containing 50 mg and 150 mg tolperisone hydrochloride as active ingredient) marketed by Gedeon Richter Plc., approved for more than 10 years within the European Economic Area.

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for tolperisone 50 mg and 150 mg film-coated tablets from Meditop Pharmaceutical Co. Ltd.

The product is indicated for: symptomatic treatment of post-stroke spasticity in adults.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Merisone 50 mg and 150 mg film-coated tablets via mutual recognition procedure according to Article 10.1 of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Meditop Pharmaceutical Co. Ltd.

The reference products of the original marketing authorisation were Mydeton film-coated tablets (containing 50 mg and 150 mg tolperisone hydrochloride as active ingredient) which were the original products of Gedeon Richter Plc.

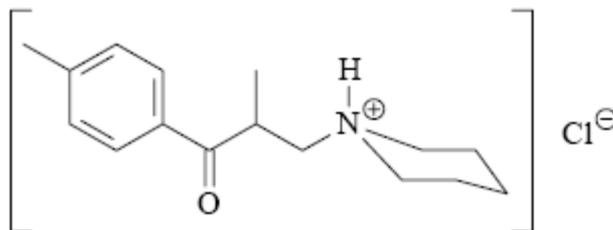
II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: tolperisone hydrochloride

Chemical name: 2-methyl-1-(4-methylphenyl)-3-(1-piperidiny)-1-propanone hydrochloride

Structure:



The active substance is white crystalline powder, very soluble in glacial acetic acid, freely soluble in water and in ethanol, soluble in acetic anhydride, slightly soluble in acetone and practically insoluble in ether. Polymorphism of the drug substance is not relevant as up to now only one crystal form is known. The racemic form is produced by the manufacturer.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by NMR, MS, IR, and by UV spectroscopy. The impurity profile of the API contains detailed information about genotoxic impurities and residual solvents.

Tolperisone hydrochloride is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, solubility, pH, melting range, identification by chemical reactions and IR,

absorbance, clarity and colour of solution, sulphate, heavy metals, loss on drying, residue on ignition, assay, residual solvents, impurities, bulk and tapped density and particle size.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Conference on Harmonisation (ICH) Q6A guideline. The specification reflects all relevant quality attributes of the active substance and was found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period and storage conditions are acceptable.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop film-coated tablets containing tolperisone hydrochloride as drug substance in 50 mg and 150 mg doses pharmaceutically equivalent and bioequivalent to the reference medicinal product Mydeton 50 mg and 150 mg film-coated tablets, the branded original products of Gedeon Richter Plc.

A satisfactory package of data on development pharmaceuticals has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

Merisone 50 mg film-coated tablets are white, round, biconvex, film-coated tablets with the diameter of about 7 mm and with the height of about 2.8 mm. They are engraved with "50" on one side and with special code on the other side.

Merisone 150 mg film-coated tablets are white, round, biconvex film-coated tablets with the diameter of about 10 mm and with the height of about 4.7 mm. They are engraved with “150” on one side and with special code on the other side.

The excipients used in the finished product are betaine hydrochloride, microcrystalline cellulose, mannitol, crospovidone, stearic acid, talc, and Opadry white (lactose monohydrate, macrogol, titanium dioxide and hypromellose). All excipients used comply with their respective Ph. Eur. monograph or the USP monograph, respectively. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 5 years when stored up to 30°C, in the original package is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From quality aspects the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of tolperisone are well known and widely used. To support this generic application no further non-clinical studies were required and the applicant provided none. The appended overview based on literature review is, thus, appropriate.

III.2 Pharmacology

Tolperisone is a centrally acting skeletal muscle relaxant. The precise mechanism of action is not known.

The most important effect of tolperisone is the inhibition of the reflex arcs. Supposedly, this effect and the inhibition of the descending tracts is, what results in the therapeutic efficacy of tolperisone.

The chemical structure of tolperisone is very similar to that of lidocaine. Like this local anaesthetic agent, tolperisone, too, possesses with membrane stabilising effect and reduces the excitability of primary afferents and motor neurons. Tolperisone dose-dependently inhibits the voltage-gated sodium channels, reducing this way the amplitude and frequency of the action potential. (This effect is the strongest in neurons of the posterior horn of the spinal cord.)

Additionally, tolperisone has an inhibitory effect on the voltage-gated calcium channels, by which transmitter release from the primary afferents may be reduced.

Finally, tolperisone is a weak alpha-adrenergic antagonist and has an antimuscarin effect.

III.3 Pharmacokinetics

Tolperisone undergoes P450-dependent and P450-independent microsomal biotransformation to the same extent. On the basis of metabolites formed and indirect evidences of inhibition studies, a considerable involvement of a microsomal reductase is assumed.

Tolperisone absorbs well from the small intestine. Its bioavailability is moderate due to the significant first pass metabolism.

Tolperisone is metabolised extensively in the liver and the kidney. Elimination takes place via the kidneys, almost exclusively (in more than 99%) in the form of metabolites.

III.4 Toxicology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety

pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Embryo toxic variations were observed in rats at 500 mg/kg body weight and in rabbits at 250 mg/kg body weight oral doses.

These doses are several times higher than the human dose-range.

III.5 Ecotoxicology/environmental risk assessment

Since Merisone film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Tolperisone is a central myorelaxant with solid non-clinical pharmacological and toxicological background. The non-clinical data support the clinical use of tolperisone in the currently approved indication and posology. The original product Mydeton (Gedeon Richter Plc.) is on the market for decades in several countries.

Abridged applications avoid the need for repetitive tests on animals and humans. Therefore, no further preclinical studies are required.

From non-clinical aspects the products are approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical development programme aimed to prove the bioequivalence of Merisone 50 mg and 150 mg film-coated tablets and the original product Mydeton 50 mg and 150 mg film-coated tablets. To support this application the MAH submitted two bioequivalence studies, one for each requested strength.

IV.2 Pharmacokinetics

IV.2.1 Literature data

The absorption of orally administered tolperisone from the small intestine is good. Peak plasma concentration is observed 0.5 – 1.5 hour after the oral intake. Bioavailability is about 20% due to significant first-pass metabolism.

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 approximately 30 minutes.

Tolperisone is extensively metabolised in the liver and kidneys. Its elimination takes place via the kidneys, almost exclusively (in more than 99%) in the form of metabolites. Pharmacological activity of the metabolites is not known.

Elimination half-life after intravenous administration is about 1.5 hours, while after oral administration is about 2.5 hours.

IV.2.2 Bioequivalence studies

The first study MDTP-T20091B was a single dose, open label, randomized, two-period, two-sequence, crossover design human one in healthy male volunteers under fasting conditions. Single doses (2x 50 mg) of the investigational products (Test, T and reference R, i.e. Mydeton 50 mg film-coated tablets, Gedeon Richter) were administered orally to each subject in each period with water after an overnight fast. A washout period was maintained between the two dosing days in each group.

The plasma samples were assayed for tolperisone in human plasma by a validated LC-MS/MS method. Pharmacokinetic parameters: AUC_{0-t} , AUC_{inf} , C_{max} and T_{max} , were estimated based on tolperisone plasma levels for each subject included in the statistical analysis.

The results are summarised in the next Table.

Pharmacokinetic parameter	Ratio (T/R)	90% Confidence interval
AUC _{0-t}	1.00	0.88 – 1.14
AUC _{inf}	1.01	0.89 – 1.14
C _{max}	1.07	0.92 – 1.25

The second study was an open-label, single-dose, randomized, 3-period, two-sequence, two-treatment, crossover one. The subjects were randomly assigned to one of the two dosing sequences ABA or BAB under fasting conditions. Single doses (1x 150 mg) of the investigational products (T or R, i.e. Mydeton 150 mg film-coated tablets of Gedeon Richter) were administered orally to each subject in each period with 200 ml of water after an overnight fast. As the study had a replicated cross-over design, data were analysed within a repeated mixed model framework, allowing for different between- and within-subject variances for the two formulations. The fixed effects in the model were sequence, period and formulation. All additional details were identical with that of the former study.

The next Table shows the results.

Pharmacokinetic parameter	Ratio (T/R) %	90% Confidence interval
AUC _{0-t}	100.71	92.68 – 109.44
AUC _{inf}	100.95	93.18 – 109.37
C _{max}	109.99	98.33 – 123.03

The results of these two studies show that the 90% confidence intervals for the log-transformed parameters AUC and C_{max} for tolperisone were within the 80-125% acceptable range. No new or unexpected safety concerns were reported in this study.

Conclusion on bioequivalence studies

Based on the results of the submitted bioequivalence studies Merisone 50 and 150 mg tablets can be considered bioequivalent to Mydeton 50 and 150-mg tablets (Gedeon Richter Plc, Hungary). However, it seemed to be a valid concern that the bioequivalence studies were carried out in fasting state while the SmPC states that Merisone tablets should be taken with food and the food effect is not negligible. However, this is an MRP procedure and Merisone 50 and 150 mg tablets already had been authorized by the RMS. Two bioequivalence studies were carried out in fasting state, one with the 50 mg tablet and another one with the 150 mg tablet. In both cases bioequivalence has been demonstrated according the requirements of the EMA bioequivalence guideline valid at the time of the approval in the RMS. Both studies were carried out before 01. 08. 2010, the date when the currently valid, new bioequivalence requirements came into force. But the originator recently updated the SmPC which now states:

“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 approximately 30 minute.”

Therefore, because the SmPC recommends taking Merisone tablets after food, according to the currently valid *Guideline On The Investigation Of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1) section 4.1.4, the studies should have been conducted in fed and not in fasting states. But actually the Guideline states that “the bioequivalence study should generally be conducted under fed conditions.” The word *generally* reflects the regulators’ concerns that, particularly in MRP procedures, that unconditional requirement regarding the fed studies might prohibit approval of products with bioequivalence studies which were designed according to the requirements of the previous guideline. Still, when there is a deviation from the general principles, further justifications are needed. Fortunately the CHMP already has done this assessment during a referral procedure EMEA/H/A-31/1311. The CHMP assessment stated that

“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 marketing authorisation holders 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} ."

The assessment highlights the fact that the food effect is characteristic for the molecule and not for the formulation because different formulations had similar food effect. In overall, based on the CHMP assessment report, the RMS believes that approval is still possible based on the results of the fasting studies.

IV.3 Pharmacodynamics

Tolperisone is a centrally acting myorelaxant which is marketed since the early 1960s. This category of myorelaxants (including tolperisone) is marketed in Japan, Germany and in Central and Eastern European countries.

IV.4 Clinical efficacy

There is only one indication approved by the European Commission as follows: treatment of pathologically elevated skeletal muscle tone in organic neurological disorders.

IV.5 Clinical safety

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 (Commission Decision - Annex III 2013).

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

<i>Summary of safety concerns</i>	
Important identified risks	hypersensitivity
Important potential risks	<ul style="list-style-type: none">• myasthenia gravis• off -label use in the withdrawn indications
Missing information	lack of clinical trials on special populations such as <ul style="list-style-type: none">• patients with renal impairment• patients with hepatic impairment• pregnant or lactating women

Pharmacovigilance plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to the products of tolperisone 50 mg and 150 mg film-coated tablets of Meditop. No additional activities are proposed.

Routine risk minimisation measures (i.e. wording in SmPC, package leaflet and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to products of tolperisone 50 mg and 150 mg film-coated tablets of Meditop. No additional activities are proposed.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

Merisone 50 mg and 150 mg film-coated tablets proved to be bioequivalent with the reference medicinal product Mydeton 50 mg and 150 mg film-coated tablets, therefore no further clinical studies are required.

The benefit-risk balance of tolperisone-containing oral formulations is positive in the symptomatic treatment of post-stroke spasticity in adults in agreement with Commission Implementing Decision of 21.1.2013 concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations for the medicinal products for human use which contain the active substance "tolperisone", Brussels, 21. 01. 2013 C(2013)369 (final).

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present mutual recognition applications concern Merisone 50 mg and 150 mg film-coated tablets, generic versions of tolperisone hydrochloride. The holder of authorisation is Meditop Pharmaceutical Co. Ltd. in the RMS.

The indication is symptomatic treatment of post-stroke spasticity in adults.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The original reference products were Mydeton 50 mg and 150 mg film-coated tablets (Gedeon Richter Plc.).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

V.2 Classification in the RMS

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after granting the original marketing authorisation with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Type IIB.1.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	15014/2014 15015/2014	no	10.04.2014	24.11.2014	approval	no
Type IA in C.1.1 Change in the Summary of Product Characteristics, Labelling or Package Leaflet following a procedure in accordance with Articles 30 or 31 of Directive 2001/83/EC or Articles 34 or 35 of Directive 2001/82/EC (referral procedure)	7807/2013 7806/2013	yes	21.02.2013	08.07.2013	approval	no