SUMMARY OF PRODUCT CHARACTERISTICS

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.

1. NAME OF MEDICINAL

MuscorRil 4mg rigid capsule
MuscoRil 8mg rigid capsule
MuscoRil 8mg orodispersible tablets
MuscoRil 4mg/2ml injectable solution for intramuscular use.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MuscoRil 4mg rigid capsules
Every capsule contains:
Active ingredient: thiocolchicoside 4mg
Excipients with noted effects: lactose 218,3mg

MuscoRil 8mg rigid capsules
Every capsule contains:
Active ingredient: thiocolchicoside 8mg
Excipients with noted effects: lactose 214,3mg

MuscoRil 8mg orodispersible tablets
Every capsule contains:
Active ingredient: thiocolchicoside 8mg
Excipients with noted effects: aspartame 7,6mg

MuscoRil 4mg/2ml injectable solution for intamuscular use
Each vial contains:
Active ingredient: thiocolchicoside 4mg
Excipients with noted effects: sodium chloride 16,8mg equivalent to 6,66mg of sodium(0,3mmol)

For the full list of excipients see paragraph 6.1

3. PHARMACEUTICAL FORM

Rigid capsules:
Transparent capsules containing 4mg granules
Whitish-yellow capsules containing 8mg granules
Orodispersible tablets:
Flat,round,bevelled, slightly yellow tablets
Injectable solution for intramuscular use.
2ml glass vial containing a yellow clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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
Muscoril should not be used in children and adolescents under 16 years of age because of safety concerns (see section 5.3).

Method of administration
MuscoRil 8mg orodispersible tablets:
Dissolve the orodispersible tablet in the mouth with or without water.

4.3 Contraindications
Thiocolchicoside must not be used
- in patients hypersensitive to the active substance or to any of the excipients listed in section 6.1
- in patients with flaccid paralysis, hypotone muscle.
- during the entire pregnancy period
- during lactation
- in women of childbearing potential not using contraception.

4.4 Special warnings and precautions for use

The dose must be reduced in case of presence of diarrhoea following oral administration.
After administration by intramuscular route episodes were observed of vasovagal syncope, thus the patient has to be monitored after being injected (see paragraph 4.8)
Post marketing cases of cytolytic hepatitis and cholestatic were reported with thiocolchicoside.
The serious cases (for example fulminant hepatitis) were observed in patients that had taken FANS or paracetamol at the same time. The patients have to be informed to report any sign of hepatic toxicity (see paragraph 4.8).
Thiocolchicoside may precipitate seizures especially in epileptic patients or those at risk of convulsions (see paragraph 4.8).
The maximum daily oral dose of 16mg must not be exceeded and must be split in two doses at 12 hour interval.
In case you forget to take a dose take the next dose avoiding taking doses close to each other.

Preclinical studies showed that one of thiocolcoside metabolites (SL59.0955) induced aneuploidy (i.e. alterations in the 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.

Important information on some excipients
MuscoRil 4mg rigid capsules and MuscoRil 8mg rigid capsules contain lactose. Patients affected with rare hereditary problems of intolerance to galactose, deficit of Lapp lactose, or malabsorption of glucose/galactose, should not take this medicine.
MuscoRil 8mg orodispersible tablets contain aspartame. This medicine contains a source of phenylalanine. It could cause harm if if you have phenylketonuria.
MuscoRil 4mg/2ml injectable solution for intamuscular use contains less than 1 mmol (23mg), of sodium per dose, therefore it is practically ‘sodium free’

4.5 Interaction with other medicines and other forms of interaction
No studies on interactions were carried out.

4.6 Fertility, pregnancy and lactation

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).
Muscoril 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).

4.7 Effects on ability on driving and the use of machinery

No studies were carried out on the ability to drive or use of machinery.
So if drowsiness is a common occurrence, this must be taken in account when driving or using machinery.

4.8 Undesirable effects

Disturbances in immunity system

Anaphylactic reactions:
Uncommon: pruritis,
Rare: urticarial
Very rare: hypotension
Not noted: angiodoema and anaphylactic shock after intramuscular administration.

Pathology of the nervous system

Common: drowsiness (see paragraph 4.7)
Rare: agitation and clouding
Not noted: malaise associated or to a lesser extent vasovagal syncope in the minutes following intramuscular administration, convulsions (see paragraph 4.4).

Gastrointestinal pathology

Common: diarrhoea (see paragraph 4.4), stomach pain
Uncommon: nausea, vomiting
Rare: heartburn after oral administration

Hepatobiliary pathology

Not noted: cytolytic hepatitis and cholestatic (see paragraph 4.4).

Pathology of the skin and subcutaneous tissue

Uncommon: allergic skin reactions

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 at address www.agenziafarmaco.gov.it/it/responsabili.

4.9 Overdosage

Overdosage was not noted or reported in any literature.

In case of overdosage it is recommended to get medical attention and implement symptomatic measures (see paragraph 5.3)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacokinetic properties

Pharmacotherapeutic category: Other muscle relaxant with central action
ATC code: M03BX05
Thiocolchicoside is a semisynthetic sulphide derivative of colchicoside, showing muscle relaxant pharmacological activity.
In vitro thiocolchicoside binds solely with gaba receptors and glycinergic stricnine sensitive. From the moment that thiocolchicoside acts as an antagonist of the gaba receptors, its muscle relaxant effect may be exercised to a supraspinal level, through a regulatory mechanism even though the glycinergic mechanism of action cannot be excluded. The characteristics of interaction with the gaba receptors are qualitative and quantitative divided between thiocolchicoside and its main circulating metabolite, the derivative glucuronidated (see paragraph 5.2)
In vivo the muscle relaxant properties of thiocolchicoside and its main metabolite have been shown in various predictive models of rat and rabbit.
The lack of muscle relaxant effect of thiocolchicoside in spineless rat suggests a predominant supraspinal activity.
Also electrocephalographic studies have shown that thiocolchicoside and its main metabolite are devoid of any sedative effect.

5.2 Pharmacokinatic properties

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 SL59.0955.22
- 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
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 (3-23 demethylthiocolchicine-SL59.0955) after intramuscular administration has never been assessed, therefore its formation using this route of administration cannot 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. PHARMACEUTICAL INFORMATION

6.1 List of excipients

MuscoRil 4mg rigid capsules
Every capsule contains:
monohydrate lactose, corn starch, magnesium stearate, *excipient of the casing:* gelatin (transparent capsule)
MuscoRil 8mg rigid capsules
monohydrate lactose, corn starch, magnesium stearate, *excipient of the casing:* gelatin, titanium dioxide, yellow ferrous oxide (capsule white-yellow n.2)
MuscoRil 8mg orodispersible tablets
crospovidone, aspartame, mannitol, magnesium stearate
MuscoRil 4mg/2ml injectable solution for intamuscular use
sodium chloride, hydrochloric acid 1M, water for preparing injection

6.2 Incompatibilities
Irrelevant

It is possible for the extemporaneous association in the syringe of the MuscoRil vial for special parenteral administration of:tenoxicam,peroxicam,ketoprofen,ketorolac trometamine, diclofenac sodium, acetylsalicylate lysinate, betamethasone disodium phosphate, cyanocobalamine (vit B12) vitamin B1,B6 and B12 complex.

6.3 Validity period

MuscorRil 4mg rigid capsule: 5 years
MuscoRil 8mg rigid capsule: 2 years
MuscoRil 8mg orodispersible tablets: 3 years
MuscoRil 4mg/2ml injectable solution for intramuscular use: 3 years

6.4 Particular precautions for storage

MuscoRil 4mg rigid capsule and MuscoRil 8mg rigid capsule:
Store at temperature not more than 30^0C
Muscoril 8mg orodispersible tablets and 4mg/2ml injectable solution:
This medicine does not require any particular storage condition

6.5 Nature and contents of container

*MuscoRil 4mg rigid capsule:*Cardboard box containing 30 capsules in blister PVC/Aluminium
*MuscoRil 8mg rigid capsule:*Cardboard box containing 14 capsules in blister PVC/Aluminium
*Muscoril 8mg orodispersible tablets:*Cardboard box containing 14 tablets in blister of polyamide,aluminium,PVC/Aluminium
*MuscoRil 4mg/2ml injectable solution for intramuscular use:*Cardboard box containing 6 white glass vials of 2ml

6.6. Instructions for use and handling

No particular instructions

7. HOLDER OF THE MARKETING AUTHORIZATION

Sanofi S.p.A. – Viale L. Bodio, 37/B- Milano

8. MARKETING AUTHORISATION NUMBERS

MuscorRil 4mg rigid capsule – 30 capsules…… AIC n. 015896107
MuscoRil 8mg rigid capsule – 14 capsules…… AIC n. 015896119
MuscoRil 8mg orodispersible tablets – 14 tablets …… AIC n. 015896121
MuscoRil 4mg/2ml injectable solution for intramuscular use – 6 vials of 2ml…… AIC n. 015896018

9. DATE OF FIRST AUTHORISATION/RENEWAL

MuscoRil 4mg rigid capsules: - Authorisation: 23.01.1960. Renewal 01.06.2005
MuscoRil 4mg/2ml injectable solution for intramuscular use: Authorisation: 23.01.1959 Renewal 01.06.2005
Muscoril 8mg rigid capsule -: Authorisation: 27.02.2008.
Muscoril 8mg orodispersible tablets -: Authorisation: 05.05.2010.

10. DATE OF REVISION OF TEXT

Determined by AIFA May 2015