Product Information as approved by the CHMP on 21 November 2013, pending endorsement by the European Commission

Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflets

SUMMARY OF PRODUCT CHARACTERISTICS

[this wording should be inserted]

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards.

4.2 Posology and method of administration

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

Posology
o *For the oral form 4 mg and 8 mg:*
The recommended and maximal dose is 8 mg every 12 hours (i.e. 16 mg per day). The treatment duration is limited to 7 consecutive days.

o *For IM form:*
The recommended and maximal dose is 4 mg every 12 hours (i.e. 8 mg per day). The treatment duration is limited to 5 consecutive days.

o *Both for oral and for IM:*
Doses exceeding recommended doses or long-term use should be avoided (see section 4.4).

Paediatric population
<Invented name> should not be used in children and adolescents under 16 years of age because of safety concerns (see section 5.3).

Method of administration
[To be completed nationally]

4.3 Contraindications

[the wording below should be inserted]

Thiocolchicoside must not be used
- in patients hypersensitive to the active substance or to any of the excipients listed in section 6.1
- during the entire pregnancy period
- during lactation
- in women of childbearing potential not using contraception.

4.4 Special warnings and precautions for use

[the wording below should be inserted]

[…]
Preclinical studies showed that one of thiocolcoside metabolites (SL59.0955) induced aneuploidy (i.e.

unequal number of chromosomes in dividing cells) at concentrations close to human exposure observed at doses 8 mg twice daily per os (see section 5.3). Aneuploidy is considered as a risk factor for teratogenicity, embryo/foeto-toxicity, spontaneous abortion, and impaired male fertility and a potential risk factor for cancer. As a precautionary measure, use of the product at doses exceeding the recommended dose or long-term use should be avoided (see section 4.2).

Patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed.

4.6 Fertility, pregnancy and lactation

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

[…]

Pregnancy
There are limited data on the use of thiocolchicoside in pregnant women. Therefore, the potential hazards for the embryo and foetus are unknown.
Studies in animals have shown teratogenic effects (see section 5.3).
<Invented name> is contraindicated during pregnancy and in women of childbearing potential not using contraception (see section 4.3).

Breastfeeding
Since it passes into the mother's milk, the use of thiocolchicoside is contraindicated during breastfeeding (see section 4.3).

Fertility
In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is a risk factor for impairment of human fertility (see section 5.3).

4.8 Undesirable effects

[…]

[the wording below should be inserted]

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

*[*For the printed material, please refer to the guidance of the annotated QRD template.]*
[…]

5. PHARMACOLOGICAL PROPERTIES

5.2 Pharmacokinetic properties

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

Absorption
- After IM administration, thiocolchicoside Cmax occur in 30 min and .reach values of 113 ng/mL after a 4 mg dose and 175 ng/mL after a 8 mg dose. The corresponding values of AUC are respectively 283 and 417 ng.h/mL.
The pharmacologically active metabolite SL18.0740 is also observed at lower concentrations with a Cmax of 11.7 ng/mL occurring 5 h post dose and an AUC of 83 ng.h/mL.

No data are available for the inactive metabolite SL59.0955.
- After oral administration, no thiocolchicoside is detected in plasma. Only two metabolites are observed:
The pharmacologically active metabolite SL18.0740 and an inactive metabolite SL59.0955. For both metabolites, maximum plasma concentrations occur 1hour after thiocolchicoside administration. After a single oral dose of 8 mg of thiocolchicoside the Cmax and AUC of SL18.0740 are about 60 ng/mL and 130 ng.h/mL respectively. For SL59.0955 these values are much lower: Cmax around 13 ng/mL and AUC ranging from 15.5 ng.h/mL (until 3h) to 39.7 ng.h/mL (until 24h).
Distribution
The apparent volume of distribution of thiocolchicoside is estimated around 42.7 L after an IM administration of 8 mg. No data are available for both metabolites.
Biotransformation
After oral administration, thiocolchicoside is first metabolized in the aglycon 3-demethyltiocolchicine or SL59.0955. This step mainly occurs by intestinal metabolism explaining the lack of circulating unchanged thiocolchicoside by this route of administration.
SL59.0955 is then glucuroconjugated into SL18.0740 which has equipotent pharmacological activity to thiocolchicoside and thus supports the pharmacological activity after oral administration of thiocolchicoside. SL59.0955 is also demethylated into didemethyl-thiocolchicine.
Elimination
- After IM administration the apparent $t_{1/2}$ of thiocolchicoside is 1.5h and the plasma clearance 19.2 L/h.
- After oral administration, total radioactivity is mainly excreted in feces (79%) while urinary excretion represents only 20%. No unchanged thiocolchicoside is excreted either in urine or feces. SL18.0740 and SL59.0955 are found in urine and feces while the didemethyl-thiocolchicine is only recovered in feces.
After oral administration of thiocolchicoside, the SL18.0740 metabolite is eliminated with an apparent $t_{1/2}$ ranging from 3.2 to 7 hours and the metabolite SL59.0955 has a $t_{1/2}$ averaging 0.8h.

5.3 Preclinical safety data

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

Thiocolchicoside profile has been assessed *in vitro,* and *in vivo* following parenteral and oral administration.
Thiocolchicoside was well tolerated following oral administration for periods of up to 6 months in both the rat and the non-human primate when administered at repeated doses of less than or equal to 2 mg/kg/day in the rat and less or equal to 2.5 mg/kg/day in non-human primate, and by the intramuscular route in the primate at repeated doses up to 0.5 mg/kg/day for 4 weeks.
At high doses, thiocolchicoside induced emesis in dog, diarrhoea in rat and convulsions in both rodents and non-rodents after acute administration by oral route.
After repeated administration, thiocolchicoside induced gastro-intestinal disorders (enteritis, emesis) by oral route and emesis by IM route.
Thiocolchicoside itself did not induce gene mutation in bacteria (Ames test), *in vitro* chromosomal damage (chromosome aberration test in human lymphocytes) and *in vivo* chromosomal damage (*in vivo* micronucleus in mouse bone marrow administered intraperitoneally).
The major glucuro-conjugated metabolite SL18.0740 did not induce gene mutation in bacteria (Ames test); however it induced *in vitro* chromosomal damage (*in vitro* micronucleus test on human lymphocytes) and *in vivo* chromosomal damage (*in vivo* micronucleus test in mouse bone marrow administered orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH centromere staining), suggesting aneugenic properties. The aneugenic effect of SL18.0740 was observed at concentrations in the *in vitro* test and at AUC plasma exposures in the *in vivo* test higher (more than 10 fold based on AUC) than those observed in human plasma at therapeutic doses.
The aglycon metabolite (3-demethylthiocolchicine-SL59.0955) formed mainly after oral administration induced *in vitro* chromosomal damage (*in vitro* micronucleus test on human lymphocytes) and *in vivo* chromosomal damage (*in vivo* oral micronucleus test in rat bone marrow administred orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH or CREST centromere staining), suggesting aneugenic properties. The aneugenic effect of SL59.0955 was observed at concentrations in the *in vitro* test and at exposures in the *in vivo* test close to those observed in human plasma at therapeutic doses of 8 mg twice daily per os. Aneugenic effect in dividing cells may result in aneuploid cells. Aneuploidy is a modification in the number of chromosomes and loss of heterozygosity, which is recognized as a

risk factor for teratogenicity, embryotoxicity/ spontaneous abortion, impaired male fertility, when impacting germ cells and a potential risk factor for cancer when impacting somatic cells. The presence of the aglycon metabolite (3-demethylthiocolchicine-SL59.0955) after intramuscular administration has never been assessed, therefore its formation using this route of administration can not be excluded.
In the rat, an oral dose of 12 mg/kg/day of thiocolchicoside caused major malformations along with foetotoxicity (retarded growth, embryo death, impairment of sex distribution rate). The dose without toxic effect was 3 mg/kg/day.

In the rabbit, thiocolchicoside showed maternotoxicity starting from 24 mg/kg/day. Furthermore, minor abnormalities have been observed (supernumerary ribs, retarded ossification).

In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg/day, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is recognised as a risk factor for impairment of human fertility.
The carcinogenic potential was not evaluated.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

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

30 tablets/capsules for the 4mg dose and 14 tablets/capsules for the 8mg dose.

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for capsules, hard / tablets / orodispersible tablets and solution for injection

4. PHARMACEUTICAL FORM AND CONTENTS

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

4 mg
[up to 30] hard capsules
[up to 30] tablets

8 mg
[up to 14] hard capsules
[up to14] orodispersible tablets

4 mg/2 ml
[up to 10] vials/ampoules

PACKAGE LEAFLET

[This wording should be inserted]

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

[…]

PL

Package leaflet: Information for the patient

1. What X is and what it is used for

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

This medicine is a muscle relaxant. It is used in adults and adolescents from 16 years onwards as an adjuvant treatment for painful muscular contractions. It is to be used for acute conditions related to spinal column.

2. What you need to know before you take X

[the wording below should be inserted]

Do not take X if:
- you are allergic to thiocolchicoside or any of the other ingredients of this medicine (listed in section 6)
- you are pregnant, might become pregnant or think you may be pregnant
- you are a woman of childbearing potential not using contraception
- you are breast feeding

Warnings and precautions
[…]
Strictly respect the doses and duration of treatment detailed in section 3. You should not use this medicine at higher dose or for longer than 7 days *(for oral forms)*/5 days *(for IM forms).* This is because one of the products formed in your body when taking thiocolchicoside at high doses might cause damage to some cells (abnormal number of chromosomes). This has been shown in studies in animals and in laboratory studies. In humans, this type of damage to cells is a risk factor for cancer, harm to the unborn child, and impairment of male fertility. Please discuss with your doctor if you have further questions.

Your doctor will inform you about all measures relating to an effective contraception and about the potential risk of a pregnancy.

Children and adolescents
Do not give this medicine to children and adolescents below 16 years old because of safety concerns.

Pregnancy, breast-feeding and fertility

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

Do not take this medicine if:
- you are pregnant, might become pregnant or think you may be pregnant
- you are a woman of childbearing potential not using contraception

This is because this medicine may harm your unborn child. Do not take this medicine if you are breast-feeding. This is because the medicine passes into your breast-milk.
This medicine might cause problems to the male fertility due to potential damage to sperm cells (abnormal number of chromosomes). This is based on laboratory studies (see section 2 “Warnings and precautions”).

3. How to take X
[the currently approved wording should be deleted and replaced by the following]

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
o *For the oral form 4 mg and 8 mg:*
The recommended and maximal dose is 8 mg every 12 hours (i.e. 16 mg per day). The treatment duration is limited to 7 consecutive days.
o *For intramuscular form:*
The recommended and maximal dose is 4 mg every 12 hours (i.e. 8 mg per day). The treatment duration is limited to 5 consecutive days.
o *Both for oral and for intramuscular forms:*
Do not exceed the recommended doses and treatment duration.
This medicine should not be used for long-term treatment (see section 2 “Warnings and precautions”).
Use in children and adolescents
Do not give this medicine to children and adolescents below 16 years old because of safety concerns.
If you take more X than you should
If you accidentally take more X than you should talk to your doctor, pharmacist or nurse.
If you forget to take X
Do not take a double dose to make up for a forgotten dose.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

[This wording should be inserted]

Like all medicines, this medicine can cause side effects, although not everybody gets them.
[…]
[the wording below should be inserted]

> **Reporting of side effects**
> If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via {the national reporting system listed in Appendix V}*. By reporting side effects you can help provide more information on the safety of this medicine.
>
> *[*For the printed material, please refer to the guidance of the annotated QRD template.]*

6. Contents of the pack and other information

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

30 tablets/capsules for the 4mg dose and 14 tablets/capsules for the 8mg dose.