National Institute of Pharmacy

Public Assessment Report

Mutual Recognition Procedure

Name of the Product:

Tolperisone STADA

Tolperisone MEDITOP

Tolperistad

DCP Number:
HU/H/0199/01-02/MR
HU/H/0200/01-02/MR
HU/H/0201/01-02/MR

Applicant: Meditop Pharmaceutical Co. Ltd.

Table of contents

Modul 1
Information about the initial procedure

Product name	Tolperisone STADA 50-150 mg filmcoated tablet Tolperisone MEDITOP 50-150 mg filmcoated tablet Tolperistad 50-150 mg filmcoated tablet
Type of application:	Bibliographic Art 10 a Dir 2001/83/EC
level 1	Known active substance
level 2	Initial application
level 3	Bibliographic Art 10 a Dir 2001/83/EC
level 4	Chemical substance
level 5	Prescription only
Active substance	Tolperisone hydrochloride
Pharmaceutical form	Film-coated tablets
Strength	50 mg, 150 mg
MA holder	Meditop Pharmaceutical Co. Ltd.
RMS	Hungary
CMS	HU/H/0199/001-002/MR: DE HU/H/0200/001-002/MR: DE HU/H/0201/001-002/MR: DE
Procedure number	HU/H/0199/001-002/MR HU/H/0200/001-002/MR HU/H/0201/001-002/MR

Timetable	day0	2008.07.02
	day45	2008.08.16
	day50	2008.08.21
	day60	2008.08.31
	day75	2008.09.15
	day85	2008.09.25
	day90	2008.09.30

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 2
Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Tolperison-HCl STADA 50 mg film-coated tablets
Tolperison-HCl STADA 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tolperison-HCl STADA 50 mg film-coated tablets
Each film-coated tablets contains 50 mg tolperisone hydrochloride.

Tolperison-HCl STADA 150 mg film-coated tablets
Each film-coated tablet contains 150 mg tolperisone hydrochloride.

For a full list of excipients, see section 6.1.

Tolperison-HCl STADA 50 mg film-coated tablet
It contains 1.37 mg lactose in each .film-coated tablet.

Tolperison-HCl STADA 150 mg film-coated tablet
It contains 5.13 mg lactose in each .film-coated tablet.

3. PHARMACEUTICAL FORM

Tolperison-HCl STADA 50 mg
Film-coated tablet
White, round, biconvex, film-coated tablets, debossed with ‘50’ in one side and on the other side with special code.

Tolperison-HCl STADA 150 mg
Film-coated tablet
White, round, biconvex, film-coated tablets, debossed with ‘150’ in one side and on the other side with special code.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spasticity of the skeletal muscles

4.2 Posology and method of administration

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.

According to the available data no special dosage adjustment is required in renal or liver insufficiency.
For doses not realisable/practicable with this strength another strength of this medicinal product is available.

For oral use.
It is recommended to take ***Tolperison-HCl STADA tablets*** after meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Myasthenia gravis.
- Lactation.

4.4 Special warnings and precautions for use

The medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose-malabsorption should not take this medicine.

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 Hgmm 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 interindividual variations may require attention and the oral doses of tolperisone might need to be individualized.

Interindividual 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.

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 tranquillizers. However, dose reduction may be considered when ***Tolperison-HCl STADA 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 Na2+ and in lesser extent on the Ca2+ channels in experimental conditions. However, reports showed that the Ca2+ antagonistic action occurring generally in higher concentrations, compared to the action on Na2+ channels. The sites and extent of possible intercations need to be elucidated.

Tolperison-HCl STADA tablets do not cause either somatic or psychical dependency.

On the basis of human investigations, effects of alcohol on the functions of the central nervous system are not enhanced or altered by tolperisone.

According to present data ***Tolperison-HCl STADA tablets*** do not have any influence on the results of clinical laboratory examinations.

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.

4.8 Undesirable effects

Undesirable effects of ***Tolperison-HCl STADA*** 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.

Nervous system disorders:
Uncommon: dizziness, sleepiness
Rare: headache, sleep disturbance

Gastrointestinal disorders:
Uncommon: abdominal discomfort, nausea, vomiting, dry mouth, abdominal pain
Rare: constipation, diarrhoea, gastrointestinal disturbance

Skin and subcutaneous tissue disorders:
Rare: increased sweating

Psychiatric disorders:
Uncommon: fatigue, lassitude, weakness
Uncommon:

Immune system dysorders:
Rare: hypersensitivity reaction with erythema, exanthema, pruritus, blood pressure decreased and increased heart rate
Very rare: hypersensitivity reaction with urticaria, dyspnoea, angioneurotic oedema in single cases, anaphylactic shock
In cases of any hypersensitivity reaction, the administration of ***Tolperison-HCl STADA*** should be discontinued.

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 600 mg tolperisone in children without any severe toxic symptom. In some children 300 – 600 mg/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, ATC code: M03B X04

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±0.4 l/h/kg. The overall binding rate of tolperisone racemate to human plasma proteins is 95%.
Food increases the bioavailability. Therefore it is recommended to take ***Tolperison-HCl STADA tablets*** after meals.

5.3 Preclinical safety data

In acute animal toxicity studies large doses of tolperisone caused ataxia, tonic-clonic seizures, dysnpoe 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

Tolperison-HCl STADA 50 mg film-coated tablets
Core:
Talc,
Stearic acid,
Crospovidone,
Betaine hydrochloride,
Mannitol,
Microcrystalline cellulose.
Film coating:
Opadry II. white
- Titanium dioxide E 171,
- Macrogol 4000,
- Hypromellose,
- Lactose monohydrate.

Tolperison-HCl STADA 150 mg film-coated tablets
Core:
Talc,
Stearic acid,
Crospovidone,
Betaine hydrochloride,
Mannitol,
Microcrystalline cellulose.
Film coating:
Opadry II. White:
- Titanium dioxide E 171,
- Macrogol 4000,
- Hypromellose,
- Lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Tolperison-HCl STADA 50 mg film-coated tablets: 5 years

Tolperison-HCl STADA 150 mg film-coated tablets: 4 years

6.4 Special precautions for storage

Do not store above 30 ^{o}C.

Store in the original package.

6.5 Nature and contents of container

20 or 30 or 50 or 100 film-coated tablets in colourless, transparent PVC/Al by blister and carton box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

To be completed nationally.

1. NAME OF THE MEDICINAL PRODUCT

Tolperison-HCl dura 50 mg film-coated tablets
Tolperison-HCl dura 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tolperison-HCl dura 50 mg film-coated tablets
Each film-coated tablets contains 50 mg tolperisone hydrochloride.

Tolperison-HCl dura 150 mg film-coated tablets
Each film-coated tablet contains 150 mg tolperisone hydrochloride.

For a full list of excipients, see section 6.1.

Tolperison-HCl dura 50 mg film-coated tablet
It contains 1.37 mg lactose in each .film-coated tablet.

Tolperison-HCl dura 150 mg film-coated tablet
It contains 5.13 mg lactose in each .film-coated tablet.

3. PHARMACEUTICAL FORM

Tolperison-HCl dura 50 mg
Film-coated tablet
White, round, biconvex, film-coated tablets, debossed with ‘50’ in one side and on the other side with special code.

Tolperison-HCl dura 150 mg
Film-coated tablet
White, round, biconvex, film-coated tablets, debossed with ‘150’ in one side and on the other side with special code.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spasticity of the skeletal muscles

4.2 Posology and method of administration

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.

According to the available data no special dosage adjustment is required in renal or liver insufficiency.

For doses not realisable/practicable with this strength another strength of this medicinal product is available.

For oral use.
It is recommended to take ***Tolperison-HCl dura tablets*** after meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Myasthenia gravis.
- Lactation.

4.4 Special warnings and precautions for use

The medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose-malabsorption should not take this medicine.

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 Hgmm 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 interindividual variations may require attention and the oral doses of tolperisone might need to be individualized.

Interindividual 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.

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 tranquillizers. However, dose reduction may be considered when ***Tolperison-HCl dura 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 Na2+ and in lesser extent on the Ca2+ channels in experimental conditions. However, reports showed that the Ca2+ antagonistic action occurring generally in higher concentrations, compared to the action on Na2+ channels. The sites and extent of possible intercations need to be elucidated.

Tolperison-HCl dura tablets do not cause either somatic or psychical dependency.

On the basis of human investigations, effects of alcohol on the functions of the central nervous system are not enhanced or altered by tolperisone.

According to present data ***Tolperison-HCl dura tablets*** do not have any influence on the results of clinical laboratory examinations.

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.

4.8 Undesirable effects

Undesirable effects of ***Tolperison-HCl dura*** 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.

Nervous system disorders:

Uncommon:	dizziness, sleepiness
Rare:	headache, sleep disturbance

Gastrointestinal disorders:

Uncommon: abdominal discomfort, nausea, vomiting, dry mouth, abdominal pain
Rare: constipation, diarrhoea, gastrointestinal disturbance

Skin and subcutaneous tissue disorders:
Rare: increased sweating

Psychiatric disorders:
Uncommon: fatigue, lassitude, weakness
Uncommon:

Immune system dysorders:
Rare: hypersensitivity reaction with erythema, exanthema, pruritus, blood pressure decreased and increased heart rate
Very rare: hypersensitivity reaction with urticaria, dyspnoea, angioneurotic oedema in single cases, anaphylactic shock

In cases of any hypersensitivity reaction, the administration of ***Tolperison-HCl dura*** should be discontinued.

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 600 mg tolperisone in children without any severe toxic symptom. In some children 300 – 600 mg/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, ATC code: M03B X04

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±0.4 l/h/kg. The overall binding rate of tolperisone racemate to human plasma proteins is 95%.
Food increases the bioavailability. Therefore it is recommended to take ***Tolperison-HCl dura tablets*** after meals.

5.3 Preclinical safety data

In acute animal toxicity studies large doses of tolperisone caused ataxia, tonic-clonic seizures, dysnpoe 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

Tolperison-HCl dura 50 mg film-coated tablets
Core:
Talc,

Stearic acid,
Crospovidone,
Betaine hydrochloride,
Mannitol,
Microcrystalline cellulose.
Film coating:
Opadry II. white
- Titanium dioxide E 171,
- Macrogol 4000,
- Hypromellose,
- Lactose monohydrate.

Tolperison-HCl dura 150 mg film-coated tablets
Core:
Talc,
Stearic acid,
Crospovidone,
Betaine hydrochloride,
Mannitol,
Microcrystalline cellulose.
Film coating:
Opadry II. White:
- Titanium dioxide E 171,
- Macrogol 4000,
- Hypromellose,
- Lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Tolperison-HCl dura 50 mg film-coated tablets: 5 years

Tolperison-HCl dura 150 mg film-coated tablets: 4 years

6.4 Special precautions for storage

Do not store above 30 ^{o}C.

Store in the original package.

6.6 Nature and contents of container

20 or 30 or 50 or 100 film-coated tablets in colourless, transparent PVC/Al by blister and carton box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

To be completed nationally.

1. NAME OF THE MEDICINAL PRODUCT

Tolperisonhydrochlorid AL 50 mg film-coated tablets
Tolperisonhydrochlorid AL 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tolperisonhydrochlorid AL 50 mg film-coated tablets
Each film-coated tablets contains 50 mg tolperisone hydrochloride.

Tolperisonhydrochlorid AL 150 mg film-coated tablets
Each film-coated tablet contains 150 mg tolperisone hydrochloride.

For a full list of excipients, see section 6.1.

Tolperisonhydrochlorid AL 50 mg film-coated tablet
It contains 1.37 mg lactose in each .film-coated tablet.

Tolperisonhydrochlorid AL 150 mg film-coated tablet
It contains 5.13 mg lactose in each .film-coated tablet.

3. PHARMACEUTICAL FORM

Tolperisonhydrochlorid AL 50 mg
Film-coated tablet
White, round, biconvex, film-coated tablets, debossed with ‘50’ in one side and on the other side with special code.

Tolperisonhydrochlorid AL 150 mg
Film-coated tablet
White, round, biconvex, film-coated tablets, debossed with ‘150’ in one side and on the other side with special code.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spasticity of the skeletal muscles

4.2 Posology and method of administration

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.

According to the available data no special dosage adjustment is required in renal or liver insufficiency.

For doses not realisable/practicable with this strength another strength of this medicinal product is available.

For oral use.
It is recommended to take ***Tolperisonhydrochlorid AL tablets*** after meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Myasthenia gravis.
- Lactation.

4.4 Special warnings and precautions for use

The medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose-malabsorption should not take this medicine.

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 Hgmm 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 interindividual variations may require attention and the oral doses of tolperisone might need to be individualized.

Interindividual 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.

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 tranquillizers. However, dose reduction may be considered when ***Tolperisonhydrochlorid AL 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 Na2+ and in lesser extent on the Ca2+ channels in experimental conditions. However, reports showed that the Ca2+ antagonistic action occurring generally in higher concentrations, compared to the action on Na2+ channels. The sites and extent of possible intercations need to be elucidated.

Tolperisonhydrochlorid AL tablets do not cause either somatic or psychical dependency.

On the basis of human investigations, effects of alcohol on the functions of the central nervous system are not enhanced or altered by tolperisone.

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

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.

4.8 Undesirable effects

Undesirable effects of ***Tolperisonhydrochlorid AL*** 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.

Nervous system disorders:

Uncommon:	dizziness, sleepiness
Rare:	headache, sleep disturbance

Gastrointestinal disorders:

Uncommon:	abdominal discomfort, nausea, vomiting, dry mouth, abdominal pain
Rare:	constipation, diarrhoea, gastrointestinal disturbance

Skin and subcutaneous tissue disorders:

Rare:	increased sweating

Psychiatric disorders:

Uncommon:	fatigue, lassitude, weakness
Uncommon:	

Immune system dysorders:

Rare:	hypersensitivity reaction with erythema, exanthema, pruritus, blood pressure decreased and increased heart rate
Very rare:	hypersensitivity reaction with urticaria, dyspnoea, angioneurotic oedema in single cases, anaphylactic shock

In cases of any hypersensitivity reaction, the administration of ***Tolperisonhydrochlorid AL*** should be discontinued.

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 600 mg tolperisone in children without any severe toxic symptom. In some children 300 – 600 mg/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, ATC code: M03B X04

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.

5.3 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±0.4 l/h/kg. The overall binding rate of tolperisone racemate to human plasma proteins is 95%.
Food increases the bioavailability. Therefore it is recommended to take ***Tolperisonhydrochlorid AL tablets*** after meals.

5.3 Preclinical safety data

In acute animal toxicity studies large doses of tolperisone caused ataxia, tonic-clonic seizures, dysnpoe 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

Tolperisonhydrochlorid AL 50 mg film-coated tablets
Core:
Talc,

Stearic acid,
Crospovidone,
Betaine hydrochloride,
Mannitol,
Microcrystalline cellulose.
Film coating:
Opadry II. white
- Titanium dioxide E 171,
- Macrogol 4000,
- Hypromellose,
- Lactose monohydrate.

Tolperisonhydrochlorid AL 150 mg film-coated tablets
Core:
Talc,
Stearic acid,
Crospovidone,
Betaine hydrochloride,
Mannitol,
Microcrystalline cellulose.
Film coating:
Opadry II. White:
- Titanium dioxide E 171,
- Macrogol 4000,
- Hypromellose,
- Lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Tolperisonhydrochlorid AL 50 mg film-coated tablets: 5 years

Tolperisonhydrochlorid AL 150 mg film-coated tablets: 4 years

6.4 Special precautions for storage

Do not store above 30 ^{o}C.

Store in the original package.

6.7 Nature and contents of container

20 or 30 or 50 or 100 film-coated tablets in colourless, transparent PVC/Al by blister and carton box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

To be completed nationally.

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 3
Package leaflets

Tolperison-HCl STADA 50 mg film-coated tablets
Tolperison-HCl STADA 150 mg film-coated tablets
tolperisone hydrochloride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT TOLPERISON-HCL STADA IS AND WHAT IT IS USED FOR

It is used for the treatment of spasticity of the skeletal muscles.

2. BEFORE YOU TAKE TOLPERISON-HCL STADA

Do not take Tolperison-HCl STADA
- if you are allergic (hypersensitive) to tolperisone or any of the other ingredients of Tolperison-HCl STADA;
- if you suffer from myasthenia gravis (an immunological disease associated with muscle weakness);
- if you breastfeed your child.

Take special care with Tolperison-HCl STADA
If you are already receiving antihypertensive therapy please consult your doctor before treatment with this product.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Interactions may occur, if Tolperison-HCl STADA is used concomitantly with one of the following drugs:

- certain other medicines, to relax the muscles (centrally acting muscle relaxants)

- certain medicines to treat pain and inflammation (non-steroidal anti-inflammatory drugs - NSAIDs)
- other medicines, which may influence the metabolism of tolperison.

Please ask your doctor. He may decide to adjust the dosage.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Pregnancy
Tell your doctor if you think you are pregnant or planning pregnancy. Although there is no evidence that tolperisone is harmful to the foetus, your doctor should decide based on careful evaluation of the benefit/risk ratio weather you can use this preparation or not, especially in the first three months of pregnancy.
Breast-feeding
Tolperison-HCl STADA must not be used during breast-feeding.

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

Important information about some of the ingredients of Tolperison-HCl STADA
This medicine contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE TOLPERISON-HCL STADA

Always take Tolperison-HCl STADA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If not instructed otherwise, the usual dose of Tolperison-HCl STADA 50 mg film-coated tablets for adults and adolescents from age 15 is 3 x 1-3 film-coated tablets (3 x 50-150 mg tolperisone hydrochloride) daily. The daily dose of Tolperison-HCl STADA 150 mg film-coated tablets for adults and adolescents from age 15 is 3 x 1 (3 x 150 mg tolperisone hydrochloride) film-coated tablets.

For oral use.
It is recommended to take ***Tolperison-HCl STADA*** after meals.

If you take more Tolperison-HCl STADA than you should
In case of overdose you should contact your doctor immediately.

If you forget to take Tolperison-HCl STADA
Do not take a double dose to make up for a forgotten tablet. Skip the missed dose and take your next tablet at the ususal time.

If you stop taking Tolperison-HCl STADA
Do not stop taking Tolperison-HCl STADA if you feel well, only if your doctor instructs you to do so. Your doctor tells you how long you should take Tolperison-HCl STADA for.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tolperison-HCl STADA can cause side effects, although not everybody gets them.

Side effects are arranged according to frequency as follows:

very common: affects more than 1 user in 10
common: affects 1 to 10 users in 100
uncommon: affects 1 to 10 users in 1,000
rare: affects 1 to 10 users in 10,000
very rare: affects less than 1 user in 10,000
not known: frequency cannot be estimated from the available data

Nervous system disorders:
Uncommon: dizziness, sleepiness
Rare: headache, sleep disturbance

Gastrointestinal disorders:
Uncommon: abdominal discomfort, nausea, vomiting, dry mouth, abdominal pain
Rare: constipation, diarrhoea, gastrointestinal disturbance

Skin and subcutaneous tissue disorders:
Rare: increased sweating

Psychiatric disorders:
Uncommon: fatigue, lassitude, weakness
Uncommon:

Immune system dysorders:
Rare: hypersensitivity reaction with erythema, exanthema, pruritus, blood pressure decreased and increased heart rate
Very rare: hypersensitivity reaction with urticaria, dyspnoea, angioneurotic oedema in single cases, anaphylactic shock
In cases of any hypersensitivity reaction, the administration of ***Tolperison-HCl STADA*** should be discontinued.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TOLPERISON-HCL STADA

Keep out of the reach and sight of children.

Do not use Tolperison-HCl STADA after the expiry date which is stated on the blister and the carton after (EXP). The expiry date refers to the last day of that month.

Do not store above 30 ^{o}C.

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tolperison-HCl STADA contains

- The active substance is tolperisone hydrochloride.

Tolperison-HCl STADA 50 mg film-coated tablets
Each tablet contains 50 mg tolperisone hydrochloride.

Tolperison-HCl STADA 150 mg film-coated tablets
Each tablet contains 150 mg tolperisone hydrochloride.

- The other ingredients are:

Tolperison-HCl STADA 50 mg film-coated tablets
Core: talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline cellulose.
Film coating: Opadry II. white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate).

Tolperison-HCl STADA 150 mg film-coated tablets
Core: talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline cellulose.
Film coating: Opadry II. white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate).

What Tolperison-HCl STADA looks like and contents of the pack

What Tolperison-HCl STADA looks like:

Tolperison-HCl STADA 50 mg film-coated tablet
White, round, biconvex, film-coated tablets, debossed with “50” in one side and on the other side with special code.

Tolperison-HCl STADA 150 mg film-coated tablet
White, round, biconvex, film-coated tablets, debossed with “150” in one side and on the other side with special code.

Contents of the pack:

20 or 30 or 50 or 100 film-coated tablets in colourless, transparent PVC/Al blister pack and carton box.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

To be completed nationally.

This medicinal product is authorised in the Member States of the EEA under the following names

Germany	Tolperison-HCl STADA 50 mg Filmtabletten Tolperison-HCl STADA 150 mg Filmtabletten
Hungary	Tolperisone STADA 50 mg filmtabletta Tolperisone STADA 150 mg filmtabletta

This leaflet was last approved in

To be completed nationally.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tolperison-HCl dura 50 mg film-coated tablets
Tolperison-HCl dura 150 mg film-coated tablets
tolperisone hydrochloride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

2. WHAT TOLPERISON-HCL DURA IS AND WHAT IT IS USED FOR

It is used for the treatment of spasticity of the skeletal muscles.

4. BEFORE YOU TAKE TOLPERISON-HCL DURA

Do not take Tolperison-HCl dura
- if you are allergic (hypersensitive) to tolperisone or any of the other ingredients of Tolperison-HCl dura;
- if you suffer from myasthenia gravis (an immunological disease associated with muscle weakness);
- if you breastfeed your child.

Take special care with Tolperison-HCl dura
If you are already receiving antihypertensive therapy please consult your doctor before treatment with this product.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Interactions may occur, if Tolperison-HCl dura is used concomitantly with one of the following drugs:

- certain other medicines, to relax the muscles (centrally acting muscle relaxants)
- certain medicines to treat pain and inflammation (non-steroidal anti-inflammatory drugs - NSAIDs)

- other medicines, which may influence the metabolism of tolperison.

Please ask your doctor. He may decide to adjust the dosage.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Pregnancy
Tell your doctor if you think you are pregnant or planning pregnancy. Although there is no evidence that tolperisone is harmful to the foetus, your doctor should decide based on careful evaluation of the benefit/risk ratio weather you can use this preparation or not, especially in the first three months of pregnancy.
Breast-feeding
Tolperison-HCl dura must not be used during breast-feeding.

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

Important information about some of the ingredients of Tolperison-HCl dura
This medicine contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

5. HOW TO TAKE TOLPERISON-HCL DURA

Always take Tolperison-HCl dura exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If not instructed otherwise, the usual dose of Tolperison-HCl dura 50 mg film-coated tablets for adults and adolescents from age 15 is 3 x 1-3 film-coated tablets (3 x 50-150 mg tolperisone hydrochloride) daily. The daily dose of Tolperison-HCl dura 150 mg film-coated tablets for adults and adolescents from age 15 is 3 x 1 (3 x 150 mg tolperisone hydrochloride) film-coated tablets.

For oral use.
It is recommended to take ***Tolperison-HCl dura*** after meals.

If you take more Tolperison-HCl dura than you should
In case of overdose you should contact your doctor immediately.

If you forget to take Tolperison-HCl dura
Do not take a double dose to make up for a forgotten tablet. Skip the missed dose and take your next tablet at the ususal time.

If you stop taking Tolperison-HCl dura
Do not stop taking Tolperison-HCl dura if you feel well, only if your doctor instructs you to do so. Your doctor tells you how long you should take Tolperison-HCl dura for.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tolperison-HCl dura can cause side effects, although not everybody gets them.

Side effects are arranged according to frequency as follows:

very common: affects more than 1 user in 10
common: affects 1 to 10 users in 100
uncommon: affects 1 to 10 users in 1,000
rare: affects 1 to 10 users in 10,000
very rare: affects less than 1 user in 10,000
not known: frequency cannot be estimated from the available data

Nervous system disorders:
Uncommon: dizziness, sleepiness
Rare: headache, sleep disturbance

Gastrointestinal disorders:
Uncommon: abdominal discomfort, nausea, vomiting, dry mouth, abdominal pain
Rare: constipation, diarrhoea, gastrointestinal disturbance

Skin and subcutaneous tissue disorders:
Rare: increased sweating

Psychiatric disorders:
Uncommon: fatigue, lassitude, weakness
Uncommon:

Immune system dysorders:
Rare: hypersensitivity reaction with erythema, exanthema, pruritus, blood pressure decreased and increased heart rate
Very rare: hypersensitivity reaction with urticaria, dyspnoea, angioneurotic oedema in single cases, anaphylactic shock
In cases of any hypersensitivity reaction, the administration of ***Tolperison-HCl dura*** should be discontinued.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TOLPERISON-HCL DURA

Keep out of the reach and sight of children.

Do not use Tolperison-HCl dura after the expiry date which is stated on the blister and the carton after (EXP). The expiry date refers to the last day of that month.

Do not store above 30 ^{o}C.

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tolperison-HCl dura contains

- The active substance is tolperisone hydrochloride.

Tolperison-HCl dura 50 mg film-coated tablets
Each tablet contains 50 mg tolperisone hydrochloride.

Tolperison-HCl dura 150 mg film-coated tablets
Each tablet contains 150 mg tolperisone hydrochloride.

- The other ingredients are:

Tolperison-HCl dura 50 mg film-coated tablets
Core: talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline cellulose.
Film coating: Opadry II. white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate).

Tolperison-HCl dura 150 mg film-coated tablets
Core: talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline cellulose.
Film coating: Opadry II. white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate).

What Tolperison-HCl dura looks like and contents of the pack

What Tolperison-HCl dura looks like:

Tolperison-HCl dura 50 mg film-coated tablet
White, round, biconvex, film-coated tablets, debossed with “50” in one side and on the other side with special code.

Tolperison-HCl dura 150 mg film-coated tablet
White, round, biconvex, film-coated tablets, debossed with “150” in one side and on the other side with special code.

Contents of the pack:

20 or 30 or 50 or 100 film-coated tablets in colourless, transparent PVC/Al blister pack and carton box.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

To be completed nationally.

This medicinal product is authorised in the Member States of the EEA under the following names

Germany	Tolperison-HCl dura 50 mg Filmtabletten Tolperison-HCl dura 150 mg Filmtabletten
Hungary	Tolperisone STADA 50 mg filmtabletta Tolperisone STADA 150 mg filmtabletta

This leaflet was last approved in

To be completed nationally.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tolperisonhydrochlorid AL 50 mg film-coated tablets
Tolperisonhydrochlorid AL 150 mg film-coated tablets
tolperisone hydrochloride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

3. WHAT TOLPERISONHYDROCHLORID AL IS AND WHAT IT IS USED FOR

It is used for the treatment of spasticity of the skeletal muscles.

6. BEFORE YOU TAKE TOLPERISONHYDROCHLORID AL

Do not take Tolperisonhydrochlorid AL
- if you are allergic (hypersensitive) to tolperisone or any of the other ingredients of Tolperisonhydrochlorid AL;
- if you suffer from myasthenia gravis (an immunological disease associated with muscle weakness);
- if you breastfeed your child.

Take special care with Tolperisonhydrochlorid AL
If you are already receiving antihypertensive therapy please consult your doctor before treatment with this product.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Interactions may occur, if Tolperisonhydrochlorid AL is used concomitantly with one of the following drugs:

- certain other medicines, to relax the muscles (centrally acting muscle relaxants)
- certain medicines to treat pain and inflammation (non-steroidal anti-inflammatory drugs - NSAIDs)

- other medicines, which may influence the metabolism of tolperison.

Please ask your doctor. He may decide to adjust the dosage.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Pregnancy
Tell your doctor if you think you are pregnant or planning pregnancy. Although there is no evidence that tolperisone is harmful to the foetus, your doctor should decide based on careful evaluation of the benefit/risk ratio weather you can use this preparation or not, especially in the first three months of pregnancy.
Breast-feeding
Tolperisonhydrochlorid AL must not be used during breast-feeding.

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

Important information about some of the ingredients of Tolperisonhydrochlorid AL
This medicine contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

7. HOW TO TAKE TOLPERISONHYDROCHLORID AL

Always take Tolperisonhydrochlorid AL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

If not instructed otherwise, the usual dose of Tolperisonhydrochlorid AL 50 mg film-coated tablets for adults and adolescents from age 15 is 3 x 1-3 film-coated tablets (3 x 50-150 mg tolperisone hydrochloride) daily. The daily dose of Tolperisonhydrochlorid AL 150 mg film-coated tablets for adults and adolescents from age 15 is 3 x 1 (3 x 150 mg tolperisone hydrochloride) film-coated tablets.

For oral use.
It is recommended to take ***Tolperisonhydrochlorid AL*** after meals.

If you take more Tolperisonhydrochlorid AL than you should
In case of overdose you should contact your doctor immediately.

If you forget to take Tolperisonhydrochlorid AL
Do not take a double dose to make up for a forgotten tablet. Skip the missed dose and take your next tablet at the ususal time.

If you stop taking Tolperisonhydrochlorid AL
Do not stop taking Tolperisonhydrochlorid AL if you feel well, only if your doctor instructs you to do so. Your doctor tells you how long you should take Tolperisonhydrochlorid AL for.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tolperisonhydrochlorid AL can cause side effects, although not everybody gets them.

Side effects are arranged according to frequency as follows:

very common: affects more than 1 user in 10
common: affects 1 to 10 users in 100
uncommon: affects 1 to 10 users in 1,000
rare: affects 1 to 10 users in 10,000
very rare: affects less than 1 user in 10,000
not known: frequency cannot be estimated from the available data

Nervous system disorders:
Uncommon: dizziness, sleepiness
Rare: headache, sleep disturbance

Gastrointestinal disorders:
Uncommon: abdominal discomfort, nausea, vomiting, dry mouth, abdominal pain
Rare: constipation, diarrhoea, gastrointestinal disturbance

Skin and subcutaneous tissue disorders:
Rare: increased sweating

Psychiatric disorders:
Uncommon: fatigue, lassitude, weakness
Uncommon:

Immune system dysorders:
Rare: hypersensitivity reaction with erythema, exanthema, pruritus, blood pressure decreased and increased heart rate
Very rare: hypersensitivity reaction with urticaria, dyspnoea, angioneurotic oedema in single cases, anaphylactic shock
In cases of any hypersensitivity reaction, the administration of ***Tolperisonhydrochlorid AL*** should be discontinued.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TOLPERISONHYDROCHLORID AL

Keep out of the reach and sight of children.

Do not use Tolperisonhydrochlorid AL after the expiry date which is stated on the blister and the carton after (EXP). The expiry date refers to the last day of that month.

Do not store above 30 ^{o}C.

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tolperisonhydrochlorid AL contains

- The active substance is tolperisone hydrochloride.

Tolperisonhydrochlorid AL 50 mg film-coated tablets
Each tablet contains 50 mg tolperisone hydrochloride.

Tolperisonhydrochlorid AL 150 mg film-coated tablets
Each tablet contains 150 mg tolperisone hydrochloride.

- The other ingredients are:

Tolperisonhydrochlorid AL 50 mg film-coated tablets
Core: talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline cellulose.
Film coating: Opadry II. white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate).

Tolperisonhydrochlorid AL 150 mg film-coated tablets
Core: talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline cellulose.
Film coating: Opadry II. white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate).

What Tolperisonhydrochlorid AL looks like and contents of the pack

What Tolperisonhydrochlorid AL looks like:

Tolperisonhydrochlorid AL 50 mg film-coated tablet
White, round, biconvex, film-coated tablets, debossed with “50” in one side and on the other side with special code.

Tolperisonhydrochlorid AL 150 mg film-coated tablet
White, round, biconvex, film-coated tablets, debossed with “150” in one side and on the other side with special code.

Contents of the pack:

20 or 30 or 50 or 100 film-coated tablets in colourless, transparent PVC/Al blister pack and carton box.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

To be completed nationally.

This medicinal product is authorised in the Member States of the EEA under the following names

Germany	Tolperisonhydrochlorid AL 50 mg Filmtabletten Tolperisonhydrochlorid AL 150 mg Filmtabletten
Hungary	Tolperisone STADA 50 mg filmtabletta Tolperisone STADA 150 mg filmtabletta

This leaflet was last approved in

To be completed nationally.

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Tolperison-HCl STADA 50mg film-coated tablet
tolperisone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg tolperisone hydrochloride.

3. LIST OF EXCIPIENTS

Excipients:
Core: Talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline, cellulose
Film-coating: Opadry II white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate)
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS ON USE

To be completed nationally..

16. INFORMATION IN BRAILLE

Tolperison-HCl STADA 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

blister

1. NAME OF THE MEDICINAL PRODUCT

Tolperison-HCl STADA 50 mg film-coated tablet
tolperisone hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meditop

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Tolperison-HCl STADA 150 mg film-coated tablet
tolperisone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg tolperisone hydrochloride.

3. LIST OF EXCIPIENTS

Excipients:
Core: Talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline, cellulose
Film-coating: Opadry II white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate)
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ^{o}C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS ON USE

To be completed nationally.

16. INFORMATION IN BRAILLE

Tolperison-HCl STADA 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

blister

1. NAME OF THE MEDICINAL PRODUCT

Tolperison-HCl STADA 150 mg film-coated tablets
tolperisone hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meditop

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Tolperison HCl dura 50mg film-coated tablet
tolperisone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg tolperisone hydrochloride.

3. LIST OF EXCIPIENTS

Excipients:
Core: Talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline, cellulose
Film-coating: Opadry II white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate)
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ^{o}C.

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS ON USE

To be completed nationally..

16. INFORMATION IN BRAILLE

Tolperison HCl dura 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

blister

1. NAME OF THE MEDICINAL PRODUCT

Tolperison HCl dura 50 mg film-coated tablet
tolperisone hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meditop

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Tolperison HCl dura 150 mg film-coated tablet
tolperisone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg tolperisone hydrochloride.

3. LIST OF EXCIPIENTS

Excipients:
Core: Talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline, cellulose
Film-coating: Opadry II white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate)
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ^{o}C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS ON USE

To be completed nationally.

16. INFORMATION IN BRAILLE

Tolperison HCl dura 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

blister

1. NAME OF THE MEDICINAL PRODUCT

Tolperison HCl dura 150 mg film-coated tablets
tolperisone hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meditop

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Tolperisonhydrochlorid AL 50mg film-coated tablet
tolperisone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg tolperisone hydrochloride.

3. LIST OF EXCIPIENTS

Excipients:
Core: Talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline, cellulose
Film-coating: Opadry II white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate)
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ^{o}C.

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS ON USE

To be completed nationally..

16. INFORMATION IN BRAILLE

Tolperisonhydrochlorid AL 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

blister

1. NAME OF THE MEDICINAL PRODUCT

Tolperisonhydrochlorid AL 50 mg film-coated tablet
tolperisone hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meditop

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Tolperisonhydrochlorid AL 150 mg film-coated tablet
tolperisone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg tolperisone hydrochloride.

3. LIST OF EXCIPIENTS

Excipients:
Core: Talc, stearic acid, crospovidone, betaine hydrochloride, mannitol, microcrystalline, cellulose
Film-coating: Opadry II white (titanium dioxide (E 171), macrogol 4000, hypromellose, lactose monohydrate)
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS ON USE

To be completed nationally.

16. INFORMATION IN BRAILLE

Tolperisonhydrochlorid AL 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

blister

1. NAME OF THE MEDICINAL PRODUCT

Tolperisonhydrochlorid AL 150 mg film-coated tablets
tolperisone hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meditop

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 5
Scientific discussion during the initial procedure

I. INTRODUCTION

Problem statement

The Marketing Application of Myderison 50 mg and 150 film-coated tablets (tolperisone hydrochloride) has been submitted to the National Institute of Pharmacy in the well established use category by Meditop Pharmaceutical Ltd, Hungary.

The Application for Myderison 50 mg film-coated tablet is submitted under Directive 2001/83/EC Article 10 (1) (a) (ii). For medicinal products with a well established use demonstrated in accordance with Article 10 (1) (a) (ii) of Directive 2001/83/EC as amended (bibliographical application) the mutual recognition procedure is applicable.

About the product

The pharmacologically active substance is the tolperisone (1-piperidino-2-methyl-3-p-totyl-propano-3 hydrochloride). Tolperisone is a centrally acting muscle relaxant which was first synthesized and patented in 1956. Clinical trials have demonstrated in more than four decades that tolperisone is an effective active agent. Tolperisone has been widely used for more than 40 years (from 1959 in Hungary) in the clinical practice in many European and other countries. Many pharmaceutical companies manufacture tolperisone-containing finished products.

The application is based on well-established used of the active pharmaceutical ingredient. The aim of the development was to formulate oral, solid pharmaceutical products containing tolperisone hydrochloride as active ingredient with proper in vitro dissolution. The quantitative composition of the film-coated tablets are proportional.

General comments on the submitted dossier

The dossier was submitted in CTD format. The legal basis for marketing authorization of the products is Consolidated Directive 2001/83/EC Article 10a.
Clinical and non-clinical parts are based on bibliographic data. Most of the pharmacological and clinical examinations with tolperisone were preformed at the end of 1950s and at the beginning of the 1960s. Some non-clinical studies were performed in the recent years by Gedeon Richter Ltd. to clarify the mechanism of action and the metabolic pathways of tolperisone.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The products are manufactured and the bioequivalence study has been conducted in compliance with GMP, GLP, GCP rules, respectively, and agreed ethical principles.

The general quality of the contents of the submitted dossier meets the requirements to well established use applications under Article 10 (1) (a) (ii) of Directive 2001/83/EC.

The Non clinical Overview and the Clinical Overview are of acceptable quality.

II. QUALITY ASPECTS

II.1 Introduction

Tolperisone STADA, Tolperidone MEDITOP and Tolperistad 50 and 150 mg film-coated tablets containing 50 and 150 mg Tolperisone hydrochloride as active substance have been developed for the centrally acting muscle relaxant. The active substance has been widely used for more than forty years in the clinical practice.
The Marketing Authorization Applications of Tolperisone STADA, Tolperidone MEDITOP and Tolperistad 50 mg and 150 mg film-coated tablets are in compliance with the legal category of "well-established medicinal use" according to article 10a of consolidated Directive 2001/83/EC. The innovator's (Gedeon Richter Ltd., Hungary) finished products Mydeton 50 mg and 150 mg film-coated tablets have been registered in Hungary since 1997.
The film-coated tablets will be marketed in dosage strengths of 50 and 150 milligrams and packaged in a clear, colourless PVC//Al blister.

II.2 Discussion on chemical, pharmaceutical and biological aspects

Drug Substance

Data on the quality and manufacture of the active substance was provided in the applicant's dossier/ via European DMF procedure. A letter of access to the DMF was submitted.
INN name: Tolperisone Hydrochloride
Chemical names:
- 2-Methyl-1-(4-methylphenyl)-3-(1-piperidinyl)-1-propanone hydrochloride
- 2,4-Dimethyl-3-piperidinopropiophenone hydrochloride
- (*RS*)-2-Methyl-1-(4-methylphenyl)-3-piperidin-1-ylpropan-1-one monohydrochloride

CAS-No.: 3644-61-9
The active substance is a white, hygroscopic crystalline powder and very soluble in glacial acetic acid, freely soluble in water and ethanol, soluble in acetic anhydride, slightly soluble in acetone, and practically insoluble in water. It has a slight, characteristic odour.
The molecule has a chiral center. The manufacturer consistently produces the racemic form, which has a monograph in the JP.
The proposed manufacturing process has been adequately described, critical steps and accompanying in-process controls have been defined to ensure quality of the final compound. In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.
Evidence of the structure has been confirmed by thermal analysis, FT-IR, NMR, UV and MS spectroscopy.
Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in relation to their origin and potential carry-over into the final drug substance. Residual solvents and heavy metals are routinely controlled.
The substance is not official in the Ph.Eur. Therefore, specification has been set according to current JP and in-house standards for Tolperisone Hydroloride, which includes tests for appearance, solubility, pH, melting range, identification, absorbance, sulphate, heavy metals, loss on drying, residue on ignation, assay (titration), purity (in-house HPLC), residual solvents (in-house GC) and IR spectra.
The specification is in accordance with the Ph.Eur. general monograph on Substances for pharmaceutical use and the ICH Q6A guideline. The substance complies with the requirements of the EMEA guideline on genotoxic impurities.

The specifications reflect all relevant quality attributes of the active substance and were 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
Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.
During the stability studies no significant changes in any parameters were observed. The proposed retest period of 4 years is supported by the supplemented stability data in the typified container with the storage condition: "Store below 25°C."
GMP compliance of the API manufacture is demonstrated by the applicant.

Medicinal Product

The application is based on well-established use of the active pharmaceutical ingredient.
The aim of the development was to formulate oral, solid pharmaceutical products containing Tolperisone Hydrochloride as active ingredient with proper in vitro dissolution.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
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 composition, appearance and packaging was obtained. The used excipients in the finished product are: talc, stearic acid, crospovidone, betaine hydrochloride, mannitol and microcrystalline cellulose. The white film-coating contains titanium dioxide (E 171), macrogol 4000, hypromellose and lactose monohydrate. All excipients used comply with their respective European Pharmacopoeia monograph, (with exception of betaine hydrocloride, which comply with USP). Compliance of the product with the general monograh of the European Pharmacopoeia on the Products with the risk of TSE has been demonstrated by the applicant.
The 50 mg film-coated tablet is white, round, biconvex, film-coated tablets, debossed with '50' in one side and on the other side with special code, diameter ~7.0 mm.
The 150 mg film-coated tablet is white, round, biconvex, film-coated tablets, debossed with '150' in one side and on the other side with special code, diameter ~10 mm.
The tablets are packaged in clear, colorless PVC/Al blister.
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 European pharmacopoeia 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. Certificates of analysis was also provided for the working standard used.
The container clousure system of the product is as follows: clear, colorless PVC/Al blister.
Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results , a shelf-life of 5 years (50 mg) or 4 years (150 mg) with storage condition of "Do not store above 30 ^{o}C. The preparation should be stored in the original package." is approved.
The SPC, PIL and label are pharmaceutically acceptable.
.

II.3 Conclusion on the quality of the product

The product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The Applicant collected and summarised non clinical literature data on tolperisone hydrochloride with special regard to scientific data published by the originator, Gedeon Richter Ltd.

III.2 Pharmacology

Tolperisone is a centrally acting muscle relaxant. The precise mechanism of action is not known. Due to its membrane stabilising and local anaesthetic effects tolperisone inhibits conductance of the primary afferent nerve fibres, therefore inhibits spinal mono- and polysynaptic reflexes. Besides, tolperisone supposedly inhibits neurotransmitter release due to secondary mechanism by inhibiting synaptic calcium inflow. Tolperisone inhibits reticulospinal reflex facilitation in the brain stem. In animal models tolperisone reduces decerebration muscle tone elevation and rigidity.
Tolperisone increases peripheral blood circulation. The circulation enhancing effect is independent from the effects on the central nervous system. The weak spasmolytic and anti-adrenerg effects of tolperisone may have some role in the development of the circulation enhancing effect.

III.3 Pharmacokinetics

Pharmacokinetics of oral tolperisone hydrochloride has been evaluated in *in vivo* in animal and human studies and *in vitro* in human liver microsomes and recombined enzymes.
In rats administered by 10 mg/kg tolperisone iv.
Results from the published literature are summarised in the Nonclinical Overview.

III.4 Toxicology

Animal toxicity and human safety data on tolperisone were generated by the originator, Gedeon Richter Ltd. A detailed clinical safety review is presented in the Clinical Overview (safety, interactions and adverse effects). In human clinical trials tolperison has had very favourable and benign safety profile.

III.5 Ecotoxicity/environmental risk assessment

N/A

III.6 Discussion on the non-clinical aspects

The non-clinical dossier based on literature data. The Applicant has not conducted any toxicological and/or pharmacological studies with Myderison 50 mg film-coated tablet or any other tolperisone hydrochloride preparations.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Marketing Application of Tolperison Stada, Tolperison Meditop and Tolperistad 50 mg and 150 film-coated tablets (tolperisone hydrochloride) has been submitted to the National Institute of Pharmacy in the well established use category by Meditop Pharmaceutical Ltd, Hungary.

IV.2 Pharmacokinetics

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.
Tolperisone is extensively metabolised in the liver and kidneys. 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.

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 the Central and Eastern-European countries.

IV.4 Discussion on the clinical aspects

Tolperison is a well known drug and therefore the risk/benefit ratio is also well known.
Based on the available data the NIP concluded that the benefits of Tolperison Stada, Tolperison Meditop and Tolperistad 50 mg and 150 film-coated tablets outweigh the risks. The CMS agreed.

IV.5 Clinical efficacy

Current indications of tolperisone 50 mg and 150 mg film-tablet are supported by clinical studies (partly in randomised, blinded, placebo controlled trials), retrospective and observational studies and open trials:

IV.6 Clinical safety

In human clinical trials tolperisone has had a benign safety profile. In rare cases muscular weakness, headache, hypotension, nausea, fatigue, sleepiness and diarrhoea were observed. However, in a double-blind study neither tolperisone-related sedation, nor interaction between alcohol and tolperisone was observed.

Hypersensitivity reactions may occur. The symptoms in some cases can be as severe as anaphylactic shock.

Environmental Risk Assessment
The possible environmental risk of tolperisone HCL was evaluated by ECOSAR program developed by US EPA (Environmental Protection Agency). The structure-activity relationships (SARs) are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class

program are based upon the octanol/water partition coefficient (Kow). The estimated organic carbon sorption coefficient (Koc) is 8.6 for tolperisone. Regarding this and the relatively high water solubility of this molecule, **no bio-concentration is expected**. This means that **this substance will concentrate in the aquatic environment,** so ground water assessment was not done. The predicted no effects concentration (PNEC) was determined by taking the Chronic Value of the most sensitive species [green algae, chronic value (ChV) = 67 mg/L)] and dividing this value by an assessment safety factor of 1000 (worst case) giving a Predicted No Effect Concentration (PNEC) aquatic of 0.067mg/L (67 microgram/L. The PEC/PNEC (2,25/67 = 0,033) ration determined for the aquatic environment is significantly less than 1, indicating no immediate concern to the aquatic compartment.

Pharmacovigilance System

The submitted Description of Pharmacovigilance system (June 2008) was supplemented during the procedure thus it can be stated that it fulfils the fundamental requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance (QPPV) and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

Due to its long lasting (40-year) , to its relative positive benefit-risk ratio and as neither the innovator nor any other MAHs have implemented any special measures for risk minimisation, the applicant proposed to use the routine pharmacovigilance system as described in Volume 9 and has not plan to install special measures for risk minimisation of Myderison 50 mg and 150 mg film-coated tablets. This conception was accepted.

Periodic Safety Update Report (PSUR) cycle

The applicant has stated to submit PSUR every six month after authorisation during the first two years and once a year for the following two years. Thereafter, the reports will be submitted at three –yearly intervals. This statement was accepted but it was completed that PSUR shall be submitted immediately upon request.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application contains an adequate review of published clinical data and the bioequivalence with reference product has been shown. Safety profile of tolperison hydrochlorid is well known and an appropriate system is available at the MAH to monitor and report clinical safety of the product. Quality of the products is adequately drawn up to support the consistent safety and efficacy of the tablets. Approval was recommended by the RMS and agreed by the CMSs.

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 6
Steps taken after the initial procedure with an influence on the Public Assessment Report

Module 6: Steps taken after the initial procedure with an influence on the Public Assessment Repor (Type II variations, PSURs, commitments) Scope	Procedure number	Type of modification [1]	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
	HU/H/0200/001/II/003	Type II	20.05.2009.	05.11.2009.	Approved	
Y/N (version)						