

## **Annex II**

### **Scientific conclusions and grounds for variation to the terms of the marketing authorisations**

## Scientific conclusions

### Overall summary of the scientific evaluation of thiocolchicoside containing medicinal products for systemic use (see Annex I)

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. Widely used by prescribers in the concerned Member States (see Annex I), the benefits of TCC containing medicinal products are recognised in clinical practice.

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 cells<sup>1</sup>. 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. A relevant summary is presented hereinafter.

### 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<sup>2</sup> and 2003<sup>3</sup>.

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.

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 oral 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.

<sup>1</sup> Parry 2000 & 2002; Kirsch-Volders 2002

<sup>2</sup> Kirkland DJ Et al. 2001

<sup>3</sup> Gouy D., 2003

### 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 (Whitwell J., 2012);
- 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 (Wase K., October 2012).

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 hybridization (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.

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 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. 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 (AUC<sub>0-24</sub> and C<sub>max</sub>) 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. Hence no safety margin could be calculated. The aneugenic effect was observed at LOEL corresponding to only 1.6 x human C<sub>max</sub> and 4.1 x AUC (8mg bid, Per Os (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, 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. The submitted data did not allow establishing a NOEL for aneuploidy, thus not excluding the potential for a human risk.

### **Clinical Safety**

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

#### Clinical studies

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.
- 1 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 2 cases with unknown exposure period:
  - 1 case of teratogenic effects (malformations) associated with exposure in early pregnancy,
  - 1 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 considers 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.

The CHMP was therefore 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 16-18 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 SmPC 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 and periodic safety update reports (PSURs) will be submitted every 3 years. 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 any safety signal 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. A mock-up of the above-mentioned pregnancy reporting form should be provided in the RMP and a report on these collected data should be submitted within PSURs.

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.

### **Benefit –risk balance**

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.

## Grounds for the maintenance of the marketing authorisations

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for thiocolchicoside containing medicinal products for systemic use (see annex I).
- The Committee considered all available data from pre-clinical, clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience on the safety of thiocolchicoside containing medicinal products for systemic use with regards to its genotoxicity.
- The Committee considered 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, thiocolchicoside 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 thiocolchicoside 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 thiocolchicoside 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.