PASS INFORMATION

Study title	**Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey mong Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Thiocolchicoside containing Medicinal Products for Systemic Use in France, Greece, Italy and Portugal**
Protocol Version identifier	Version 2
Date of last version of protocol	8 August 2016
EU PAS Register number	ENCEPP/SDPP/11765
Active substance	Thiocolchicoside: - ATC code: M03BX05
Medicinal product	Thiocolchicoside containing medicinal products for systemic use* *All substances will be summarized under the term "systemic thiocolchicoside"
Product reference	Information is detailed in the cover letter's Annex.
Procedure number	EMEA/H/N/PSP/j/0030
Marketing authorization holder (MAH) or sponsor company	Consortium of companies. The full list of all MAHs (Companies and/or their Affiliates and licensors) and address is provided in Annex 3. Acarpia services farmaceuticos Lda, Alter laboratoire, Angelini, Angenerico SpA, Arrow Generiques, Biogaran, Cristers, Daiichi Sankyo, Doc Generici, Dompe Farmaceutici SpA, EG labo, EG SpA, Epifarma Srl, Farmaceutici Caber SpA, Generis Farmaceutica, Korangi, Laboratorio Farmaceutico CT Srl, MDM, Mylan, Sandoz, Sanofi Aventis Groupe, SF Group Srl, SPA, Teofarma Srl, Union Health Srl.
Brand names of the systemic thiocolchicoside containing medicinal products marketed by the consortium MAHs	France: COLTRAMYL, MIOREL, THIOCOLCHICOSIDE ALMUS, THIOCOLCHICOSIDE ALTER, THIOCOLCHICOSIDE ARROW, THIOCOLCHICOSIDE BIOGARAN, THIOCOLCHICOSIDE CRISTERS, THIOCOLCHICOSIDE EG, THIOCOLCHICOSIDE MYLAN, THIOCOLCHICOSIDE SANDOZ, THIOCOLCHICOSIDE ZENTIVA. Italy: ADALGUR, DECONTRIL, MIOREXIL, MIOTENS, MOVERIL, MUSCOFLEX, MUSCORIL, SCIOMIR, STRIALISIN, TERASIDE, TIOSIDE, TIOCOLCHICOSIDE ANGENERICO, TIOCOLCHICOSIDE DOC GENERICI, TIOCOLCHICOSIDE EG, THIOCOLCHICOSIDE MYLAN GENERICS, THIOCOLCHICOSIDE SANDOZ, TIOCOLCHICOSIDE UNION HEALTH, THIOCOLCHICOSIDE ZENTIVA. Portugal: ADALGUR N, COLTRAMYL, MOVERIL, RELMUS, TIOCOLQUICOSIDO GENERIS. Greece: MUSCO-RIL.
Joint PASS	Yes
Research question and objectives	Research question: Whether the dear healthcare professionals communication (DHPC) and educational materials (EM), implemented as risk minimisation measures (RMM), were effective to ensure: - correct knowledge of physicians about prescribing conditions and safe use when prescribing systemic thiocolchicoside - appropriate attitude when prescribing systemic thiocolchicoside. Objective: to measure the effectiveness of the DHPC and EM, implemented as part of RMM, by ascertaining the proportion of targeted

	physicians who understood and implemented the latest prescribing conditions and safety information about systemic thiocolchicoside provided in the DHPC and EM. Specific objectives were to evaluate the proportion of physicians who: • prescribe systemic thiocolchicoside only as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards. • do not prescribe systemic thiocolchicoside for long-term treatment of chronic conditions. • follow the recommendations regarding the doses and duration restriction: - for oral forms: 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. - for IM forms: 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. • do not prescribe systemic thiocolchicoside during pregnancy and lactation. • do not prescribe systemic thiocolchicoside in women of childbearing potential not using adequate contraception.
Countries of study	France, Greece, Italy and Portugal.
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MAH(s)	Consortium of companies. The full list of all MAHs (Companies and/or their Affiliates and licensors) and address is provided in Annex 3.
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MARKETING AUTHORISATION HOLDERS

IMS is a partner centre of the ENCePP scientific network which is coordinated by the European Medicines Agency. IMS is dedicated to excellence in research by adhering to the ENCePP Guide on Methodological Standards and promoting scientific independence and transparency.

This document is for the exclusive use of the consortium (Annex 3; List of Companies (and/or their Affiliates and licensors)). The information about this project is confidential and may not be reproduced or disclosed to any third party without the agreement of the consortium.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AIFA	Agenzia Italiana del Farmaco: Italian Medicines Agency
AR	Adverse reaction
ASOCS	Association of Opinion and Behaviour in health field research companies
CI	Confidence interval
CHMP	Committee of for Medicinal Products for Human Use
DHPC	Direct healthcare professional communication
EM	Educational Materials
EMA	European Medicines Agency
EphMRA	European Pharmaceutical Marketing Research Association
EU	European Union
HEOR	Health Economics and Outcomes Research
GVP	Good pharmacovigilance practices
GP	General practitioner
HCP	Health care professional
IM	Intramuscular
MAH	Marketing Authorization Holder
PASS	Post-authorization safety study
PI	Prescribing Insights
PRAC	Pharmacovigilance and Risk Assessment Committee
RMM	Risk minimisation measures
RMP	Risk management plan
RWES	Real World Evidence Solutions
SOP	Standard operating procedures
SmPC	Summary of product characteristics
STROBE	Strengthening the reporting of observational studies in epidemiology
TCC	Thiocolchicoside

3. RESPONSIBLE PARTIES

Sponsor:

Marketing Authorisation Holders (MAHs) represented by the following companies are involved in the study via a consortium (the full list of all MAHs is provided in Annex 3):

Acarpia services farmaceuticos Lda, Alter laboratoire, Angelini, Angenerico SpA, Arrow Generiques, Biogaran, Cristers, Daiichi Sankyo, Doc Generici, Dompe Farmaceutici SpA, EG labo, EG SpA, Epifarma Srl, Farmaceutici Caber SpA, Generis Farmaceutica, Korangi, Laboratorio Farmaceutico CT Srl, MDM, Mylan, Sandoz, Sanofi Aventis Groupe, SF Group Srl, SPA, Teofarma Srl, Union Health Srl.

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The steering committee comprises representatives of each MAH and of IMS Health.
This committee is chaired by Sanofi-Aventis R&D.

The roles of the scientific committee are to supervise activities and obligations related to the governance of the cooperation of the parties under the agreement, and to ensure an optimal coordination among parties with respect to the scientific part of the study.

4. ABSTRACT

4.1 Title:

Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey and Drug Utilisation Study among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Thiocolchicoside-containing Medicinal Products for Systemic Use in France, Greece, Italy and Portugal

Version n°2: 26 April 2016

Protocol supervised by: Massoud Toussi, Medical Director, IMS Health, HEOR/RWES
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4.2 Rationale and background

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity, used in the management of non-specific low back pain. TCC is indicated as adjuvant treatment of painful muscular contractures in acute spinal pathology, in adults and adolescents from 16 years onwards. The benefits of TCC containing medicinal products are recognised in clinical practice, and they are widely used by prescribers in the concerned Member States (see Annex 3).

An Article 31 referral on thiocolchicoside-containing medicinal products for systemic use was initiated in February 2013. The CHMP has concerns with regard to the potential genotoxicity of thiocolchicoside-containing medicinal products for systemic use. Within the context of minimization measures as per European Commission decision dated 17 January 2014, including a Dear Healthcare Professional Communication, changes to the SmPC, Labelling and Package Leaflet. As per EMA request the present survey will be conducted in complement to a Joint Drug Utilization Study.

4.3 Research question and objectives

Research question: whether the DHPC and EM, implemented as risk minimisation measures, were effective to ensure:

- correct knowledge of physicians about prescribing conditions and safe use when prescribing systemic thiocolchicoside
- appropriate attitude when prescribing systemic thiocolchicoside, in particular as concerns pregnancy, lactation and contraception.

Objective: to measure the effectiveness of the DHPC and EM, by ascertaining the proportion of targeted physicians who understood and implemented the latest prescribing conditions and safety information about systemic thiocolchicoside provided in the DHPC and EM.

Specific objectives were to evaluate the proportion of physicians who:

- prescribe systemic thiocolchicoside only as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.
- do not prescribe systemic thiocolchicoside for long-term treatment of chronic conditions.
- follow the recommendations regarding the doses and duration restriction:
  - for oral forms: 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.
  - for IM forms: 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.
- do not prescribe systemic thiocolchicoside during pregnancy and lactation.
- Do not prescribe systemic thiocolchicoside in women of childbearing potential not using adequate contraception.

4.4 Study design

Cross-sectional, multinational and non-interventional survey conducted through a web-questionnaire in an anonymous way among physicians in 4 selected European countries (France, Greece, Italy and Portugal).

4.5 Population

Inclusion criteria:

- Physicians who prescribed systemic thiocolchicoside within the last 12 months
- GPs and specialists (rheumatologists and orthopedists / orthopedic surgeons).

Exclusion criteria:

- Physicians who do not treat patients
- Those who may have conflicts of interest with the survey.

4.6 Variables

The collected information includes:

- physician's demographics and practice information (e.g. age, gender, specialty, setting)
- prescription of systemic thiocolchicoside containing medicinal products within the last 12 months (yes/no)
- knowledge about the latest prescribing conditions and safety information/warnings about systemic thiocolchicoside presented in the DHPC and EM (e.g. indication, contraindicated conditions, recommended maximal dose, posology and duration of use for oral and IM forms, information to be communicated to a patient before prescribing the drug, specific information to be advised to a female of childbearing potential)
- awareness and attitude towards the latest prescribing conditions and safety information (main concerns perceived, sources of knowledge, DHPC reception and EM awareness, intention to consider the prescribing conditions and safety warnings)
- recent prescriptions details for patients (e.g. patient' age at the time of prescription, gender, indication, form, number and dose per administration per day, concomitant treatment(s) ongoing or written at the time of prescription, main reason for choosing systemic thiocolchicoside, information and recommendations provided to the patient when prescribing systemic thiocolchicoside).

The proportion of correct and appropriate answers about the prescribing conditions and safety information/warnings of systemic thiocolchicoside given by the physicians will be assessed overall, per country and among subgroups of specialties.

4.7 Data sources

The survey is a primary data collection conducted through a web questionnaire.

4.8 Study size

The sample survey will include physicians from the IMS OneKey reference lists.
The sample size calculation is based on the survey objective, *i.e*. to measure the effectiveness of the DHPC and EM, on the awareness and understanding of prescribers of systemic thiocolchicoside about the latest prescribing conditions and safety information/warnings of systemic thiocolchicoside provided in the DHPC and EM.

Since the expected proportion of physicians who received and understood the latest prescribing conditions and safety information of systemic thiocolchicoside is not known and there is no evidence supporting it, the worst case hypothesis will assume a proportion of 50%. For a confidence interval of 95% and a precision of 4%, a total of 600 analysable web-questionnaires will be needed for the overall sample: 180 in France and Italy, and 120 in Greece and Portugal.

4.9 Data analysis

The statistical analysis will be conducted using the SAS® softwareV9.3 on Windows™ (SAS Institute, North Carolina, USA).

Results will be presented, overall and at country level per specialty.

Continuous variables will be described by the number of valid cases and missing data, mean, standard deviation, median, Q1, Q3, minimum, and maximum. No missing data will be replaced. Categorical variables will be described as the total number and relative percentage per category. Confidence intervals of 95% will be calculated when relevant.

Calculations will first be performed on raw data per specialty, and weighted according to the real proportion of targeted physicians in each country to accurately reflect the population the survey seeks to measure.

Possible selection bias will be assessed by comparing the distributions of available characteristics (e.g. region, age, gender, type of practice and specialty) between respondent and non-respondent physicians.

4.10 Milestones

- Start of data collection: September 2016
- End of data collection: November 2016
- Submission of study report to EMA: June 2017

5. AMENDMENTS AND UPDATES:

None

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	November 2015
Start of data collection	September 2016
End of data collection	November 2016
Final report of study results	June 2017

The table below summarises per country the time schedule of distribution of DHPC and EM.

	France	**Greece**	**Italy**	**Portugal**
Distribution of DHPC	April 2014	February 2014	February 2014	February 2014
Distribution of EM	26 April 2016	2 August 2016	October 2015	September 2015

7. RATIONALE AND BACKGROUND

7.1 BACKGROUNG

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity. Muscle relaxants are one of the many treatments currently used in the management of non-specific low back pain. TCC is indicated as adjuvant treatment of painful muscular contractures in acute spinal pathology, in adults and adolescents from 16 years onwards. The benefits of TCC containing medicinal products are recognised in clinical practice, and they are widely used by prescribers (Annex 3).

The Italian medicines agency (AIFA) requested one of the Marketing Authorisation Holders (MAHs) of TCC to further investigate the genotoxic potential of TCC, and in particular of its metabolites. This request was addressed after discontinuation by a Company of a phase I clinical trial with TCC because of new non-clinical findings.
The results showed that thiocolchicoside was broken down into 3-demethylthiocolchicine (M2 : SL59.0955) and could damage dividing cells, resulting in aneuploidy (an abnormal number or loss of heterozygosity).
Aneuploidy is recognised as a potential risk factor for teratogenicity, embryo-toxicity/spontaneous abortions and impaired male fertility when impacting germ cells, and cancer when impacting somatic cells (1,2,3,4).

As a result, AIFA asked the European Medicines Agency's Committee on Human Medicinal Products (CHMP) to examine the safety profile of this medicine and consider what regulatory action might be appropriate.
The CHMP reviewed the evidence (5), including the opinions of experts in the field of medicines safety, and concluded that aneuploidy could occur with M2 at levels not much greater than those seen after recommended doses of thiocolchicoside taken by mouth.

On 15 February 2013, AIFA, the Italian Medicines Agency, requested the Committee of for Medicinal Products for Human Use (CHMP), under Article 31 of Directive 2001/83/EC, to assess the above concerns regarding aneuploidy and its impact on the benefit-risk balance of TCC containing medicinal products for systemic use and to give its opinion on whether the indication of TCC containing medicinal products should be restricted and/or other regulatory measures should be taken.
In April 2013, for the purpose of the review of this risk, the MAH provided, as per CHMP request, 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.

On November 21st 2013, based on the scientific conclusions of the review (Annex II), the CHMP recommended that the authorised uses for thiocolchicoside containing medicines for systemic use (oral or injection) should be restricted across the European Union (EU) (5).

The implementation of risk minimisation measures (RMMs) to ensure that thiocolchicoside containing medicines are used as safely as possible, and address the risks of teratogenicity, embryo/foeto-toxicity, spontaneous abortion, impaired male fertility and cancer (5), and also agreed on the need of a risk management plan (RMP).

These include restricting the maximum dose and number of days of treatment when given by mouth or injection. Use is also contra-indicated in pregnancy and lactation or in women of childbearing potential not using contraception, as well as in children or for chronic (long-term) conditions. (Topic forms, which do not produce substantial levels of M2 in the body, are not affected by this review).

Since November 21st 2013, the modified indication, restrictions and indications for systemic thiocolchicoside containing medicinal products are the following:

- Systemic TCC should only be used as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.
- It is not to be used for long-term treatment of chronic conditions.
- Doses should be restricted as follows and the recommended dose and duration should not be exceeded:
  - Oral forms: 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.
  - Intramuscular (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.
- It should not be used in pregnancy and lactation.
- It should not be used in women of childbearing potential not using adequate contraception.

(Local Direct Healthcare Professional Communications (DHPC) and updated Summaries of Product characteristics (SmPC) are provoded in the annex).

The European Commission (EC) implementing decision was issued on 17January 2014 (6), and required the distribution of a direct healthcare professional communication (DHPC) (6) to inform prescribers on the updated indication and highlight the genotoxic risk of systemic (oral and intramuscular) thiocolchicoside containing medicinal products.

In addition, further Risk Minimisation Measures were requested: changes to the summary of product characteristics (SmPC) information and patient's information leaflet including information on fertility and potential risk for cancer, adequate educational materials (EM) for patients and prescribers, as further RMMs (7), and a drug utilisation study (DUS) to characterise the prescribing practices during typical clinical use were also requested to evaluate the effectiveness of RMMs.
These measures were included in the MAHs risk management plan (RMP).

Patients being treated with systemic thiocolchicoside should have their treatment reviewed at the next scheduled appointment, and appropriate alternative treatments should be considered.

7.2 RATIONALE

This joint post-authorisation safety study (PASS) survey, requested by PRAC on 8 October 2015, will be conducted in complement to a Joint DUS. Through the prescription details collected, it will also assess the information rarely reported in databases (e.g. pregnancy, lactation and contraception).

This survey is designed to assess the effectiveness of the DHPC and EM, and whether physicians received the updated prescribing conditions and safety warnings/information, understood and follow them when prescribing systemic thiocolchicoside, in four selected European countries (France, Greece, Italy, Portugal).

7.3 RATIONALE FOR COUNTRY SELECTION

The survey will be conducted in four European countries: France, Greece, Italy and Portugal. The selection of countries to be involved in the survey takes into account the following criteria:

- where thiocolchicoside for systemic use is currently registered and marketed,

- where the physicians and HCPs have been targeted for the DHPC and EM,
- conducted in the countries involved in the DUS (France and Italy) and including the two following countries with significant sales volume (Greece and Portugal).

Table 7.1–1: Prescriptions of systemic thiocolchicoside in European countries

	Distribution of systemic thiocolchicoside containing medicinal products prescriptions per country (thousands) MAT/6/2015	% of prescriptions per country MAT/6/2015
Total selected Market	6,051.410	100.0%
France retail	3,072.412	50.8%
Italy retail	1,899.171	31.4%
Portugal retail	473.337	7.8%
Greece retail	400.976	6.6%
Spain retail	143.145	2.4%
Czech retail	62.369	1.0%

Source: MIDAS Prescribing Insights - IMS Health international databases
MAT: Moving annual total.

7.4 RATIONALE FOR THE SELECTION OF THE SPECIALTIES

The MAHs were required to conduct a study to assess the effectiveness of the DHPC and EM in order to strengthen the risk minimisation measures for systemic thiocolchicoside.

The survey will be conducted among the following physicians who were targeted for the DHPC and EM:

- GPs
- Rheumatologists
- Orthopedists / orthopedic surgeons

The distribution of systemic thiocolchicoside containing medicinal products prescriptions per specialty in Prescribing Insights (PI) panel for countries of interest is shown in Table 7.2–1. It is to be noted that in France and Italy the panel does not cover all specialties (e.g. Orthopedists / orthopedic surgeons in France and Rheumatologists in Italy).

The three selected specialties represent more than 92% of the patient-exposure to systemic thiocolchicoside containing medicinal products among France and Italy. The breakdown per specialty differs from one country to another, partly due to a difference in the coverage of the specialties of interest across countries. Nevertheless, GPs and orthopedists appear as the major prescribers. In contrast, rheumatologists seem to be in minor proportions.

For Greece and Portugal, since no quantitative information is available, the same specialists as in other countries will be involved in the study.

Table 7.2–1: Main prescribers of systemic thiocolchicoside in the selected countries (Source: IMS Health†)

	Distribution of systemic thiocolchicoside containing medicinal products prescriptions per specialty (thousands) MAT/6/2015	% of prescriptions per specialty MAT/6/2015
France	3,072.387	100.0%
Gen.Practitionners	2,981.504	97.0%
Rheumatologists	73.152	2.4%

	Distribution of systemic thiocolchicoside containing medicinal products prescriptions per specialty (thousands) MAT/6/2015	% of prescriptions per specialty MAT/6/2015
Ent specialists	5.444	0.2%
Gastro/Enterologists	4.785	0.2%
Neurologists	3.631	0.1%
Cardiologists	1.903	0.1%
Psychiatrists	1.655	0.1%
Dermatologists	0.313	0.01%
Italy	1,899.256	100.0%
Gen.Practitionners	1,365.608	71.9%
Orthopedists	388.895	20.5%
Neurologists	43.937	2.3%
Geriatrics	28.658	1.5%
Ent specialist	21.914	1.2%
Cardiologists	20.848	1.1%
Pediatricians	11.037	0.6%
Pneumologists	6.918	0.4%
Psychiatrists	6.773	0.4%
Gastro/Enterologists	2.562	0.1%
Gynaecologists	1.209	0.1%
Urologists	0.752	0.04%
Diabetologists	0.145	0.01%
Greece	NA*	NA*
Portugal.	NA*	NA*

[†]*Source:MIDAS Prescribing Insights - IMS Health international databases.*

Prescribing Insights databases contain the evolution of IMS Medical Indices, which had as objective to provide a detailed analysis of prescriptions, diagnoses and therapy patterns based on the records of practicing physicians (both GPs and specialists).

MAT: Moving annual total.

NA: Not available, i.e. country not covered.*

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

The research question is whether the DHPC and EM, implemented as RMMs, were effective to ensure:

- correct knowledge of physicians about prescribing conditions and safe use when prescribing systemic thiocolchicoside,
- appropriate attitude when prescribing systemic thiocolchicoside, in particular as concerns pregnancy, lactation and contraception.

8.2 OBJECTIVE

The survey objective is to measure the effectiveness of the DHPC and EM, implemented as part of RMMs, by ascertaining the proportion of targeted physicians who understood and implemented the latest prescribing conditions and safety information about systemic thiocolchicoside provided in the DHPC and EM.

Specific objectives were to evaluate the proportion of physicians who:

- prescribe systemic thiocolchicoside only as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.
- do not prescribe systemic thiocolchicoside for long-term treatment of chronic conditions.
- follow the recommendations regarding the doses and duration restriction:
  - for oral forms: 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.
  - for IM forms: 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.
- do not prescribe systemic thiocolchicoside during pregnancy and lactation.
- do not prescribe systemic thiocolchicoside in women of childbearing potential not using adequate contraception.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This survey will be cross-sectional, multinational, non-interventional and conducted among physicians in anonymous way.

9.2 SETTING

The survey will be conducted through a web questionnaire among prescribers of systemic thiocolchicoside in settings of the selected countries (France, Greece, Italy and Portugal).

Physicians will be identified according to their specialty as specified in the IMS OneKey lists. They will be sent an email to present them the survey and invite them to participate.

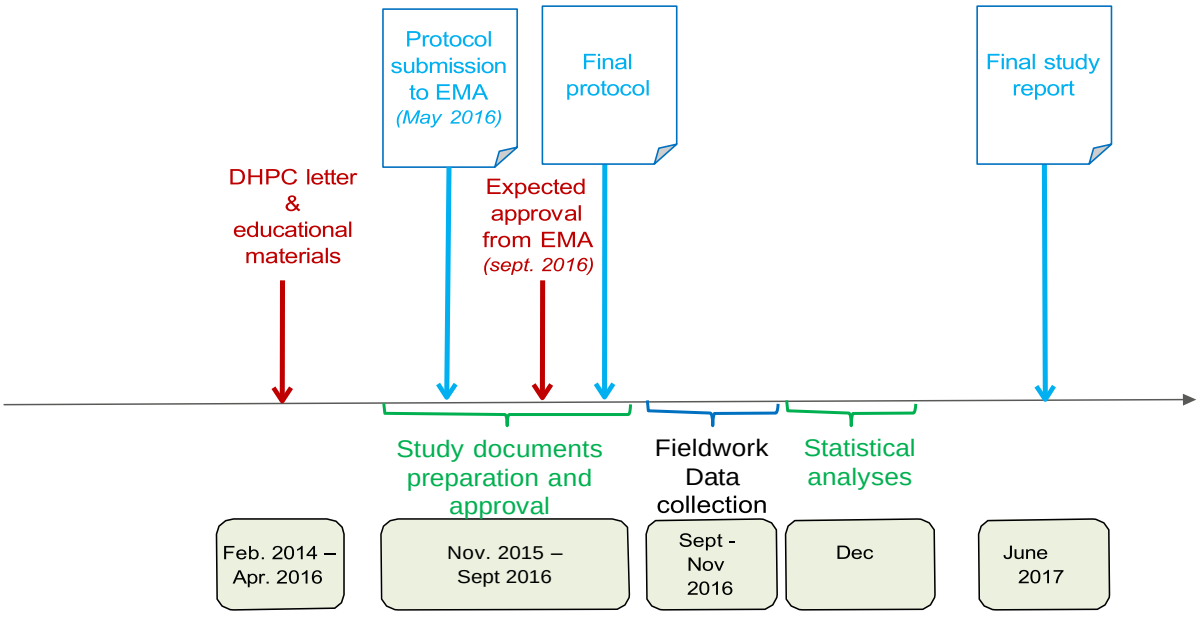

Figure 1: Study scheme and main timelines

9.2.1 Inclusion criteria

The survey will be conducted among physicians meeting the following inclusion criteria:

- Physicians who prescribed systemic thiocolchicoside within the 12 months prior to the survey
- GPs and specialists of any of those targeted for the DHPC and EM:
  - Rheumatologists
  - Orthopedists / orthopedic surgeons

9.2.2 Exclusion criteria

Inactive and retired physicians (when documented information is available to identify them) will be deleted from the contact lists before randomisation.

The following exclusion criteria will be checked at the beginning of the web questionnaire:

- Physicians who do not treat patients
- Physicians who may have conflicts of interest with the survey (i.e. physicians employed by regulatory bodies, pharmaceutical industries).

9.3 VARIABLES

Physician related data about their knowledge and prescribing attitude for systemic thiocolchicoside containing medicinal products and drug utilisation data will be collected.

1) Physicians demographics and practice information:
   Physician's related data include:
   - Demographics (age, gender)
   - Duration of practice
   - Specialty
   - Type of setting

2) Screener:
   - Prescription of systemic thiocolchicoside containing medicinal products within the last 12 months (yes/no)

3) Question to evaluate the physician experience in treating patients presenting with painful muscle contractures:
   - Number of prescriptions (not patients) of systemic (oral and/or intramuscular) thiocolchicoside containing medicinal products written within the last 12 months

The following information will also be assessed:

4) Prescribing conditions and safety information/warnings of systemic thiocolchicoside containing medicinal products:
   - Knowledge of the prescribing conditions and safety information about systemic thiocolchicoside presented in the DHPC and EM:
     - Indication
     - Contraindicated conditions
     - Recommended maximal dose, posology and duration of use for oral and IM forms
     - Information to be communicated to a patient before prescribing the drug
     - Specific information to be advise to females of childbearing potential

5) Awareness of and attitude towards the latest prescribing conditions and safety information:
   - Awareness of the prescribing conditions and safety information about systemic thiocolchicoside presented in the DHPC and EM:

- Awareness of the prescribing conditions and safety information: main concerns perceived
- Sources of knowledge
- Reception of the DHPC by the physician and awareness about the EM
- Physician's intention to consider the prescribing conditions and safety warnings

6) Recent prescriptions details:

The following information related to up to the last five prescriptions to patients will be collected upon physician's recall memory:

- Approximate date of prescription of systemic thiocolchicoside
- Approximate patient' age at the time of prescription (age ranges: <16 or ≥16 years old)
- Gender
- Status at the visit for females of childbearing potential (using or not an effective method of contraception, pregnant or not, planning to be pregnant, breastfeeding)
- Indication for which the drug was prescribed
- Form, number of administrations and dose per administration per day
- Duration of use prescribed
- Concomitant treatment(s) ongoing or written at the time of prescription
- Main reasons for choosing systemic thiocolchicoside
- Information and recommendations provided to the patient when prescribing systemic thiocolchicoside containing medicinal products.

9.4 DATA SOURCES

Physicians will be identified according to their specialty as specified in the IMS OneKey lists. They will be sent an email to present them the survey and invite them to participate.

The survey is a primary data collection conducted through a web questionnaire.

The questionnaire will be developed and tested among 6 physicians for its comprehensibility, consistency and the appropriateness of medical terms. Physicians' comments will be implemented in the final version.

The translated versions of the questionnaire from English into local language will be done using the back and forth method (from English into local language and then from local language into English) to ensure an accurate translation.

The web questionnaire completion is estimated to take 10 to 15 minutes for the core questionnaires and around 5 minutes per prescription details reported.

9.5 STUDY SIZE

9.5.1 Sampling plan

The statistical unit considered is the physician who prescribes systemic thiocolchicoside. For each selected country, the sample survey will include physicians identified and recruited from one source: IMS OneKey reference lists of required specialists.

These lists may not cover all of the physicians who received the DHPC and EM or may include physicians who were not targeted for the DHPC and EM. Consequently a screening question will check whether the physician has prescribed systemic thiocolchicoside within the last 12 months and therefore can be considered as a prescriber. These lists will be restricted to the targeted specialists' population, i.e. selected specialists who are currently active and not retired in 2016 at the time of the survey.

As per sample size defined below and the number of selected countries and specialities, physicians will be stratified only per country and specialty (Table 9.5.1–1). Other criteria such

as region, age and gender of the prescriber are less relevant than country and specialty, since they may not be available in all countries or not be a determinant as important as country or specialty. The use of more strata would have needed a larger sample size.

A random stratified sampling method will be applied. As a first step, all lists will be merged, and then the eligible physicians will be divided into homogeneous groups, called strata, which are mutually exclusive (a physician can only belong to one stratum). This stratification will be based on the following criteria:

- Country: 4 possibilities,
- Specialty: 3 possibilities.

Thus, 4 x 3 = 12 strata will be formed.

Table 9.5.1–1: Strata definition

Stratum ID	Country	Specialty
1	France	GPs
2	France	Rheumatologists
3	France	Ortopedists / ortopedic surgeons
4	Greece	GPs
5	Greece	Rheumatologists
6	Greece	Ortopedists / ortopedic surgeons
7	Italy	GPs
8	Italy	Rheumatologists
9	Italy	Ortopedists / ortopedic surgeons
10	Portugal	GPs
11	Portugal	Rheumatologists
12	Portugal	Ortopedists / ortopedic surgeons

The physicians' allocation to a stratum is explained in the section below (§9.5.2. Study size calculation). However, eligible physicians are not evenly distributed across these four specialties. The GPs are much more prevalent..

9.5.2 Study size calculation

The sample size formula, based on the normal approximation to the binomial distribution, for calculating the number of subjects required for a proportion is the following:

$$n = \frac{P \cdot (1-P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where *P* is the expected proportion, *e* is one half the desired width of the confidence interval (CI), and $Z_{1-\alpha/2}$ is the standard normal *Z* value corresponding to a cumulative probability of 1 – α/2. The following table provides the margin of error for 95% CI based on various sample sizes and proportions of interest (Table 9.5.2–1).

Table 9.5.2–1: Sample size obtained for various precisions and proportions

	Margin of error for 95% CI			
Proportion	**5%**	**4%**	**3%**	**2%**
10%	139	216	384	864

30%	323	504	896	2,017
50%	384	**600**	1,067	2,401
70%	323	504	896	2,017
90%	139	216	384	864

Since the proportion of physicians informed about the updated prescribing conditions and recommendations for safe use of systemic thiocolchicoside is not known and there is no evidence supporting the expected proportion, the worst case hypothesis will be assumed considering that 50% of physicians will have received and understood the safety information distributed recently. This assumption yields the largest sample size.

Considering this hypothesis and in order to achieve a CI of 95% with a half-width of 4%, a total of 600 analysable physician questionnaires will be needed for the overall sample. Considering a margin of error of 5% (or 3% respectively) instead of 4%, the required sample size would be 384 (or 1,067) analysable physician questionnaires for the overall sample.

Based on IMS Medical Radar experience from previous similar surveys and estimates and the evaluation of the survey feasibility with four countries, the sample size of 600 is considered for this study. Indeed, the elected sample size should be sufficient to be divided between 4 countries and further between 3 groups of specialities.

It is estimated that about 30% of physicians will not complete the questionnaire until the end or not be analysable (i.e. physicians who respond to questions regarding their knowledge on the updated safety concerns of systemic thiocolchicoside or physicians without any prescription of systemic thiocolchicoside in the last 12 months or physicians who have to interrupt the interview due to an emergency (rare)). Taking into account these respondent physicians without analysable questionnaires, the overall sample size of 780 participating physicians will be required to reach 600 analysable questionnaires (i.e. recruitment of physicians should continue until 600 analysable questionnaires have been reached).

For the conduct of survey, ideally this overall sample of 780 participating physicians (and 600 analysable questionnaires) should be proportionally split between the selected countries and specialties based on the number of physicians in each country. However, due to large variance of the number of physicians in targeted countries (Table 9.5.2–2) such a distribution would yield a too small number of interviews in smaller countries (such as Greece or Portugal) / specialties (such as rheumatologists) and would not allow the applicability of common statistical methods in those countries / specialties. For instance, an allocation of 600 analysable questionnaires using the true weight of each country (see column 'All % C') would yield the following sub-sample sizes per country: 353 physicians for France, 21 for Greece, 200 for Italy and 26 for Portugal.

Table 9.5.2–2: Distribution of the specialties involved in the survey per country (Source: Eurostat†)

		Family pratice (GPs)	Rheumatologists	Orthopedists / orthopedic surgeons	All	All %C
France‡	#	90,630	2,353	2,936	95,919	58.8%
	%L	94.5%	2.5%	3.1%	100%	
Greece†	#	3,494	NA	2,314	5,808	3.6%
	%L	60.2%	NA	39.8%	100%	
Italy†	#	45,203	NA	9,234	54,437	33.4%
	%L	83.0%	NA	17.0%	100%	
Portugal†	#	5,943	NA	1 071	7,014	4.3%

		Family pratice (GPs)	Rheumatologists	Orthopedists / orthopedic surgeons	All	All %C
	%L	84.7%	NA	15.3%	100%	
All	#	145.270	NA	15.555	163.178	100%

†Source: Eurostat http://ec.europa.eu/eurostat/web/products-datasets/-/hlth_rs_spec. Data for the year of 2013 (most recent year with data for all selected countries).

‡Source : CNOM (Conseil National de l'Ordre des Médecins) for France in 'Atlas de la démographie médicale en france situation au 1er janvier 2014' http://www.conseil-national.medecin.fr/sites/default/files/atlas_2014.pdf

number of physicians. %L: percentages per line, %C percentages per column. NA: Not available.

A pragmatic split will be therefore implemented (Table 9.5.2–3) to allocate a sufficient sub-sample size to the less represented countries (Greece and Portugal). To allow this over-sampling of Greece (objective of 120 analysable questionnaires instead of 21 with a proportional allocation) and Portugal (objective of 120 instead of 26, respectively), an under-sampling of the most represented countries France (objective of 180 instead of 353) and Italy (objective of 180 instead of 200) is needed in compensation.

With this sample, it will be necessary to weight the results according to the real proportion of physicians from IMS reference lists or available public information obtained through external sources (e.g. Eurostat or CNOM for France) to allow the representativeness of the overall sample.

Table 9.5.2–3: Number of physician interviews required per country

	Sample size objectives			
Country	**Analysable questionnaires**			**ns**
France	180	(30.0%)	234	(30.0%)
Greece	120	(20.0%)	156	(20.0%)
Italy	180	(30.0%)	234	(30.0%)
Portugal	120	(20.0%)	156	(20.0%)
All	600	(100.0%)	780	(100.0%)

* Note: The country-distributions of the 'Number of participating physicians required' and the 'Number of participating physicians with complete analysable questionnaire expected' are the same, since the second one is deducted from the first one through the application of a 30% inflation rate due to physicians who will not complete the questionnaire.

At each country level, the sample size will be further divided into the selected groups of specialties.

Usually, to ensure the robustness of statistical estimations at a wished level of analysis (e.g. specialty or aggregated specialties per country), the sample size should not be lower than a threshold of 40 statistical units in each entity of this level.

For analysis, less common specialties as orthopedists or orthopedic surgeons need to be grouped. Moreover, for other less common specialties as rheumatologists, given their very limited contribution within the total of prescriptions of systemic thiocolchicoside (less than 2.5% (Table 7.2–1), the recruitment of a threshold of 40 rheumatologists and 40 orthopedists/ orthopedic surgeons who have prescribed systemic thiocolchicoside per country will be too difficult.

It will be necessary to weight the results according to the real proportion of physicians in order to determine the representativeness of the overall sample. If the threshold of 40 statistical units (physicians per specialty in a country) would not be reached, then additional

physicians of other groups will be recruited to compensate and preserve the sample size at country level.

To comply with this constraint, an arbitrary split per specialty in each selected country will be implemented as follows (Table 9.5.2–4). Whenever possible, the real breakdown of targeted specialists was used to determine the split per specialty. But most of the time, building a sample proportionally distributed by the number of specialists would yield very small numbers for less frequent specialties, mainly in Greece and Portugal.

As a consequence, an over-sampling of less frequent specialties will be applied in order to provide a sufficient number of analysable questionnaires (threshold of 30). This allocation is applied to the number of analysable questionnaires. Then, the number of required participating physicians is deducted taking into account 30% of respondents without analysable questionnaires.

Table 9.5.2–4: Sample size per country and per specialty

n (vertical % per country)*	France	Greece	Italy	Portugal	All
Number of physicians with an analysable questionnaire	**180**	**120**	**180**	**120**	**~~600~~**
GPs	90 (50.0%)	60 (50%)	90 (50.0%)	60 (50%)	300 (50%)
Rheumatologists	40 (22.2%)	30 (25%)	40 (22.2%)	30 (25%)	140 (23.3%)
Orthopedists / orthopaedic surgeons	50 (27.8%)	30 (25%)	50 (27.8%)	30 (25%)	160 (26.7%)
Number of participating physicians required	**234**	**156**	**234**	**156**	**~~780~~**
GPs	117 (50%)	78 (50%)	117 (50%)	78 (50%)	390 (50%)
Rheumatologists	52 (22.2%)	39 (25%)	52 (22.2%)	39 (25%)	182 (23.3%)
Orthopedists / orthopaedic surgeons	65 (27.8%)	39 (25%)	65 (27.8%)	39 (25%)	208 (26.7%)

** To be aligned with the n by country, numbers n per specialty have been rounded to the most closed integer.*

Since the relative weight of each country and of each specialty in the sampling plan is different from its real relative weight in estimations, the extrapolation of the raw survey results to the overall target population would not be relevant.

A sample adjustment will be performed. The survey results will be weighted to reflect the real proportion of the four countries and within each country to reflect the real proportion of each specialty in order to extend the survey results to the overall target population. Both unweighted (i.e. raw data) and weighted results will be presented in the report.

A weight variable will be applied to each statistical unit (i.e. the analysable physician) during the results calculation in order to correct any over-or under-sampling that may have occurred for a country or specialty. This weight variable will indicate how many unit(s) of the population of interest an observation will count in a statistical procedure. Its value will change per country and per specialty. The weights will be normalised to obtain their sum equal to the sample size.

In order to fill-in each stratum of the sample survey from the IMS OneKey reference files, an independent sample will be selected per stratum through a simple random sampling without replacement.

In each specific stratum, physicians will be contacted according to the order of draw in this stratum. If a physician does not want to participate in the survey, the next one in order of

draw will be contacted, and so on until the required number of physicians is met. If the target for a stratum is not achieved after the end of the initial list, an additional randomly sampled list will be prepared and the physicians contacted until the goal is reached or no names are left in that stratum. If the complete list of the IMS OneKey reference files has been exhausted in any particular stratum, a strategy will be determined to adjust the sample size within stratum with associated weighting.

In web surveys, the number of physicians to be contacted for reaching the required number of physicians with analysable questionnaires is usually around ten times more than the expected final number.

It is to be noted that this sample is calculated to be representative as a whole (including all countries), not per country or specialty. Thus the subgroup analyses will not guarantee the same confidence intervals as the whole sample. Indeed per country, a sub-sample of 180 analysable questionnaires for France and Italy will allow the estimation of the unknown expected proportion (supposed to be 50% for the sample size calculation) with a margin error of 7%. For Greece and Portugal, with 120 analysable questionnaires, the expected margin error will be around 9%.

Sample of collected prescriptions:

For the data on prescriptions, the statistical unit considered will be the individual drug prescription to patient. Although the level of contribution to this section per interviewed physician is not known and will depend both on the market sells of systemic thiocolchicoside in each country and for each specialty, and on the percentage of interviewed physicians who prescribed the drug to patients. Physicians are requested to report up to 5 last prescriptions of systemic thiocolchicoside written over the last 12 months before the survey, each pertaining to a unique patient.

As a result, the sampling method (systematic sampling) is expected to allow generalisability of results once the overall sample of physicians can be shown to be generalisable.

Based on IMS Medical Radar experience from previous similar surveys, it is estimated that in average each interviewed physician who prescribed systemic thiocolchicoside to patients will contribute with 3 prescriptions on average.

If a conservative rate of 50% is assumed to evaluate the part of interviewed physicians who prescribed systemic thiocolchicoside to patients, the sample size for prescriptions will be about 900, thus largely sufficient for the study of proportions of appropriate use of drug under the same assumptions of confidence interval and precision as described above.

Note that a sample adjustment will be also implemented for the sample of collected prescriptions using the same methodology as for analysable questionnaires but with different weights.

9.6 DATA MANAGEMENT

The survey will be conducted according to the Standard Operating Procedures (SOPs) of IMS Medical Radar and IMS Real World Evidence Solutions.

Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by merging of databases of each country.

Data will be checked in terms of consistency before data analysis:

- removal of duplicates (if required),
- data labelling and data formatting,
- range and consistency checks for each variable to identify potential non admissible values,
- cross-check the consistency of data for related variables (if feasible).

The number of variables with missing values will be indicated. Missing values are excluded from the calculation of percentages.
The study database will be locked once validated.

9.6.1 Data collection

The data collection period will last six to seven weeks, and will be conducted in parallel in the four countries.

The survey will be conducted by IMS Medical Radar, a division of IMS Health specialising in the conduct of phone and web surveys for more than 20 years. IMS Medical Radar will create a web-based instance survey. The lists of physicians will be loaded into separate databases for the management of the survey. Physicians' answers/data will be collected through a web questionnaire. The survey will collect data in an anonymous way.

As described previously (§9.5.1: Sampling plan and §9.5.2: Study size calculation), physicians will be randomly contacted, mainly by email and also by letters or phone calls when needed, according to their stratum by the IMS Medical Radar team. Their recruitment will be done as follows:

- Physicians will be invited to participate in the survey (via emails/mails or phone calls). The survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the physicians at this step. If they agree to participate in the survey, they will receive a link to access the survey and the instructions for the web questionnaire completion.
- If the questionnaire is not completed and sent to IMS Medical Radar, the physicians will be sent a reminder by email one week after the start of the survey.
- If the target is not achieved in the stratum, a reminder by phone will be conducted 1.5 week after the start of the survey.
- If the questionnaire is still not completed and sent to IMS Medical Radar, the physicians will be sent a last reminder by email two weeks after the start of the survey.

If necessary, i.e. if the minimum number of needed responders is still not reached, the recruitment will be continued by phone to achieve the target in a specific stratum.

A physician will be considered as contacted if he/she has:

- completed the web questionnaire and sent it back to IMS Medical Radar
- refused to participate,
- was tentatively reached out at least 3 times and up to 5 times.

Moreover, a physician will be considered as unreachable if he/she has been contacted between three and five times without any answer.

For each physician of the sample file, the number of contacts, and the date and time when he/she completed the web questionnaire will be recorded. The recruitments in each stratum will be stopped when the target is reached. If the files have been exhausted in any particular stratum, the recruitments in this stratum will be prematurely ended and a strategy will be determined to adjust the sample size with associated weighting.

9.6.2 Approaches for increasing the response rate

Physicians are increasingly contacted to participate in web or phone surveys. Their overall response rate of participation remains low according to international studies (8)(9)(10). Holbrook et al. showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey (10). VanGeest et al. conducted a systematic review of 66 published reports on efforts to perform for improving response rates (11). Two general strategies were explored: incentives-based approaches and survey design-based approaches. Financial incentives, even little ones,

were effective in improving physician response rates while non-monetary incentives were much less effective. These measures include the use of a short questionnaire, and questionnaires personalised, and approved by professional associations.

In order to increase the response rate, three actions will be applied to this survey:

1) A compensation fee will be proposed to physicians for their participation in the survey.
2) All physicians will be sent an email or contacted by experienced operators of IMS Medical Radar with extensive experience in conducting health related surveys.
3) Each physician will be emailed or called up to 3-5 times before being considered as "not reachable", and reminders will be sent by email if IMS Medical Radar does not receive the web questionnaire.

9.7 DATA ANALYSIS

9.7.1 General statistical consideration

The statistical analysis will be conducted using the SAS® softwareV9.4 on Windows™ (SAS Institute, North Carolina, USA).

The statistical results of the four countries will be presented in the same report, overall, per country and per physician's specialty group (Table 9.7.1–1 as an example).

Table 9.7.1–1: Mock table to implement in the statistical and study reports

			Question 1…		
Country	**General practitioners**	**Rheumatologists**	**Orthopedists / orthopedic surgeons**	**All (unweighted)**	**All (weighted)**
France	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Greece	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Italy	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Portugal	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall - unweighted results	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall - weighted results	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: the table structure may be adjusted in the final study report.

All the analysis will be descriptive in nature and no statistical comparison will be done in this study, as it does not appear to be necessary to answer suitably the survey objectives. Besides as the DHPC and EM were already distributed to all physicians of the selected specialties, a before-after study design with comparison to baseline values is not possible, as well as a case-control study.
Continuous variables will be described by their number (of valid cases, of missing values), mean, standard deviation, and median, Q1, Q3, minimum and maximum.

Categorical variables will be described as the total number and relative percentage per category. These will be the percentage per category.

Free text answers to open-ended questions will be categorised by theme, listed according to the frequency.

Confidence intervals of 95% will be evaluated, when relevant.

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be expressed among physicians with complete analysable web questionnaires. The endpoint will be assessed overall, by country and among subgroups of physicians' specialty.

In a first step, calculations will be performed on raw data. No projection factor will be applied to generalize the results to the entire prescribers' universe. As a consequence, the line "Overall - unweighted results" will show only the results observed on the overall sample, and will not reflect the countries' universe since this sample is not proportional to the size of IMS OneKey reference files in each country.

In a second step, the results will be weighted according to the real proportion of physicians in each specialty and country in order to accurately reflect the population that the survey seeks to measure.

For each country, the results will be reported according to the prescribers' specialty distributed proportionally to their weight within IMS OneKey reference lists.

Study objective:
The proportion of targeted physicians who received, understood and agreed to implement the latest prescribing conditions and safety information about systemic thiocolchicoside provided in the DHPC and EM will be evaluated. Analysis will be done in total and separately by specialty (GPs, rheumatologists and orthopaedists / orthopaedic surgeons) using proportions and the corresponding 95% Wald confidence intervals.

Analysis of the collected prescriptions:
The variables will be analysed separately for GPs, rheumatologists and orthopaedists / orthopaedic surgeons according to the information provided, as detailed above in § 9.3: Variables.
Possible selection bias will be assessed by comparing the distributions of available characteristics (e.g. country, age, gender, type of practice and specialty) between respondent and non-respondent physicians.

Handling of missing data:
The number of missing data will be indicated. Missing data will not be replaced by imputation methods. They are expected to be few and distributed at random.

9.7.2 Analysis of non-participation or refusal to participate rate

As often required by the Authorities, the following different cases of total non-response will be distinguished and analysed:

- Targeted physicians: Physicians reached to whom an email or mail has been sent, or have been called.

- Contacted physicians: Physicians who have been reached out by phone or have opened their email (if technically available in their country).
- Physicians who agreed to participate: Physicians willing to participate in the survey (e.g. by phone or by clicking on the link provided in the recruitment email).
- Physicians with complete questionnaire: Physicians who actually completed the questionnaire until its end**.**

The physicians' participation in the survey will be examined via different ratios:

- Contact rate = contacted physicians / targeted physicians
- Response rate = Physicians who agreed to participate / contacted physicians
- Cooperation rate = Physicians with complete questionnaire / Physicians who agreed to participate
- Refusal rate = (contacted physicians-physicians who agreed to participate) / Physicians reached

The reasons for non-response will be sought, especially from all observed variables. This will ensure that missing data are reported with enough details to strengthen the results validity, as recommended by the STROBE guidelines (12).

9.7.3 Questionnaire analysis

The general statistical considerations described above (§9.7.1) will be applied for quantitative and qualitative variables. The number of missing data will be indicated. Missing values are expected to be few and distributed at random. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data (13).

Confidence intervals of 95% will be evaluated for endpoint variables.

Physicians' answers will be analysed by subgroups of physician's specialty per country, and on the overall dataset.
For each question associated to the outcomes included in the main objective, a criterion will be calculated to separate physicians with an appropriate answer (or at least one appropriate response if the corresponding question allows multiple answers or is an open-ended question). These proportions of appropriate answers will be expressed among physicians with complete web-questionnaires.

9.8 QUALITY CONTROL

9.8.1 Approaches for validating the questionnaire

The questionnaire will be tested among 6 physicians for its comprehensibility, consistency and the appropriateness of medical terms. The questionnaire will be translated from English into local language using the back and forth method to ensure an accurate translation of the local versions of the questionnaire will be validated by the MAHs.

9.8.2 Approaches for validating the results

The quality control for validating the results will be conducted at five levels:

1) At IMS Medical Radar management level, every efforts will be undertaken to collect complete and valid data:
   - Verification of the reliability and security of the web questionnaire interface by a qualified web-master for each country,
   - Monitoring of the quality and datasets definition by a qualified data manager. In the background of the web questionnaire, real-time checks of the answers provided by the respondents will be developed. Non admissible answers (i.e. incorrect or unusual values, outlying values) will be detected and queries sent to the physician.
2) At the study database level (after merging datasets of each country), final data quality checks will be applied (beyond data management process):
   - Distribution of each variable in order to count the number of missing values and estimate the associated relative percentage,
   - Identification and count of non-analysable questionnaires:
     - estimation of the percentage of physicians without complete analysable questionnaire.

Any changes in the database will be tracked and documented. The country-datasets will be stored in a dedicated database. Once data validated and quality checked, the database will be locked.

3) At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.
4) At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewers' comments.
5) At the study level, all aspects of the study will be conducted according to the SOPs of IMS Real World Evidence Solutions and IMS Medical Radar divisions.
   The study documents have been approved by people competent in medical and safety areas of IMS. According to the SOPs, an independent review of the survey results and report will be conducted by a person who was not in charge of their preparation.

9.8.3 Safeguards, security and traceability of contacts

Operators of the call centre specialised in health surveys, will be assigned to the project and trained on the survey methodology prior to fieldwork. The emails contacts and phone calls will be traced using the management software. All survey aspects from protocol development to the reporting of the results will be conducted according to the Standard Operating Procedures (SOPs) of IMS Real World Evidence Solutions and IMS Medical Radar divisions. These SOPs can be consulted on site (14).

9.9 STRENGTHS AND LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Strengths:

1) use of IMS OneKey reference lists of physicians

The IMS OneKey file used to target interviewed physicians is an international database that cover more than 80 countries and 8.5 millions of HCPs/health facilities. In each country, the database is fully representative of the HCPs population.

The information contained in the file of each country is updated constantly with proactive updates. Quality controls are implemented on a regular basis.

2) The sampling of physicians follows a stratified randomised method which guarantees the representativeness of the contacted population in order to limit selection bias due to voluntary participation. Batches of physicians will be contacted up to five times before moving forward to other physicians in the lists.

3) The questionnaire includes general questions followed by specific ones in order to limit a learning process during the survey. It included both open- and closed questions. As the physicians may understand the right answer in subsequent questions, it would not be possible to go back in the questionnaire and edit answers in former questions.
The questionnaire is tested for its clarity and absence of questions raisons social desirability bias. The translation of the questionnaire is tested before implementation.

4) The study is conducted by an experienced team specialised in the design and conduct in such survey in safety area. It follows IMS SOPs (14) as well as the methodological guidelines on ENCePP and EMA GVP.

9.9.2 Possible selection bias due to voluntary participation

The potential for selection bias of physicians participating in a survey is an inherent bias/limitation to any study based on volunteer participation. In order to quantify any selection bias, the distribution of each stratification criterion of physicians (country and specialty) will be compared between participants and non-participants.

9.9.3 Limits inherent to web surveys

In such surveys, the generalisation and external validity of the results is restricted to physicians who have an active email address and willing (and able) to answer a questionnaire online. These physicians may not be fully representative of the whole targeted population (15).

Among non-response bias, targeted physicians may also have activated filters in their mail box in order to block spams and unsolicited emails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple email addresses could also be a critical situation. If the one used is not the primary address or if the physicians do not check their email box frequently they will not receive the invitation during the recruitment period. Some physicians who were sent a letter may not have received it. This is one of the reasons why some physicians will also be contacted by phone.

Moreover, web surveys may promote social desirability bias which refers to the tendency of physicians to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behavior, e.g. physicians can copy-paste information gathered online instead of giving their own opinions (15).

Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire could/tends to reduce this bias (16).

The access to the web questionnaire interface will be strictly limited to the invited participants, with the possibility to participate only once and with a traceability system. Thus stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfill the survey in order to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable.

9.9.4 Possible recall bias for prescription details report

The physicians will be asked to provide prescription cases out of mind. The main reason for asking physicians to provide prescriptions details out of mind is that we wanted to keep the study pragmatically simple and within the definitions of a survey.

The collection of data through patient records would be categorised as chart review in most of the participating countries and would require Ethics Committee submissions, which is a time consuming process. This would delay the administration of the survey too far from the communication of the RMMs (DHPC and EM), which by itself would lead to a recall bias. The trade-off between a survey and a chart review was a difficult one. But, as the initial PRAC request was for a survey, and the present survey is complemented with a drug utilisation study using secondary data sources, to keep it as simple as possible.

However, this section of the survey is prone to both recall bias and selection bias. Physicians are asked to report prescription cases systematically and without omission.

Clinicians generally know and remember patients with chronic disease and long term follow-up, but in spite of the guideline of systematic selection they may select specific patients because they have a better memory of their conditions.

The results of this section will be interpreted with caution due to the likelyhood of biases. However these biases would not affect the core survey questionnaire which deals with physicians' knowledge and opinions.

9.9.5 Generalisation of the survey results to the overall target population with adjustment

Since the study design presents an over-sampling mainly in Greece or Portugal, and less frequent specialties as rheumatologists or orthopedists/ orthopedic surgeons and an under-sampling in France, Italy and of GPs, the raw survey results will not be generalised to the overall target population, except if a sample adjustment is applied. For more accuracy and transparency, both unweighted (i.e. raw data) and weighted results will be presented in the report.

Since the IMS lists may identify a limited number of physicians who were not targeted with the DHPC and EM, the results may be impacted.

9.10 OTHER ASPECTS

None

10. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential, and only aggregated data will be analysed and communicated in a report.

10.1 REGULATORY AND ETHICS CONSIDERATIONS

10.1.1 Ethical principles, laws and regulations

The survey will follow the regulatory and ethical requirements of each country. The survey will comply with the module VIII of the good pharmacovigilance practices (GVP).

IMS will follow the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines (17) for all countries. Since the physicians will be asked to recall out of mind the prescriptions' details, no legal approvals or information are required for the four countries.

10.2 PHYSICIANS INFORMATION

Physicians participating in the survey will be informed about the targets of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IMS keeping their data.

10.2.1 Physicians compensations

Physicians will be offered a compensation for the time spent participating in this survey (that they may refuse).The time to complete the survey is estimated between 10 to 15 minutes, plus an additional 5 minutes for each prescription reported (up to five prescriptions).

The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, and which states:

"When it is necessary to compensate a physician in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the physician for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the physician's participation in the survey. They must be declared to the tax authorities in accordance with applicable laws".

10.3 CONFIDENTIALITY

10.3.1 Patient confidentiality

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential, and only aggregated data will be communicated and analysed.

10.3.2 Data confidentiality / Data security

Participating physicians will access the website (https secured site) via a secure link using a personalised login and password. This link is unique to each physician.
The answers provided will be collected in an anonymous way, only aggregated data and presented as a synthesis will be transmitted to the MAH.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time, and will include security elements to prevent others than authorized staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the database and the application files will be made outside the server housing the web-based study. Security copies will be periodically made and stored outside this server. A copy of the data stored in the database will be transferred to MAHs at the end of the study.

Description of all elements of security and traceability will be available upon request.

10.4 RECORD RETENTION

The study documentation will be stored in the study master file.
The web questionnaires data will be stored on the survey database for 5 years.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 ADVERSE EVENT COLLECTION

The study is based on the secondary use of data. Adverse events (AE) and Adverse Drug Reactions (ADR) will not be measured.

11.2 AE management and reporting

NA

12. PLANS FOR DISSEMINATING AND COMMUNICATING SURVEY RESULTS

The survey will be registered in EU-PAS register (currently the ENCePP e-register of studies) by MAHs.

The statistical results will be discussed with and approved by MAHs.

A survey report including the results of the four countries will be written in English, using MAHs or IMS Health template (which is based on the template included in the GVP module VIII) and following STROBE recommendations in MS Word format (12).

The final survey report validated by MAHs will be communicated to EMA.

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14. ANNEXES

Annex 1: List of stand-alone documents

Number	Document reference number	Date	Title
1-Protocol	Version 2	April 2016	Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Thiocolchicoside containing Medicinal Products for Systemic Use in France, Greece, Italy and Portugal
2-Questionnaire	Version 2	April 2016	Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Thiocolchicoside-containing Medicinal Products for Systemic Use in France, Greece, Italy and Portugal

Annex 2: ENCePP checklist for study protocol

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Thiocolchicoside containing Medicinal Products for Systemic Use in France, Greece, Italy and Portugal

Study reference number:
xxxxx

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for	☒	☐	☐	
1.1.1 Start of data collection[1]	☒	☐	☐	13, 14
1.1.2 End of data collection[2]				13, 14
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	13, 14

Comments:

No progress reports are planned.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	11, 15-17
2.1.2 The objective(s) of the study?	☒	☐	☐	11, 18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12, 19
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

For 2.1.4 and 2.1.5: there is no formal hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12, 19
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☒	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

For 3.2: the objectives will be answered by descriptive analysis, but no specific endpoints are defined.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒			19-20, 21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	19
4.2.2 Age and sex?	☒	☐	☐	19,20
4.2.3 Country of origin?	☒	☐	☐	16,17
4.2.4 Disease/indication?	☒	☐	☐	15
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	21-27

Comments:

For 4.2.5 and 4.2.6: the study population presented with painful muscle contractures.
For 4.3, see § 9.5.1 Sampling plan p.21,22 of the protocol.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and	☒	☐	☐	16-17

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
categorising exposure)				
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	19
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

For 5.2, 5.4 and and 5.5: no measurement will be done on exposure data.
For 5.3: the time window of exposure considered is specified in the questionnaire.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☒	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

For 6.1 and 6.2: the survey is descriptive. No specific endpoints are defined.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				21
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	21-22
8.2.2 Endpoints? (e.g. date of occurrence, multiple event,				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
severity measures related to event) 8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)			× ×	
8.3 Is a coding system described for: 8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) 8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	 ☒ ☐ ☒	 ☐ ☐	 ☐ ☒ ☐	 1 1
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

For 8.1.2, 8.1.3, 8.2.2 and 8.3.2: the survey is descriptive. No specific endpoints are defined
For 8.2.1 and 8.3: see the survey questionnaire.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	12, 21-25

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?		×		
10.2 Is the choice of statistical techniques described?	×			12, 29-31
10.3 Are descriptive analyses included?	×			12, 29-31
10.4 Are stratified analyses included?	×			29-31
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	×			27
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	×			27,32,35
11.3 Are methods of quality assurance described?	×			31-32
11.4 Does the protocol describe possible quality issues related to the data source(s)?	×			31-32
11.5 Is there a system in place for independent review of study results?	×			32

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	32-33
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	32-33
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒			22,31
12.3 Does the protocol address other limitations?	☒			32-33

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒			34
13.2 Has any outcome of an ethical review procedure been addressed?			☒	
13.3 Have data protection requirements been described?	☒			34-35

Comments:

For 13.2: see section 9.9.4 p.33.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒			14

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒			36
15.2 Are plans described for disseminating study results externally, including publication?	☒			36

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3: Additional information - List of Companies: MAHs for generic thiocolchicoside containing medicinal products containing products that are part of the consortium.

These companies also represent their Affiliates and/or other Companies belonging to the same group and/or licensees holding Marketing Authorisations in various Member States.

1. ACARPIA
2. ALTER
3. ANGELINI
4. ANGENERICO
5. ARROW GENERIQUES
6. BIOGARAN
7. CRISTERS
8. DAIICHI SANKYO
9. DOC GENERICI
10. DOMPE FARMACEUTICI
11. EG LABO
12. EG SPA
13. EPIFARMA
14. FARMACEUTICI CABER
15. GENERIS FARMACEUTICA
16. KORANGI
17. LABORATORIO FARMACEUTICO CT
18. MDM
19. MYLAN
20. SANDOZ
21. SANOFI AVENTIS GROUPE
22. SF GROUP
23. SPA
24. TEOFARMA
25. UNION HEALTH

List of represented MAHs contact details and product names per country.

Country	MAH	Invented name Name
FRANCE	ALTER Laboratoires 3, Avenue de la Baltique ZA de Courtaboeuf 91140 Villebon-sur-Yvette France	THIOCOLCHICOSIDE ALTER
FRANCE	ARROW GENERIQUES SAS 26, avenue Tony Garnier 69007 Lyon France	THIOCOLCHICOSIDE ARROW
FRANCE	BIOGARAN SAS 15, Boulevard Charles de Gaulle 92707 Colombes Cedex France	THIOCOLCHICOSIDE ALMUS THIOCOLCHICOSIDE BIOGARAN
FRANCE	CRISTERS SAS 22, Quai Gallieni 92150 Suresnes France	THIOCOLCHICOSIDE CRISTERS
FRANCE	DAIICHI SANKYO France SAS 1, rue Eugène et Armand Peugeot 92500 Rueil-Malmaison France	MIOREL
FRANCE	EG Labo - Laboratoires Eurogenerics Le Quintet Bât.A 12 Rue Barthelemy Danjou 92100 Boulogne-Billancourt France	THIOCOLCHICOSIDE EG
FRANCE	MYLAN SAS 117, Allée des Parcs 69800 St Priest France	THIOCOLCHICOSIDE MYLAN
FRANCE	SANDOZ 49, avenue Georges Pompidou 92593 Levallois-Perret France	THIOCOLCHICOSIDE SANDOZ
FRANCE	SANOFI AVENTIS GROUPE 1-13, Boulevard Romain Rolland 75014 Paris France	COLTRAMYL THIOCOLCHICOSIDE ZENTIVA

GREECE	SANOFI-AVENTIS AEBE Syngrou Av. 348 Building A' 17674, Kallithea Athens Greece	MUSCO-RIL
ITALY	ACARPIA c/o PHAMAFAR Corso Vittorio Emanuele II, 82 10121 Torino Italy	MOVERIL
ITALY	ANGENERICO SpA Via Nocera Umbra, 75 00181 Roma Italy	TIOCOLCHICOSIDE ANGENERICO
ITALY	DOC Generici S.r.l via Turati 40 20121 Milano Italy	TIOCOLCHICOSIDE DOC Generici
ITALY	DOMPE' FARMACEUTICI S.P.A. Via San Martino 12-12/a 20122 Milan Italy	MIOTENS
ITALY	EG S.p.A. Via Domenico Scarlatti, 31 20124 Milano Italy	TIOCOLCHICOSIDE EG
ITALY	EPIFARMA S.r.l. via San Rocco, 6 85033 Episcopia (PZ), Italy	MUSCOFLEX
ITALY	FARMACEUTICI CABER S.p.A Viale Città d'Europa 681 00144 Rome Italy	TIOSIDE
ITALY	LABORATORIO FARMACEUTICO CT Srl Strada Solaro, 75/77 18038 Sanremo (IM) Italy	SCIOMIR
ITALY	MDM Viale Papiniano, 22/b 20123 Milano Italy	STRIALISIN

ITALY	MYLAN S.P.A Via Vittor Pisani, 20 20124 Milano Italy	THIOCOLCHICOSIDE MYLAN GENERICS
ITALY	SANDOZ S.P.A Largo Umberto Boccioni, 1 21040 Origgio (VA) Italy	THIOCOLCHICOSIDE SANDOZ
ITALY	SANOFI AVENTIS S.P.A Viale Luigi Bodio, 37/B 20158 Milan	MUSCORIL THIOCOLCHICOSIDE ZENTIVA
ITALY	SF GROUP S.r.l Via Beniamino Segre 59 00134 Roma Italy	DECONTRIL TERASIDE
ITALY	SPA - SOCIETA' PRODOTTI ANTIBIOTICI S.p.A. Via Biella 8 20143 Milano Italy	MIOREXIL
ITALY	ANGELINI FARMACEUTICA Lda c/o TEOFARMA Srl Via F.lli Cervi N° 8 27010 Valle Salimbene (PV) Italy	ADALGUR
ITALY	UNION HEALTH S.r.l Via Adige 5 66020 San Giovanni Teatino – Chieti Italy	TIOCOLCHICOSIDE UNION HEALTH
PORTUGAL	ACARPIA SERVIÇOS FARMACEUTICOS Lda Rua dos Murcas, 88 9000 Funchal Portugal	MOVERIL
PORTUGAL	ANGELINI FARMACEUTICA Lda Rua João Chagas, 53 - 3° piso, 1499-040 Cruz Quebrada Dafundo Portugal	ADALGUR N
PORTUGAL	GENERIS FARMACEUTICA Rua João de Deus, 19 2700-487 Amadora Portugal	TIOCOLQUICOSIDO GENERIS

PORTUGAL	KORANGI Produtos Farmacêuticos Lda Rua da Vinha, 17P 2765-388 Estoril Portugal	COLTRAMYL
PORTUGAL	SANOFI - Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park Edifício 7 3º Piso 2740-244 Porto Salvo Portugal	RELMUS

Annex 4: DHPC letter (English and local versions)

Date: <xx>

< THIOCOLCHICOSIDE- CONTAINING PRODUCTS FOR SYSTEMIC USE - IMPORTANT INFORMATION REGARDING INDICATIONS, TREATMENT REGIMEN, CONTRAINDICATIONS AND WARNINGS >

Dear Healthcare Professional,

The MAH in agreement with the European Medicines Agency and NCA {insert NCA name} would like to inform you of important restrictions regarding the use of thiocolchicoside-containing products for systemic use following the outcome of a review of new preclinical findings, which raised concerns about the activity of a thiocolchicoside metabolite on chromosomes.

Summary

New preclinical findings indicate a potential risk of genotoxicity from use of thiocolchicoside oral and intramuscular (IM) formulations.

- Systemic thiocolchicoside should only be used as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.
- Thiocolchicoside is not to be used for long-term treatment of chronic conditions.
- Doses should be restricted as follows and the recommended dose and duration should not be exceeded:
    - Oral forms: 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.
    - 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.
- Thiocolchicoside should not be used in pregnancy and lactation, nor in women of childbearing potential not using adequate contraception.

Further information

Thiocolchicoside is a muscle relaxant available as oral, injectable and topical formulations. In preclinical studies it has been shown that one of the thiocolchicoside metabolites (SL59.0955, also known as M2 or 3-demthylthiocolchicine) induced aneuploidy (i.e. unequal numbers of chromosomes in dividing cells) at concentrations close to those seen in humans who take the maximum recommended oral dose of 8 mg twice daily. Aneuploidy is reported as a risk factor for teratogenicity, embryofoetotoxicity/spontaneous abortion and impaired male fertility and a potential risk factor for cancer. The risk is greatest with long-term exposure.

Therefore, precautionary measures are to be taken in order to reduce the exposure to the metabolite SL59.0955 from systemic formulations. (Topical formulations do not produce significant systemic concentrations of the metabolite, and are not affected by these recommendations.)

Systemic thiocolchicoside should not be used for long-term treatment of chronic conditions, and treatment should be limited to 7 days for oral formulations, and to 5 days for injectable formulations. Moreover the dose should not exceed 8 mg every 12 hours for oral formulations and 4 mg every 12 hours for injectable formulations.

The benefits of systemic thiocolchicoside-containing formulations are considered to exceed their risks only when used in these dose schedules as adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards.

In order to minimise and manage the risk to the foetus, thiocolchicoside should not be used in pregnancy and lactation, nor in women of childbearing potential who are not using appropriate contraception.

Extract from the Summary of Product Characteristics (SmPC) for thiocolchicoside-containing products for systemic use is annexed.

Call for reporting
Please review carefully the revised enclosed product information and contact <MAH> if you have any additional questions.
Any adverse events experienced by your patients should be reported to the National Reporting System according to the National Regulation.
<details on how to access to the national spontaneous reporting system>

Yours sincerely,

This DHPC is distributed by <details of MAHs>

Annexes

Text of the revised local SmPC and Package leaflet (with main changes highlighted)

Section 4.1: Therapeutic indications
xx
Section 4.2: Posology and method of administration
xx
Section 4.3: Contraindications
xx
Section 4.4: Warnings and precautions for use
xx
Section 4.6: Fertility, pregnancy and lactation
xx
Section 5.3: Preclinical safety data

Xx

INFORMATIONS
SÉCURITÉ PATIENTS

INFORMATION TRANSMISE SOUS L'AUTORITE DE L'ANSM

Lettre aux professionnels de santé

Avril 2014

Spécialités contenant du thiocolchicoside administrées par voie générale : information importante relative aux indications, aux modalités de traitement, aux contre-indications et aux mises en garde

Information destinée aux rhumatologues, médecins généralistes, médecins du sport et de médecine physique, pharmaciens d'officine et hospitaliers, aux centres de rééducation fonctionnelle.

Madame, Monsieur, Cher confrère,

En accord avec l'Agence Européenne des Médicaments (EMA) et l'Agence nationale de sécurité du médicament et des produits de santé (ANSM), les titulaires des autorisations de mise sur le marché des spécialités contenant du thiocolchicoside administrées par voie générale, souhaitent vous informer des restrictions d'utilisation de ces médicaments, suite aux résultats de nouvelles études précliniques mettant en évidence les effets d'un métabolite du thiocolchicoside sur les chromosomes.

Résumé
Ces nouvelles données précliniques indiquent un risque potentiel de génotoxicité du thiocolchicoside utilisé par voie systémique et ont conduit à des restrictions d'utilisation des médicaments à base de thiocolchicoside administrés par voie orale (PO) ou intramusculaire (IM) :

- le thiocolchicoside doit uniquement être utilisé dans le traitement d'appoint des contractures musculaires douloureuses en cas de pathologies rachidiennes aiguës chez les adultes et les adolescents à partir de 16 ans ;
- Le thiocolchicoside ne doit plus être utilisé au long cours en cas de pathologies chroniques ;
- La posologie et la durée du traitement sont désormais limitées et ne doivent pas être dépassées :
    - La durée du traitement est limitée à 7 jours consécutifs pour la voie orale, avec une dose maximale recommandée de 8 mg toutes les 12 heures, soit 16 mg par jour.
    - La durée du traitement est limitée à 5 jours consécutifs pour la voie injectable (IM), avec une dose maximale recommandée de 4 mg toutes les 12 heures, soit 8 mg au total par jour.
- Le thiocolchicoside est contre-indiqué pendant la grossesse, au cours de l'allaitement, ou chez les femmes en âge de procréer sans contraception efficace.

Informations complémentaires
Le thiocolchicoside est un principe actif avec une action myorelaxante disponible en France sous forme orale et injectable.
Des études chez l'animal, réalisées à des concentrations proches de celles observées chez l'homme lors de l'administration par voie orale du thiocolchicoside aux doses maximales recommandées de 8 mg deux fois par jour, ont montré que l'un de ses métabolites (SL59.0955 aussi appelé M2 ou 3-déméthylthiocolchicine) induit une aneuploïdie (nombre inégal de chromosomes après division cellulaire).
L'aneuploïdie est reconnue comme un facteur de risque de tératogénicité, d'embryotoxicité, d'avortement spontané et d'altération de la fertilité masculine ainsi que comme un facteur de risque potentiel de cancer. Ce risque est plus important en cas d'exposition de longue durée.

Ces informations ont conduit à la prise de mesures visant à réduire l'exposition au métabolite SL59.0955 du thiocolchicoside administré par voie générale.

Le rapport bénéfice/risque du thiocolchicoside administré par voie générale a été considéré comme favorable dès lors qu'il est utilisé aux doses et durées de traitement désormais recommandées, uniquement dans le traitement d'appoint des contractures musculaires douloureuses en cas de pathologies rachidiennes aiguës chez les adultes et les adolescents à partir de 16 ans et en respectant les contre-indications.

INFORMATION TRANSMISE SOUS L'AUTORITE DE L'ANSM

Lettre aux professionnels de santé

Afin de minimiser les risques, le thiocolchicoside est contre-indiqué en cas de grossesse, d'allaitement et chez les femmes en âge de procréer n'utilisant pas de contraception efficace.

Déclaration des effets indésirables

▼Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. L'ANSM rappelle que les professionnels de santé doivent déclarer immédiatement tout effet indésirable suspecté d'être dû à un médicament dont ils ont connaissance au centre régional de pharmacovigilance dont ils dépendent géographiquement. Les patients et les associations agréées de patients peuvent également signaler tout effet indésirable à leur centre régional de pharmacovigilance.
Pour plus d'informations, consulter la rubrique « Déclarer un effet indésirable » sur le site Internet de l'ANSM : http://ansm.sante.fr

Information médicale

Pour toute question ou information complémentaire, nous vous remercions de bien vouloir contacter les laboratoires concernés (voir liste ci-dessous)

Dénomination	Titulaire de l'autorisation de mise sur le marché
THIOCOLCHICOSIDE ACTAVIS 4 mg, comprimé	Titulaire ACTAVIS GROUP PTC EHF Exploitant ACTAVIS France Information médicale et Pharmacovigilance Tel : 04 72 71 63 97
THIOCOLCHICOSIDE ALMUS 4 mg, comprimé	Exploitant ALMUS Information médicale et Pharmacovigilance Tel : 01 40 80 18 44
THIOCOLCHICOSIDE ALTER 4 mg, comprimé	Titulaire/Exploitant ALTER Information médicale Tél : 01.69.29.83.08 Pharmacovigilance Tel : 01.30.08.72.92
THIOCOLCHICOSIDE ARROW 4 mg, comprimé	Titulaire/Exploitant ARROW GENERIQUES Information médicale et Pharmacovigilance Tel : 04 72 71 63 97
THIOCOLCHICOSIDE BIOGARAN 4 mg, comprimé	Titulaire/Exploitant BIOGARAN Information médicale et Pharmacovigilance Tel : 0811 907 917
THIOCOLCHICOSIDE CRISTERS 4 mg, comprimé	CRISTERS Information médicale et Pharmacovigilance Tél : 01 42 04 94 20 / Fax : 01 42 04 94 21
MIOREL® 4 mg, gélule MIOREL® 4 mg/2 ml, solution injectable (IM) en ampoule	Titulaire/Exploitant DAIICHI SANKYO France SAS Information médicale et Pharmacovigilance Tel (n° vert) : 0 800 00 87 85
THIOCOLCHICOSIDE EG 4 mg, comprimé sécable	EG LABO - LABORATOIRES EUROGENERICS Info médicale et pharmacovigilance Tél : 01 46 94 86 96
COLTHIOZID 4 mg/2 ml, solution injectable	Titulaire/Exploitant LABORATOIRE PHARMY II Information médicale et Pharmacovigilance Tél : 01 34 51 50 97
THIOCOLCHICOSIDE MYLAN 4 mg, comprimé	Titulaire/Exploitant MYLAN SAS Information médicale et Pharmacovigilance Tel : 0810 123 550
THIOCOLCHICOSIDE SANDOZ 4 mg, comprimé	Titulaire/Exploitant SANDOZ Information médicale et Pharmacovigilance Tel : 0800 455 799
COLTRAMYL 4 mg, comprimé THIOCOLCHICOSIDE ZENTIVA 4 mg, comprimé	SANOFI-AVENTIS FRANCE Information médicale et pharmacovigilance : Numéro vert (métropole) : 0 800 394 000 (DOM – TOM) : 0 800 626 626
THIOCOLCHICOSIDE TEVA 4 mg, comprimé	Exploitant TEVA SANTE Information médicale et Pharmacovigilance Tel (n° vert) : 0800 51 34 11

Παρασκευή, 14 Φεβρουαρίου 2014

Άμεση Επικοινωνία με τους Επαγγελματίες Υγείας

MUSCO-RIL® (θειοκολχικοσίδη) ΚΑΙ ΠΡΟΪΟΝΤΑ ΓΙΑ ΣΥΣΤΗΜΑΤΙΚΗ ΧΡΗΣΗ ΠΟΥ ΠΕΡΙΕΧΟΥΝ ΘΕΙΟΚΟΛΧΙΚΟΣΙΔΗ – ΠΕΡΙΟΡΙΣΜΟΙ ΣΤΗ ΧΡΗΣΗ - ΣΗΜΑΝΤΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ ΣΧΕΤΙΚΑ ΜΕ ΤΙΣ ΕΝΔΕΙΞΕΙΣ, ΤΗ ΘΕΡΑΠΕΥΤΙΚΗ ΑΓΩΓΗ, ΤΙΣ ΑΝΤΕΝΔΕΙΞΕΙΣ ΚΑΙ ΤΙΣ ΠΡΟΕΙΔΟΠΟΙΗΣΕΙΣ

Αγαπητέ Επαγγελματία Υγείας,

Η Sanofi-aventis AEBE σε συμφωνία με τον Ευρωπαϊκό Οργανισμό Φαρμάκων (EMA) και τον Εθνικό Οργανισμό Φαρμάκων (ΕΟΦ) θα ήθελε να σας ενημερώσει σχετικά με σημαντικούς περιορισμούς που αφορούν τη συστηματική χρήση προϊόντων που περιέχουν θειοκολχικοσίδη έπειτα από τα αποτελέσματα της επανεξέτασης νέων προκλινικών ευρημάτων, τα οποία εγείρουν ανησυχίες σχετικά με τη δράση ενός μεταβολίτη της θειοκολχικοσίδης στα χρωμοσώματα.

Σύνοψη

Νέα προκλινικά ευρήματα υποδεικνύουν πιθανό κίνδυνο γονοτοξικότητας από τη χρήση σκευασμάτων θειοκολχικοσίδης που χορηγούνται από του στόματος και ενδομυϊκά (ΙΜ).

- Η συστηματικώς χορηγούμενη θειοκολχικοσίδη θα πρέπει να χρησιμοποιείται μόνο ως επικουρική θεραπεία για την αντιμετώπιση των επώδυνων μυϊκών συσπάσεων που σχετίζονται με οξεία σπονδυλική παθολογία σε ενήλικες και εφήβους ηλικίας 16 ετών και άνω.
- Η θειοκολχικοσίδη δεν πρέπει να χρησιμοποιείται για τη μακροχρόνια θεραπεία χρόνιων παθήσεων.
- Οι συνιστώμενες δόσεις και η διάρκεια χρήσης δεν θα πρέπει να υπερβαίνουν τα ακόλουθα:
  - Από του στόματος μορφές: η συνιστώμενη και μέγιστη δόση είναι 8 mg κάθε 12 ώρες, δηλ. 16 mg ανά ημέρα. **Η διάρκεια της θεραπείας περιορίζεται σε 7 συνεχόμενες ημέρες.**
  - Ενδομυϊκή μορφή: η συνιστώμενη και μέγιστη δόση είναι 4 mg κάθε 12 ώρες, δηλ. 8 mg ανά ημέρα. **Η διάρκεια της θεραπείας περιορίζεται σε 5 συνεχόμενες ημέρες.**
- Η θειοκολχικοσίδη **δεν πρέπει να χρησιμοποιείται** κατά τη διάρκεια της εγκυμοσύνης και του θηλασμού αλλά ούτε και σε γυναίκες σε αναπαραγωγική ηλικία που δεν χρησιμοποιούν αποτελεσματική μέθοδο αντισύλληψης.

Λοιπές πληροφορίες

Η θειοκολχικοσίδη είναι ένα μυοχαλαρωτικό που διατίθεται σε από του στόματος, ενέσιμα και τοπικά σκευάσματα. Προκλινικές μελέτες έδειξαν ότι ένας από τους μεταβολίτες της θειοκολχικοσίδης (SL59.0955, επίσης γνωστός ως M2 ή 3-demethylthiocolchicine) προκάλεσε ανευπλοειδία (δηλ., άνισο αριθμό χρωμοσωμάτων σε διαιρούμενα κύτταρα) σε συγκεντρώσεις κοντά σε αυτές που παρατηρούνται σε ανθρώπους που λαμβάνουν τη μέγιστη συνιστώμενη από του στόματος δόση των 8 mg δις ημερησίως. Η ανευπλοειδία αναφέρεται ως παράγοντας κινδύνου για τερατογένεση, τοξικότητα στο έμβρυο-κύημα, αυτόματη αποβολή, διαταραχή της γονιμότητας του άρρενος και δυνητικός παράγοντας κινδύνου για καρκίνο. Ο κίνδυνος είναι μεγαλύτερος κατά τη μακροχρόνια έκθεση.

Ως εκ τούτου, πρέπει να ληφθούν προληπτικά μέτρα προκειμένου να μειωθεί η έκθεση στο μεταβολίτη SL59.0955 από τα συστηματικώς χορηγούμενα σκευάσματα. Τα τοπικά σκευάσματα δεν παράγουν σημαντικές συστηματικές συγκεντρώσεις του μεταβολίτη και δεν επηρεάζονται από αυτές τις συστάσεις.

Η συστηματικώς χορηγούμενη θειοκολχικοσίδη δεν πρέπει να χρησιμοποιείται για τη μακροχρόνια αντιμετώπιση χρόνιων παθήσεων και η θεραπεία θα πρέπει να περιορίζεται σε 7 ημέρες για τα από του στόματος χορηγούμενα σκευάσματα και σε 5 ημέρες για τα ενέσιμα σκευάσματα. Επιπλέον, η δόση δεν θα πρέπει να υπερβαίνει τα 8 mg κάθε 12 ώρες για τα από του στόματος σκευάσματα και τα 4 mg κάθε 12 ώρες για τα ενέσιμα σκευάσματα.

Τα οφέλη των συστηματικώς χορηγούμενων σκευασμάτων που περιέχουν θειοκολχικοσίδη θεωρείται ότι υπερτερούν των κινδύνων μόνο όταν χρησιμοποιούνται σε αυτά τα δοσολογικά σχήματα ως επικουρική θεραπεία για την αντιμετώπιση μυϊκών συσπάσεων σε οξεία σπονδυλική παθολογία σε ενήλικες και εφήβους ηλικίας 16 ετών και άνω.

Για την ελαχιστοποίηση και τη διαχείριση του κινδύνου για το έμβρυο, η θειοκολχικοσίδη δεν πρέπει να χρησιμοποιείται κατά τη διάρκεια της εγκυμοσύνης και του θηλασμού αλλά ούτε και σε γυναίκες σε αναπαραγωγική ηλικία που δεν χρησιμοποιούν κατάλληλη μέθοδο αντισύλληψης.

Για περισσότερες πληροφορίες, ανατρέξτε στην Περίληψη των Χαρακτηριστικών του Προϊόντος (ΠΧΠ) και στο Φύλλο Οδηγιών Χρήσης (ΦΟΧ), που έχουν αξιολογηθεί από τον Ευρωπαϊκό Οργανισμό Φαρμάκων, βρίσκονται υπό έγκριση στον Εθνικό Οργανισμό Φαρμάκων (ΕΟΦ) και επισυνάπτονται με επισήμανση των κυριότερων αλλαγών (Παραρτήματα I και II).

Τα Musco-ril καψάκια 4 mg και το ενέσιμο διάλυμα 4 mg/2 ml AMP κυκλοφόρησαν στην Ελλάδα το Μάιο του 1993.

Παρακαλείσθε να μοιραστείτε αυτές τις πληροφορίες με τους αρμόδιους συναδέλφους σας και με το υγειονομικό προσωπικό.

Πρόσκληση για αναφορά εικαζόμενων/πιθανολογούμενων ανεπιθύμητων ενεργειών του φαρμάκου

Παρακαλείσθε να αναφέρετε οποιεσδήποτε ανεπιθύμητες ενέργειες που παρουσιάζονται στους ασθενείς σας οι οποίοι λαμβάνουν Musco-ril. Κατά την αναφορά, παρακαλείσθε να παρέχετε όσο το δυνατόν περισσότερες πληροφορίες, συμπεριλαμβανομένων των πληροφοριών σχετικά με

το ιατρικό ιστορικό, οποιαδήποτε συγχορήγηση άλλου φαρμάκου, καθώς και τις ημερομηνίες εμφάνισης και θεραπείας.
Υπενθυμίζεται ότι οι ανεπιθύμητες ενέργειες που συνδέονται με τη χρήση του Musco-ril μπορούν να αναφέρονται σύμφωνα με το εθνικό σύστημα αυθόρμητων αναφορών στον Εθνικό Οργανισμό Φαρμάκων, Τμήμα Ανεπιθύμητων Ενεργειών, με την υποβολή της Κίτρινης Κάρτας με τους εξής τρόπους:

- Ηλεκτρονική υποβολή της Κίτρινης Κάρτας μέσω της ιστοσελίδας του ΕΟΦ http://www.eof.gr/web/guest/yellowgeneral
- Έντυπη μορφή, αποστολή μέσω ταχυδρομείου, ατελώς, στο Τμήμα Ανεπιθύμητων Ενεργειών του ΕΟΦ (Μεσογείων 284, 15562) τηλέφωνο επικοινωνίας: 213-2040380 ή 213-2040337.
- Υποβολή μέσω ΦΑΞ στο 210-6549585

Επιπλέον, αυτές οι πληροφορίες μπορούν να αναφερθούν στη Sanofi-aventis ΑΕΒΕ, τηλ. 210-9001600.

Στοιχεία επικοινωνίας της εταιρίας
Για περισσότερες πληροφορίες παρακαλούμε απευθυνθείτε στην Ιατρική Διεύθυνση.
Αθηνά Παπαπαύλου, Υπεύθυνη Φαρμακοεπαγρύπνησης
Σοφία Βρέττα, Επιστημονικός Σύμβουλος

Sanofi-aventis ΑΕΒΕ
Λεωφ. Συγγρού 348 – Κτίριο Α
176 74 Καλλιθέα – Αθήνα
Τηλ.: 210 9001 600
Fax.: 210 9249 140

Με εκτίμηση,

Δρ. Βαρβάρα Μπαρούτσου, Παθολόγος
Medical & Scientific Director – Greece & Cyprus

Παραρτήματα
I. Περίληψη των χαρακτηριστικών του προϊόντος
II.Φύλλο οδηγιών χρήσης

NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON L'AGENZIA EUROPEA DEI MEDICINALI (EMA) E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

7 febbraio 2014

MEDICINALI A BASE DI TIOCOLCHICOSIDE PER USO SISTEMICO
INFORMAZIONI IMPORTANTI SU INDICAZIONI, REGIME DI TRATTAMENTO, CONTROINDICAZIONI E AVVERTENZE

Gentile Dott.ssa/Egregio Dottore,

l'Agenzia Europea dei Medicinali e l'AIFA in accordo con i titolari dell'autorizzazione all'immissione in commercio desiderano informarla di importanti limitazioni relative all'uso dei medicinali a base di tiocolchicoside per uso sistemico, imposte a seguito dei risultati derivanti dalla revisione di nuovi dati preclinici che hanno sollevato dubbi sull'attività di un metabolita di tiocolchicoside sui cromosomi.

Riassunto

Nuovi dati preclinici indicano un potenziale rischio di genotossicità derivante dall'uso di tiocolchicoside per via orale e intramuscolare (IM).

- Tiocolchicoside per via sistemica deve essere usata solo come trattamento adiuvante delle contratture muscolari dolorose associate a patologie acute della colonna, negli adulti e negli adolescenti di età superiore a 16 anni.
- Tiocolchicoside non deve essere usata per il trattamento a lungo termine di patologie croniche.
- Le seguenti posologie devono essere rispettate; le dosi e la durata raccomandate non devono essere superate:
  - Forme orali: la dose raccomandata, che non deve essere superata, è di 8 mg ogni 12 ore, ossia 16 mg/die. La durata del trattamento non deve superare i 7 giorni consecutivi.
  - Forma IM: la dose raccomandata, che non deve essere superata, è di 4 mg ogni 12 ore, ossia 8 mg/die. La durata del trattamento non deve superare i 5 giorni consecutivi.
- Tiocolchicoside non deve essere usata in gravidanza e durante l'allattamento, né in donne in età fertile che non adottano un adeguato metodo contraccettivo.

Ulteriori informazioni

Tiocolchicoside è un miorilassante disponibile in formulazione orale, iniettabile e topica. Studi preclinici hanno evidenziato che uno dei metaboliti della tiocolchicoside (SL59.0955, noto anche come M2 o 3-demetiltiocolchicina) induce aneuploidia (formazione di un numero anomalo di cromosomi durante la divisione cellulare) a concentrazioni vicine a quelle osservate nell'uomo con l'assunzione della dose orale massima raccomandata di 8 mg due volte al giorno. L'aneuploidia è stata evidenziata come fattore di rischio di teratogenicità, embriofetotossicità/aborto spontaneo, compromissione della fertilità maschile e come potenziale fattore di rischio di cancro. Il rischio è maggiore con l'esposizione a lungo termine.

Pertanto è necessario adottare misure precauzionali per ridurre l'esposizione al metabolita SL59.0955 delle formulazioni sistemiche (le formulazioni topiche non producono

concentrazioni sistemiche significative del metabolita e non sono interessate da queste raccomandazioni).

Tiocolchicoside per via sistemica non deve essere usata per il trattamento a lungo termine di condizioni croniche e il trattamento deve essere limitato a 7 giorni, per le formulazioni orali, e a 5 giorni, per quelle iniettabili. Inoltre la posologia non deve superare la dose di 8 mg ogni 12 ore, per le formulazioni orali, e di 4 mg ogni 12 ore per quelle iniettabili.

Il beneficio delle formulazioni orali a base di tiocolchicoside è considerato superiore ai rischi solo se l'uso avviene secondo questi regimi terapeutici, come adiuvante nel trattamento delle contratture muscolari dolorose nelle patologie acute della colonna vertebrale, in pazienti adulti e adolescenti di età da 16 anni in su.

Per poter minimizzare e gestire il rischio per il feto, tiocolchicoside non deve essere usata in gravidanza e durante l'allattamento, né da donne in età fertile che non adottano un adeguato metodo contraccettivo.

I testi delle modifiche ed integrazioni al riassunto delle caratteristiche del prodotto (RCP) e al foglio illustrativo (FI) dei farmaci a base di tiocolchicoside per uso sistemico sono allegati alla presente Nota.

Richiamo alla segnalazione

I medici e gli altri operatori sanitari sono tenuti a segnalare qualsiasi sospetta reazione avversa associata a medicinali.

I medici e gli altri operatori sanitari devono, a norma di legge, trasmettere le segnalazioni di sospette reazioni avverse, tramite l'apposita scheda cartacea (reperibile sul sito http://www.agenziafarmaco.gov.it/sites/default/files/tipo_filecb84.pdf) o compilando on-line la scheda elettronica (http://www.agenziafarmaco.gov.it/sites/default/files/Scheda_elettronica_AIFA_operatore_sanitario_25.09.2013.doc) tempestivamente, al Responsabile di Farmacovigilanza della struttura sanitaria di appartenenza o, qualora operanti in strutture sanitarie private, tramite la Direzione sanitaria, al responsabile di farmacovigilanza della ASL competente per territorio.

L'AIFA coglie l'occasione per ricordare a tutti gli Operatori Sanitari l'importanza della segnalazione delle reazioni avverse da farmaci, quale strumento indispensabile per confermare un rapporto beneficio rischio favorevole nelle reali condizioni di impiego.

Le Segnalazioni di Sospetta Reazione Avversa da Farmaci devono essere inviate al Responsabile di Farmacovigilanza della Struttura di appartenenza dell'Operatore stesso.

17 de fevereiro de 2014

Comunicação Dirigida aos Profissionais de Saúde

Tiocolquicosido - Medicamentos contendo tiocolquicosido, para uso sistémico – nova informação de segurança importante relativa a indicações terapêuticas, posologia, contraindicações e precauções de utilização

▼Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas.

Exmo(a). Senhor(a) Doutor(a),

Os Titulares das Autorizações de Introdução no Mercado (AIM) dos medicamentos contendo tiocolquicosido autorizados em Portugal, após acordo com a Agência Europeia do Medicamento (EMA) e o INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P., gostariam de informa-lo das importantes restrições de utilização aprovadas no seguimento de uma revisão de novos dados pré-clinicos que sugerem preocupação sobre a atividade do metabolito do tiocolquicosido a nível dos cromossomas.

Resumo

Os novos dados pré-clinicos indicam um potencial risco de genotoxicidade na utilização de formulações oral e intramuscular (IM) de tiocolquicosido.

- O tiocolquicosido para uso sistémico é recomendado apenas para o tratamento adjuvante de contraturas musculares dolorosas na patologia aguda da coluna vertebral em adultos e adolescentes com idade superior a 16 anos.
- O tiocolquicosido não é recomendado para o tratamento prolongado de situações crónicas.
- As doses devem ser restringidas e a dose e duração recomendadas não devem ser excedidas:
  - Formulações orais: a dose máxima recomendada é de 8 mg de 12 em 12 h, ou seja 16 mg por dia. A duração do tratamento não deve exceder os 7 dias consecutivos.
  - Formulações intramusculares: a dose máxima recomendada é de 4 mg de 12 em 12h, ou seja 8 mg por dia. A duração do tratamento não deve exceder os 5 dias consecutivos.
- O tiocolquicosido não deve ser administrado durante a gravidez, a amamentação ou a mulheres em idade fértil que não utilizam métodos contracetivos adequados.

Informação adicional

O tiocolquicosido é um relaxante muscular disponível nas formulações oral e injetável. Os dados pré-clinicos sugerem que um dos metabolitos do tiocolquicosido (SL59.0955, também designado por M2 ou 3-dimetiltiocolchicina) pode causar aneuploidia (número desigual de cromossomas em células em divisão) em concentrações próximas às detetadas em humanos que tomam a dose oral máxima recomendada de 8 mg duas vezes por dia. A aneuploidia é considerada um fator de risco para teratogenicidade, embrio/fetotoxicidade, aborto espontâneo, problemas de fertilidade nos homens e um potencial fator de risco para cancro. O risco é maior com a utilização prolongada.

Deste modo, devem ser tomadas medidas de precaução para redução da exposição ao metabolito SL59.0955 das formulações sistémicas. (As formulações tópicas não produzem concentrações significativas de metabolito pelo que não se aplicam estas recomendações.)

O tiocolquicosido sistémico não deve ser utilizado para tratamento prolongado das situações crónicas e, o tratamento não deve exceder os 7 dias para as formulações orais e os 5 dias para as formulações injetáveis. Por outro lado, as doses não devem exceder os 8 mg de 12 em 12h para as formulações orais e os 4 mg de 12 em 12h para as formulações injetáveis.

Os benefícios das formulações sistémicas contendo tiocolquicosido são considerados superiores aos riscos, desde que sejam utilizadas nas doses recomendadas para o tratamento adjuvante de contraturas musculares dolorosas em patologia aguda da coluna vertebral em adultos e adolescentes com idade superior a 16 anos.

Para minimizar o risco para o feto, o tiocolquicosido não deve ser administrado durante a gravidez, a amamentação ou a mulheres em idade fértil que não utilizam métodos contracetivos adequados.

Para mais informações consulte o Anexo 1 que indica quais as alterações que irão ser efectuadas no Resumo das Características do Medicamento (RCM) e no Folheto Informativo (FI) para os medicamentos de uso sistémico contendo tiocolquicosido.

Contactos para notificação

Por favor notifique qualquer suspeita de reação adversa a estes medicamentos ao INFARMED, I.P. e/ou aos respetivos Titulares de AIM, referidos no anexo 2, através dos seguintes contactos:

INFARMED, I.P
formulário online do Portal RAM (preferencialmente) disponível no sítio do. em:
http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil, 53
1749-004 Lisboa
Telefone: 21 798 71 40/41
Fax: 21 798 73 97
E-mail: farmacovigilancia@infarmed.pt

Contactos das empresas
Ver Anexo 2

Ficamos ao dispor para qualquer informação complementar que considere necessária e apresentamos os melhores cumprimentos.

Anexos:
1. Alterações ao Resumo das Características do Medicamento (RCM)
2. Contactos dos Titulares das Autorizações de Introdução no Mercado (AIM) dos medicamentos contendo tiocolquicosido autorizados em Portugal

Annex 5: SmPc (English and local versions)

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 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.

ANNEXE III

Modifications apportées aux rubriques pertinentes du résumé des caractéristiques du produit, de l'étiquetage et de la notice

RÉSUMÉ DES CARACTÉRISTIQUES DU PRODUIT

[la formulation ci-dessous doit être insérée]

▼ Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique 4.8 pour les modalités de déclaration des effets indésirables.

4. DONNÉES CLINIQUES

4.1 1 Indications thérapeutiques

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Traitement d'appoint des contractures musculaires douloureuses en pathologie rachidienne aiguë chez les adultes et les adolescents à partir de 16 ans.

4.2 2 Posologie et mode d'administration

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Posologie
o *Pour les formes orales dosées à 4 mg et 8 mg :*
La dose recommandée et maximale est de 8 mg toutes les 12 heures (soit 16 mg par jour). La durée du traitement est limitée à 7 jours consécutifs.

o *Pour la forme IM (intramusculaire) :*
La dose recommandée et maximale est de 4 mg toutes les 12 heures (soit 8 mg par jour). La durée du traitement est limitée à 5 jours consécutifs.

o *Pour l'administration orale et IM :*
Des doses supérieures aux doses recommandées ou l'utilisation à long terme doivent être évitées (voir rubrique 4.4).

Population pédiatrique
<Nom de fantaisie> ne doit pas être utilisé chez les enfants et les adolescents âgés de moins de 16 ans pour des raisons de sécurité (voir rubrique 5.3).

Mode d'administration
[À remplir pour chaque pays]

4.3 Contre-indications

[la formulation ci-dessous doit être insérée]

- hypersensibilité à la substance active ou à l'un des excipients (voir rubrique 6.1)
- Grossesse et femmes en âge de procréer n'utilisant pas de contraception (voir rubrique 4.6)
- Allaitement maternel (voir rubrique 4.6)

4.4 Mises en garde spéciales et précautions d'emploi

[la formulation ci-dessous doit être insérée]

[…]
Les études précliniques ont montré que l'un des métabolites du thiocolcoside (SL59.0955) induit de l'aneuploïdie (soit un nombre anormal de chromosomes dans les cellules après division cellulaire) à des concentrations proches de celles observées chez l'homme exposé à des doses de 8 mg deux fois par jour par voie orale (voir rubrique 5.3). L'aneuploïdie est considérée comme un facteur de risque de tératogenèse, d'embryo/fœtotoxicité, d'avortement spontané, et d'altération de la fertilité chez l'homme ainsi qu'un facteur de risque potentiel de cancer. Par mesure de précaution, l'utilisation du produit à des doses supérieures à la dose recommandée ou l'utilisation à long terme doit être évitée (voir rubrique 4.2).

Les patients doivent être soigneusement informés du risque potentiel d'une éventuelle grossesse et des mesures de contraception efficaces à suivre.

4.6 Fertilité, grossesse et allaitement

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

[…]

Grossesse
Les données sur l'utilisation du thiocolchicoside chez la femme enceinte sont limitées. Par conséquent, les risques potentiels pour l'embryon et le fœtus ne sont pas connus.
Les études chez l'animal ont montré des effets tératogènes (voir rubrique 5.3).
<Nom de fantaisie> est contre-indiqué pendant la grossesse et chez les femmes en âge de procréer n'utilisant pas de contraception (voir rubrique 4.3).

Allaitement
Compte tenu du passage du thiocolchicoside dans le lait maternel, son utilisation est contre-indiquée pendant l'allaitement (voir rubrique 4.3).

Fertilité
Dans une étude de toxicité sur la fertilité chez le rat, aucune altération de la fertilité n'a été observée à des doses allant jusqu'à 12 mg/kg, correspondant à des niveaux de dose n'induisant aucun effet clinique. Le thiocolchicoside et ses métabolites exercent une activité aneugène à différents niveaux de dose, ce qui est un facteur de risque d'altération de la fertilité chez l'homme (voir rubrique 5.3).

4.8 Effets indésirables

[…]

[la formulation ci-dessous doit être insérée]

Déclaration des effets indésirables suspectés
La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration – voir Annexe V*.

*[*Pour le matériel imprimé, veuillez vous référer au guide annoté du modèle QRD.]*
[…]

5. PROPRIÉTÉS PHARMACOLOGIQUES

5.2 Propriétés pharmacocinétiques

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Absorption

- Après administration intramusculaire (IM), la concentration plasmatique maximale (C_{max}) de thiocolchicoside survient en 30 min et atteint des valeurs de 113 ng/mL après une dose de 4 mg, et de 175 ng/mL après une dose de 8 mg. Les valeurs correspondantes de l'AUC (surface sous la courbe) sont respectivement de 283 et 417 ng.h/mL.

Le métabolite pharmacologiquement actif SL18.0740 est également observé à des concentrations plus faibles avec une C_{max} de 11,7 ng/mL survenant 5 h après administration de thiocolchicoside et une AUC de 83 ng.h/mL.
Il n'existe pas de données concernant le métabolite inactif SL59.0955.

- Après administration orale, le thiocolchicoside n'est pas détecté dans le plasma. Seuls deux métabolites sont observés : le métabolite pharmacologiquement actif SL18.0740 et le métabolite inactif SL59.0955.
Pour ces deux métabolites, les concentrations plasmatiques maximales surviennent 1 heure après administration de thiocolchicoside. Après une dose orale unique de 8 mg de thiocolchicoside, les C_{max} et AUC du SL18.0740 sont respectivement d'environ 60 ng/mL et 130 ng.h/mL. Pour SL59.0955 ces valeurs sont beaucoup plus faibles : C_{max} d'environ 13 ng/mL et AUC allant de 15,5 ng.h/mL (AUC calculée jusqu'à 3 h) à 39,7 ng.h/mL (AUC jusqu'à 24 h).

Distribution
Le volume de distribution apparent du thiocolchicoside est estimé à environ 42,7 Ll après une administration IM de 8 mg. Il n'existe pas de données sur les deux métabolites.
Biotransformation
Après administration orale, le thiocolchicoside est d'abord métabolisé en aglycone 3-déméthyl-thiocolchicine ou SL59.0955. Cette étape se produit principalement par métabolisme intestinal expliquant l'absence de thiocolchicoside inchangé circulant par cette voie d'administration.
SL59.0955 est ensuite glucuro-conjugué en SL18.0740 qui possède une activité pharmacologique équipotente à celle du thiocolchicoside, et contribue donc à l'activité pharmacologique après administration orale de thiocolchicoside. SL59.0955 est également déméthylé en didéméthyl-thiocolchicine.

Élimination
- Après administration IM, la demi-vie apparente d'élimination ($t_{½}$) du thiocolchicoside est de 1,5 h et sa clairance plasmatique de 19,2 L/h.
- Après administration orale de thiocolchicoside radiomarqué, la radioactivité totale est principalement excrétée dans les fèces (79 %) alors que l'excrétion urinaire ne représente que 20 %. Le thiocolchicoside inchangé n'est pas excrété dans l'urine ni dans les fèces. SL18.0740 et SL59.0955 sont retrouvés dans l'urine et les fèces alors que le didéméthyl-thiocolchicine n'est retrouvé que dans les fèces.
Après administration orale de thiocolchicoside, le métabolite SL18.0740 est éliminé avec un $t_{1/2}$ apparent allant de 3,2 à 7 heures, et le métabolite SL59.0955 à un $t_{1/2}$ d'environ 0,8 h.

5.3 Données de sécurité préclinique

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Le profil toxicologique du thiocolchicoside a été évalué *in vitro,* et *in vivo* après administration parentérale et orale.

Le thiocolchicoside est bien toléré après administration orale répétée jusqu'à 6 mois chez le rat et le primate non-humain et ce, à des doses inférieures ou égales à 2 mg/kg/jour chez le rat et 2,5 mg/kg/jour chez le primate non humain, ainsi qu'après administration intramusculaire répétée pendant 4 semaines chez le primate à des doses allant jusqu'à 0,5 mg/kg/jour.

À fortes doses, après administration unique par voie orale, le thiocolchicoside provoque des vomissements chez le chien, des diarrhées chez le rat et des convulsions chez les rongeurs et les non rongeurs..

Après administration répétée, le thiocolchicoside a provoqué des troubles gastro-intestinaux (entérite, vomissements) par voie orale et des vomissements par voie IM.

Le thiocolchicoside lui-même n'induit pas de mutation génique sur bactéries (test d'Ames), d'aberration chromosomique *in vitro* (test d'aberration chromosomique sur lymphocytes humains) ni d'aberration chromosomique *in vivo* (test du micronoyau *in vivo* sur moelle osseuse de souris après administration par voie intrapéritonéale).

Le principal métabolite glucuro-conjugué SL18.0740 n'induit pas de mutation génique sur bactéries (test d'Ames) ; il provoque cependant des aberrations chromosomiques *in vitro* (test du micronoyau *in vitro* sur lymphocyte humain) et des aberrations chromosomiques *in vivo* (test du micronoyau *in vivo* sur moelle osseuse de souris après administration orale). Les micronoyaux résultaient principalement d'une perte de chromosome (présence de centromère dans les micronoyaux révélée par une coloration FISH spécifique du centromère), suggérant des propriétés aneugènes. L'effet aneugène de SL18.0740 a été observé à des concentrations (dans le test *in vitro)* et à des expositions plasmatiques (dans le test *in vivo)* plus élevées (plus de 10 fois sur la base de l'AUC) que celles observées dans le plasma humain à doses thérapeutiques.

Le métabolite aglycone (3-déméthyl-thiocolchicine ou SL59.0955), formé principalement après administration orale, induit des aberrations chromosomiques *in vitro* (test du micronoyau *in vitro* sur lymphocyte humain) et des aberrations chromosomiques *in vivo* (test du micronoyau *in vivo* sur moelle osseuse de rat après administration orale). Les micronoyaux résultaient principalement d'une perte de chromosome (présence de centromère dans les micronoyaux révélée par une coloration FISH ou CREST spécifique du centromère), suggérant des propriétés aneugènes. L'effet aneugène de SL59.0955 a été observé à des concentrations (dans le test *in vitro)* et à des expositions (dans le test *in vivo)* proches de celles observées dans le plasma humain à des doses thérapeutiques de 8 mg deux fois par jour par voie orale. L'effet aneugène dans les cellules en division peut aboutir à des cellules aneuploïdes. L'aneuploïdie est une modification du nombre de chromosomes et une perte d'hétérozygotie, qui est reconnue comme un facteur de risque de tératogenèse, d'embryotoxicité/d'avortement spontané et d'altération de la fertilité masculine, en cas d'effet sur les cellules germinales et comme facteur de risque potentiel de cancer en cas d'effet sur les cellules somatiques. La présence du métabolite aglycone (3 déméthyl-thiocolchicine ou SL59.0955) après administration intramusculaire n'ayant jamais été évaluée, sa formation en utilisant cette voie d'administration ne peut donc être exclue.

Chez le rat, une dose orale de 12 mg/kg/j. de thiocolchicoside a entraîné des malformations majeures ainsi qu'une fœtotoxicité (retard de croissance, mort embryonnaire, altération du taux de distribution par sexe). La dose sans effet toxique était de 3 mg/kg/jour.

Chez le lapin, le thiocolchicoside a montré une toxicité maternelle à partir de 24 mg/kg/jour. En outre, des anomalies mineures ont été observées (côtes surnuméraires, retard d'ossification).

Dans une étude de toxicité sur la fertilité chez le rat, aucune altération de la fertilité n'a été observée à des doses allant jusqu'à 12 mg/kg/jour, soit à des doses n'induisant aucun effet clinique. Le thiocolchicoside et ses métabolites exercent une activité aneugène à différents niveaux de dose, ce qui est reconnu comme un facteur de risque d'altération de la fertilité humaine.

Le potentiel cancérogène n'a pas été évalué.

6.5 Nature et contenu de l'emballage <et équipement spécial pour l'utilisation, l'administration ou l'implantation>

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

30 comprimés/gélules pour la dose de 4 mg et 14 comprimés/gélules pour la dose de 8 mg.
10 flacons / ampoules pour la dose de 4 mg / 2 ml.

ÉTIQUETAGE

MENTIONS DEVANT FIGURER SUR L'EMBALLAGE EXTÉRIEUR

Emballage extérieur pour capsules, comprimés durs/comprimés orodispersibles et solution pour injection

4. FORME PHARMACEUTIQUE ET CONTENU

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

4 mg
[jusqu'à 30] capsules dures
[jusqu'à 30] comprimés

8 mg
[jusqu'à 14] capsules dures
[jusqu'à 14] comprimés orodispersibles

4 mg/2 ml
[jusqu'à 10] flacons/ampoules

NOTICE

[la formulation ci-dessous doit être insérée]

▼ Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Vous pouvez y contribuer en signalant tout effet indésirable que vous observez. Voir en fin de rubrique 4 comment déclarer les effets indésirables.

[…]

Notice : Information du patient

1. Qu'est-ce que X et dans quel cas est-il utilisé

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Ce médicament est un relaxant musculaire. Il est utilisé chez les adultes et les adolescents de plus de 16 ans en tant que traitement d'appoint des contractures musculaires douloureuses. Il doit être utilisé pour des affections aiguës liées à la colonne vertébrale.

2. Quelles sont les informations à connaître avant de prendre X

[la formulation ci-dessous doit être insérée]

Ne prenez jamais X:
- si vous êtes allergique au thiocolchicoside ou à l'un des autres composants contenus dans ce médicament (mentionnés dans la rubrique 6)
- si vous êtes enceinte, pourriez tomber enceinte ou pensez que vous pourriez être enceinte
- si vous êtes une femme en âge d'avoir des enfants n'utilisant pas de contraception
- si vous allaitez

Avertissements et précautions
[…]
Respectez rigoureusement les doses et la durée du traitement décrites à la rubrique 3. Vous ne devez pas utiliser ce médicament à une dose plus élevée ou pour une durée dépassant 7 jours *(pour les formes orales)*/5 jours *(pour les formes IM).* Ceci est dû au fait que les produits formés dans votre organisme lorsque vous prenez thiocolchicoside à des doses élevées peuvent provoquer des lésions sur certaines cellules (nombre anormal de chromosomes). Cela a été mis en évidence lors d'études chez l'animal et d'études en laboratoire. Chez l'homme, ce type de lésions cellulaires est un facteur de risque de cancer, d'altération de la fertilité masculine et peut-être dangereux pour un enfant à naître. Parlez-en avec votre médecin si vous avez plus de questions.

Votre médecin vous renseignera sur toutes les mesures relatives à une contraception efficace et sur les risques potentiels d'une grossesse.

Enfants et adolescents
N'administrez pas ce médicament à des enfants ou des adolescents âgés de moins de 16 ans pour des raisons de sécurité.

Grossesse, allaitement et fertilité

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Ne prenez pas ce médicament :
- si vous êtes enceinte, pourriez tomber enceinte ou pensez que vous pourriez être enceinte.
- si vous êtes une femme en âge d'avoir des enfants n'utilisant pas de contraception.

Ce médicament peut mettre en danger votre enfant à naître. Ne prenez pas ce médicament si vous allaitez car ce médicament passe dans le lait maternel.
Ce médicament peut entraîner des problèmes de fertilité masculine par altération potentielle des cellules spermatiques (nombre anormal de chromosomes) ; ceci a été mise en évidence lors d'études en laboratoire (voir en rubrique 2 «Avertissements et précautions»).

3. Comment prendre X
[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Veillez à toujours prendre ce médicament en suivant exactement les instructions de votre médecin ou pharmacien. Vérifiez auprès de votre médecin ou pharmacien en cas de doute.
o *Pour les formes orales dosées à 4 mg et 8 mg :*
La dose recommandée et maximale est de 8 mg toutes les 12 heures (soit 16 mg par jour). La durée du traitement est limitée à 7 jours consécutifs.
o *Pour la forme intramusculaire :*
La dose recommandée et maximale est de 4 mg toutes les 12 heures (soit 8 mg par jour). La durée du traitement est limitée à 5 jours consécutifs.
o *Pour les formes orale et intramusculaire :*
Ne dépassez pas la dose recommandée ni la durée du traitement.
Ce médicament ne doit pas être utilisé pour un traitement à long terme (voir la rubrique 2 «Avertissements et précautions).
Utilisation chez les enfants et les adolescents
N'administrez pas ce médicament à des enfants ou des adolescents âgés de moins de 16 ans pour des raisons de sécurité.
Si vous avez pris plus de X que vous n'auriez dû
Si vous avez pris accidentellement plus de X que vous n'auriez dû, parlez-en à votre médecin, pharmacien ou infirmier/ère.
Si vous oubliez de prendre X
Ne doublez pas une dose pour compenser une dose que vous avez oubliée de prendre.
Si vous avez d'autres questions sur l'utilisation de ce médicament, demandez à votre médecin, à votre pharmacien ou à votre infirmier/ère.

4. Quels sont les effets indésirables éventuels

[la formulation ci-dessous doit être insérée]

Comme tous les médicaments, ce médicament peut provoquer des effets indésirables, mais ils ne surviennent pas systématiquement chez tout le monde.
[…]
[la formulation ci-dessous doit être insérée]

Déclaration des effets secondaires
Si vous ressentez un quelconque effet indésirable, parlez-en à votre médecin, votre pharmacien ou votre infirmier/ère. Ceci s'applique aussi à tout effet indésirable qui ne serait pas mentionné dans cette notice. Vous pouvez également déclarer les effets indésirables directement via le système national de déclaration décrit en Annexe V*. En signalant les effets indésirables, vous contribuez à fournir davantage d'informations sur la sécurité du médicament.

*[*Pour le matériel imprimé, veuillez vous référer au guide annoté du modèle QRD.]*

6. Contenu de l'emballage et autres informations

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

30 comprimés/gélules pour la dose de 4 mg et 14 comprimés/gélules pour la dose de 8 mg.
10 flacons / ampoules pour la dose de 4 mg / 2 ml.

Παράρτημα III

Τροποποιήσεις στις σχετικές παραγράφους της περίληψης των χαρακτηριστικών του προϊόντος, της επισήμανσης και του φύλλου οδηγιών χρήσης

ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΙΟΝΤΟΣ

[η παρακάτω διατύπωση πρέπει να εισαχθεί]

▼Το φάρμακο αυτό τελεί υπό συμπληρωματική παρακολούθηση. Αυτό θα επιτρέψει τον ταχύ προσδιορισμό νέων πληροφοριών ασφάλειας. Ζητείται από τους επαγγελματίες του τομέα της υγειονομικής περίθαλψης να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες. Βλ. παράγραφο 4.8 για τον τρόπο αναφοράς ανεπιθύμητων ενεργειών.

4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ

4.1 Θεραπευτικές ενδείξεις

[οι ισχύουσες εγκεκριμένες ενδείξεις πρέπει να διαγραφούν και να αντικατασταθούν από το παρακάτω]

Επικουρική θεραπεία για την αντιμετώπιση των επώδυνων μυϊκών συσπάσεων σε οξεία σπονδυλική παθολογία σε ενήλικες και εφήβους ηλικίας 16 ετών και άνω.

4.2 Δοσολογία και τρόπος χορήγησης

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

Δοσολογία

- *Για την από του στόματος μορφή των 4 mg και 8 mg:*

Η συνιστώμενη και μέγιστη δόση είναι 8 mg κάθε 12 ώρες (δηλ. 16 mg ανά ημέρα). Η διάρκεια της θεραπείας περιορίζεται σε 7 συνεχόμενες ημέρες.

- *Για την ενδομυϊκή μορφή:*

Η συνιστώμενη και μέγιστη δόση είναι 4 mg κάθε 12 ώρες (δηλ. 8 mg ανά ημέρα). Η διάρκεια της θεραπείας περιορίζεται σε 5 συνεχόμενες ημέρες.

- *Για την από του στόματος και ενδομυϊκή μορφή:*

Πρέπει να αποφεύγονται οι δόσεις που υπερβαίνουν τις συνιστώμενες δόσεις ή η μακροχρόνια χρήση (βλ. παράγραφο 4.4).

Παιδιατρικός πληθυσμός
Το <επινοηθείσα ονομασία> δεν πρέπει να χρησιμοποιείται σε παιδιά και εφήβους ηλικίας κάτω των 16 ετών εξαιτίας ανησυχιών ως προς την ασφάλεια (βλ. παράγραφο 5.3).

Τρόπος χορήγησης

[Να συμπληρωθεί σε εθνικό επίπεδο]

4.3 Αντενδείξεις

[η παρακάτω διατύπωση ο πρέπει να εισαχθεί]

Η θειοκολχικοσίδη δεν πρέπει να χρησιμοποιείται:
- σε ασθενείς με υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα που αναφέρονται στην παράγραφο 6.1.
- καθ' όλη τη διάρκεια της κύησης
- κατά τη γαλουχία
- σε γυναίκες με δυνατότητα τεκνοποίησης που δεν χρησιμοποιούν αντισύλληψη.

4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση

[η παρακάτω διατύπωση πρέπει να εισαχθεί]

[…]
Προκλινικές μελέτες έδειξαν ότι οι μεταβολίτες της θειοκολχικοσίδης (SL59.0955) προκάλεσαν ανευπλοειδία (δηλ. άνισο αριθμό χρωμοσωμάτων σε διαιρούμενα κύτταρα) σε συγκεντρώσεις κοντά στην ανθρώπινη έκθεση, που παρατηρήθηκαν σε από του στόματος δόσεις των 8 mg δις ημερησίως (βλ. παράγραφο 5.3). Η ανευπλοειδία θεωρείται παράγοντας κινδύνου για τερατογένεση, τοξικότητα στο έμβρυο/κύημα, αυτόματη αποβολή, διαταραχή της γονιμότητας του άρρενος και δυνητικό παράγοντα κινδύνου για καρκίνο. Ως προληπτικό μέτρο, η χρήση του προϊόντος σε δόσεις που υπερβαίνουν τη συνιστώμενη δόση ή η μακροχρόνια χρήση θα πρέπει να αποφεύγεται (βλ. παράγραφο 4.2).

Οι ασθενείς θα πρέπει να ενημερώνονται προσεκτικά σχετικά με το δυνητικό κίνδυνο μίας πιθανής κύησης και για τα αποτελεσματικά μέτρα αντισύλληψης που θα πρέπει να ακολουθούνται.

4.6 Γονιμότητα, κύηση και γαλουχία

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

[…]

Εγκυμοσύνη
Υπάρχουν περιορισμένα δεδομένα από τη χρήση της θειοκολχικοσίδης σε έγκυες γυναίκες. Ως εκ τούτου, οι δυνητικοί κίνδυνοι για το έμβρυο και το κύημα είναι άγνωστοι.
Οι μελέτες σε ζώα έδειξαν τερατογόνες επιδράσεις (βλ. παράγραφο 5.3).
Η χρήση του <επινοηθείσα ονομασία> αντενδείκνυται κατά τη διάρκεια της κύησης, καθώς και σε γυναίκες με δυνατότητα τεκνοποίησης που δεν χρησιμοποιούν αντισύλληψη (βλ. παράγραφο 4.3).

Θηλασμός
Δεδομένου ότι περνά στο μητρικό γάλα, η χρήση της θειοκολχικοσίδης αντενδείκνυται κατά τη διάρκεια του θηλασμού (βλ. παράγραφο 4.3).

Γονιμότητα
Σε μία μελέτη γονιμότητας που πραγματοποιήθηκε σε αρουραίους, δεν παρατηρήθηκε διαταραχή της γονιμότητας σε δόσεις έως και 12 mg/kg, δηλ. σε δόσεις που δεν προκαλούν κλινική επίδραση. Η θειοκολχικοσίδη και οι μεταβολίτες της ασκούν ανευπλοειδογόνο δράση σε διαφορετικά επίπεδα συγκέντρωσης, γεγονός που αποτελεί παράγοντα κινδύνου για διαταραχή της γονιμότητας στον άνθρωπο (βλ. παράγραφο 5.3).

4.8 Ανεπιθύμητες ενέργειες

[…]

[η παρακάτω διατύπωση πρέπει να εισαχθεί]

Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών
Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους/κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες του τομέα της υγειονομικής περίθαλψης να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω του εθνικού συστήματος αναφοράς που αναγράφεται στο Παράρτημα V*.

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

5. ΦΑΡΜΑΚΟΛΟΓΙΚΕΣ ΙΔΙΟΤΗΤΕΣ

5.2 Φαρμακοκινητικές Ιδιότητες

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

Απορρόφηση
- Μετά από ενδομυϊκή χορήγηση, οι μέγιστες συγκεντρώσεις της θειοκολχικοσίδης εμφανίζονται σε 30 λεπτά και φθάνουν τις τιμές των 113 ng/mL έπειτα από δόση 4 mg και των 175 ng/mL έπειτα από δόση 8 mg. Οι ανάλογες τιμές της AUC είναι 283 και 417 ng.h/mL, αντίστοιχα.
Ο φαρμακολογικά ενεργός μεταβολίτης SL18.0740 παρατηρείται, επίσης, σε χαμηλότερες συγκεντρώσεις με Cmax της τάξεως των 11,7 ng/mL 5 ώρες μετά τη δόση και AUC 83 ng.h/mL.
Δεν υπάρχουν διαθέσιμα δεδομένα για τον ανενεργό μεταβολίτη SL59.0955.

- Μετά την από του στόματος χορήγηση η θειοκολχικοσίδη δεν ανιχνεύεται στο πλάσμα. Μόνο δύο μεταβολίτες παρατηρούνται: Ο φαρμακολογικά ενεργός μεταβολίτης SL18.0740 και ένας ανενεργός μεταβολίτης, ο SL59.0955. Και για τους δύο μεταβολίτες, οι μέγιστες συγκεντρώσεις στο πλάσμα εμφανίζονται 1 ώρα μετά τη χορήγηση της θειοκολχικοσίδης. Μετά από εφάπαξ από του στόματος δόση θειοκολχικοσίδης 8 mg, οι Cmax και AUC του SL18.0740 είναι περίπου 60 ng/mL και 130 ng.h/mL αντίστοιχα. Για τον SL59.0955 οι τιμές αυτές είναι πολύ χαμηλότερες: Η Cmax είναι περίπου 13 ng/mL και η AUC κυμαίνεται από 15,5 ng.h/mL (έως τις 3 ώρες) έως 39,7 ng.h/mL (έως τις 24 ώρες).

Κατανομή
Ο φαινομενικός όγκος κατανομής της θειοκολχικοσίδης υπολογίζεται σε περίπου 42,7 L μετά από ενδομυϊκή χορήγηση 8 mg. Δεν υπάρχουν διαθέσιμα στοιχεία για τους δύο μεταβολίτες.

Βιομετασχηματισμός
Μετά την από του στόματος χορήγηση, η θειοκολχικοσίδη μεταβολίζεται αρχικά στην αγλυκόνη 3-demethyltiocolchicine ή SL59.0955. Το στάδιο αυτό λαμβάνει χώρα κυρίως μέσω μεταβολισμού στο έντερο, γεγονός που εξηγεί την απουσία αμετάβλητης θειοκολχικοσίδης στη συστηματική κυκλοφορία μέσω αυτής της οδού χορήγησης.
Εν συνεχεία πραγματοποιείται γλυκουρονική σύζευξη του SL59.0955 σε SL18.0740 που έχει ισοδύναμη φαρμακολογική δράση με τη θειοκολχικοσίδη και, ως εκ τούτου, υποστηρίζει τη φαρμακολογική δράση μετά την από του στόματος χορήγηση της θειοκολχικοσίδης. Ο SL59.0955 επίσης απομεθυλιώνεται σε didemethyl-thiocolchicine.

Αποβολή
- Μετά από ενδομυϊκή χορήγηση, ο φαινομενικός χρόνος ημίσειας ζωής ($t_{1/2}$) της θειοκολχικοσίδης είναι 1,5 ώρες και η κάθαρση στο πλάσμα 19,2 L/h.

- Ύστερα από χορήγηση από του στόματος, η συνολική ραδιενέργεια αποβάλλεται κυρίως στα κόπρανα (79%) ενώ η απέκκριση στα ούρα αντιπροσωπεύει μόνο το 20%. Δεν απεκκρίνεται αμετάβλητη θειοκολχικοσίδη στα ούρα ή στα κόπρανα. Ο SL18.0740 και ο SL59.0955 εμφανίζονται στα ούρα και στα κόπρανα ενώ η didemethyl-thiocolchicine ανακτάται μόνο στα κόπρανα.
Μετά από την από του στόματος χορήγηση θειοκολχικοσίδης, ο μεταβολίτης SL18.0740 αποβάλλεται με φαινομενική $t_{1/2}$ που κυμαίνεται από 3,2 έως 7 ώρες ενώ ο μεταβολίτης SL59.0955 έχει μέση τιμή $t_{1/2}$ της τάξεως των 0,8 ωρών.

5.3 Προκλινικά δεδομένα για την ασφάλεια

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

Το προφίλ της θειοκολχικοσίδης έχει αξιολογηθεί *in vitro,* και *in vivo* μετά από παρεντερική και από του στόματος χορήγηση.

Η θειοκολχικοσίδη ήταν καλά ανεκτή μετά από χορήγηση από το στόμα για περιόδους έως και 6 μηνών τόσο σε αρουραίους όσο και σε μη ανθρώπινα πρωτεύοντα κατά τη χορήγηση επαναλαμβανόμενων

δόσεων μικρότερων ή ίσων των 2 mg/kg/ημέρα στους αρουραίους και μικρότερων ή ίσων των 2,5 mg/kg/ημέρα σε μη ανθρώπινα πρωτεύοντα, καθώς και μέσω της ενδομυϊκής οδού σε πρωτεύοντα σε επαναλαμβανόμενες δόσεις έως και 0,5 mg/kg/ημέρα για διάστημα 4 εβδομάδων.
Σε υψηλές δόσεις, η θειοκολχικοσίδη προκάλεσε έμεση σε σκύλους, διάρροια σε αρουραίους και σπασμούς σε τρωκτικά και μη τρωκτικά μετά από οξεία χορήγηση δια της στοματικής οδού.
Μετά από επαναλαμβανόμενη χορήγηση, η θειοκολχικοσίδη προκάλεσε γαστρεντερικές διαταραχές (εντερίτιδα, έμεση) δια της στοματικής οδού και έμεση δια της ενδομυϊκής οδού.
Η θειοκολχικοσίδη καθαυτή δεν επήγαγε γονιδιακή μετάλλαξη σε βακτήρια (δοκιμασία Ames), χρωμοσωμική βλάβη *in vitro* (δοκιμασία χρωμοσωμικής παρέκκλισης σε ανθρώπινα λεμφοκύτταρα) και χρωμοσωμική βλάβη *in vivo* (ενδοπεριτοναϊκώς χορηγούμενη μικροπυρηνική δοκιμασία *in vivo* σε μυελό των οστών σε ποντικούς).
Ο κύριος, συζευγμένος με γλυκουρονικό οξύ μεταβολίτης SL18.0740 δεν επήγαγε γονιδιακή μετάλλαξη σε βακτήρια (δοκιμασία Ames) αλλά επήγαγε χρωμοσωμική βλάβη *in vitro* (μικροπυρηνική δοκιμασία *in vitro* σε ανθρώπινα λεμφοκύτταρα) και χρωμοσωμική βλάβη *in vivo* (από του στόματος χορηγούμενη μικροπυρηνική δοκιμασία *in vivo* σε μυελό των οστών σε ποντικούς). Οι μικροπυρήνες προέκυψαν κυρίως από χρωμοσωμική απώλεια (μικροπυρήνες θετικοί για κεντρομερίδιο μετά από χρώση κεντρομεριδίου FISH), γεγονός που υποδηλώνει ανευπλοειδογόνες ιδιότητες. Η ανευπλοειδογόνος δράση του SL18.0740 παρατηρήθηκε σε συγκεντρώσεις στη δοκιμασία *in vitro* και σε εκθέσεις AUC στο πλάσμα στη δοκιμασία *in vivo* μεγαλύτερες (πάνω από 10 φορές με βάση την AUC) από εκείνες που έχουν παρατηρηθεί στο ανθρώπινο πλάσμα σε θεραπευτικές δόσεις.
Ο άγλυκος μεταβολίτης (3-demethylthiocolchicine-SL59.0955) που σχηματίζεται κυρίως μετά από χορήγηση από το στόμα, επήγαγε χρωμοσωμική βλάβη *in vitro* (μικροπυρηνική δοκιμασία *in vitro* σε ανθρώπινα λεμφοκύτταρα) και χρωμοσωμική βλάβη *in vivo* (από του στόματος χορηγούμενη μικροπυρηνική δοκιμασία *in vivo* σε μυελό των οστών σε ποντικούς). Οι μικροπυρήνες προέκυψαν κυρίως από χρωμοσωμική απώλεια (μικροπυρήνες θετικοί για κεντρομερίδιο μετά από χρώση κεντρομεριδίου FISH ή CREST), γεγονός που υποδηλώνει ανευπλοειδογόνες ιδιότητες. Η ανευπλοειδογόνος δράση του SL59.0955 παρατηρήθηκε σε συγκεντρώσεις στη δοκιμασία *in vitro* και σε εκθέσεις στη δοκιμασία *in vivo* κοντά σε εκείνες που έχουν παρατηρηθεί στο ανθρώπινο πλάσμα στις θεραπευτικές δόσεις των από του στόματος χορηγούμενων 8 mg δις ημερησίως. Η ανευπλοειδογόνος επίδραση στα διαιρούμενα κύτταρα μπορεί να οδηγήσει σε ανευπλοειδή κύτταρα. Η ανευπλοειδία είναι μία μεταβολή στον αριθμό των χρωμοσωμάτων και απώλεια της ετεροζυγωτίας, η οποία αναγνωρίζεται ως παράγοντας κινδύνου για τερατογένεση, εμβρυοτοξικότητα/αυτόματη αποβολή, διαταραχή της γονιμότητας του άρρενος όταν επιδρά στα γεννητικά κύτταρα και δυνητικός παράγοντας κινδύνου για καρκίνο όταν επιδρά στα σωματικά κύτταρα. Η παρουσία του άγλυκου μεταβολίτη (3-demethylthiocolchicine-SL59.0955) μετά από ενδομυική χορήγηση δεν έχει αξιολογηθεί ποτέ, επομένως ο σχηματισμός του, όταν χρησιμοποιείται αυτή η οδός χορήγησης δεν μπορεί να αποκλειστεί.
Στους αρουραίους, μία από του στόματος δόση θειοκολχικοσίδης των 12 mg/kg/ημέρα προκάλεσε μείζονες δυσπλασίες μαζί με εμβρυοτοξικότητα (καθυστέρηση της ανάπτυξης, θάνατο του εμβρύου, διαταραχή του ποσοστού κατανομής του φύλου). Η δόση που δεν προκάλεσε τοξική επίδραση ήταν 3 mg/kg/ημέρα.

Σε κουνέλια, η θειοκολχικοσίδη επέδειξε μητρική τοξικότητα ξεκινώντας από τα 24 mg/kg/ημέρα. Επιπλέον, έχουν παρατηρηθεί ήσσονος σημασίας ανωμαλίες (υπεράριθμα πλευρά, καθυστερημένη οστεοποίηση).

Σε μία μελέτη γονιμότητας που πραγματοποιήθηκε σε αρουραίους, δεν παρατηρήθηκε διαταραχή της γονιμότητας σε δόσεις έως και 12 mg/kg/ημέρα, δηλ. σε δόσεις που δεν προκαλούν κλινική επίδραση. Η θειοκολχικοσίδη και οι μεταβολίτες της ασκούν ανευπλοειδογόνο δράση σε διαφορετικά επίπεδα συγκέντρωσης, γεγονός που αναγνωρίζεται ως παράγοντας κινδύνου για διαταραχή της γονιμότητας στον άνθρωπο.
Η καρκινογόνος δυνατότητα δεν αξιολογήθηκε.

6.5 Φύση και συστατικά του περιέκτη <και ειδικός εξοπλισμός για τη χρήση, τη χορήγηση ή την εμφύτευση>

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

30 *δισκία/καψάκια για τη δόση των 4 mg και 14 δισκία/καψάκια για τη δόση των8 mg*
10 φιαλίδια / αμπούλες για τη δόση των 4 mg / 2 ml.

ΕΠΙΣΗΜΑΝΣΗ

ΕΝΔΕΙΞΕΙΣ ΠΟΥ ΠΡΕΠΕΙ ΝΑ ΑΝΑΓΡΑΦΟΝΤΑΙ ΣΤΗΝ ΕΞΩΤΕΡΙΚΗ ΣΥΣΚΕΥΑΣΙΑ

Εξωτερικό κουτί για καψάκια, σκληρά/δισκία/διασπειρόμενα στο στόμα δισκία και ενέσιμο διάλυμα

4. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ ΚΑΙ ΠΕΡΙΕΧΟΜΕΝΟ

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

4 mg
[έως 30] σκληρά καψάκια
[έως 30] δισκία

8 mg
[έως 14] σκληρά καψάκια
[έως 14] διασπειρόμενα στο στόμα δισκία

4 mg/2 ml
[έως 10] φιαλίδια/φυσίγγια

ΦΥΛΛΟ ΟΔΗΓΙΩΝ ΧΡΗΣΗΣ

[η παρακάτω διατύπωση πρέπει να εισαχθεί]

▼ Το φάρμακο αυτό τελεί υπό συμπληρωματική παρακολούθηση. Αυτό θα επιτρέψει τον γρήγορο προσδιορισμό νέων πληροφοριών ασφάλειας. Μπορείτε να βοηθήσετε μέσω της αναφοράς πιθανών ανεπιθύμητων ενεργειών που ενδεχομένως παρουσιάζετε. Βλ. τέλος της παραγράφου 4 για τον τρόπο αναφοράς ανεπιθύμητων ενεργειών.

[…]

ΦΟΧ

Φύλλο οδηγιών χρήσης: Πληροφορίες για τον ασθενή

1. Τι είναι το Χ και ποια είναι η χρήση του

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

Το φάρμακο αυτό είναι μυοχαλαρωτικό. Χρησιμοποιείται σε ενήλικες και εφήβους ηλικίας 16 ετών και άνω ως επικουρική θεραπεία για την αντιμετώπιση των επώδυνων μυϊκών συσπάσεων. Χρησιμοποιείται για οξείες καταστάσεις που σχετίζονται με τη σπονδυλική στήλη.

2. Τι πρέπει να γνωρίζετε προτού πάρετε το Χ

[η παρακάτω διατύπωση πρέπει να εισαχθεί]

Μην πάρετε το Χ:
- σε περίπτωση αλλεργίας στη θειοκολχικοσίδη ή σε οποιοδήποτε άλλο από τα συστατικά αυτού του φαρμάκου (αναφέρονται στην παράγραφο 6)
- εάν είστε έγκυος, μπορεί να μείνετε έγκυος ή νομίζετε ότι μπορεί να είστε έγκυος
- εάν είστε γυναίκα με δυνατότητα τεκνοποίησης που δεν χρησιμοποιείτε αντισύλληψη
- εάν θηλάζετε

Προειδοποιήσεις και προφυλάξεις

[…]

Ακολουθείτε αυστηρά τις δόσεις και τη διάρκεια θεραπείας που περιγράφονται στην παράγραφο 3. Δεν πρέπει να χρησιμοποιείτε αυτό το φάρμακο σε υψηλότερες δόσεις ή για μεγαλύτερο χρονικό διάστημα από 7 ημέρες *(για τις από του στόματος μορφές)*/5 ημέρες *(για τις ενδομυϊκές μορφές).* Αυτό οφείλεται στο γεγονός ότι ένα από τα προϊόντα που σχηματίζονται στον οργανισμό σας όταν παίρνετε θειοκολχικοσίδη σε υψηλές δόσεις μπορεί να προκαλέσει βλάβη σε ορισμένα κύτταρα (μη φυσιολογικό αριθμό χρωμοσωμάτων). Αυτό έχει αποδειχθεί σε μελέτες σε ζώα και σε εργαστηριακές μελέτες. Στον άνθρωπο, αυτό το είδος της βλάβης στα κύτταρα αποτελεί παράγοντα κινδύνου για καρκίνο, βλάβη στο αγέννητο παιδί και διαταραχή της γονιμότητας στον άντρα. Παρακαλούμε συζητήστε με το γιατρό σας σε περίπτωση που έχετε περαιτέρω ερωτήσεις.

Ο γιατρός σας θα σας ενημερώσει αναφορικά με όλα τα μέτρα που σχετίζονται με την αποτελεσματική αντισύλληψη καθώς και για το δυνητικό κίνδυνο μίας κύησης.

Παιδιά και έφηβοι
Μην δίνετε αυτό το φάρμακο σε παιδιά και εφήβους ηλικίας κάτω των 16 ετών εξαιτίας ανησυχιών ως προς την ασφάλεια.

Κύηση, θηλασμός και γονιμότητα

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

Μην πάρετε αυτό το φάρμακο:
- εάν είστε έγκυος, μπορεί να μείνετε έγκυος ή νομίζετε ότι μπορεί να είστε έγκυος
- εάν είστε γυναίκα με δυνατότητα τεκνοποίησης και δεν χρησιμοποιείτε αντισύλληψη

Αυτό συμβαίνει διότι αυτό το φάρμακο μπορεί να προκαλέσει βλάβη στο αγέννητο παιδί σας. Μην πάρετε αυτό το φάρμακο εάν θηλάζετε. Αυτό συμβαίνει διότι το φάρμακο περνά στο μητρικό γάλα.

Το φάρμακο αυτό μπορεί να προκαλέσει προβλήματα στην αντρική γονιμότητα λόγω της δυνητικής βλάβης στα κύτταρα του σπέρματος (μη φυσιολογικός αριθμός χρωμοσωμάτων). Αυτό βασίζεται σε εργαστηριακές μελέτες (βλ. παράγραφο 2 «Προειδοποιήσεις και προφυλάξεις»).

3. Πώς να πάρετε το X

[η ισχύουσα εγκεκριμένη διατύπωση πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

Πάντοτε να παίρνετε το φάρμακο αυτό αυστηρά σύμφωνα με τις οδηγίες του γιατρού ή του φαρμακοποιού σας. Εάν έχετε αμφιβολίες, ρωτήστε το γιατρό ή το φαρμακοποιό σας.

- *Για την από του στόματος μορφή 4 mg και 8 mg:*

Η συνιστώμενη και μέγιστη δόση είναι 8 mg κάθε 12 ώρες (δηλ. 16 mg ανά ημέρα). Η διάρκεια της θεραπείας περιορίζεται σε 7 συνεχόμενες ημέρες.

- *Για την ενδομυϊκή μορφή:*

Η συνιστώμενη και μέγιστη δόση είναι 4 mg κάθε 12 ώρες (δηλ. 8 mg ανά ημέρα). Η διάρκεια της θεραπείας περιορίζεται σε 5 συνεχόμενες ημέρες.

- *Για την από του στόματος και ενδομυϊκή μορφή:*

Μην υπερβαίνετε τις συνιστώμενες δόσεις και τη διάρκεια της θεραπείας.
Το φάρμακο αυτό δεν πρέπει να χρησιμοποιείται για μακροχρόνια θεραπεία (βλ. παράγραφο 2 «Προειδοποιήσεις και προφυλάξεις»).

Χρήση σε παιδιά κι εφήβους
Μην δίνετε αυτό το φάρμακο σε παιδιά και εφήβους ηλικίας κάτω των 16 ετών εξαιτίας ανησυχιών ως προς την ασφάλεια.

Εάν πάρετε μεγαλύτερη δόση X από την κανονική
Εάν πάρετε κατά λάθος μεγαλύτερη δόση X από την κανονική, απευθυνθείτε στο γιατρό, το φαρμακοποιό ή το νοσοκόμο σας.

Εάν ξεχάσετε να πάρετε το X
Μην πάρετε διπλή δόση για να αναπληρώσετε τη δόση που ξεχάσατε.
Εάν έχετε περισσότερες ερωτήσεις σχετικά με τη χρήση αυτού του φαρμάκου, ρωτήστε το γιατρό, το φαρμακοποιό ή το νοσοκόμο σας.

4. Πιθανές ανεπιθύμητες ενέργειες

[η διατύπωση αυτή πρέπει να εισαχθεί]

Όπως όλα τα φάρμακα, έτσι και αυτό το φάρμακο μπορεί να προκαλέσει ανεπιθύμητες ενέργειες, αν και δεν παρουσιάζονται σε όλους τους ανθρώπους.
[…]
[η παρακάτω διατύπωση πρέπει να εισαχθεί]

Αναφορά ανεπιθύμητων ενεργειών
Εάν παρατηρήσετε κάποια ανεπιθύμητη ενέργεια, ενημερώστε το γιατρό, το φαρμακοποιό ή το νοσοκόμο σας. Αυτό ισχύει και για κάθε πιθανή ανεπιθύμητη ενέργεια που δεν αναφέρεται στο παρόν φύλλο οδηγιών χρήσης. Μπορείτε επίσης να αναφέρετε ανεπιθύμητες ενέργειες απευθείας, μέσω του εθνικού συστήματος αναφοράς που αναγράφεται στο Παράρτημα V*. Μέσω της αναφοράς ανεπιθύμητων ενεργειών μπορείτε να βοηθήσετε στη συλλογή περισσότερων πληροφοριών σχετικά με την ασφάλεια του παρόντος φαρμάκου.

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

6. Περιεχόμενο της συσκευασίας και λοιπές πληροφορίες

[*η ισχύουσα εγκεκριμένη διατύπωση* πρέπει να διαγραφεί και να αντικατασταθεί από το παρακάτω]

30 δισκία/καψάκια για τη δόση των 4 mg και 14 δισκία/καψάκια για τη δόση των 8 mg
10 φιαλίδια / αμπούλες για τη δόση των 4 mg / 2 ml.

ALLEGATO III

Modifiche ai paragrafi rilevanti del riassunto delle caratteristiche del prodotto, etichettatura e foglio illustrativo

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

[il testo sotto riportato deve essere inserito]

▼Medicinale sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta. Vedere paragrafo 4.8 per informazioni sulle modalità di segnalazione delle reazioni avverse.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

[le indicazioni attualmente autorizzate devono essere eliminate e sostituite con le seguenti]

Trattamento adiuvante di contratture muscolari dolorose nelle patologie acute della colonna vertebrale negli adulti e negli adolescenti dai 16 anni in poi.

4.2 Posologia e modo di somministrazione

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Posologia

- *Per la forma orale di 4 mg e 8 mg*:

La dose raccomandata e massima è di 8 mg ogni 12 ore (16 mg al giorno). La durata del trattamento è limitata a 7 giorni consecutivi.

- *Per la forma intramuscolare*:

La dose raccomandata e massima è di 4 mg ogni 12 ore (8 mg al giorno). La durata del trattamento è limitata a 5 giorni consecutivi.

- *Per entrambe le forme orale e intramuscolare*:

Dosi superiori a quelle raccomandate o l'uso a lungo termine devono essere evitati (vedere paragrafo 4.4).

Popolazione pediatrica
<Nome di fantasia> non deve essere usato nei bambini e negli adolescenti sotto 16 anni di età a causa di problematiche di sicurezza (vedere paragrafo 5.3).

Modo di somministrazione
[Completare con i dati nazionali]

4.3 Controindicazioni

[il testo sotto riportato deve essere inserito]

Tiocolchicoside non deve essere utilizzato
- nei pazienti con ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1
- durante tutto il periodo di gravidanza
- durante l'allattamento
- nelle donne in età fertile che non usano contraccettivi.

4.4 Avvertenze speciali e precauzioni di impiego

[il testo sotto riportato deve essere inserito]

[…]
Studi preclinici hanno dimostrato che uno dei metaboliti della tiocolchicoside (SL59.0955) ha indotto aneuploidia (alterazione del numero dei cromosomi nelle cellule in divisione) a concentrazioni vicine all'esposizione umana osservata con dosi di 8 mg due volte al giorno per os

(vedere paragrafo 5.3). L'aneuploidia viene considerata come un fattore di rischio per teratogenicità, tossicità dell'embrione/feto, aborto spontaneo, alterazione della fertilità maschile e un potenziale fattore di rischio per il cancro. Come misura precauzionale, l'uso del medicinale a dosi superiori alla dose raccomandata o l'uso a lungo termine devono essere evitati (vedere paragrafo 4.2).

I pazienti devono essere accuratamente informati circa il potenziale rischio di una possibile gravidanza e sulle misure di contraccezione efficaci da seguire.

4.6 Fertilità, gravidanza e allattamento

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

[…]

Gravidanza
I dati relativi all'uso di tiocolchicoside in donne in gravidanza sono limitati. Pertanto, i potenziali rischi per l'embrione e il feto sono sconosciuti.
Gli studi su animali hanno mostrato effetti teratogeni (vedere paragrafo 5.3).
<Nome di fantasia> è controindicato durante la gravidanza e nelle donne in età fertile che non usano contraccettivi (vedere paragrafo 4.3).

Allattamento
L'uso di tiocolchicoside è controindicato durante l'allattamento poiché è secreto nel latte materno (vedere paragrafo 4.3).

Fertilità
In uno studio sulla fertilità condotto sui ratti, nessuna alterazione della fertilità è stata osservata a dosi fino a 12 mg/kg, cioè a livelli di dose che non inducono alcun effetto clinico. Tiocolchicoside e i suoi metaboliti esercitano attività aneugenica a diversi livelli di concentrazione, il che è un fattore di rischio di alterazione della fertilità umana (vedere paragrafo 5.3).

4.8 Effetti indesiderati

[...]

[il testo sotto riportato deve essere inserito]

Segnalazione delle reazioni avverse sospette
La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione riportato nell'Allegato V*.

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

[...]

5. PROPRIETÀ FARMACOLOGICHE

5.2 Proprietà farmacocinetiche

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Assorbimento

- Dopo somministrazione per via intramuscolare, la Cmax di Tiocolchicoside si verifica in 30 minuti e raggiunge i valori di 113 ng/ml dopo una dose di 4 mg, e di 175 ng/ml dopo una dose di 8 mg. I corrispondenti valori di AUC sono rispettivamente 283 e 417 ng.h/ml.
Il metabolita farmacologicamente attivo SL18.0740 si osserva anche a concentrazioni più basse, con una Cmax di 11,7 ng/ml che si ottiene 5 ore dopo la dose e una AUC di 83 ng.h/ml.
Non sono disponibili dati per il metabolita inattivo SL59.0955.

- Dopo somministrazione orale, tiocolchicoside non viene rilevato nel plasma. Si osservano solo due metaboliti: il metabolita farmacologicamente attivo SL18.0740 e un metabolita inattivo SL59.0955. Per entrambi i metaboliti, le concentrazioni plasmatiche massime si verificano 1 ora dopo la somministrazione di tiocolchicoside. Dopo una singola dose orale di 8 mg di tiocolchicoside la Cmax e l'AUC di SL18.0740 sono rispettivamente circa 60 ng/ml e 130 ng.h/ml. Per SL59.0955 questi valori sono molto più bassi: Cmax circa 13 ng/ml e i valori di AUC sono compresi tra 15,5 ng.h/ml (fino a 3h) e 39,7 ng.h/ml (fino a 24h).

Distribuzione
Il volume apparente di distribuzione di tiocolchicoside è stimato intorno a 42,7 L dopo somministrazione intramuscolare di 8 mg. Non sono disponibili dati per entrambi i metaboliti.

Biotrasformazione
Dopo somministrazione orale, tiocolchicoside viene prima metabolizzato in aglicone 3-demetiltiocolchicina o SL59.0955. Questa trasformazione avviene principalmente mediante metabolismo intestinale e spiega la mancanza di tiocolchicoside circolante immodificata con questa via di somministrazione.
Il metabolita SL59.0955 viene poi glucuroconiugato in SL18.0740 che ha attività farmacologica equipotente a tiocolchicoside e supporta quindi l'attività farmacologica dopo somministrazione orale di tiocolchicoside.
Il metabolita SL59.0955 è inoltre demetilato a didemetil-tiocolchicina.

Eliminazione
- Dopo somministrazione intramuscolare il $t_{1/2}$ apparente di tiocolchicoside è 1,5 ore e la clearance plasmatica 19,2 l/h.

- Dopo somministrazione orale, la radioattività totale viene escreta principalmente nelle feci (79%), mentre l'escrezione urinaria rappresenta solo il 20%. Tiocolchicoside immodificato non viene escreto né nelle urine né nelle feci. I metaboliti SL18.0740 e SL59.0955 si trovano nelle urine e nelle feci, mentre il didemetil-tiocolchicina viene recuperato solo nelle feci.
Dopo somministrazione orale di tiocolchicoside, il metabolita SL18.0740 viene eliminato con un $t_{1/2}$ apparente compreso tra 3,2 e 7 ore e il metabolita SL59.0955 ha un $t_{1/2}$ medio di 0.8 ore.

5.3 Dati preclinici di sicurezza

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Il profilo di tiocolchicoside è stato valutato *in vitro* e *in vivo* dopo somministrazione parenterale ed orale.
Tiocolchicoside è stato ben tollerato dopo somministrazione orale per periodi fino a 6 mesi sia nel ratto che nel primate non umano quando somministrato a dosi ripetute inferiori o uguali a 2 mg/kg/die nel ratto e inferiori o uguale a 2,5 mg/kg/die nel primate non umano, e per via intramuscolare nel primate a dosi ripetute fino a 0,5 mg/kg/die per 4 settimane.
A dosi elevate, dopo somministrazione acuta per via orale, tiocolchicoside ha indotto emesi nel cane, diarrea nel ratto e convulsioni sia nei roditori che nei non roditori.
Dopo somministrazioni ripetute, tiocolchicoside ha indotto disturbi gastro-intestinali (enteriti, emesi) per via orale ed emesi per via intramuscolare.
Thiocolchicoside non ha indotto di per sé mutazione genica nei batteri (Ames test), danno cromosomico *in vitro* (test di aberrazione cromosomica nei linfociti umani) e danno cromosomico *in vivo* (test del micronucleo nel midollo osseo del topo dopo somministrazione intraperitoneale).
Il principale metabolita glucuroconiugato SL18.0740 non ha indotto mutazione genica nei batteri (Ames test), tuttavia ha indotto un danno cromosomico *in vitro* (test del micronucleo sui linfociti umani) e un danno cromosomico *in vivo* (test del micronucleo nel midollo osseo del topo dopo somministrazione orale). I micronuclei provenivano prevalentemente dalla perdita cromosomica (micronuclei centromero positivi dopo colorazione FISH del centromero), suggerendo proprietà aneugeniche. L'effetto aneugenico del metabolita SL18.0740 è stato osservato a concentrazioni nel test *in vitro* e a esposizioni plasmatiche (AUC) nel test *in vivo,* più elevate (maggiori di 10 volte in base alla AUC) rispetto a quelle osservati nel plasma umano a dosi terapeutiche.

Il metabolita aglicone (3-demetilthiocolchicina-SL59.0955), che si forma principalmente dopo somministrazione orale, ha indotto un danno cromosomico *in vitro* (test del micronucleo sui linfociti umani) e un danno cromosomico *in vivo* (test del micronucleo nel midollo osseo del ratto dopo somministrazione orale). I micronuclei provenivano prevalentemente dalla perdita cromosomica (micronuclei centromero positivi dopo colorazione FISH o CREST del centromero), suggerendo

proprietà aneugeniche. L'effetto aneugenico di SL59.0955 è stato osservato a concentrazioni nel test *in vitro* e ad esposizioni nel test *in vivo* vicine a quelle osservate nel plasma umano a dosi terapeutiche di 8 mg due volte al giorno per os. L'effetto aneugenico nelle cellule in divisione può causare cellule aneuploidi. L'aneuploidia è una alterazione nel numero dei cromosomi e perdita della eterozigosi, che è riconosciuta come un fattore di rischio per teratogenicità, tossicità dell'embrione/aborto spontaneo, alterata fertilità maschile, quando riguarda le cellule germinali, e un potenziale fattore di rischio per il tumore quando riguarda le cellule somatiche. La presenza del metabolita aglicone (3-demetilthiocolchicina-SL59.0955) dopo somministrazione intramuscolare non è mai stata valutata, quindi la sua formazione attraverso questa via di somministrazione non può essere esclusa.
Nel ratto, una dose orale di 12 mg/kg/giorno di tiocolchicoside ha provocato malformazioni maggiori insieme a tossicità fetale (ritardo nella crescita, morte dell'embrione, alterazione del tasso di distribuzione del sesso). La dose senza effetto tossico è stata di 3 mg/kg/giorno.

Nel coniglio, tiocolchicoside ha mostrato tossicità materna a partire da 24 mg/kg/giorno. Inoltre, sono state osservate anomalie minori (costole soprannumerarie, ossificazione ritardata).

In uno studio sulla fertilità condotto sui ratti, nessuna alterazione della fertilità è stata osservata a dosi fino a 12 mg/kg/giorno, cioè livelli di dose che non inducono alcun effetto clinico.
Tiocolchicoside e i suoi metaboliti esercitano attività aneugenica a diversi livelli di concentrazione, ciò è riconosciuto come fattore di rischio di alterazione della fertilità umana.

Il potenziale cancerogeno non è stato valutato.

6.5 Natura e contenuto del contenitore < e strumentazione particolare per l'uso, la somministrazione o l'impianto>

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

30 compresse/capsule per la dose di 4 mg e 14 compresse/capsule per la dose di 8 mg
10 fiale / flaconi per la dose di 4 mg / 2 ml.

ETICHETTATURA

INFORMAZIONI DA APPORRE SUL CONFEZIONAMENTO SECONDARIO

Astuccio per capsule rigide/ compresse / compresse orodispersibili e per la soluzione iniettabile }

4. FORMA FARMACEUTICA E CONTENUTO

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

4 mg[fino a 30] capsule rigide[fino a 30] compresse

8 mg
[fino a 14] capsule rigide
[fino a 14] compresse orodispersibili

4 mg/2 ml
[fino a 10] flaconcini/fiale

FOGLIO ILLUSTRATIVO

[il testo sotto riportato deve essere inserito]

▼Medicinale sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Lei può contribuire segnalando qualsiasi effetto indesiderato riscontrato durante l'assunzione di questo medicinale. Vedere la fine del paragrafo 4 per le informazioni su come segnalare gli effetti indesiderati.

[…]

PL

Foglio illustrativo: informazioni per il paziente

1. Che cos'è X e a cosa serve

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Questo medicinale è un rilassante muscolare. Viene utilizzato negli adulti e negli adolescenti da 16 anni in poi come trattamento adiuvante per le contratture muscolari dolorose. Deve essere utilizzato per condizioni acute legate alla colonna vertebrale.

2. Cosa deve sapere prima prima di prendere X

[il testo sotto riportato deve essere inserito]

Non prenda X se:
- è allergico a tiocolchicoside o ad uno qualsiasi degli eccipienti di questo medicinale (elencati nel paragrafo 6)
- è in gravidanza, sospetta di esserlo o potrebbe andare incontro a gravidanza
- è una donna in età fertile che non usa contraccettivi
- sta allattando al seno

Avvertenze e precauzioni

[...]

Rispetti rigorosamente le dosi e la durata del trattamento riportati al paragrafo 3. Non deve usare questo medicinale a dosi più alte o per più di 7 giorni (*per le forme orali*) /5 giorni (*per le forme* intramuscolari). Questo perché una delle sostanze che si formano nel corpo quando prende tiocolchicoside a dosi elevate potrebbe causare danni ad alcune cellule (numero anomalo di cromosomi). Ciò è stato dimostrato in studi su animali e in studi di laboratorio. Negli esseri umani, questo tipo di danno cellulare è un fattore di rischio per il cancro, danneggia il nascituro, e altera la fertilità maschile. Si rivolga al medico se ha ulteriori domande.

Il medico la informerà su tutte le misure in materia di contraccezione efficace e sul rischio potenziale di una gravidanza .

Bambini e adolescenti
Non somministri questo medicinale a bambini e adolescenti sotto 16 anni a causa di problemi di sicurezza.

Gravidanza, allattamento e fertilità

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Non prenda questo medicinale se:
- è in gravidanza, sospetta di esserlo o potrebbe andare incontro a gravidanza
- è una donna in età fertile che non usa contraccettivi

Infatti questo medicinale può causare danni al nascituro.

Non assuma questo medicinale se sta allattando in quanto il medicinale passa nel latte materno.

Il medicinale può causare problemi alla fertilità maschile a causa di potenziali danni alle cellule spermatiche (numero anormale di cromosomi). Questo si basa su studi di laboratorio (vedere paragrafo 2 "Avvertenze e precauzioni").

3. Come prendere X

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Prenda questo medicinale seguendo sempre esattamente le istruzioni del medico o del farmacista. Se ha dubbi consulti il medico o il farmacista.

- *Per la forma orale di 4 mg e 8 mg*:

La dose raccomandata e massima è di 8 mg ogni 12 ore (cioè 16 mg al giorno). La durata del trattamento è limitata a 7 giorni consecutivi.

- *Per la forma intramuscolare*:

La dose raccomandata e massima è di 4 mg ogni 12 ore (cioè 8 mg al giorno). La durata del trattamento è limitata a 5 giorni consecutivi.

- *Per entrambe le forme orale e intramuscolare*:

Non superare le dosi raccomandate e la durata del trattamento.
Questo medicinale non deve essere usato per trattamento a lungo termine (vedere paragrafo 2 "Avvertenze e precauzioni").

Uso nei bambini e negli adolescenti
Non somministrare questo medicinale a bambini e adolescenti al di sotto di 16 anni di età a causa di problemi di sicurezza.

Se prende più X di quanto deve
Se accidentalmente prende più X di quanto deve, si rivolga al medico, al farmacista o all'infermiere.

Se dimentica di prendere X
Non prenda una dose doppia per compensare la dimenticanza della dose.
Se ha qualsiasi dubbio sull'uso di questo medicinale, si rivolga al medico, al farmacista o all'infermiere.

4. Possibili effetti indesiderati

[il testo sotto riportato deve essere inserito]

Come tutti i medicinali, questo medicinale può causare effetti indesiderati sebbene non tutte le persone li manifestino.
[...]

[il testo sotto riportato deve essere inserito]

Segnalazione degli effetti indesiderati
Se manifesta un qualsiasi effetto indesiderato, compresi quelli non elencati in questo foglio, si rivolga al medico o al farmacista o all'infermiere. Lei può inoltre segnalare gli effetti indesiderati direttamente tramite il sistema nazionale di segnalazione riportato nell'Allegato V*.
Segnalando gli effetti indesiderati lei può contribuire a fornire maggiori informazioni sulla sicurezza di questo medicinale.

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

6. Contenuto della confezione e altre informazioni

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

30 compresse/capsule per la dose di 4 mg e 14 comprese/capsule per la dose di 8 mg
10 fiale / flaconi per la dose di 4 mg / 2 ml.

Anexo III

Alterações às secções relevantes do resumo das características do medicamento, rotulagem e folheto informativo

RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO

[O texto abaixo deve ser inserido]

▼Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas. Para saber como notificar reações adversas, ver secção 4.8.

4. INFORMAÇÕES CLÍNICAS

4.1 Indicações terapêuticas

[as indicações atualmente aprovadas devem ser eliminadas e substituídas pelas seguintes]

Tratamento adjuvante de contraturas musculares dolorosas na patologia aguda da coluna vertebral em adultos e adolescentes a partir dos 16 anos.

4.2 Posologia e modo de administração

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

Posologia*Para a formulação oral 4 mg e 8 mg:*

A dose recomendada e máxima é de 8 mg a cada 12 horas (isto é, 16 mg por dia). A duração do tratamento está limitada a 7 dias consecutivos.

- *Para a formulação IM:*

A dose recomendada e máxima é de 4 mg a cada 12 horas (isto é, 8 mg por dia). A duração do tratamento está limitada a 5 dias consecutivos.

- *Para ambas as formulações oral e IM:*

Devem ser evitadas doses superiores às recomendadas ou a utilização a longo prazo (ver secção 4.4).

População pediátrica
<Nome de fantasia> não deve ser utilizado em crianças e adolescentes com menos de 16 anos devido a questões de segurança (ver secção 5.3).
Modo de administração
[A ser completado nacionalmente]

4.3 Contraindicações

[o texto abaixo deve ser inserido]

O tiocolquicosido não deve ser utilizado
- em doentes com hipersensibilidade à substância ativa ou a qualquer um dos excipientes mencionados na secção 6.1
- durante todo o período da gravidez
- durante a amamentação
- em mulheres com potencial para engravidar que não utilizam métodos contracetivos.

4.4 Advertências e precauções especiais de utilização

[o texto abaixo deve ser inserido]

[…]

Os estudos pré-clínicos mostraram que um dos metabolitos de tiocolquicosido (SL59.0955) induziu aneuploidia (isto é, número desigual de cromossomas em células em divisão) em concentrações próximas da exposição em humanos observadas em doses de 8 mg duas vezes ao dia por via oral (ver secção 5.3). A aneuploidia é considerada um fator de risco para teratogenicidade, embrio/fetotoxicidade, aborto espontâneo e problemas de fertilidade nos homens e um fator de risco potencial para cancro. Como medida de precaução, a utilização do medicamento em doses que excedam a dose recomendada ou o uso a longo prazo devem ser evitados (ver secção 4.2).

Os doentes devem ser cuidadosamente informados sobre o risco potencial de uma possível gravidez e sobre as medidas de contraceção eficazes a seguir.

4.6 Fertilidade, gravidez e aleitamento

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

[…]

Gravidez
Os dados sobre a utilização de tiocolquicosido em mulheres grávidas são limitados. Por conseguinte, os potenciais perigos para o embrião e feto não são conhecidos.
Os estudos em animais revelaram efeitos teratogénicos (ver secção 5.3).
<Nome de fantasia> está contraindicado durante a gravidez e em mulheres com potencial para engravidar que não utilizam métodos contracetivos (ver secção 4.3).

Amamentação
Uma vez que passa para o leite materno, o uso de tiocolquicosido está contraindicado durante a amamentação (ver secção 4.3).

Fertilidade
Num estudo de fertilidade realizado em ratos, não foi observado qualquer alteração na fertilidade em doses até 12 mg/kg, isto é, em níveis de doses que não induzam qualquer efeito clínico. O tiocolquicosido e respetivos metabolitos exercem atividade aneugénica em diferentes níveis de concentração, o que representa um fator de risco para alterações na fertilidade nos humanos (ver secção 5.3).

4.8 Efeitos indesejáveis

[…]

[o texto abaixo deve ser inserido]

Notificação de suspeitas de reações adversas
A notificação de suspeitas de reações adversas após a autorização do medicamento é importante, uma vez que permite uma monitorização contínua da relação benefício-risco do medicamento. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do sistema nacional de notificação mencionado no Apêndice V*.

[*Para o material impresso, ver o document de orientação do templare QRD anotado.]

5. PROPRIEDADES FARMACOLÓGICAS

5.2 Propriedades farmacocinéticas

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

Absorção-
- Após administração IM, a Cmax de tiocolquicosido ocorre em 30 min e atinge valores de 113 ng/ml após uma dose de 4 mg e 175 ng/ml após uma dose de 8 mg. Os valores correspondentes de AUC são, respetivamente, 283 e 417 ng.h/m.
O metabolito farmacologicamente ativo SL18.0740 é também observado em concentrações mais baixas com uma Cmax de 11,7 ng/ml 5 h após a dose e uma AUC de 83 ng.h/ml.
Não existem dados disponíveis para o metabolito ativo SL59.0955.
- Após administração oral, não é detetado qualquer tiocolquicosido no plasma. Apenas são observados dois metabolitos:
O metabolito farmacologicamente ativo SL18.0740 e um metabolito inativo SL59.0955. Para ambos os metabolitos, as concentrações plasmáticas máximas ocorrem 1 hora após a administração de tiocolquicosido. Após uma dose única oral de 8 mg de tiocolquicosido, a Cmax e AUC de SL18.0740 são de cerca de 60 ng/ml e 130 ng.h/ml, respetivamente. Para o SL59.0955 estes valores são muito inferiores: Cmax de cerca de 13 ng/ml e AUC entre 15,5 ng.h/ml (até 3 h) e 39,7 ng.h/ml (até 24 h).

Distribuição
O volume aparente de distribuição de tiocolquicosido é calculado em cerca de 42,7 l após uma administração IM de 8 mg. Não existem dados disponíveis para ambos os metabolitos.

Biotransformação
Após administração oral, o tiocolquicosido é primeiro metabolizado na aglição 3-demetiltiocolquicina ou SL59.0955. Este passo ocorre sobretudo através do metabolismo intestinal, o que explica a falta de tiocolquicosido inalterado em circulação através desta via de administração.
O SL59.0955 é então glucoroconjugado em SL18.0740, que tem atividade farmacológica equipotente ao tiocolquicosido e, portanto, suporta a atividade farmacológica após administração oral de tiocolquicosido. O SL59.0955 passa também por uma demetilação para didemetil-tiocolquicina.

Eliminação
- Após administração IM, o t1/2 aparente de tiocolquicosido é de 1,5 h e a depuração plasmática é de 19,2 l/h.
- Após administração oral, a radioatividade total é sobretudo excretada nas fezes (79%), enquanto a excreção urinária representa apenas 20%. Não é excretado qualquer tiocolquicosido inalterado quer na urina quer nas fezes. O SL18.0740 e o SL59.0955 encontram-se na urina e nas fezes, enquanto a didemetil-tiocolquicina se encontra apenas nas fezes.
Após a administração oral de tiocolquicosido, o metabolito SL18.0740 é eliminado com um t1/2 aparente variando entre 3,2 a 7 horas e o metabolito SL59.0955 tem um t1/2 médio de 0,8 h.

5.3 Dados de segurança pré-clínica

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

O perfil do tiocolquicosido foi avaliado in vitro e in vivo após administração parentérica e oral.
O tiocolquicosido foi bem tolerado após administração oral por períodos de até 6 meses quer em ratos e primatas não humanos, quando administrado em doses repetidas inferiores ou iguais a 2 mg/kg/dia em ratos e 2,5 mg/kg/dia em primatas não humanos, e pela via intramuscular nos primatas em doses repetidas até 0,5 mg/kg/dia durante 4 semanas.
Em doses elevadas, o tiocolquicosido induziu emese em cães, diarreia em ratos e convulsões quer em roedores e não roedores após administração aguda por via oral.
Após administração repetida, o tiocolquicosido induziu alterações gastrointestinais (enterite, emese) por via oral e émese por via IM.
O tiocolquicosido em si não induziu mutação genética em bactérias (teste de Ames), danos cromossómicos in vitro (teste de aberração cromossómicas em linfócitos humanos) e danos

cromossómicos in vivo (micronúcleo in vivo na medula de ratinhos administrado por via intraperitoneal).

O principal metabolito glucoroconjugado SL18.0740 não induziu mutação genética em bactérias (teste de Ames); no entanto, induziu danos nos cromossomas *in vitro* (teste de micronúcleo *in vitro* em linfócitos humanos) e danos em cromossomas *in vivo* (teste de micronúcleo *in vivo* em medula de ratinhos administrado oralmente). Os micronúcleos resultaram predominantemente da perda de cromossomas (micronúcleos com centrómero positivo após coloração de centrómero com hibridização in situ fluorescente [FISH]), sugerindo propriedades aneugénicas. O efeito aneugénico de SL18.0740 foi observado em concentrações no teste *in vitro* e exposições plasmáticas de AUC no teste *in vivo* superiores (mais de 10 vezes com base na AUC) do que as observadas no plasma humano em doses terapêuticas.

O metabolito de aglição (3-demetiltiocolquicina-SL59.0955) formado sobretudo após administração oral induziu danos nos cromossomas *in vitro* (teste de micronúcleo *in vitro* em linfócitos humanos) e danos nos cromossomas *in vivo* (teste de micronúcleo oral *in vivo* em medula óssea de ratos administrado oralmente). Os micronúcleos resultaram predominantemente da perda de cromossomas (micronúcleos com centrómero positivo após coloração de centrómero FISH ou CREST), sugerindo propriedades aneugénicas. O efeito aneugénico de SL59.0955 foi observado em concentrações no teste *in vitro* e em exposições de teste *in vivo* próximas das observadas no plasma humano em doses terapêuticas de 8 mg duas vezes ao dia por via oral. O efeito aneugénico nas células em divisão poderá resultar em células aneuplóides. A aneuploidia é uma modificação do número de cromossomas e perda de heterozigosidade, que é reconhecida como um fator de risco para a teratogenicidade, embriotoxicidade/aborto espontâneo, problemas de fertilidade nos homens, com impacto nas células germinativas e um potencial fator de risco para cancro com impacto nas células somáticas. A presença do metabolito de aglição (3-demetiltiocolquicina-SL59.0955) após administração intramuscular nunca foi avaliada, por conseguinte, a sua formação utilizando esta via de administração não pode ser excluída.

Nos ratos, uma dose oral de 12 mg/kg/dia de tiocolquicosido causou malformações graves juntamente com fetotoxicidade (atrasos no crescimento, morte do embrião, problemas da taxa de distribuição de género). A dose sem efeitos tóxicos foi de 3 mg/kg/dia.

Em coelhos, o tiocolquicosido apresentou maternotoxicidade a partir de 24 mg/kg/dia. Além disso, foram observadas anomalias menores (costelas supranumerárias, atrasos na ossificação).

Num estudo de fertilidade realizado em ratos, não foi observado qualquer problema de fertilidade em doses até 12 mg/kg/dia, isto é, em níveis de doses que não induzam qualquer efeito clínico. O tiocolquicosido e respetivos metabolitos exercem atividade aneugénica em diferentes níveis de concentração, o que representa um fator de risco de problemas de fertilidade nos humanos.

O potencial carcinogénico não foi avaliado.

6.5 Natureza e conteúdo do recipiente <e equipamento especial para utilização, administração ou implantação>

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

30 comprimidos/cápsulas para a dose de 4 mg e 14 comprimidos/cápsulas para a dose de 8 mg.

10 frascos / ampolas para a dose de 4 mg / 2 ml.

ROTULAGEM

INDICAÇÕES A INCLUIR NO ACONDICIONAMENTO SECUNDÁRIO

Embalagem secundária para cápsulas duras, comprimidos/comprimidos orodispersíveis e solução injetável

4. FORMA FARMACÊUTICA E CONTEÚDO

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

4 mg
[até 30] cápsulas duras
[até 30] comprimidos

8 mg
[até 14] cápsulas duras
[até 14] comprimidos orodispersíveis

4 mg/2 ml
[até 10] frascos/ampolas

FOLHETO INFORMATIVO

[o texto abaixo deve ser inserido]

▼Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Poderá ajudar, comunicando quaisquer efeitos secundários que tenha. Para saber como comunicar efeitos secundários, veja o final da secção 4.

[…]

FI

Folheto informativo: Informação para o doente

1. O que é X e para que é utilizado

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

Este medicamento é um relaxante muscular. É utilizado em adultos e adolescentes a partir dos 16 anos como um tratamento adjuvante para contrações musculares dolorosas. É utilizado para episódios agudos relacionados com a coluna vertebral.

2. O que precisa de saber antes de tomar X

[o texto abaixo deve ser inserido]

Não tome X se:

- se tem alergia ao tiocolquicosido ou a qualquer outro componente deste medicamento (indicados na secção 6)
- se está grávida,se puder ficar grávida ou pensar que pode estar grávida
- se é uma mulher com potencial para engravidar que não utiliza métodos contracetivos
- se estiver a amamentar

Advertências e precauções

[…]

Respeite rigorosamente as doses e duração do tratamento detalhadas na secção 3. Não deverá utilizar este medicamento numa dose superior ou durante mais tempo do que 7 dias *(para formas orais)*/5 dias *(para formas IM).* Isto porque um dos produtos que se formam no seu corpo ao tomar tiocolquicosido em doses elevadas poderá causar danos em algumas células (número anormal de cromossomas). Isto foi provado em estudos com animais e estudos em laboratório. Em humanos, este tipo de danos em células é um fator de risco para o cancro, lesões em fetos e problemas de fertilidade nos homens. Fale com o seu médico se tiver mais perguntas.

O médico irá informá-lo sobre todas as medidas relacionadas com uma contraceção eficaz e acerca do risco potencial de uma gravidez.

Crianças e adolescentes
Não dê este medicamento a crianças e adolescentes com menos de 16 anos devido a preocupações com a segurança.

Gravidez, amamentação e fertilidade

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

Não tome este medicamento se:
- está grávida, se puder ficar grávida ou se pensa poder estar grávida
- é uma mulher com potencial para engravidar que não utiliza métodos contracetivos
Isto porque este medicamento poderá causar lesões no feto. Não tome este medicamento se estiver a amamentar. Isto porque o medicamento passa para o leite materno.

Este medicamento pode causar problemas de fertilidade nos homens devido ao danos potenciais nos espermatozoides (número anormal de cromossomas). Este facto baseia-se em estudos laboratoriais (ver secção 2 "Advertências e precauções").

3. Como tomar X

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

Tome este medicamento exatamente de acordo como indicado pelo seu médico ou farmacêutico. Fale com o seu médico ou farmacêutico se tiver dúvidas.

- *Para a formulação oral 4 mg e 8 mg:*

A dose recomendada e máxima é de 8 mg a cada 12 horas (isto é, 16 mg por dia). A duração do tratamento está limitada a 7 dias consecutivos.

- *Para a formulação intramuscular:*

A dose recomendada e máxima é de 4 mg a cada 12 horas (isto é, 8 mg por dia). A duração do tratamento está limitada a 5 dias consecutivos.

- *Para ambas as formulações oral e intramuscular:*

Não exceda as doses recomendadas e a duração do tratamento.

Este medicamento não deve ser utilizado para tratamento de longa duração (ver secção 2 "Advertências e precauções").

Utilização em crianças e adolescentes
Não dê este medicamento a crianças e adolescentes com menos de 16 anos devido a questões de segurança.

Se tomar mais X do que deveria
Se tomar acidentalmente mais X do que deveria, fale com o seu médico, farmacêutico ou enfermeiro.

Caso se tenha esquecido de tomar X
Não tome uma dose a dobrar para compensar uma dose que se esqueceu de tomar.
Caso ainda tenha dúvidas sobre a utilização deste medicamento, fale com o seu médico, farmacêutico ou enfermeiro.

4. Efeitos secundários possíveis

[este texto deve ser inserido]

Como todos os medicamentos, este medicamento pode causar efeitos secundários, embora estes não se manifestem em todas as pessoas.
[…]
[o texto abaixo deve ser inserido]

Comunicação de efeitos secundários
Se tiver quaisquer efeitos secundários, incluindo possíveis efeitos secundários não indicados neste folheto, fale com o seu médico, ou farmacêutico ou enfermeiro. Também poderá comunicar efeitos secundários diretamente através do sistema nacional de notificação mencionado no Apêndice V*. Ao

comunicar efeitos secundários, estará a ajudar a fornecer mais informações sobre a segurança deste medicamento.

[*Para o material impresso, ver o document de orientação do templare QRD anotado.]

6. Conteúdo da embalagem e outras informações

[o texto atualmente aprovado deve ser eliminado e substituído pelo seguinte]

30 comprimidos/cápsulas para a dose de 4 mg e 14 comprimidos/cápsulas para a dose de 8 mg.
10 frascos / ampolas para a dose de 4 mg / 2 ml.