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SCIENCE MEDICINES HEALTH

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Assessment report

Thiocolchicoside containing medicinal products for systemic use

Referral under Article 31 of Directive 2001/83/EC

INN: thiocolchicoside

Procedure number: EMEA/H/A-1361

Note

Assessment Report as adopted by the CHMP with all the information of a commercially confidential nature deleted.



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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 15 February 2013, Italy triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the indication of thiocolchicoside-containing medicinal products for systemic use should be restricted and/or other regulatory measures should be taken.

The procedure described in Article 32 of Directive 2001/83/EC, was applicable.

2. Scientific discussion

2.1. Introduction

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity. Muscle relaxants are one of the many treatments currently employed in the management of non-specific low back pain. TCC is indicated for the treatment of painful muscular contractures in different settings (in rheumatological and/or orthopaedic conditions). Widely used by prescribers in the concerned Member States (MSs) (see Annex I), the benefits of TCC containing medicinal products are recognised in clinical practice. In addition, an indication for symptoms in Parkinson's disease was registered in one Member State.

Thiocolchicoside is available under different pharmaceutical forms for systemic use: hard capsules, tablets and solution for intramuscular injection (IM). The use of oral (PO) versus parenteral formulation varies considerably between MSs, as well as treatment duration. Short-term use is 5 to 7 days; long term use exceeds 15 days. For PO, the daily recommended dose is 16 mg (5 MSs). Only in one case (2 MSs) a daily dose of 24 mg is reported. For IM, the daily dose is 8 mg in most of the cases. In only one case the maximum daily dosage is 12 mg.

The majority of the TCC-containing medicinal products are contraindicated during pregnancy and lactation. Paediatric use is contraindicated in only 2 MSs, all other MSs either include it as a warning (1 MS), or do not recommend use below 15 years old (5 MSs). In general there are differences in contraindications and warnings and precaution among different products and MSs.

After discontinuation by a Company of a phase I clinical trial with TCC because of new non-clinical findings, the Italian medicines agency (AIFA) requested one of the Marketing Authorisation Holders (MAH) of TCC to further investigate the genotoxic potential of TCC and in particular of its metabolites; the MAH was requested to perform *in vivo* and *in vitro* preclinical studies to address the potential genotoxicity of the metabolites of TCC. The results obtained from one of the metabolites' studies (metabolite SL59.0955, M2) led to concerns: new data on the aneugenic effect of the M2 metabolite of TCC generated from the submitted preclinical studies indicated a signal of genotoxic potential.

In view of the above, on 15 February 2013, Italy requested the CHMP, under Article 31 of Directive 2001/83/EC, to assess the above concerns regarding aneuploidy and its impact on the benefit-risk balance for TCC containing medicinal products for systemic use. The CHMP was asked to give its opinion on whether the indication of TCC containing medicinal products should be restricted and/or other regulatory measures should be taken. On 21 February 2013, the CHMP started a referral procedure for TCC containing medicinal products.

Aneuploidy (variation in the number of chromosomes and loss of heterozygosity) is recognised as a potential risk factor for cancer when impacting somatic cells, and teratogenicity, embryo-toxicity/spontaneous abortions and impaired male fertility when impacting germ cells¹. For the purpose of the review of this risk, the MAHs provided an analysis of this genotoxic potential for each systemic route of administration, together with an analysis of possible risk factors, including relevant criteria such as dose and duration of treatment. The CHMP reviewed all available data from pre-clinical and clinical studies, literature and post-marketing experience on aneuploidy for TCC containing medicinal products for systemic use.

¹ Parry 2000 & 2002; Kirsch-Volders 2002

2.2. Pre-clinical studies

The preclinical development of TCC was mainly performed during the 1980s, and then complemented in the 1990s to be compliant with the European guidelines on the non-clinical documentation for mixed marketing authorisation applications (CPMP/SWP/799/95) and to investigate a new active metabolite SL18.0740 (M1) identified at that time. Subsequent safety assessments focusing on genotoxic potential were issued in 2001 and 2003 .

After discontinuation of the above-mentioned phase I clinical trial with TCC, the genotoxic potential of the aglycone metabolite SL59.0955 (M2) was further investigated. New studies were performed in 2011 and 2012 regarding the genotoxicity of the parent compound (TCC), its main circulating metabolite SL18.0740 and the aglycone metabolite SL59.0955.

Genotoxicity data on TCC and its main circulating metabolite SL18.0740 (M1):

Various genetic toxicology studies were conducted on TCC and on its major identified metabolite 3-O-glucuronidated aglycone (SL18.0740), which is the active metabolite.

The available genotoxicity safety data on TCC and its metabolite SL18.0740 were assessed in an expert report in 2001 <confidential information deleted>.

The genotoxicity data results of TCC and its metabolite SL18.0740 are summarised hereafter.

Table 1: Genotoxicity studies performed with TCC and SL18.0740

Study type	Test system	Doses/concentrations (Route)	GLP status	Results
Thiocolchicoside				
Unscheduled DNA repair synthesis	Rat hepatocytes	3 to 5000 µg/mL	Yes	No genotoxic effect
Unscheduled DNA repair synthesis	Human embryonal epithelial cells	5 to 1000 µg/mL -S9 10 to 500 µg/mL +S9	No	No genotoxic effect
Reverse mutation in bacteria (Ames test)	<i>Salmonella typhimurium</i> ¹⁾	15 to 5000 µg/plate ±S9	Yes	No mutagenic effect
Reverse mutation in bacteria (Ames test)	<i>Salmonella Typhimurium</i> ¹⁾	312.5 to 5000 µg/plate ±S9	Yes	No mutagenic effect
Gene mutation in mammalian cells	Chinese Hamster Ovary cells <i>hgp^{rt}</i> ⁺	81.25 to 2600 µg/mL±S9	Yes	No mutagenic effect
In vitro Chromosome aberration	Human lymphocytes	3 to 5000 µg/mL-S9 100 to 5000 µg/mL+S9 (3 hours)	Yes	No increase in the incidence of cells with structural chromosome aberrations Increased incidence of polyploid and endoduplicated cells at 5000+S9 only
In vivo Micronucleus	Mouse bone marrow	20 mg/kg (single dose) Intraperitoneal route	Yes	No clastogenic/aneugenic effect
SL18.0740				
Reverse mutation in bacteria (Ames test)	<i>Salmonella typhimurium</i> ¹⁾	312.5 to 5000 µg/plate ±S9	Yes	No mutagenic effect

Study type	Test system	Doses/concentrations (Route)	GLP status	Results
Gene mutation in mammalian cells	L5178Y mouse lymphoma cells (<i>tk</i> ⁺)	9.77 to 5000 µg/mL-S9 (3- or 24- hours) 4.88 to 156.25 µg/mL+S9 (3 hours)	Yes	No effect without S9 Increased incidence of mutant colonies with S9 from 4.88 µg/mL
<i>In vitro</i> Micronucleus	Human lymphocytes	48.44 to 5000 µg/mL-S9 (3- or 24- hours) 10.24 to 24.49 µg/mL+S9 (3 hours)	Yes	Aneugenic effect, increased incidence of micronucleated cells with and without S9 from 10.24 µg/mL Micronuclei predominantly contained centromere (FISH)
<i>In vivo</i> Micronucleus	Mouse bone marrow	200, 400 and 800 mg/kg single dose PO	No	Increased incidence of micronucleated polychromatic erythrocytes (PCE)s at all doses
<i>In vivo</i> Micronucleus	Mouse bone marrow	3.3, 6.6, 13.2, 26.4, 39.6 and 52.8 mg/kg single dose PO	No	Increased incidence of micronucleated PCEs at 52.8 mg/kg No effect at 39.6 mg/kg and below

DNA: deoxyribonucleic acid

GLP: Good Laboratory Practice

1) *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537.

It was concluded that M1 (SL18.0740) is devoid of mutagenic (gene mutations) and clastogenic (structural chromosome damage) potential, but is able to induce aneuploidy (numerical chromosome damage). However a follow-up study (*in vivo* micronucleus test) defined a no-effect level of 39.6 mg/kg. This was associated with M1 plasma AUC of 4073 ng.h/mL, which is more than 20 times higher than M1 exposure observed in human after a 8 mg bid PO dose of TCC (175 ng.h/mL at 30 min).

Therefore, on the basis of the above-mentioned available data, the CHMP considered the safety margins and benefit/risk for TCC and SL18.0740 (M1) acceptable.

Genotoxicity data on aglycone metabolite SL59.0955 (M2)

Since no relevant genetic toxicology studies were previously performed with the aglycone metabolite SL59.0955, complementary studies (chromosome damage assays) were performed in order to investigate the genotoxic profile of this metabolite and its ability to induce aneuploidy in nonclinical *in vitro* (up to 600 µg/mL) and *in vivo* (up to 150 mg/kg):

- an *in vitro* micronucleus (MN) test in primary culture of human lymphocytes with the aglycone metabolite (SL59.0955), with centromere staining <confidential information deleted>;
- an *in vivo* MN test in rat bone marrow following administration of aglycone metabolite (SL59.0955) by oral route in rats with centromere staining and with a full assessment of exposure to SL59.0955 and to 3-O-glucuronidated aglycone metabolite (SL18.0740) to better assess the threshold of exposure <confidential information deleted>.

Hereafter, Table 2 summarises the 2 new studies performed.

Table 2: Genotoxicity studies performed with SL59.0955

Study type	Test system	Doses Concentrations (Route)	GLP status	Results Incidence of micronucleated cells (MN) (presence of centromeres in micronuclei)
In vitro micronucleus test	Primary culture of human peripheral blood lymphocytes	5 to 600 ng/mL	Yes	Increased incidence of MN from 15-20 ng/mL (24-hour treatment) No effect at 5-10 ng/mL Increased incidence of MN from 60 ng/mL (3- hour treatment) No effect at 40-50 ng/mL (Presence of centromeres in micronuclei)
In vivo micronucleus test	Rat bone marrow	25, 50, 70, 100 (F) 150 (M) Oral by gavage	Yes	No effect in males based on group mean and individual values Increased incidence of MN from 25 mg/kg/day in females (individual values) and from 70 mg/kg/day (group mean values) (Presence of centromeres in micronuclei)

Both reports are adequate and robust, and the obtained findings are considered reliable by the CHMP.

In vitro micronucleus test in human lymphocytes

The *in vitro* MN test in human lymphocytes showed that M2 induced micronuclei in cultured human peripheral blood lymphocytes in all treatment conditions. Subsequent mechanistic analysis via the use of fluorescence in situ hybridisation (FISH) with pan centromeric DNA probes demonstrated that micronuclei were predominantly generated via an aneugenic (numerical chromosome abnormality) mechanism under all treatment conditions; aneuploidy was clearly confirmed by centromere staining. A high proportion of micronuclei evaluated with CREST staining contained a centromere, strongly indicating an aneugenic effect.

Aneuploidy is the consequence of a variety of errors occurring during chromosome segregation, leading to either chromosome non-disjunction (CND) or chromosome loss (CL). With regards to the biological significance of the tests, the use of the *in vitro* experimental data in lymphocytes to determine a

NOAEL dose (between 5 and 10 ng / ml) is rather forced since the method employed although being certainly the most widely used, is based on the detection of micronuclei in interphase cells and their subsequent analysis by immunostaining or FISH and thus is only suitable for the analysis of CL. The calculation of the NOAEL for aneuploidy based only on the CL-component may lead to underestimation of the toxic effect. Data from the literature² strongly indicate that, in cultured human lymphocytes, CND is a major mechanism of aneuploidy induction by spindle inhibitors (COL). Since CND occurs at lower concentrations than chromosome loss, the aneuploidy threshold should be estimated on the basis of CND rather than on micronuclei frequencies (CL). It is therefore considered that CND may be the most appropriate end-point to investigate when looking for low-dose effects of spindle poisons, such as in the search for threshold doses for aneuploidy induction. Published studies³ show that by applying FISH in cytokinesis-blocked cells it is possible to detect and quantify both end-points (CND and CL) in the same cell population⁴. The simultaneous analysis of CND and CL in cultured human lymphocytes demonstrated that ND is the prevalent damage resulting from exposure to low, sub-inhibitory doses COL⁵.

Under the assay conditions, the No Observed Adverse Effect Level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) were also considered but while acknowledging that chromosome non disjunction (CND) is the most appropriate end-point to investigate when looking for low-dose effects of spindle poisons, conclusion on the search for threshold doses for aneuploidy induction was not possible to draw.

In vivo rat bone marrow micronucleus test

In the *in vivo MN test in rat bone marrow*, after M2 oral administration once daily for two consecutive days at doses of 25, 50, 70, 100 or 150 mg/kg/d, the rats bone marrow micronucleus test was found negative in males. In females, a positive response was observed at doses of 25, 50, 70 and 100 mg/kg/d based on group mean and individual data. A high proportion of micronuclei evaluated with antikinetochore antibody staining (CREST staining) contained a centromere, strongly indicating an aneugenic effect. The maximum M2 plasma concentrations were observed between 0.5 and 6 hours after administration, while the maximum M1 plasma concentrations were observed between 0.5 and 2 hours after administration. The mean ratio female/male for AUC₀₋₂₄ was 1.22 for M2 and 1.28 for M1 indicating a slightly higher exposure in case of the female rats.

Genotoxic mechanisms, such as aneuploidy, involving cell division and non-DNA targets, are known to occur above a certain threshold of exposure. But no NOAEL for aneugenic effects was identified in rat females (LOEL = 25 mg/kg) and no clear dose related effect was observed because only slight difference in exposure (AUC₀₋₂₄ and C_{max}) with 3-demethylthiocolchicine (SL59.0955) were observed between the different doses in males and females. No clear dose related effect was observed because only a slight difference in exposure (AUC₀₋₂₄ and C_{max}) with M2 was observed between the different doses in males and females. In addition males and females showed only a slight gender difference in exposure. The lack of effect in male is not explained and cannot be due to the slight difference in exposure between animals of two sexes. In addition males and females showed only a slight gender difference in exposure. Hence no safety margin could be calculated. The aneugenic effect was observed at LOEL corresponding to only 1.6 x human C_{max} and 4.1 x AUC (8mg bid, PO).

After parenteral use, the plasma concentration of M2 is expected to be much lower as the M2 transformation occurs after oral administration mainly by intestinal metabolism. However, whether the exposure to M2 would be below a threshold of aneugenicity (including a sufficient safety margin) is unknown since M2 has not been analysed in the available clinical kinetic studies.

In conclusion, under these experimental conditions, 3-demethylthiocolchicine (SL59.0955) administered by the oral route once daily for two consecutive days at doses of 25, 50, 70, 100 or 150 mg/kg/d was found negative in the rat bone marrow micronucleus test in males. In females, a positive response was observed at doses of 25, 50, 70 and 100, based on group mean and individual data. No clear dose related effect was observed because only slight differences in exposure (AUC₀₋₂₄ and C_{max}) with 3-demethylthiocolchicine (SL59.0955) were observed between the different doses in males and females. In addition males and females showed only a slight gender difference in exposure. Considering all available data of this study, 3-demethylthiocolchicine (M2) can be considered as an aneugenic compound.

² Elhajouji et al., Environmental and Molecular Mutagenesis, 26, 292, 1995

³ Zijno et al., Mutagenesis 9, 225-232, 1994; Zijno et al., Mutagenesis 11, 335, 1996.

⁴ Zijno et al., 1994)

⁵ Zijno et al., Mutagenesis 11, 335, 1996

Conclusion

In conclusion, the results of the above pre-clinical studies showed that M2 (SL59.0955) induced micronuclei *in vitro* and *in vivo*, generated via a predominantly aneugenic mechanism under all treatment conditions. In the two *in vitro* and *in vivo* preclinical studies conducted, the findings (increase in the incidence of micronucleated cells) were observed at concentrations/exposures close to the exposures measured in human at therapeutic doses. The CHMP was therefore of the view that the available data allow to confirm a clear aneugenic effect of the thiocolchicoside metabolite M2 at concentrations which are 4 fold the human exposure in plasma after oral 8 mg TCC treatment bid (recommended dose) and starting from 25 mg/kg dose.

A comparative table of TCC metabolite M2 plasma levels at therapeutic dose (8 mg TCC, PO) in humans versus exposure in genotoxicity studies is provided below.

Table 3: Comparison of TCC metabolite M2 plasma levels at therapeutic dose (8 mg TCC, PO) in humans versus exposure in genotoxicity studies

		C_{max} (ng/mL)	Ratio versus Human	AUC (ng.h/mL)	Ratio versus Human
Human (TCC 8 mg bid oral route, daily exposure)		13.0		79.4	
In vitro micronucleus study (human lymphocytes)	NOEL (3 h-treatment)	50	X 3.8		
	LOEL (3 h-treatment)	60	X 4.6		
	NOEL (24 h-treatment)	5-10	X 0.4-0.8		
	LOEL (24 h-treatment)	15-20	X 1.2-1.5		
In vivo bone marrow rats micronucleus study	LOEL (females at 25 mg/kg/day)	21.9 No clear difference in C _{max} values between positive and negative animals	No safety ratio can be calculated based on C _{max}	327 No clear difference in AUC values between positive and negative animals	No safety ratio can be calculated based on AUC

Abbreviations: AUC: area under the curve, C_{max}: maximum plasma concentration, LOEL: lowest observed effect level, NOEL: no-observed effect level, TCC: thiocolchicoside.

The submitted data did not allow establishing a NOEL for aneuploidy, thus a potential risk in humans could not be excluded. To define an effect threshold, the CHMP considered if a rat MN study on a larger number of doses and animals with lower dose range and non-disjunction as additional endpoint could be performed but was of the opinion that such study would not provide additional information in terms of the safety margin and therefore did not recommended it.

Given the known genotoxic effect of TCC metabolite M2, a long-term follow-up non-clinical study to address the concern on teratogenicity, impaired fertility and carcinogenicity was also discussed by the CHMP. The CHMP considers that such pre-clinical study would not provide any additional useful information in terms of quantifying the risk.

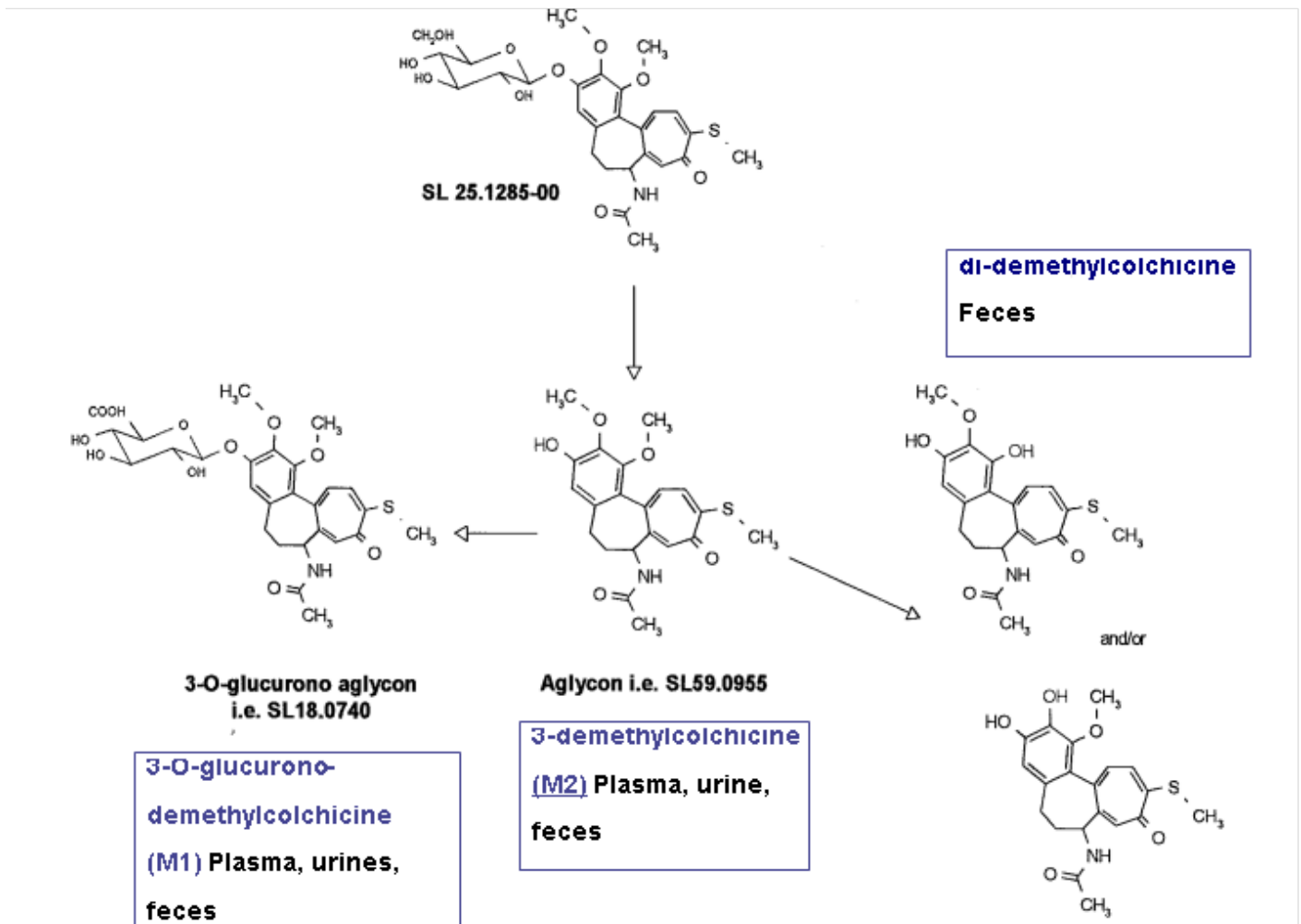
Metabolism and pharmacokinetics of TCC

The metabolism and pharmacokinetic of TCC was presented by the MAHs.

After oral administration TCC is first metabolised in M2 (SL59.0955). This step mainly occurs by intestinal metabolism, explaining the lack of circulating unchanged TCC by this route of administration. M2 (SL59.0955) is then glucuroconjugated into M1 (SL18.0740), which has equipotent pharmacological activity to TCC and thus supports the pharmacological activity after oral administration of TCC. M2 (SL59.0955) is also demethylated into didemethyl-thiocolchicine.

M2 and M1 are observed in plasma, urine and faeces while didemethyl-thiocolchicine is only recovered in faeces.

Figure 1: Metabolic pathways of thiocolchicoside



After intramuscular administration of TCC (8 mg):

- The main circulating entity is TCC, with a maximum concentration occurring within 30 minutes after injection (175 ng/mL) and corresponding to an AUC of 417 ng.h/mL.
- The metabolite M1 is also observed but at lower concentrations with a C_{max} of 11.7 ng/mL occurring 5 hours post dose and an AUC of 83 ng.h/mL after a 8 mg dose of TCC.
- The M2 was never assessed in the available studies. However, based on the metabolic scheme and oral data, SL59.0955 is likely formed mainly in the intestine and first path metabolism and then transformed in M1 in the liver. Taking into account that exposure to M1 formed by glucuroconjugation of the aglycone metabolite M2 is lower when TCC is given by IM administration than by oral route, the exposure to the M2 should be lower when TCC is given by IM administration than by oral route. This is noted specifically for C_{max}, since the t_{max} of M1 occurs much later (5h) by IM than by oral route (0.5h).

2.3. Clinical Safety

Clinical trials and post marketing spontaneous reports were submitted by the MAHs.

Clinical studies

A review was performed in order to identify if cases of cancer, congenital abnormalities, spontaneous abortion and impaired male fertility had been reported in clinical trials.

No cases of cancer, congenital abnormalities, spontaneous abortion and impaired male fertility were retrieved from a review of clinical trials and literature.

Post marketing experience

Postmarketing spontaneous cases were collected based on the reports recorded in two MAHs' global pharmacovigilance databases (cut-off dates of 15 February 2013 and 29 April 2013 respectively).

In the first database, 11 cases secondary to exposure during pregnancy were reported:

- six cases of congenital abnormalities (i.e. one multiple malformations leading to abortion, one pulmonary hypoplasia, one cleft palate, one spina bifida, one Poland's syndrome, one patent ductus arteriosus),
- four cases of spontaneous abortion,
- one case of threat of premature delivery.

Case review reports from 2004 up to 29 April 2013 from the second database reported 23 cases secondary to exposure during pregnancy and / or exposition in utero:

- 20 cases due to exposure during the embryonic period, of which:
 - two cases of teratogenic effects (malformations) associated with exposure in early pregnancy (the first quarter is the period during which the risk is the greatest),
 - four cases resulting in discontinuation of the pregnancy (3 spontaneous abortions and one voluntary abortion not due to medical reason),
 - five cases with a favourable evolution (no effect on the new born),
 - nine cases with an unknown evolution of the pregnancy due to lack of documentation.
- One case due to exposure during the foetal period (i.e. a case of foetotoxic effects that resulted in foetal or neonatal type of achieving growth impact, or histological or functional maturation of organs in place (the period during which the greatest risk begins in the second quarter of pregnancy),
- and two cases with unknown exposure period:
 - One case of teratogenic effects (malformations) associated with exposure in early pregnancy,
 - One case with an unknown evolution of the pregnancy due to lack of documentation.

No case was registered for neonatal effects related to exposure occurred in late pregnancy or during childbirth.

The CHMP considered that the clinical evidence within the cases reported by the MAHs concerning the consequences of aneuploidy in humans does not allow drawing definitive conclusions. Aneuploidy is a common characteristic of cancer cells. However it is still controversial if aneuploidy is a contributing cause or merely a consequence of neoplastic transformation. In addition, the lack of evidence for the correlation between the use of TCC and cancer could be due to the difficulty of establishing a causal relationship between the medicine and the effect, which may occur years after intake. In most cases the treatment is for short-term use and not associated with the perception of increased cancer risk for both physicians and patients, therefore a causal relationship between cancer occurrence and treatment is difficult to establish.

The CHMP also noted that the limited number of cases of malformations/embryo-foetal toxicities may be due to the fact that, in most of the Member States, the medicine is contraindicated in pregnancy.

Taking the totality of data into account, the CHMP considered that causality cannot be excluded and that aneuploidy should be considered as a cancer risk factor on theoretical grounds.

2.4. Discussion

On the basis of all the evidence available, the CHMP was of the view that risk minimisation measures (RMMS) should be undertaken in order to address the risks of teratogenicity, embryo-toxicity/spontaneous abortions, impaired male fertility and cancer.

Firstly, since the TCC metabolite M2 has been shown to be aneugenic at exposure levels close to human therapeutic exposure, the CHMP considered that the dose should be restricted (to 8 mg bid PO and 4 mg bid by IM) and long-term use avoided. In that respect the CHMP was of the view that the

indication in *"Parkinson's disease and drug-induced Parkinsonism with special consideration to neurodyslectic syndrome"* should be removed as this is an indication for chronic use.

The CHMP also considered that the use of TCC should be avoided during puberty (12 to 16 years) due to potential risk on fertility. The use of the product should therefore be limited to acute conditions in patients over 16 years old; an updated product information with restriction for use and duration therapy was endorsed accordingly. Based on common use in acute settings, other recommendations for the posology were included as the limitation of the treatment duration to 7 days in case of oral administration and to 5 days in case of IM administration; a reference to the maximum dose allowed was also recommended.

Finally a 12 hours interval between 2 consecutive administrations was requested in view of the elimination half-life of the M2 metabolite. The corresponding product information sections were updated accordingly. In addition, the CHMP was of the view that the package size should be restricted according to the new treatment-days scheme recommended (up to 30 tablets or capsules/4 mg pack, up to 14 tablets or capsules/8 mg pack and up to 10 vials/ampoules).

Teratogenicity is classified as an important identified risk. To address the risks of teratogenicity and embryo-toxicity/spontaneous abortions the CHMP agreed on contraindicating TCC during the entire pregnancy period, during lactation, and in women of childbearing potential not using contraception. Amendments to the warnings and pregnancy and lactation sections of the product information were also endorsed.

Carcinogenicity and impaired fertility are categorised as important potential risks. Concerning the risk of male infertility: elevated sperm chromosome aneuploidy is known to be associated with male infertility. However, more concern was raised in relation to the potential risk of foetal anomalies due to elevated sperm aneuploidy rather than to the male infertility per se. Given the treatment conditions with TCC (short-term, potentially aneugenic at maximum doses) effects on male fertility will be low and a rapid recover to normal levels can be expected. . An amendment to the product information was agreed to address this concern.

Lastly, evidence for carcinogenicity of aneugens is limited. A significantly increased cancer risk would in general be dependent on long-term/chronic exposure/dosing with the aneugen. Carcinogenicity is an important potential risk. To address it, the proposed RMM (indication limited to acute conditions, treatment duration limited to seven consecutive days, avoidance of long-term use) were considered appropriate by the CHMP.

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to inform on the outcome of the present review, including the updated indication, the clinical use for these products (short-term) and to highlight the genotoxic risk.

A risk management plan (RMP) will be submitted to national competent authorities in accordance with agreed timelines.

In addition the CHMP reviewed the PSUR frequency for TCC containing medicines for systemic use and requested PSURs to be submitted on a three-yearly basis (instead of a 13-yearly basis as it is currently recommended). Continuous monitoring of safety signals correlated with aneuploidy (i.e. teratogenicity, embryo-foetal toxicity / spontaneous abortion, impaired male fertility and cancer) and pregnancy reporting to collect structured data on accidental exposure to the drug should be performed.

Furthermore the CHMP requested a drug utilisation study (DUS) to be conducted in order to better characterise prescribing practices for these medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription. This DUS should be conducted over a three year period. The study protocol should be provided within the RMP.

Finally educational material for prescribers and for patients highlighting the risks and warnings of genotoxicity reactions will also be submitted to national competent authorities within the RMP.

2.4.1. Risk management plan

As part of the risk minimisation measures the CHMP considered there was a need to ensure that all relevant information for the safe use of these products should be applied across authorised products and therefore agreed on the wording for all relevant sections of the products information dealing with the risk of genotoxicity reactions.

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to inform on the outcome of the present review, including the updated indication, the clinical use for these products (short-term) and to highlight the genotoxic risk. A risk management plan (RMP) will be submitted to national competent authorities in accordance with agreed timelines and periodic safety update reports (PSURs) will be submitted every 3 years.

In addition the CHMP proposed a three-year PSUR cycle and continuous monitoring of safety signals correlated with aneuploidy and pregnancy reporting.

A drug utilisation study (DUS) will be conducted to better characterise prescribing practices for these medicinal products. This DUS should be conducted over a three year period. The study protocol should be provided within the RMP. Educational material for prescribers and for patients highlighting the risks and warnings of genotoxicity reactions will also be submitted to national competent authorities within the RMP.

2.5. Overall benefit/risk assessment

The Committee reviewed all available data from pre-clinical, clinical studies, published literature, post-marketing experience on the safety of TCC containing medicinal products for systemic use with regards to genotoxicity potential.

The preclinical data confirmed an aneugenic effect of TCC, but they were scarcely informative for the determination of a threshold dose. The CHMP considered that the TCC metabolite M2 has been shown to be aneugenic at exposure levels very close to human therapeutic exposure dose of 8 mg bid PO, and therefore a potential risk for genotoxicity in humans exists.

Since aneuploidy is a risk factor for teratogenicity, foetotoxicity/spontaneous abortion and impaired male fertility and a potential risk factor for cancer, the CHMP considered that RMMs were necessary in order to reduce the exposure to the metabolite SL59.0955 from systemic formulations. In that respect amendments to the Product Information were proposed to mitigate the risk. Restrictions for use and duration therapy were endorsed. The medicinal products should only be used in acute conditions in patients over 16 years old and for no longer than 7 days in case of oral administration and to 5 days in case of IM administration; the indication in Parkinson's disease was removed and the package size was adapted to new recommended treatment-days. The CHMP also advised that TCC containing medicinal products should not be given to pregnant women, in women of childbearing potential not using contraception and during lactation. The CHMP requested the MAHs to perform a DUS to address this particular safety concern. In addition, the PSUR cycle will be reduced from 13 to 3 years and a RMP should be submitted to national competent authorities addressing the safety profile of TCC and the pharmacovigilance activities agreed.

The CHMP endorsed a DHPC to communicate the outcome of the present review.

Having noted the above, the CHMP concluded that the benefit-risk balance of TCC containing medicinal products indicated as adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards remains favourable subject to the restrictions, warnings, other changes to the product information, additional pharmacovigilance activities and RMMs agreed.

2.6. Communication plan

As part of this referral procedure, the MAHs and the CHMP agreed the wording of a 'Dear healthcare professional' communication designed to inform prescribers of the genotoxic risk associated with these TCC containing medicinal products and the amendments to the Product information. This communication should be circulated within 30 days of the Commission decision of this referral procedure.

2.7. Changes to the product information

Summary of product characteristics

Section 4.1 Therapeutic indications

The CHMP recommended that the indication should be revised in order to highlight that thiocolchicoside containing medicinal products for systemic use remain an effective adjuvant treatment of painful muscle contractures in acute spinal pathology. However, having considered the risks and its potential effect on fertility during puberty, thiocolchicoside containing medicinal products for systemic use should only be administered to patients over 16 years of age in acute conditions. Besides, the CHMP was of the view that the indication in *"Parkinson's disease and drug-induced Parkinsonism with special consideration to neurodyslectic syndrome"* should be removed as this is a chronic condition which requires longer treatment duration.

Section 4.2 Posology and method of administration

The CHMP emphasised the restriction for use and the limitation to the duration of therapy.

The dose should be restricted (maximum daily dose of 8 mg bid PO and 4 mg bid by IM) and long-term use avoided.

Based on common use in acute settings, recommendations for the posology were included together with limitations to the treatment duration to 7 days in case of oral administration and to 5 days in case of IM administration.

Finally a 12 hours interval between 2 consecutive administrations was requested in view of the elimination half-life of the M2 metabolite.

Section 4.3 Contraindications

The CHMP agreed on contraindicating TCC during the entire pregnancy period, during lactation, and in women of childbearing potential not using contraception. Amendments to the warnings and pregnancy and lactation sections of the product information were also endorsed.

Section 4.4 Special warnings and precautions for use

The CHMP concluded that carcinogenicity and impaired fertility are important potential risks and therefore endorsed amendments to include warnings and precautions for use.

It is known that elevated sperm chromosome aneuploidy is associated with male infertility. However, more concern was raised in relation to the potential risk of foetal anomalies due to elevated sperm aneuploidy rather than to the male infertility per se. Given the treatment conditions with TCC (short-term, potentially aneugenic at maximum doses) effects on male fertility will be low and a rapid recover to normal levels can be expected.

Section 4.6 Fertility, pregnancy and lactation

In view of the above, the CHMP amended this section to reflect the pregnancy and lactation concerns. In addition, the CHMP concluded that a wording on effects on male fertility should be added.

Section 4.8 Undesirable effects

The statement for the encouragement and the modalities to report adverse reaction was included in this section according to version 9 of the QRD template.

Section 5.2 Pharmacokinetic properties

The CHMP concluded that since pharmacokinetic and metabolism data were reviewed within the context of this procedure, the section should be revised to address the new findings.

Section 5.3 Preclinical safety data

A wording to include the outcomes of the new preclinical data was endorsed by the CHMP.

Section 6.5 Nature and contents of container

In view of the restricted package size, an updated wording was agreed accordingly by the CHMP.

Labelling

The package size should be restricted according to the new treatment-days scheme recommended (up to 30 tablets or capsules/4 mg pack, up to 14 tablets or capsules/8 mg pack and up to 10 vials/ampoules).

Package Leaflet

The corresponding sections of the package leaflet were amended accordingly.

3. Overall conclusion

Having considered all available data from pre-clinical, clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience on the safety of thicolchicoside containing medicinal products for systemic use with regards to its genotoxicity, the Committee considered that thicolchicoside containing medicinal products for systemic use remain an effective adjuvant treatment of painful muscle contractures in acute spinal pathology.

However, having considered the risks, thicolchicoside containing medicinal products for systemic use should only be administered to patients over 16 years of age in acute conditions, with treatment duration limited to 7 (oral) and 5 (IM) consecutive days. In that respect, the CHMP was of the view that the indication in *"Parkinson's disease and drug-induced Parkinsonism with special consideration to neurodyslectic syndrome"* should be removed as this is a chronic condition which requires longer treatment duration. The package size should be adapted to new recommended treatment-days. .

The Committee considered also that thicolchicoside containing medicinal products for systemic use should be contraindicated during the entire pregnancy period. These products should also be contraindicated in women of childbearing potential not using contraception and during lactation. The CHMP also recommended further changes to the product information including information on fertility.

The CHMP also agreed on the need of a RMP. In addition, three-yearly PSURs should be submitted by all MAHs of these products. These PSURs should include a report compiling continuous monitoring of any safety signal correlated with aneuploidy and pregnancy on accidental exposure to the drug.

The Committee concluded that there was a need for further risk minimisation measures such as a drug utilisation study to characterise the prescribing practices during typical clinical use, as well as adequate educational materials to be developed for patients and prescribers. These measures are to be included in the RMP.

The Committee as consequence concluded that the benefit-risk balance of thicolchicoside containing medicinal products for systemic use as adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards remains favourable, subject to the restrictions, warnings, other changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed.

The conditions affecting the marketing authorisations are set out in Annex IV.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion