POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

TITLE: : Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study

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COMPOUND: Thiocolchicoside

STUDY NAME: Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study

The Study is conducted by QuintilesIMS Health 90-92 route de la Reine, 92773 Boulogne Billancourt, France

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PASS Information

Title	Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records databases study
Protocol version identifier	Version 5.0
Date of last version of protocol	2nd March 2017
EU PAS register number	EUPAS11081
Active substance	M03BX05 Thiocolchicoside
Medicinal Product	See Annex 3
Product reference	See Annex 3
Procedure number	EMEA/H/N/PSP/j/0030
Marketing authorization holder(s) or Sponsor company	**1. SANOFI AVENTIS GROUPE,** a French company having its registered office at 54 rue La Boétie, 75008 Paris, France; **2. TEOFARMA Srl**, Via F.lli Cervi N° 8, I-27010 valle Salimbene, 27010 Pavia, Italy; **3. MYLAN** SAS with legal address at 117 Allée des Parcs, 69800 St Priest, France; **4. ANGELINI** with legal address at Angelini Farmacêutica Lda, Rua João Chagas, 53 - 3° piso, 1499-040 Cruz Quebrada – Dafundo, Portugal; **5. DOMPE' FARMACEUTICI S.P.A**., with legal address in Via San Martino 12-12/a, 20122 Milan- Italy and Operative office: Via Santa Lucia 6, 20122 Milan, Italy; **6. GENERIS FARMACEUTICA** with legal address in Rua João de Deus, 19, 2700-487 Amadora, Portugal; **7. KORANGI,** with legal address at Produtos Farmacêuticos Lda. Rua da Vinha, 17P 2765-388 Estoril, Portugal; **8. DAIICHI Sankyo France SAS** with legal address at 1, rue Eugène et Armand Peugeot, 92500 Rueil-Malmaison, France; **9. BIOGARAN SAS** wth legal address 15, Boulevard Charles de Gaulle, 92707 Colombes Cedex, France; **10. SANDOZ SAS** with legal address 49, avenue Georges Pompidou, 92593 Levallois-Perret, France;

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Joint PASS	Yes

Research question and objectives	The aim of this drug utilization study is to characterise prescribing practices of TCC-containing medicinal products during typical clinical use in representative groups of prescribers and assess main reasons for prescription. The study objectives are: • To describe the demographic and clinical characteristics of the treated patients (i.e. age and gender, co-medications, pregnancy, contraceptive use, lactation) • To describe for which indication TCC is prescribed in routine clinical practice (overall and by age/gender) • To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration • To compare patients characteristics pre- and post-implementation of RMMs
Country(-ies) of study	France and Italy
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2 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AESI	Adverse Event of Special Interest
AIFA	Italian Medicines Agency
CI	Confidence Interval
CHMP	Committee on Human Medicinal Products
eCRF	Electronic Case Report Form
DA	Disease Analyzer
DHPC	Direct Healthcare Professional Communication
DREES	Direction de la recherche, des études, de l'évaluation et des statistiques (French National Statistical Institute)
DUS	Drug Utilization Study
EC	European Community
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUQPPV	European Qualified Person for Pharmacovigilance
EMA	European Medicines Agency
EMR	Electronic Medical Record
GP	General Practitioners
HAS	Haute Autorité de Santé (French Health Authority)
LPD	Longitudinal Patient Databases
RMMs	Risk Minimization Measures
SC	Scientific Committee
SmPc	Summary of Product Characteristics
TCC	Thiocolchicoside

3 RESPONSIBLE PARTIES

The Scientific Committee:

a) The SC shall be composed of one representative of each MAH and one representative of QuintilesIMS. If the nominated representative is not able to attend an SC meeting on a given date, the MAH shall nominate another representative able to participate in the discussions.

b) QuintilesIMS shall participate in meetings of the SC and shall be responsible for organizing and coordinating such meetings and shall not hold any voting rights.

c) During the meetings of the SC, the MAHs undertake their best efforts to agree to any necessary actions or take any necessary decisions regarding the Services.

d) The decisions taken during the SC shall include, without limitation:

i) Preparation and final validation of the Protocol
ii) Submission of documents, communications, such as interim reports and the Final Report by QuintilesIMS to the MAHs, and
iii) Any subject matters in relation to the management of the Study.

4 ABSTRACT

Title

Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records databases study.

Version 5.0 dated on 2nd March 2017 by Sophie L. Jouaville

Rationale and background

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, a Joint Drug Utilization Study will be conducted.

Research question and objectives

The aim of this Drug Utilization Study is to characterise prescribing practices of systemic TCC-containing medicinal products during typical clinical use in representative groups of prescribers and assess main reasons for prescription.

The study objectives are:

- To describe the demographic and clinical characteristics of the treated patients (i.e. age and gender, co-medications; pregnancy, contraceptive use, lactation)
- To describe for which indication TCC is prescribed in routine clinical practice (overall and by age/gender)
- To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration
- To compare patients characteristics pre- and post-implementation of RMMs

Study design:

Cross sectional study based on existing databases in France and Italy.

Study period: The study will cover 3 years starting from effective date of implementation (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France) of minimization measures.

In addition, a baseline period spanning over year 2013, will be used to describe prescribing practices of systemic TCC-containing medicinal products before implementation of minimization measures.

Population:

Study population:

The study population will include patients with at least one prescription of TCC-containing medicinal products for systemic use during the study period, i.e. before (baseline: year 2013) or after the implementation of the minimization measures. The effective date of implementation of minimization measures will be considered per country (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

Prescriber population:

A national representative sample of Generalist Practitioners (GPs) will be considered for each country. In addition and for France only, a panel of specialists (Rheumatologists) will be considered as well.

Variables

Age, gender, treatment indication, dose, duration, route of administration, concomitant treatments, use of appropriate contraceptive measures, pregnancy and lactation, during the study period.

Data Sources

Longitudinal electronic medical records (EMR) databases will be used in France and Italy (IMS LPD® and DA). The data are collected routinely from GPs and rheumatologists (for France only) in the outpatient setting.

Study size

Over 50,000 patients in France (GPs + Rheumatologists), 17,000 in Italy (GPs) are expected.

Data analysis

The analysis will be done annually for the 3 years of study and once for the baseline period. The statistical analysis will be mainly descriptive. Patient's demographic and clinical characteristics available from the selected databases will be used to describe the study population.
Distribution of drug patterns will be done considering the overall sample and by country:

- Distribution of the treatment indication by age groups and gender
- Duration of prescription at index date
- Distribution of daily dose and treatment duration at index date
- Distribution of TCC use in the subgroup of women of childbearing age only:
  - Pregnancy
  - Using appropriate contraceptive measures
  - Lactation
- Distribution of co-medications used along with TCC scripts
- Description of prevalent and incident patients

In order to better characterize the impact of risk minimization measures (RMMs) on prescribing practices for thiocolchicoside, patient characteristics will be compared between the two study periods.

Milestones*

*Estimated timelines pending approval of the DUS protocol and Educational Material by the respective competent regulatory authorities.

Draft Study protocol: 3 months after contract signature between all MAHs

Study period: 3 years study (covering data collected from Q3 2015 to Q3 2018 for Italy, and from Q2 2016 to Q2 2019 for France)

Two annual interim reports (Q4 2017, Q4 2018)

Final report in Q4 2019

5 AMENDMENTS AND UPDATES

5.1 AMENDMENT # 1

This amendment, Version 4.0, dated 13th October 2016, is to reflect changes that have occurred since the last version of the protocol (V3.0 dated 26th April 2016) and in particular the removal of the French RH data base, the changes in MAH information and the changes in QuintilesIMS personal.

a) Removal of RH database

The French HEAD database will not be available anymore for use in this study, due to routine ongoing evaluations that were required following quality control tests.

Therefore the following sections have been amended:

- PASS information / Research question and objectives
- List of abbreviations
- Abstract/ Research question and objectives, Variables, Data sources, data analysis
- 8.1 Primary objective
- 9.3 Variables (9.3.2, 9.3.3)
- 9.4 Data Sources
- 9.6 Data Management
- 9.8 Primary Analysis
- 9.10 Limitations of the research methods
- 13 References

b) Change in MAHs information

Therefore the following section has been amended:

- PASS Information / Marketing authorization holder(s)

c) Change in IMS personal

Therefore the following section has been amended:

- Name and Address of study management

5.2 AMENDMENT # 2

This amendment, Version 5.0, dated 2nd March 2017, is to reflect changes that have occurred since the last version of the protocol (4.0 dated 13th October 2016) as a consequence of the demand of the PRAC to collect data about concomitance of a TCC prescription with pregnancy and lactation as well as thechange of company conducting the study's name.

a) Replacement of IMS Health LPD® France GP database by IMS ®Disease Analyzer (DA) France GP

In order to be able to collect data about concomitance of a TCC prescription with pregnancy or with lactation, IMS Health LPD® France GP database will be replaced by IMS ®DA France GP.

Therefore the following section has been amended:

- Pass information
- List of abbreviations
- Abstract/ Research question and objectives, Variables, Data sources, data analysis
- 8.1 Primary objective
- 9.3 Variables (9.3.2, 9.3.3)
- 9.4 Data Sources
- 9.6 Data Management
- 9.8 Primary Analysis
- 9.10 Limitations of the research methods

b) Change of company name

The merge between IMS Health and Quintiles which occurred on May 2016 results with a change in company name from IMS Health to QuintilesIMS. Therefore the change from IMS Health to QuintilesIMS has been implemented thorough the entire protocol.

6 MILESTONES

Milestone	Planned date
Start of data collection	Oct 2015 for Italy and April 2016 for France
End of data collection	Oct 2018 for Italy and April 2019 for France
Registration in the EU PASS register	Q3 2015
Two annual interim reports	Q4 2017, Q4 2018
Final report of study results	Q4 2019

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity. Muscle relaxants are one of the many treatments currently employed in the management of non-specific low back pain. TCC for systemic use is indicated as adjuvant treatment of painful muscle contractures associated with acute spinal pathology. Widely used by prescribers in the concerned Member States (Czech Republic, France, Greece, Italy, Malta, Portugal and Spain.), the benefits of TCC containing medicinal products are recognized in clinical practice.

The review of thiocolchicoside was triggered by the Italian medicines regulatory agency, AIFA, following new experimental evidence which suggested that thiocolchicoside was broken down into 3-demethylthiocolchicine (M2 or SL59.0955) that could damage dividing cells, resulting in aneuploidy (an abnormal number or loss of heterozygosity).

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 [European Medicines Agency. Assessment Report][1], 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. Aneuploidy is a risk factor for harm to the developing fetus, reduced fertility in men and in theory could increase the risk of developing cancer. On November 21th 2013 the CHMP recommended that the authorized uses for thiocolchicoside-containing medicines for use by mouth or injection should be restricted across the European Union (EU) [European Medicines Agency. Article 31 referral[2]]. The CHMP therefore recommended measures to ensure thiocolchicoside-containing medicines are used as safely as possible. 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 adequate contraception, as well as in children below 16 years old or for chronic (long-term) conditions. Topical cutaneous preparations for local application to the skin, which do not produce substantial levels of M2 in the body, are not affected by this review. The European Commission implementing decision was issued on January 17, 2014.

Since this date, the modified indication statement for systemic TCC use is as follow:

- Systemic thiocolchicoside is indicated only as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and adolescents from 16 years of age.
- Systemic thiocolchicoside should not be used for long-term treatment of chronic conditions
- The maximum recommended oral dose is 8 mg every 12 hours; treatment duration should be no more than 7 consecutive days. When given intramuscularly, the maximum dose should be 4 mg every 12 hours, for up to 5 days.
- Medicines containing thiocolchicoside should not be used during pregnancy and lactation, nor in women of childbearing potential who are not taking appropriate contraception.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Thiocolchicoside-containing_medicines/WC500162337.pdf

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Thiocolchicoside-containing_medicines/human_referral_000356.jsp&mid=WC0b01ac05805c516f

Local modified SmPC and Direct Healthcare Professional Communication (DHPC) are appended in Annex 4.

European Commission decision included the distribution of educational material for prescribers and for patients, highlighting the risks and warnings of genotoxicity reactions.

7.2 RATIONALE

This drug utilization study (DUS) is being conducted, per regulatory request, following the Article 31 referral on thiocolchicoside-containing medicinal products for systemic use. It is to be included in the Risk Management Plan, as part of the assessement of effectiveness of risk minimization measures, including a Dear Healthcare Professional Communication, educational materials distribution to health care professionals and patients, as well as changes to the SmPC, Labelling and Package Leaflet.

This drug utilization study aims to characterize the prescribing practices during typical clinical use of systemic thiocolchicoside in Italy and France.

Epidemiological studies on the use of drugs are essential to evaluate the intended and adverse effects of prescription medications as they are used in clinical practice. Drug use and patient characterisation studies allow for characterisation of users of the medication in terms of age and sex, treatment indication, use of concurrent medications, prior morbidity and other characteristics.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The aim of this drug utilization study is to characterise prescribing practices of TCC-containing medicinal products for systemic use during typical clinical use in representative groups of prescribers and assess main reasons for prescription.

The study objectives are:

- To describe the demographic and clinical characteristics of the treated patients (i.e. age and gender, co-medications, pregnancy, use of appropriate contraceptive measures, lactation),
- To describe for which indication TCC is prescribed in routine clinical practice (overall and by age/gender),
- To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration.

8.2 SECONDARY OBJECTIVES

- Comparison of patient characteristics, pre- and post- implementation of RMMs as a measurement of the efficacy of the risk minimization measures

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is

- An international: France and Italy.
- A multicenter:

Data will be collected from Electronic Medical Record (EMR) databases: IMS Longitudinal Patient databases (LPD) Italy and France-Rheumatologists, and Disease Analyzer (DA) France. These databases collect the electronic Medical Record information obtained from the general practice management software utilized during physician office visits. Approximately 1,000 GPs (DA France) and 100 rheumatologists (LPD France-Rheumatologists) in France and 900 GPs (LPD-Italy) in Italy contribute to the databases. Physician panels in each database are designed to be representative of the physician population in each country by age, gender and localization.

- A non-interventional:

Data from EMR is submitted daily to a coordinating center, cleaned, de-identified, and made available for research. Since data is collected in a non-interventional manner, IMS database mirror real life clinical practice.

- A retrospective: Data will be retrospectively collected
- A cross-sectional study: all patients having systemic TCC prescription during study periods (before or after the implementation of the risk minimization measures) will be included

9.2 SETTING

The study will take place in 2 European countries: France and Italy.

9.2.1 Baseline Period

A one-year baseline period spanning over year 2013, will be used to describe prescribing practices of systemic TCC-containing medicinal products before implementation of risk minimization measures.

9.2.2 Study Follow-up Period

No follow-up period is planned for this study.

9.2.3 Duration of the study

The study will describe the utilization pattern of systemic thiocolchicoside during the first three years after the effective date of implementation of all the risk minimization measures following the CHMP decision in France and Italy. The effective date of implementation of minimization measures will be considered per country (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

This analysis will be repeated at 12 (interim analysis 1), 24 (interim analysis 2) and 36 (Final report) months from the implementation of all the minimization measures.

In addition, a **baseline period** spanning over year 2013 (January 1st to December 31st), will be used to describe prescribing practices of systemic TCC-containing medicinal products before implementation of minimization measures.

9.2.4 Eligibility criteria

9.2.4.1 Inclusion criteria

The study population will include all patients with at least one prescription of TCC-containing medicinal products for systemic use in the selected databases during the study periods, i.e. before or after the implementation of the risk minimization measures.

The "prescription index date" for each patient included in the study will be defined as first date in each study period a patient is prescribed systemic thiocolchicoside.

9.2.4.2 Exclusion criteria

No age restrictions or exclusion criteria will be applied. This will allow for the characterization of all users of TCC-containing medicinal products for systemic use according to each indication for which the medication is being used. This will include any pediatric population and patients with contraindications (e.g., pregnant woman).

9.2.4.3 Analysis population(s)

Analysis will be done on all eligible patients with at least one year of enrollment in the database before index date. However, in order to assess the effect of including patients prescribed systemic TCC but not analyzed because of enrollment less than one year before index date, these patients will be counted, and their main characteristics (age, gender, dose, duration, treatment indication, co-medications) at index date, will be described together with the characteristics of patients included in the study.

9.2.5 Modalities of recruitment

9.2.5.1 Physician selection

In the selected EMR-databases, a panel of contributing physicians is maintained as a representative sample of the national physician population.
The EMR-databases contain physicians' daily practice automated records. These physicians are software users of the data provider in each country. They are contacted according to the needs of representativity of the panel based on national statistics and according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. In addition for specialist panels, the type (semi-liberal, liberal) of practice is also considered. As compensation for their participation to the panel, preferential rates on their software subscription or subscription to other services that are part of their medical practice are offered.
A larger panel is therefore maintained from which a stable subset of physicians (1,000 GPs in France, 900 GPs in Italy,100 rheumatologists in France) is selected and maintained on the basis of representativity needs and the reliability of their data. This subset is used in epidemiological studies such as this one (more details § 9.4).

9.2.5.2 Patient selection

Not applicable.

9.3 VARIABLES

9.3.1 Exposures

The exposure of interest is obtained through systemic TCC prescription.

9.3.1.1 Treatment duration

Use of systemic TCC will be assessed through the recorded prescriptions (prescriptions "issued" or "written") in databases. Since EMR-databases report issued prescriptions rather than dispensed medication, there is no information indicating if, or, when a prescription was filled. We will assume that all the prescriptions and their associated dates recorded in both databases reflect actual prescription fills, and subjects will begin exposure at the index date (= prescription issued) and be exposed continuously for the number of days indicated by the days of supply for that prescription.

Note: If the days-of-supply field for a given prescription is missing or zero, or the value recorded has been determined to be implausible based on the quantity dispensed for that prescription, the days of supply will be calculated by dividing the total quantity dispensed by the daily prescribed dose.

9.3.1.2 Dose

The distribution of the daily prescribed dose (for oral form and IM form) at the index date will be described for all users of systemic TCC. The dose described will be the one associated to the index prescription. The daily dose of medications is recorded in the EMR-databases. Dose will be ascertained from the numeric daily dose derived from the dosing instructions. The proportion of missing values will be described.
However, the degree of completeness is variable across databases. Missing values for doses are expected. The missing information will be specified.

9.3.1.3 Treatment indications

Following the Article 31 referral on thiocolchicoside-containing medicinal products for systemic use, systemic thiocolchicoside use is recommended only as adjuvant treatment for acute muscle contractures in spinal pathology.

All diagnoses associated to a systemic TCC prescription will be recorded and classified according to ICD-10-CM. An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication. Of note, Table 1 displays the lists of diseases, conditions, and procedures mapped to the ICD-10-CM codes for identification of the current approved indication.

Table 1. List of diagnoses and corresponding ICD-10-CM codes for identification of the current approved indications

ICD-10-CM description	***ICD-10-CM code***	***Use of codes in indication definitions***
Other deforming dorsopathies including: • Spondylolysis • Spondylolisthesis • Recurrent atlantoaxial dislocation with myelopathy • Other recurrent atlantoaxial dislocation • Other recurrent vertebral dislocation • Torticollis • Other specified deforming dorsopathies • Deforming dorsopathy, unspecified	M 43 M43.0 M43.1 M43.3 M43.4 M43.5 M43.6 M43.8 M43.9	Primary code for the broad definition of the clinical indication
Dorsalgia • Radiculopathy • Cervicalgia • Sciatica • Lumbago with sciatica • Low back pain • Pain in thoracic spine • Other dorsalgia • Dorsalgia, unspecified	M 54 M 54.1 M 54.2 M 54.2 M 54.3 M.54.4 M54 .5 M54 .6 M54 .8 M54 .9	Primary code for the broad definition of the clinical indication

9.3.2 Pregnancy, contraceptive use and lactation: for women of child bearing potential

Use of appropriate contraceptive measures during the study period:

In the GP EMR databases contraceptive use is not well recorded (see Study limitations, § 9.10). Therefore it is expected that the recording of prescriptions of contraceptive measures up to a year before and concomitantly to TCC prescription is going to underestimate the population that is using appropriate contraceptive measures.

Pregnancy:

All of the diagnoses related to pregnancies will be searched in databases according to data availability.

Some of these diagnoses precise the pregnancy trimester or are related to exams specific of a trimester. If the information on trimester or start date or delivery/end of pregnancy date is available, the pregnancy will be considered exposed if at least one TCC prescription was recorded in the period between assumed dates of pregnancy start and delivery/end of pregnancy. In case information on pregnancy trimester or start date or delivery/end of pregnancy date is not available in the EMR-database, a pregnancy will be considered as exposed to TCC if at least one TCC prescription was issued within 90 days before or within 180 days after the first record of a given pregnancy.

Lactation:

Diagnoses related to breastfeeding will be searched in databases according to data availability.

Lactation will be considered as concomitant to TCC use if at least one TCC prescription is issued in a window of 90 days before and after any breast-feeding record.

9.3.3 Operational variables and definition of off-label

In summary, all variables to be collected for the purpose of the study and definition of off-label are the following:

Table 2. Summary of variables

Characteristic	***Variable Definition***	***Off label definition****
Patient Demographics, at initiation of systemic TCC use:	Patient Demographics, at initiation of systemic TCC use:	
• Age categories	• <16, ≥16 years	• Age at prescription <16 years
• Gender	• Male, female	
• Pregnancy	• Pregnancy diagnosis	• At least one TCC prescription issued in the period between assumed dates of pregnancy start and delivery/end of pregnancy, or, – when no information on pregnancy start or end is available-, within 90 days before or within 180 days after the first record of a given pregnancy
• Contraceptive use	• Prescription of contraceptive medications/devices	• No record of contraceptive use before, at initiation of, and during systemic TCC use
• Lactation status	• Lactation	• At least one TCC prescription issued in a window of 90 days before and after any diagnosis of lactation
• Country	• France, Italy	

Concomitant medications and /or health services, medical devices, before, at initiation of and during systemic TCC use:	Medications: • All analgesics (ATC code :N02) and specifically among them: o Salicylic combinations (NO2A) o Paracetamol (N02B) o Opioids (N02A) • Tricyclic antidepressants (N06A,mitriptyline type) • Benzodiazepine (ATC code: N03A, clonazepam type) • Muscle relaxants (ATC code : M03) • NSAIDs/Cox-2 inhibitors (ATC code : M01A) • Corticosterioids (ATC code : MO1B) • Topical products for joint and muscular pain (ATC code: M02A) • Phytotherapy (harpagophyton, ATC code : V03A), Health services/medical devices and others : • Functionnal rehabilitation (V57 (ICD-9), Z50 (ICD-10)) • Osteo-therapies (V57 (ICD-9), Z50 (ICD-10)) • Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10)) • Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	• No concomitant medications and /or health services, medical devices, before, at initiation of, and during systemic TCC use

Systemic TCC daily doses prescribed	• Oral form: ≤ 16 mg per day, >16 mg per day • IM form: ≤ 8 mg per day, >8 mg per day	• Oral form: >16 mg per day • IM form: >8 mg per day
Duration of systemic TCC treatment episode	• Oral form: ≤ 7 consecutive days, >7 consecutive days • IM form: ≤ 5 consecutive days, >5 consecutive days	• Oral form: >7 consecutive days • IM form: >5 consecutive days • Long term treatment: duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
Treatment indication for systemic TCC prescription	• clinical diagnosis recorded at the time of prescription	• Other than painful muscle contractures associated with acute spinal pathology

* Off-label definition is defined as any occurrence of the situations listed in the table 2 (in the last column) in a prescription

9.4 DATA SOURCES

- Longitudinal Patient Database (LPD): Rheumatologists France and GPs Italy

The LPDs collect medical information from proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in electronic medical records. A panel of physicians using this software volunteers to make available anonymized, patient-level information from their practices for clinical research purposes. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in the country.

The panel of contributing physicians is maintained as a representative sample of the primary care physician population according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile. Additionally, the patient population is representative of the country population according to age and gender distribution, as provided by national statistic authorities [Istituto di ricerca della SIMG, 2014] (see also Annex 2).

Repeated prescriptions can be refilled at the pharmacy without seeing the doctor. The number of allowed refills is recorded in the database. The database is not used for payment purposes, and the recorded prescriptions cover both reimbursed and unreimbursed medications. An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication.

In France, data from panels of primary care physicians and data from specialist panels are available. Panels of specialists are independent of GP panel; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, it is not possible to link individual patients across the two types of practitioners.

For this study, it is planned to record information gathered by a panel of French rheumatologists for a better coverage of patients prescribed TCC. Both LPD panels have been validated through previous published works. Indeed, French panel of Rheumatologists (LPD France-rheumatologists) has been used by French National Authority for Health [Has, 2009; HAS, 2010] and Italian LPD (LPD-Italy) have been used in peer reviewed publications [Lapi et al, 2012; Coloma et al, 2013].

- Disease Analyzer (DA) France: GPs France

Disease Analyzer provides a nationally representative sample of about 1,000 primary care physicians (GPs) and includes over 5 million anonymous patient records and 152 million prescriptions in France.

Physicians are contacted among GPs who are using one of the five practice management software selected by IMS and according to the needs of representativity of the panel based on national statistics. Physicians included in the panel are those who volunteer to make available anonymized, patient-level information from their practices for clinical research purposes.

The panel of contributing physicians is maintained as a representative sample of the primary care physician population according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile. Additionally, the patient population is representative of the country population according to age and gender distribution, as provided by national statistic authorities [Becher et al., 2009] (see also Annex 2).

DA was recently used in a PASS study involving the attainment of exposure of pregnant women to sodium valproate and related substances [ENCEPP/SDPP/9678]

Characteristics of the three databases are summarized in Table 3 and Table 4.

Table 3. Summary of variables available in LPD and DA

Demographic and Medical Profile		***Treatment and other medical data***	
Gender	Yes	Drug	Yes
Year of Birth	Yes	Diagnosis	Yes
Socia-Economics Status	No	Molecule	Yes
Ethnicity	No	Rx in INN	Yes
Death Recording	Partial	Brand Name	Yes
Registration Date	Yes	Dosage	Yes
"Transferred out" date	No	Duration of script	Yes
Diet	Partial	Repeat	Yes
Exercise	Partial	Cost	Partial
Life style (smoking etc .)	Partial		
Height	Yes	Allergies	Yes
Weight	Yes	Immunization	Yes
Blood pressure	Yes	Lab Tests	Yes
Date of events	Yes	Lab Tests Results	Partial
Home visit	Partial	Referrals	Partial
Medical History	Yes	Hospitalization	Partial
Signs and Symptoms	Yes	Reasons for Hospitalization	Partial

Table 4. Characteristics of data sources.

Characteristics	***DA France***	***LPD France-Rheumatologist***	***LPD Italy***
Database type	Primary health care electronic medical record database	Electronic medical record database	Primary health care electronic medical record database
Possibility of linkage	None	None	None
Possibility to request additional information	• Possibility of pop-up screens filled by physician • Possibility of questionnaires filled by patients and/or physicians	• Possibility of pop-up screens filled by physician • Possibility of questionnaires filled by patients and/or physicians	None
Physicians population	GPs: 1,000 (of 54,000 in France)	Rheumatologists: 100 (of 1,749 in France)	GPs: 900 (of 46,000 in Italy)
Data availability	Metropolitan France Since 2004	Metropolitan France. Since 2002 for Rheumatologist panel	All Italy Since 2004
Database population	1,160,000 active patients*	115,000 active patients*	1,000,000 active patients*
Approximate proportion of the country physician population covered by the database	1.85%	5.7 %	1.96%
Active international principle coding system	Proprietary thesaurus (*mapped to ATC)*	Proprietary thesaurus (*mapped to ATC)*	Proprietary thesaurus (*mapped to ATC)*
Disease classification	Proprietary thesaurus *(mapped to ICD-10)*	Proprietary thesaurus *(mapped to ICD-10)*	Proprietary thesaurus *(mapped to ICD-9)*

*active patients: patients having visited their physician at least once a year

9.5 STUDY SIZE

The aim of this study is to provide a description of real life treatment patterns. The study size will be driven primarily by the uptake of systemic TCC in the populations from which the automated databases obtain data for France and Italy.

The sample size is calculated in order to ensure that the study obtains meaningful data for descriptive purposes. The primary objectives are mainly descriptive. The primary objective of this study is to assess the distribution of drug patterns in the overall sample and across countries.

Approximately 50,000 patients in France (GPs + Rheumatologists) and 17,000 in Italy (GPs) are expected.

9.5.1 Determination of sample size

The sample size calculation is determined by the desired accuracy/precision of the estimation by confidence interval of the observed proportions. The Table 5 shows that to achieve a sufficient accuracy, i.e. within a marge of accuracy < +/- 5%, of the estimation by a two-sided 95% confidence interval (CI) for proportions (p) between 10 % and 50 % (or from 90 % to 50 % for complementary percentage), a minimum sample size of around 400 patients is required. The precision for an observed percentage with 95%CI will be determined by the formula below:

Calculation use the following formula (normal approximation):

$$e = \sqrt{\frac{p(1-p)}{n} \times \varepsilon_{\alpha}}$$

With n sample size, p observed percentage, ε_{α} 1.96 for 95% CI, e Precision.

Table 5. Required number of patients (1) by acceptable precision (95% confidence interval) for proportions (normal approximation)

	Observed percentage (accuracy): p(1-p)				
Precision	10% (90%)	20% (80%)	30% (70%)	40% (60%)	50% (50%)
± 2.0%	864	1537	2017	2305	2401
± 2.5%	553	983	1291	1475	1537
± 3.0%	384	683	896	1024	1067
± 3.5%	282	502	659	753	784
± 4.0%	216	384	504	576	600
± 5.0%	139	246	323	369	384

9.5.2 Sample size for France and Italy

For the study, investigators will register all consecutive TCC patientsvisiting GPs or specialists, whatever the reason. For the study, the analyzed patients' data set will consist of all registered patients, excluding patients for whom year of birth and/or gender are missing. As no published data are available on the practice of such physicians/sites, it was decided to assess the number of followed subjects from LPD and DA feasibility results. No hypothesis was made on the total number of subjects that will be registered. Thus, based on the feasibility results, for France, approximatively 40,000 patients were prescribed TCC in 2012 from GP panel and 2,800 in specialists. Besides, in Italy, more than 17,000 patients were prescribed TCC in 2012. Thus, based on a percentage of missing data on age and gender lower than 5 %, the maximal expected sample size will be over 60,000 patients per year from all data sources.

Table 6. Summary of the available number of users of TCC in each database in 2012 and 2013

	LPD France-Rheumatologists	DA France	LPD Italy
Number of GPs (panel size)	-	1,000	900
Number of Rheumatologists (panel size)	100	Not covered	Not covered
Patients on TCC cmp* - 2012-GP's	-	~40,000	>17,000
Patients on TCC cmp* -2012-Rheumatologists	>2,800	Not covered	Not covered
Patients on TCC cmp* - 2013-GP's	-	~50,000	>16,800
Patients on TCC cmp* -2013-Rheumatologists	>3,100	Not covered	Not covered

*: cmp: cumulative measurement period

9.6 DATA MANAGEMENT

Data collected by physicians in usual routine practice into the patient EMR are anonymized and transferred daily in accordance with national legislation. The data will be hosted on servers located in datacenters belonging to IMS, which ensures a high level of data security and confidentiality in accordance with the methods and good practices currently defined (CMMI, ISO 27001 and ITIL) and European regulation.

9.6.1 Data collection schedule

Not applicable.

9.6.2 Data collected

The following patients' data will be collected from the databases:

- Patient demography: age at the time of the visit, gender
- Pregnancy associated diagnoses for women of child bearing potential
- Lactation associated diagnoses for women of child bearing potential
- Date of prescription of TCC: name of the TCC-containing medicinal product for systemic use, posology, duration of treatment
- Diagnosis associated to prescription of the TCC-containing medicinal product for systemic use
- Concomitant medications/products: Concomitant medications/devices, including contraceptive medication/devices will be collected using list of therapeutic classes or drugs commonly prescribed.

Concerning concomitant medications/products prescribed in population with acute muscle contractures in spinal pathology, the predefined list, as exhaustive as possible, covers the concomitant medications of interest and the main therapeutic classes i.e. pain management prescription including: analgesics, tricyclic antidepressants, benzodiazepine, antiepileptics.

9.6.3 Site / Physician questionnaire

Not applicable. However, prescribing physicians may be analyzed and compared to panel population in term of age, gender and localization.

9.6.4 Screening log (if applicable)

Not applicable.

9.6.5 Procedure for withdrawal of patients from study follow-up schedule

Not applicable.

9.6.6 Logistic aspects

Not applicable

9.7 DATA ANALYSIS

A Statistical Analysis Plan (SAP) will be developed and validated prior to database extraction. A final version of the SAP will be provided at the end of the study. Statistical analysis will be performed using SAS® software with SAS enterprise guide 6.1 (SAS Institute, version 6.1, SAS 9.4, North Carolina, USA) and R© R Foundation for Statistical Computing, version 3.0 and later. Analyses will be performed by statistician and quality control by a senior statistician. Statistical analyses will follow the tables shell validated by the client and will be displayed using tables, listings and/or graphs.

Given the objectives, analyses will be mainly descriptive. To evaluate the differences between sub-groups by indication, proportions for categorical variables and means for continuous variables will be estimated (with 95% confidence intervals) within each sub-group. If appropriate, medians will be used instead of means when the variables of interest do not assume a normal distribution.

Besides, because of the likelihood of some degree of allocation bias, comparative statistical testing will be performed in a descriptive manner. Comparison will be provided for groups of interest, as long as the number of patients in each sub-group is sufficient ($n>30$ in each group). The Fisher's exact test will be used for comparison of categorical data. Continuous data will be compared by Wilcoxon rank-sum test. All tests where two-sided and $p<0.05$ will be considered to indicate significance. Adjustments on statistical analyses modelling will be performed limiting the danger of spurious statistically significant findings with the numbers of people studied and taking into account the effect of potential confounders.

Continuous variables will be described by the usual statistics: number (number of valid cases, number of missing values), mean, standard deviation, median, minimum, maximum, first and third quartiles.

Categorical variables will be described for each modality and the associated percentages. The numbers of data entered and missing values will be indicated. Missing values will be excluded from the calculation of percentages.

9.8 PRIMARY ANALYSIS

The description of drug use patterns (overall description by country and by age and gender and incident or prevalent patients) will be performed for the baseline period (year 2013) and each year over the 3 years of inclusion for both countries.

Analysis will be done overall and by sub-group of prevalent and incident patients. Prevalent patients will be defined by the total number of treated patients per year during 3 years, and incident patients will be defined as the total number of new treated patients per year.

For each country, a descriptive analysis of TCC utilization and potential off-label use (as defined in table 2) will be performed:

- Indication,
- Dosage,
- Duration,
- Therapeutic regimen: mono-therapies or adjuvant therapies (use of TCC along with other pre-specified co-medications).

The prescribed daily dose will be defined as the average dose prescribed overall and by indications.

In addition descriptive analyses will be performed according to:

- Age and gender
- In the subgroup of women of childbearing potential: in case of pregnancy, use of contraceptive measures, or lactation during the study period. Proportion of pregnancies exposed to TCC (at least one TCC prescription during pregnancy within the defined study period) will be calculated over the total number of pregnancies in patients included in the study within the defined study periods. Proportion of breastfeeding patients exposed to TCC (at least one TCC prescription concomitant to a lactation record within the defined study period) will be calculated over the total number of breastfeeding patients included in the study within the defined study periods.

In order to assess the impact of RMMs on the target population, the main characteristics of patients (demographic and clinical) will be compared between pre- and post-implementation of RMMs.

9.8.1 Secondary analysis

A comparison of patient characteristics and proportion of off-label use, pre- and post- implementation of RMMs as a measurement of the effectiveness of the risk minimization measures will be performed. The off label patients' proportion at baseline (year 2013) will be estimated on both the basis of the 2013 SmPC (A) and the post-RMMs SmPC (B). Off label patients' proportion for each year post-implementation of RMMs will be estimated on the basis of the post-RMMs SmPC (C). "Off-label use" definition will be based on the collected variables on relevant characteristics of use which are presented in Section 9.3.3

To estimate RMMs impact on off-label patients' rate, the overall difference (Δ = C - B) in off-label before and after RMMs will be estimated.

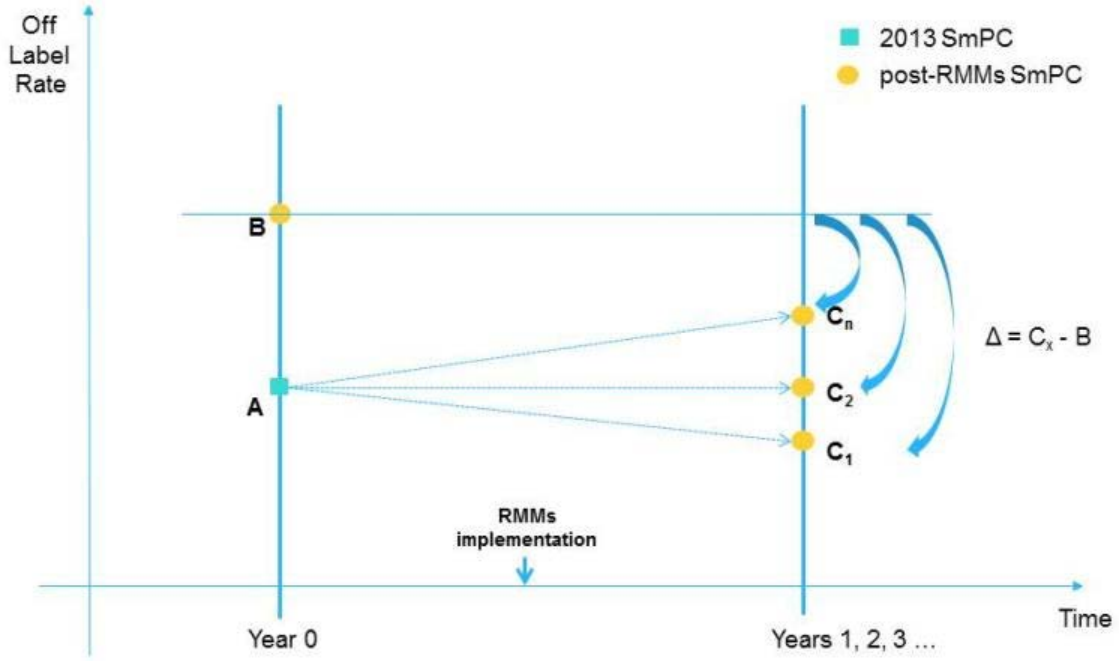

Figure 1: Estimation of RMMs impact on off-label rate

Furthermore, the effect of RMMs on off label incidence will be performed. The analysis will use a segmented regression analysis using a Poisson model [Wagner et al., 2002]. In this analysis, incidence rates will be computed by months before (baseline: 2013) and after RMMs (according to each country). The model will include an intercept (mean outcome rate at beginning of the study) and main period (before / after RMMs) effect and separate time trends before and after RMMs.

9.8.2 Interim analysis

Two annual interim reports are planned for this study.

9.9 QUALITY CONTROL

9.9.1 Data collection, validation and data quality control at MAH/MAH representative level

The data will be hosted on servers located in datacentres belonging to IMS, which ensures a high level of data security and confidentiality in accordance with the methods and good practices currently defined (CMMI, ISO 27001 and ITIL) and European regulation.

All data transfers will be verified by IMS according to SOPs for electronic file acquisition and checking practices.

All programming will be independently reviewed by one of the QuintilesIMS statisticians. The study reports will undergo quality-control review, senior scientific review, and editorial review.

Analysis data sets and program output will be checked for accuracy and integrity according to SOPs of QuintilesIMS that include the following steps:

- Checking program logs for errors and warnings
- Checking output for errors and inconsistencies
- Running quality-control programs to verify that specifications were implemented correctly and that any output generated accurately reflects the data
- Checking all results tables for accuracy

None of the extracted data sets will contain data that allow identification of subjects included in the study. Each electronic record will be completely anonymised and will not contain any personally identifying data.

9.9.2 Data quality control at site level

Not applicable: Data are collected by physicians in usual routine practice into the patient EMR. Since data are collected directly by physicians and uploaded in an anonymized way, it is not possible to refer back to patients' files and perform any site quality control.

Information is recorded by the physicians whenever they deem it relevant for their clinical practice and some information (e.g. family history, test results) may be partially available.

9.10 LIMITATIONS OF THE RESEARCH METHODS

The study will be conducted using health information recorded in population-based databases that collect and record data on a regular basis, thereby minimising bias related to differential reporting of prescriptions or impacts of contacts with patients and health care professionals. Although misclassification of clinical indication is recognized as a potential issue for all these databases, studies evaluating data already collected may be the most efficient way to assess potential off-label use.

However, there are limitations in the conduct of this study

- Potential for missing/incomplete data: No individual patient identifiers will be available. It is therefore impossible to query the physicians providing the data for any missing information. There is no availability of information on death, or date transferred out of the system.

  Recording of the indication of each prescribed treatment is mandatory in the physician software, but the physicians are free to enter any diagnosis and can for instance enter the reason of visit (e.g. flu) as indication for all treatments prescribed at the visit.

  Pregnancies are estimated by diagnoses codes in the patient's EMR but cannot always be reliably dated. There is therefore not always a possibility for us to state definitively the concomitance of a TCC prescription with a pregnancy. The same is true for lactation.

  Contraceptive use, as researched in women of childbearing potential trough the prescription of contraceptive medications or device, will be underestimated. The reasons are (i) a substantial number of women may see a gynaecologist for this purpose (ii) devices may have been inserted in a time period not encompassed by this study or removed elsewhere (iii) contraception may be insured by other means than a prescribed devices or medications. There is therefore no possibility for us to state definitively the concomitance of a TCC prescription and contraceptive use.

  Nevertheless, an accompanying survey performed at the PRAC request (PRACLOQN.8) in the most representative countries for TCC sales (France, Italy, Portugal and Greece) will be an additional source of information on contraception, lactation, and pregnancy for this study.
- Representativity of physicians: while representativeness of EMR-databases used in the present study is established on administrative criteria [Becher et al, 2009; Istituto di ricerca della SIMG, 2014] one

cannot exclude that the voluntary basis of physician's participation to the database leads to a potential bias in physicians' representativity.

- In France: no link between the panel of GPs and Rheumatologists is possible. Panels of specialists are independent of GP panels; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, the risk is minimal.

- Bias to be explained:

  - Selection Bias: Health care utilization patterns are best described when they include data from all potential prescribers of a drug. In this instance, the Italian LPD and DA data source will capture patients prescribed TCC only in a GP setting. However this bias will be assessed in France, where a panel of rheumatologists will be available.

  - Misclassification bias can result if study subjects are not categorized correctly with regards to exposure or selected patient characteristics. We expect minimal misclassification with respect to exposure, since this is determined from each database's prescribing records. However, actual adherence to TCC cannot be confirmed. In addition, misclassification bias can occur at the level of associated diagnosis since physician can enter the reason of the visit (e.g. flu) as indication for all treatments prescribed at the visit.
  -
  - Assessment of representativeness:

    - Representativity assessment of the participating physicians:

      Characteristics of participating GPs (gender, age class, region) will be compared to those of the national statistics. In case of discrepancy with national statistics information, weighted analysis could be applied.

    - Representativity assessment of the participating patients:

      In order to assess the effect of excluding patients prescribed TCC but for whom there was less than one year of enrolment before the index date, patients exposed to TCC but not meeting this inclusion requirement will be counted and their main characteristics at index date (age, gender) will be described together with the characteristics of patients included in the study.

9.11 OTHER ASPECTS

NA

10 PROTECTION OF HUMAN SUBJECTS

As per Module VIII of the 2013 EMA Guideline on Good Pharmacovigilance Practices (GVP) [EMA GPV, Module VIII, 2016], this study has been included in the EU PASS register (EUPAS11081, ENCePP: Website: encepp.eu/encepp_studies/indexRegister.shtml) prior to the start of data collection.

10.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS

Not applicable.

10.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.2.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments, and the guidelines for Good Epidemiology Practice [2013 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) methodological standards for study protocols].

In addition, according to the Guidelines for good Pharmacoepidemiology Practices (GPP) [International Society for Pharmacoepidemiology, 2015] the archive of the study should be maintained for at least five years after final report or first publication of study results, whichever comes later.

10.2.2 Laws and regulations

Approval for use of encrypted and aggregated data from LPD-Italy is granted by the Italian College of General Practitioners, and from LPD-France – rheumatologists and DA France by the CNIL (French National Commission for Data Protection).

10.2.3 Data protection

None of the extracted datasets will contain data that allow identification of subjects included in the study. Each electronic record will be completely anonymised and will not contain any personally identifying data. QuintilesIMS will ensure a high level of stored data protection according to European regulations.

10.2.4 Insurance

Not applicable.

10.2.5 Secrecy agreement

Not applicable.

10.2.6 Record retention

Not applicable.

10.2.7 Discontinuation of the study

Not applicable.

10.2.8 MAH/MAH representative audits and inspections by competent authorities

Not applicable.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As per the EMA Guideline on Good Pharmacovigilance Practices [Module VI–Management and reporting of adverse reactions to medicinal products (Rev 1) 2014] for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The estimated timelines for the study report, pending approval of the DUS protocol and Educational Material by the respective competent regulatory authorities, are provided below.

The first submitted interim report will analyze data collected within 1 year after starting from effective date of implementation (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

The second interim report will be submitted within 2 years after starting from effective date of implementation (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

The final report will be submitted in Q4 2019. This report will contain all study data of the pre- and post-implementation periods.

The study protocol and final study report will be included in regulatory communications in line with the risk management plan, Periodic Benefit Risk Evaluation Reports (PBRER), and other regulatory milestones and agreed requirements.

Any amendments to the protocol and plans for communication/publication will be made in accordance with procedures outlined in ENCePP guidance.

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the MAH/MAH REPRESENTATIVE conducting the study.

12.2 PUBLICATIONS

As per Module VIII of the 2016 EMA Guideline on Good Pharmacovigilance Practices (GVP) [EMA GPV, Module VIII, 2016], this study is included (ENCEPP/SDPP/11081) in the EU PASS register (Website: encepp.eu/encepp_studies/indexRegister.shtml).

Dissemination and communication of findings from this study will be in accordance with the Guidelines for Good Pharmacoepidemiology Practices [GPP,2008] and the EMA Guideline on Good Pharmacovigilance Practices (GVP), Module VIII [EMA GPV, Module VIII, 2013]. Study results will be published following the guidelines of the International Committee of Medical Journal Editors [ICMJE, 2013].

The MAHs will communicate to the EMA and the competent authorities of the Member States in which the product is authorized, the final manuscript of the article within two weeks after first acceptance for publication.

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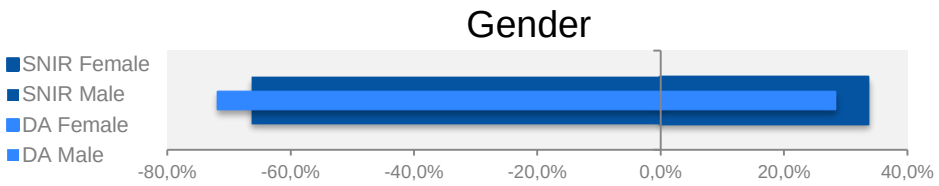
ANNEXES

Annex 1 List of stand-alone documents

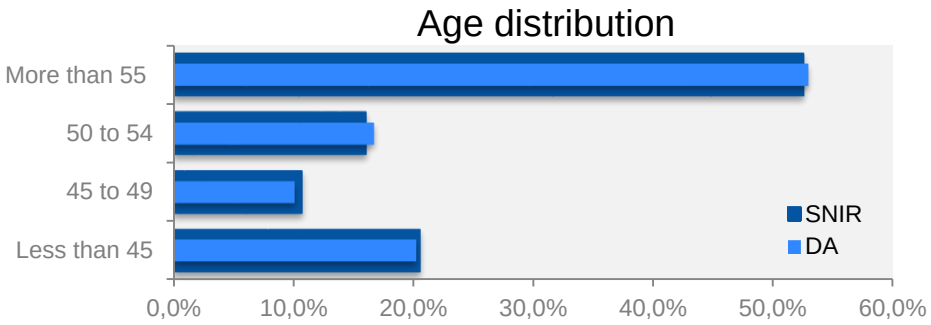
None

Annex 2 Representativity of physician and patient population for GPs database DA-France and LPD- Italy, and for -LPD-France- Rheumatologist database.

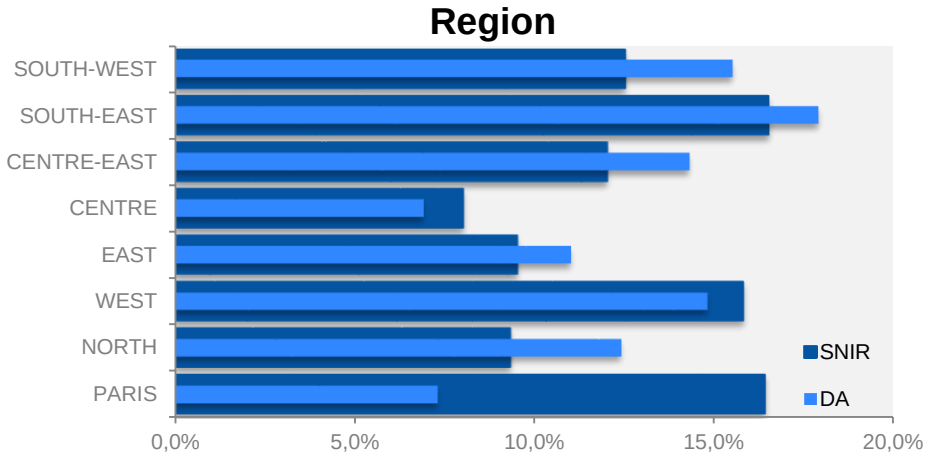
DA-FRANCE: characteristics of physicians and patient population compared to national statistics (SNIR, 2014)



	DA	SNIR*
Female	28.3%	33.7%
Male	71.7%	66.3%



	DA	SNIR*
More than 55	52.5%	52,9%
50 to 54	16.0%	16.7%
45 to 49	10.7%	10.1%
Less than 45	20.5%	20,2%



	DA	SNIR*
SOUTH-WEST	15.5%	12.5%
SOUTH-EAST	17.9%	16.5%
CENTRE-EAST	14.3%	12.0%
CENTRE	6.9%	8.0%
EAST	11.0%	9.5%
WEST	14.8%	15.8%
NORTH	12.4%	9.3%
PARIS	7,3%	16.4%

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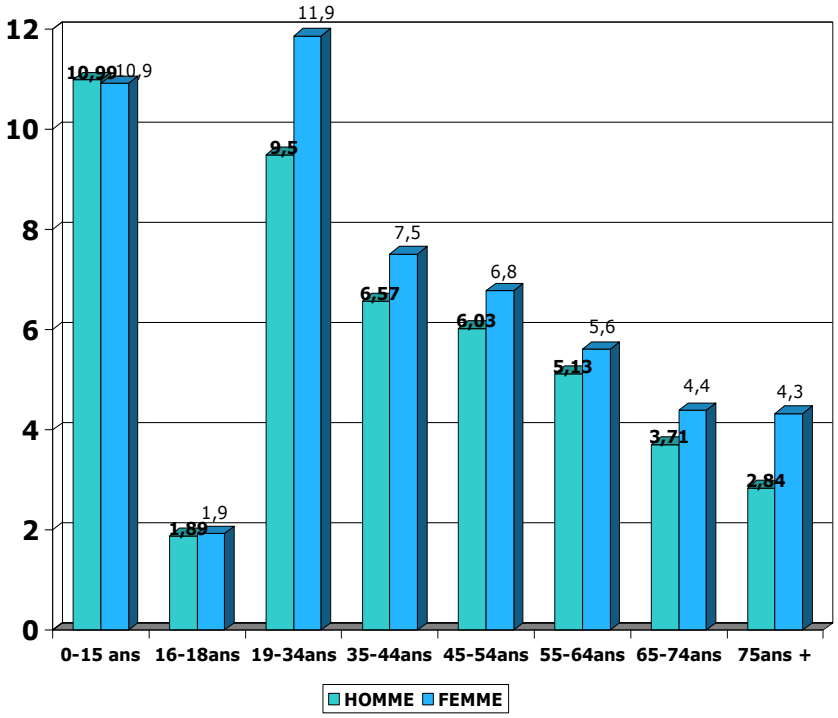
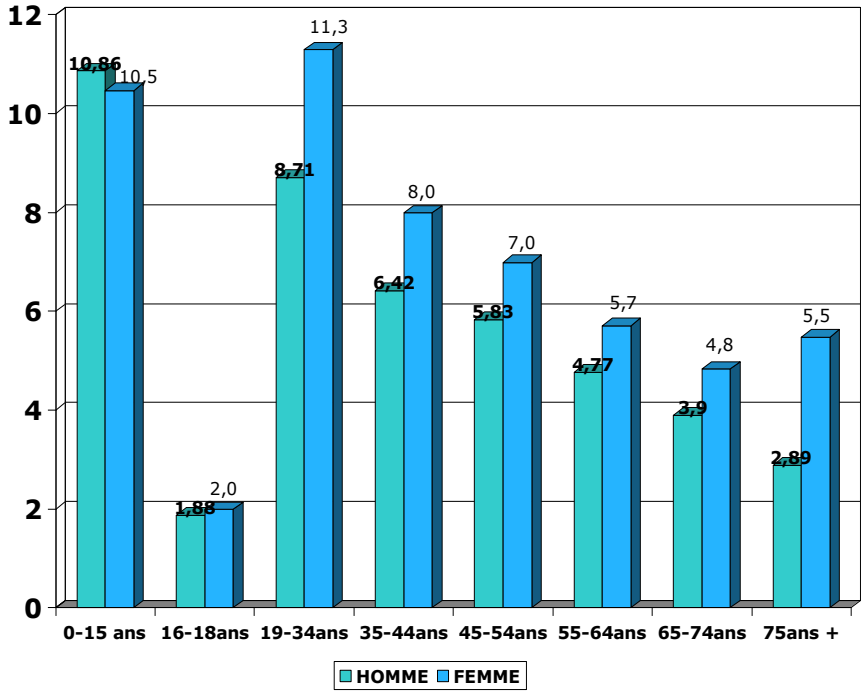
*: Système National Inter-Régimes (SNIR) 2014

DA-FRANCE: Patients distribution by age and gender and comparison to National statistics (EPAS, 2013)

NATIONAL STATISTICS
(Echantillon Permanent Assurés Sociaux)



DA-FRANCE
(Patient with at least 1 Gp visit during the year)



From expert group (Drees, Irdes and Afssaps) : Da France content and methodology assessment

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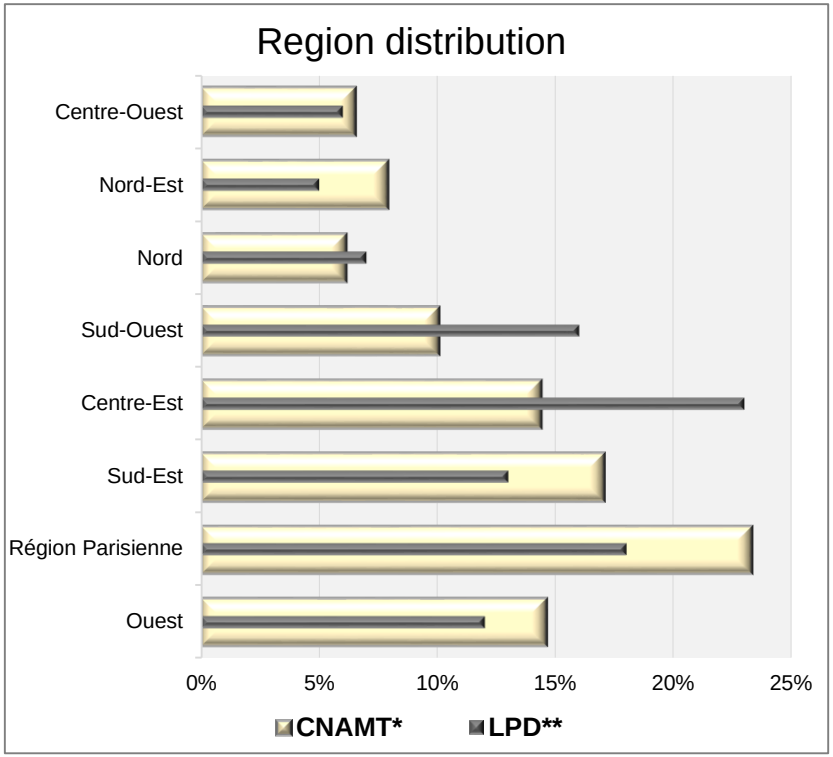
LPD FRANCE-RHEUMATOLOGISTS: Physician demographics and comparison to National Statistics (CNAMTS, 2013)



Gender distribution

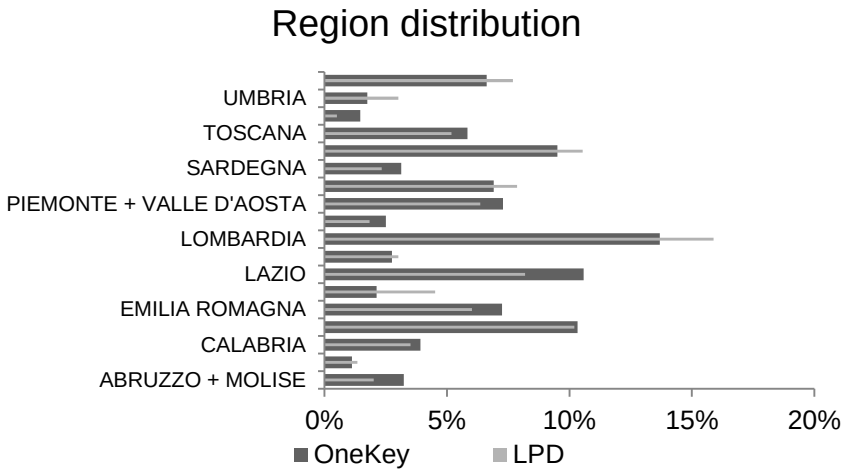
CNAMTS* Male	CNAMTS* Female	LPD Male	LPD Female
64,5%	35,5%	59,0%	41,0%

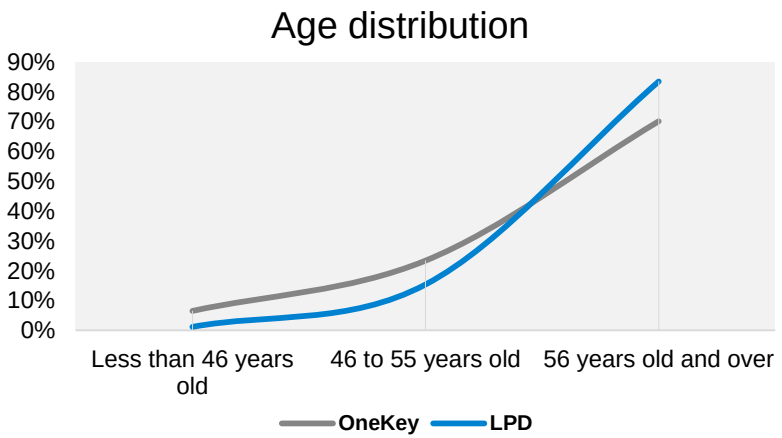
Age distribution

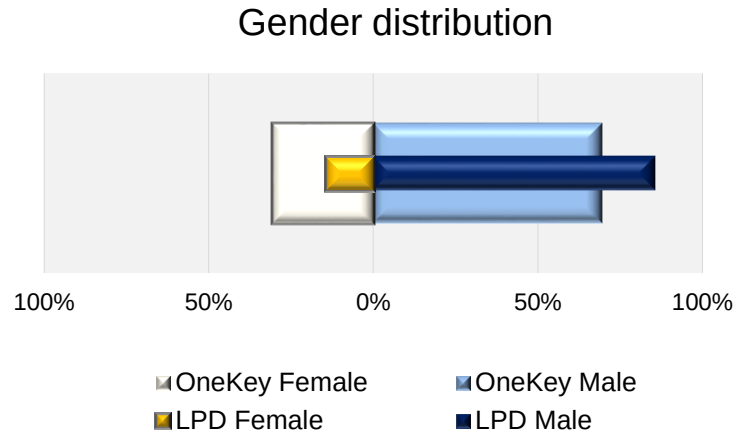
Physician age	CNAMT*	LPD**
Less than 39 years old	6,0%	1,0%
40 to 44 years old	6,5%	8,0%
45 to 49 years old	11,7%	14,0%
50 to 59 years old	41,4%	46,0%
60 years old and over	34,5%	31,0%

***: CNAMTS, French National Social Security, available at: http://www.ameli.fr/l-assurance-maladie/statistiques-et-publication**

LPD-ITALY: Physician demographics and comparison to National Onekey Physisican Register (2013)







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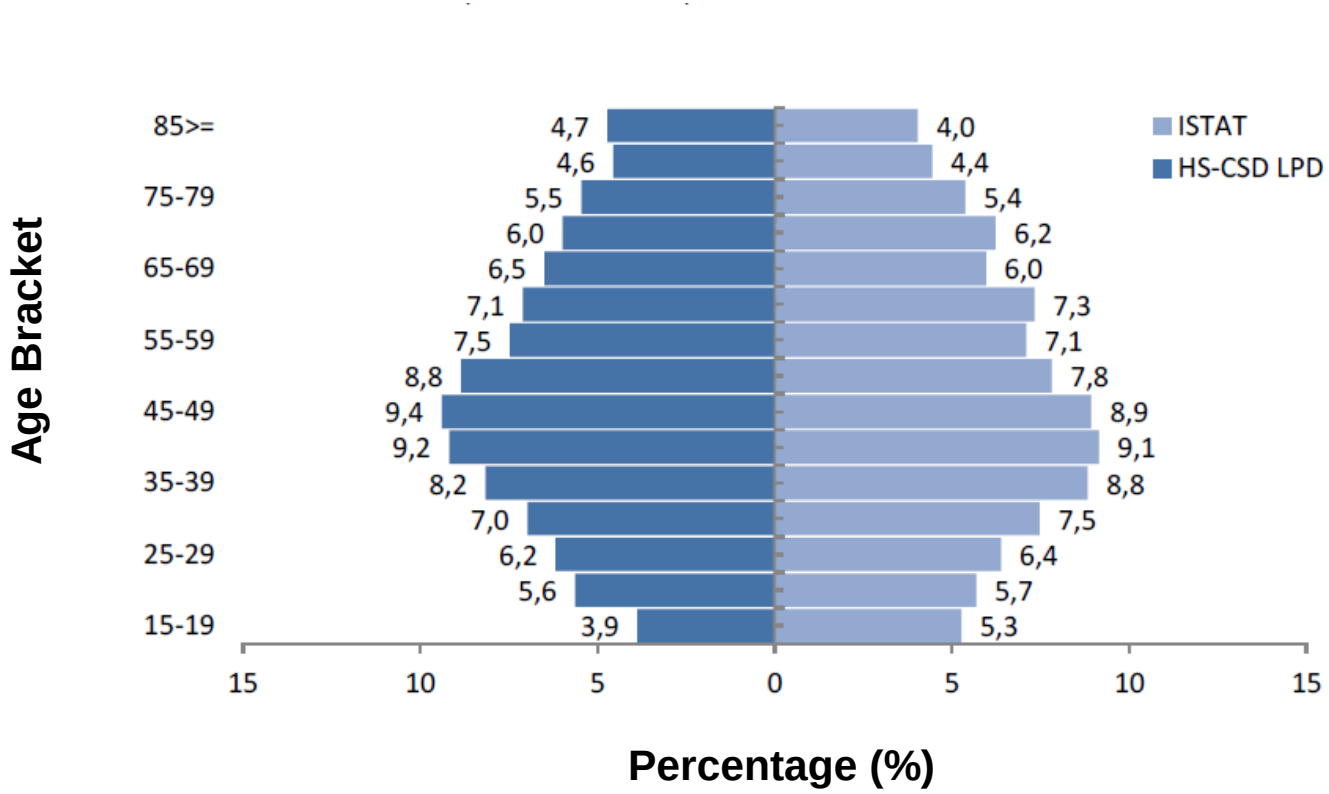
LPD-ITALY: Comparison of age distribution in the Italian-LPD and national statistics (ISTAT*) (2013)



*: Italian National Institute of Statistics

Annex 3 List of Medicinal Products / Products References

Member State (in EEA)	Marketing Authorisation Holder	Invented name Name
France	**Laboratoire Alter** 3, avenue de la Baltique ZA de Courtaboeuf 91140 Villebon Sur Yvette France	THIOCOLCHICOSIDE ALTER
France	**Arrow Generiques** 26, avenue Tony Garnier 69007 Lyon France	THIOCOLCHICOSIDE ARROW
France	**Biogaran** 15, boulevard Charles de Gaulle 92700 Colombes France	THIOCOLCHICOSIDE ALMUS
France	**Biogaran** 15, boulevard Charles de Gaulle 92700 Colombes France	THIOCOLCHICOSIDE BIOGARAN
France	**Cristers SAS** 22 quai Gallieni 92150 Suresnes France	THIOCOLCHICOSIDE CRISTERS
France	**DAIICHI SANKYO France SAS** Immeuble le Corosa 1, rue Eugene et Armand Peugeot 92508 Rueil Malmaison France	MIOREL
France	**Eg Labo - Laboratoires Eurogenerics** "Le Quintet" - bâtiment A 12, rue Danjou 92517 Boulogne Billancourt Cedex France	THIOCOLCHICOSIDE EG

France	**Mylan SAS** 117, allée des Parcs 69800 Saint-Priest France	THIOCOLCHICOSIDE MYLAN
France	**Sandoz** 49, avenue Georges Pompidou 92300 Levallois-Perret France	THIOCOLCHICOSIDE SANDOZ
France	**Sanofi Aventis France** 1-13, boulevard Romain Rolland 75014 Paris France	THIOCOLCHICOSIDE ZENTIVA
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	TIOCOLCHICOSIDE SANDOZ
Italy	**I.B.N. Savio S.r.l**., Via del Mare, 36, 00071 Pomezia (RM) Italy	TIOSIDE
Italy	**Sanofi S.p.A. / Zentiva Italia Srl** Viale Luigi Bodio, 37/B 20158 Milan Italy	MUSCORIL TIOCOLCHICOSIDE ZENTIVA
Italy	**ACRAF S.p.A.** Viale Amelia, 70 -00181 Roma, Italy	TIOCOLCHICOSIDE ANGELINI
Italy	**DOC Generici S.R.L.** Via Turati, 40 20121 Milan Italy	TIOCOLCHICOSIDE DOC Generici

Italy	**Dompe' Farmaceutici S.P.A.** Via Campo di Pile S.N.C. 67100 L'Aquila Italy Operative office: Via Santa Lucia 6 20122 Milan Italy Marketing authorization holder transfer to Dompé farmaceutici S.p.A. ongoing.	MIOTENS
Italy	**EG S.P.A.** Via Pavia, 6 20136 Milano Italy	TIOCOLCHICOSIDE EG
Italy	**Epifarma S.R.L.** Via San Rocco, 6 85033Episcopia (Potenza) Italy	MUSCOFLEX
Italy	**Laboratorio Farmaceutico C.T.** S.R.L. Strada Solaro 75/77 18038 Sanremo (IM) Italy	SCIOMIR
Italy	**MDM S.P.A.** Viale Papiniano, 22/B 20123 Milan Italy	STRIALISIN
Italy	**S.F. Group S.R.L.** Via Beniamino Segre, 59 00134 – Roma Italy	DECONTRIL TERASIDE
Italy	**SPA - Società Prodotti Antibiotici S.p.A.** Via Biella, 8 20143 Milano Italy	MIOREXIL
Italy	**Union Health S.R.L.** Via Adige, 5 66020 San Giovanni Teatino (Chieti) Italy	TIOCOLCHICOSIDE UNION HEALTH

Annex 4 SmPC / DHPC

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 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 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.

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 <u>eliminato e sostituito</u> 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.

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

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.

Annex 5 ENCePP checklist for study protocol

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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: Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study

Study reference number:
EUPAS11081

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	17
1.1.2 End of data collection[2]	☒	☐	☐	17
1.1.3 Study progress report(s)	☒	☐	☐	17
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	3
1.1.6 Final report of study results.	☒	☐	☐	17

[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.

Comments:

The study will cover 3 years starting from effective implementation of minimization measures

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	18, 19
	2.1.2 The objective(s) of the study?	☒	☐	☐	12, 20
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12, 21
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a drug utilization study focused on potential off-label use; therefore, formal hypothesis testing is not applicable.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	21, 22
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	21
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	42

Comments:

This is a cross-sectional drug utilisation study; therefore, no endpoint will be measured. Also, as a descriptive cross-sectional study, we will not measure any effects.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	21, 22
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	12, 21
	4.2.2 Age and sex?	☒	☐	☐	22

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin?	☒	☐	☐	21
4.2.4 Disease/indication?	☒	☐	☐	22
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	22

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	23
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

This is a cross-sectional drug utilisation study. Users of systemic TCC will be described at the time of TCC prescription; therefore, 5.3 to 5.4 are not applicable.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☒	☐	☐	38
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	38
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	38
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	22, 29-31
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates?	☒	☐	☐	22, 29-31
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	22, 26-31
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	24, 26-31
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	25-28
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☒	☐	☐	25-28

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Endpoint do not apply

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☐	☐	☒	
10.2 Are descriptive analyses included?	☒	☐	☐	36-39
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	36-39
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	32

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	34, 37
11.2 Are methods of quality assurance described?	☒	☐	☐	37
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	38-39
12.1.2 Information bias?	☒	☐	☐	38-39
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	33

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	40
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	40

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	15-16

Comments:

Deviation is not applicable in this protocol.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	43
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	43

Comments:

Name of the main author of the protocol: Sophie L. Jouaville

Date: 02 / March /2017

Signature: _____

Annex 6 Bibliography

Drug Saf (2013) 36:13–23
DOI 10.1007/s40264-012-0002-x

SHORT COMMUNICATION

A Reference Standard for Evaluation of Methods for Drug Safety Signal Detection Using Electronic Healthcare Record Databases

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Published online: 23 November 2012

Abstract

Background The growing interest in using electronic healthcare record (EHR) databases for drug safety surveillance has spurred development of new methodologies for signal detection. Although several drugs have been withdrawn postmarketing by regulatory authorities after scientific evaluation of harms and benefits, there is no definitive list of confirmed signals (i.e. list of all known adverse reactions and which drugs can cause them). As there is no true gold standard, prospective evaluation of signal detection methods remains a challenge.

Objective Within the context of methods development and evaluation in the EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge), we propose a surrogate reference standard of drug-adverse event associations based on existing scientific literature and expert opinion.

Methods The reference standard was constructed for ten top-ranked events judged as important in pharmacovigilance. A stepwise approach was employed to identify which, among a list of drug-event associations, are well recognized (known positive associations) or highly unlikely ('negative controls') based on MEDLINE-indexed publications, drug product labels, spontaneous reports made to the WHO's pharmacovigilance database, and expert opinion. Only drugs with adequate exposure in the

On behalf of the EU-ADR Consortium.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-012-0002-x) contains supplementary material, which is available to authorized users.

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EU-ADR database network (comprising ≈60 million person-years of healthcare data) to allow detection of an association were considered. Manual verification of positive associations and negative controls was independently performed by two experts proficient in clinical medicine, pharmacoepidemiology and pharmacovigilance. A third expert adjudicated equivocal cases and arbitrated any disagreement between evaluators.

Results Overall, 94 drug-event associations comprised the reference standard, which included 44 positive associations and 50 negative controls for the ten events of interest: bullous eruptions; acute renal failure; anaphylactic shock; acute myocardial infarction; rhabdomyolysis; aplastic anaemia/pancytopenia; neutropenia/agranulocytosis; cardiac valve fibrosis; acute liver injury; and upper gastrointestinal bleeding. For cardiac valve fibrosis, there was no drug with adequate exposure in the database network that satisfied the criteria for a positive association.

Conclusion A strategy for the construction of a reference standard to evaluate signal detection methods that use EHR has been proposed. The resulting reference standard is by no means definitive, however, and should be seen as dynamic. As knowledge on drug safety evolves over time and new issues in drug safety arise, this reference standard can be re-evaluated.

1 Background

The growing interest in the utility of electronic healthcare records (EHRs) for drug safety surveillance has spurred the development of new methodologies for quantitative and automated signal detection. Timely detection of safety signals remains a challenge because no single technique ensures identification of *all* drug-related adverse events, whether signal detection is done using spontaneous reports [1] or using healthcare records [2]. Generation of false alarms similarly constitutes a public health hazard, not only overwhelming regulatory agencies and diverting already scarce resources, but also triggering unwarranted warnings or even drug market withdrawals [3]. Thus, proper evaluation of signal detection methodologies calls for the creation of a reference standard, the purpose of which is to better define the predictive value of these new techniques, as well as their added value to the current pharmacovigilance armamentarium.

2 Signal Detection in the Context of Pharmacovigilance

The WHO has defined 'signal' as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented" [4]. An updated and more encompassing definition has been proposed recently based on a systematic review of how the term is being applied in current pharmacovigilance: a signal represents information that arises from one or multiple sources which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, and is judged to be of sufficient likelihood to justify verificatory and remedial actions [5]. Although a 'gold standard' of confirmed signals, i.e. *causal* drug-adverse event associations, does not exist, a reference standard of recognized associations based on existing published scientific literature, regulatory actions (e.g. labelling changes or withdrawal of marketing authorization), as well as expert opinion, may serve as a suitable surrogate. In this study we describe a reference standard that was put together in the context of methods development within the EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge'; http://www.euadr-project.org), which aims to exploit information from various EHR databases in Europe to produce a computerized integrated system for the early detection of drug safety signals [6]. This reference standard was developed for the primary purpose of evaluating performance of methods for signal detection using EHR.

3 Methodology

The EU-ADR network currently comprises anonymous healthcare data from eight established European databases located in four countries (Denmark, Italy, The Netherlands and the UK) [7]. Clinical and drug dispensing/prescription data used for this paper represent data from 19,647,445 individuals with 59,929,690 person-years (PYs) of follow-up.

4 Adverse Events

In the EU-ADR Project we have chosen an event-based approach to active drug safety surveillance, focusing on events considered to be important from a pharmacovigilance and public health perspective. For the construction of this reference standard, we considered the following top ten events which have been selected from a list of 23 events ranked on the basis of importance in pharmacovigilance using predefined criteria: (i) bullous eruptions; (ii) acute renal failure; (iii) anaphylactic shock; (iv) acute myocardial infarction; (v) rhabdomyolysis; (vi) aplastic anaemia/pancytopenia; (vii) neutropenia/agranulocytosis; (viii) cardiac valve fibrosis; (ix) acute liver injury; and (x) upper gastrointestinal bleeding [8].

5 Drug Selection

The procedure employed in the construction of the reference standard is outlined in Fig. 1. It was first necessary to ensure that the drug-event associations to be included in the reference standard are identifiable in clinical practice and could be investigated in the EU-ADR network. That is, there should be adequate exposure to the drugs to permit detection of an association with the adverse event of interest, if present. In another publication we described the sample size calculations used to derive the total amount of PYs of drug exposure required to detect an association between a drug and a particular event over varying magnitudes of relative risk (RR), using one-sided significance level $\alpha = 0.05$ and power of 80 %, given pooled population-based incidence rates (IR) estimated directly within the EU-ADR network [2]. For this reference standard we employed in the calculations an RR of at least two for all events except for rhabdomyolysis, bullous eruptions and anaphylactic shock, where we used an RR of at least 4. The latter was done to account for the very low background IR of these events in the population (2.5/100,000 PYs for rhabdomyolysis, 5.7/100,000 PYs for anaphylactic shock and 5.9/100,000 PYs for bullous eruptions). A series of steps was subsequently employed to select the positive drug-event associations and 'negative controls' among those potentially eligible (i.e. drugs with an adequate amount of exposure to detect the association of interest) [see Fig. 1].

6 Information Retrieval from Published Literature

To streamline the scientific literature search, we utilized a tool developed within the EU-ADR Project that automatically searches MEDLINE-indexed publications concerning adverse drug reactions (ADRs) [9]. A subset of MEDLINE was downloaded (via PubMed) and imported into a database including all the citations from December 1952 to February 2010 with the 'adverse effects' Medical Subject Heading (MeSH) subheading. For each citation, the PubMed identification (PMID), MeSH descriptors, major/minor subheadings, substances, date of creation of the citation, as well as publication type, were obtained. Co-occurrence of the drug (from 'substances' OR 'MeSH heading' fields) and the event (under the subheading 'adverse effects') in a citation were noted. Drug codes in the WHO Anatomical Therapeutic Chemical (ATC) classification were first mapped to MeSH headings or supplementary concept records using standardized concept unique identifiers from the Unified Medical Language System (UMLS) [10]. Drugs from the 'substances' field were taken into account only if their pharmacological action was qualified by the subheading 'adverse effects'. Taking the pharmacological action as an additional element for consideration was an attempt to establish a link between the adverse event of interest and the drug in the context of drug safety and not just a co-occurrence in a MEDLINE citation. This becomes particularly important when more than one drug is mentioned in the citation [10].

7 Selection of Known Positive Drug-Event Associations

The drug-event associations were ranked according to the number of MEDLINE citations with co-occurrence of the drug and the adverse event of interest. For the pool of positive drug-event associations, we considered those with the highest number of citations. This meant that more published evidence was available on these associations. Citations may refer to case reports, observational studies, clinical trials, reviews or meta-analyses. The type of publication was taken into account in the evaluation of the evidence regarding each drug-adverse event association, as subsequently described. Supplementary information was obtained from the Summary of Product Characteristics or product labels [11–16]. The aim was to select five drugs that are positively associated with each event of interest. Whenever possible, drugs belonging to different classes were included in the pool. However, the need for minimizing ambiguity (i.e. by selecting strong and well substantiated drug-adverse event associations) took precedence over the need for diversity in terms of drug class. Except for fixed-dose combinations, drug preparations with more than one active substance were excluded from the pool.

8 Selection of 'Negative Controls'

A drug-event association was considered for the pool of 'negative controls' if there were no MEDLINE citations with co-occurrence of the drug and the event of interest and if there was no explicit mention of such adverse event in the drug product label. The pool of 'negative controls' was further evaluated using the WHO spontaneous reporting database (VigiBase™) to exclude associations flagged as a potential signal using standard data mining methodology. The list of potential signals from VigiBase™ (including data up to the fourth quarter of 2010) was generated using the Oracle Health Sciences Empirica™ Signal tool (courtesy of Astellas Pharmaceuticals, Deerfield, IL, USA). Bayesian disproportionality analysis was performed using preferred terms mapped to the events of interest [17]. A value greater than 2 for the lower bound of the 90 % confidence interval (CI) of the Empirical Bayes Geometric Mean (EB_{05}) and the presence of at least one report were used as the criteria for flagging a signal [18]. The aim was to likewise obtain five drug-event associations as 'negative controls' per event of interest.

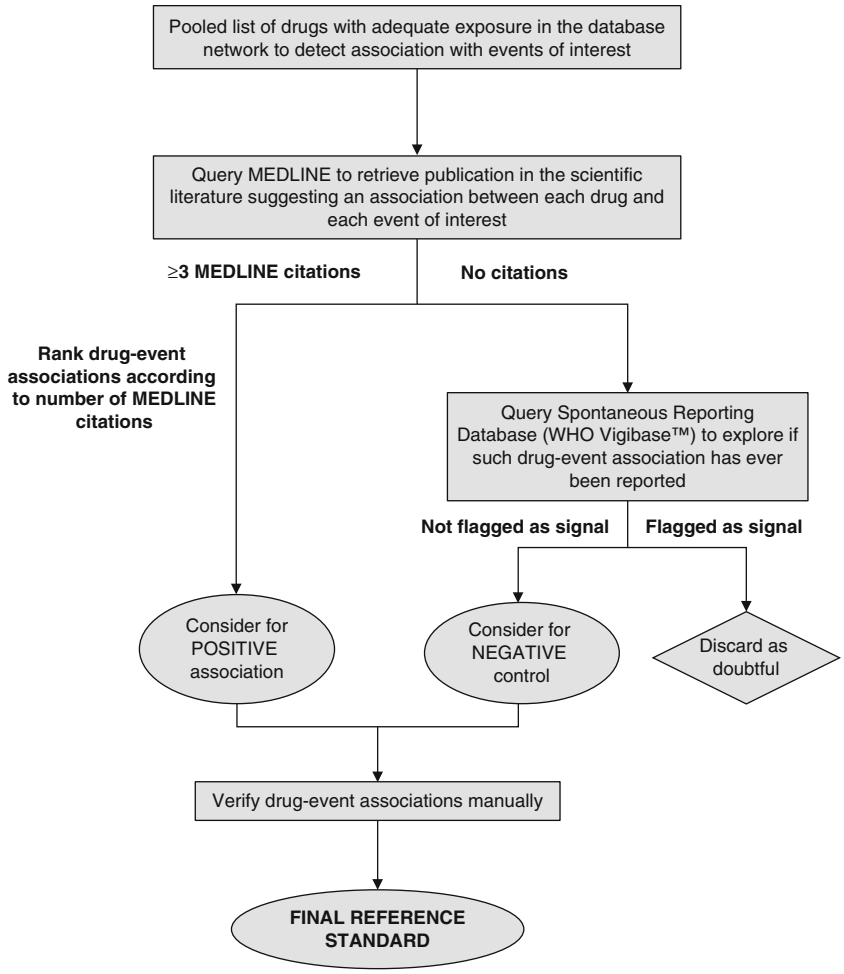

Fig. 1 Flowchart showing the process of the construction of the reference standard

9 Evaluation of the Evidence from Literature

Table 1 shows the scheme that was used as a guide to evaluate evidence from the literature. Manual verification of the positive associations and 'negative controls' was conducted by two physicians with proficiency in clinical medicine, epidemiology and pharmacovigilance. A third expert arbitrated any disagreement between evaluators. The following indices of agreement between evaluators were assessed: (i) proportion of overall agreement; (ii) proportion of specific agreement; and (iii) kappa statistic, κ, for chance-corrected agreement. The earliest date of MEDLINE citation was also noted for each drug-event association.

10 Results

The amount of drug exposure required to detect a potential signal in the EU-ADR database network for each of the events of interest is shown in Table 2. Overall, there were 893 drugs (i.e. unique ATC codes, 5th level chemical substance) with enough exposure to permit detection of an association with at least one of the ten events of interest. Out of the 893 drugs, the following are the number (i.e. count) of drugs for which there were at least three MEDLINE citations with co-occurrence of the drug and the corresponding event: acute liver injury, 21; acute myocardial infarction, 52; acute renal failure, 51; anaphylactic shock, 26; bullous eruptions, 47; cardiac valve fibrosis, 2; neutropenia/agranulocytosis, 30; aplastic anaemia/pancytopenia, 21; rhabdomyolysis, 8; upper gastrointestinal bleeding, 54. Close to 1,200 abstracts and, when necessary, the full-text journal articles pertaining to all ten events were reviewed to arrive at a shortlist of potential positive associations and 'negative controls'. Specific citations in drug product labels concerning 'undesirable effects', 'warnings', and 'adverse reactions' were used to further restrict the shortlist of associations. Table 3 shows how the manual evaluation of a positive association for acute liver injury with valproic acid and for upper gastrointestinal bleeding with indometacin were done. The complete evaluation for all the positive drug-adverse event associations of interest can be found in Appendix 1 (Online Resource 1).

Table 1 Levels of evidence used in the evaluation of drug safety information from the literature

Level of evidence	Description
I	Evidence from at least one (properly designed) randomized controlled trial or meta-analysis
II	Evidence from at least one observational study (e.g. cohort, case-control, case-crossover, self-controlled case series) OR from at least three published case reports from different sources and concerning different patients
III	Evidence from not more than two published case reports OR from unpublished reports in pharmacovigilance databases and no further substantiation in the literature
IV	Included in drug label (SPC) but no case reports or published studies
V	No evidence from published literature or from WHO spontaneous reporting database and not mentioned in the SPC

Recommendations: Levels I and II → positive association; Levels III and IV → cannot be determined → disregard as doubtful; Level V → 'negative control'

SPC summary of product characteristics

Table 2 Amount of drug exposure required to detect a potential signal in the EU-ADR database network for the events of interest

Event	Required exposure (person-years)	No. of drugs with sufficient exposure to detect association and with ≥3 MEDLINE citations
Acute liver injury	32,769	21
Acute myocardial infarction	4,706	52
Acute renal failure	30,397	51
Anaphylactic shock	21,733	26
Bullous eruptions	20,823	47
Cardiac valve fibrosis	13,604	2
Neutropenia/agranulocytosis	82,697	30
Aplastic anaemia/ pancytopenia	77,192	21
Rhabdomyolysis	49,593	8
Upper gastrointestinal bleeding	12,028	54

The final reference standard consisted of 94 drug-event associations, which included 44 positive associations and 50 'negative controls' related to the ten events of interest. Table 4 lists the positive associations, including the corresponding level of evidence. The majority of positive associations were based on Level II evidence. The associations for which there was Level I evidence included that of NSAIDs and of heparin with upper gastrointestinal bleeding, the association of the statins with rhabdomyolysis, and the association of coxibs and rosiglitazone with acute myocardial infarction. All 'negative controls', by definition, have Level V evidence and are listed in Table 5. Both positive and 'negative control' associations comprised 68 unique drugs (i.e. ATC 5th level) belonging to 42 different pharmacological subgroups (i.e. ATC 3rd level). Only four drugs having sufficient exposure in the database network satisfied the criteria for a positive association with rhabdomyolysis, all of them being HMG-CoA reductase inhibitors (statins). Fibrates, as a class (ATC 4th level, chemical subgroup), comprised enough exposure to detect an association with rhabdomyolysis, but the individual drugs did not. For cardiac valve fibrosis, no drug with adequate exposure met the criteria for a positive association after review of the literature.

11 Inter-Evaluator Agreement

The indices for agreement were computed across all drug-event pairs evaluated (179 drug-event pairs), including those that eventually did not get included in the final reference standard. The proportion of overall agreement (the proportion of cases for which both evaluators agreed across all evaluation categories) was 0.93 (95 % CI 0.89, 0.97). The proportions of specific agreement were as follows: (i) 'positive' agreement 0.96 (95 % CI 0.93, 0.98); and (ii) 'negative' agreement 0.90 (95 % CI 0.89, 0.90). There were three instances where one evaluator considered a drug-event association 'undetermined' while the other considered it a positive association (paracetamol [acetaminophen]-anaphylactic shock, bromocriptine-acute myocardial infarction and aspirin [acetylsalicylic acid]-bullous eruptions). Of these three instances only one was eventually included in the reference standard after arbitration (paracetamol-anaphylactic shock). There was a single case where one evaluator marked the association 'undetermined' while the other marked it as 'negative control' (prednisone-neutropenia/ agranulocytosis). Arbitration was done by a third expert. There was no disagreement between evaluators in the final list of 'negative control' associations. The chance-corrected agreement kappa coefficient, κ, was 0.83 (unweighted, 95 % CI 0.74, 0.92).

Table 3 Example summary of manual evaluation of positive drug-event associations for valproic acid and indometacin

ATC code	Drug name	Event type	No. of MEDLINE notices	Labelled as AE in SPC [Yes/No]? (Source and label section)
N03AG01	Valproic acid	Acute liver injury	*Total no. of citations = 31* Review[a] = 1 Clinical trial = 1 (RCT) Epidemiological study = 1 (cohort study) Case reports[b] = 28 (1 citation involving 3 cases, 1 citation involving 5 cases, 1 citation reviewing 31 cases, 2 other citations with literature review)	Yes DailyMed[c] (boxed warning, adverse reactions) eMC[d] (special warnings and precautions for use, undesirable effects) Micromedex[e] (adverse reactions)
M01AB01	Indometacin	Upper gastrointestinal bleeding	*Total no. of citations = 45* Review = 13 Clinical trial = 16 (9 RCTs) Epidemiological study = 5 (1 case control and 4 cohort studies) Case reports = 11	Yes eMC[d] (undesirable effects) Micromedex (adverse reactions)

AE adverse event, *ATC* Anatomical Therapeutic Chemical, *eMC* electronic medicines compendium, *RCT* randomized controlled trial, *SPC* summary of product characteristics

[a] Review refers to both systematic and narrative reviews

[b] Case reports involve only one case pertinent to the drug of interest, unless specified

[c] Website for drugs currently marketed and approved by the US FDA (http://dailymed.nlm.nih.gov/)

[d] For drugs licensed in the UK (http://www.medicines.org.uk)

[e] The Micromedex family of international databases provides full-text drug and substance information (http://www.thomsonhc.com/micromedex2/)

Table 4 Positive drug-event associations

Event	Positive associations		
	ATC code	Name	Level of evidence
Acute liver injury	N03AF01	Carbamazepine	II
	N03AG01	Valproic acid	II
	M01AX17	Nimesulide	II
	J01CR02	Amoxicillin and clavulanic acid	II
	A07EC01	Sulfasalazine	II
Acute myocardial infarction	M01AH02	Rofecoxib	I
	A10BG02	Rosiglitazone	I
	G03AA07	Levonorgestrel and estrogen	II
	N02CC01	Sumatriptan	II
	M01AH03	Valdecoxib	I
Acute renal failure	C09AA01	Captopril	II
	M01AE01	Ibuprofen	II
	N02BE01	Paracetamol (acetaminophen)	II
	J01MA02	Ciprofloxacin	II
	N05AN01	Lithium	II
Anaphylactic shock	B01AC06	Aspirin (acetylsalicylic acid)	II
	N02BE01	Paracetamol (acetaminophen)	II
	J01CA04	Amoxicillin	II
	J01MA02	Ciprofloxacin	II
	M01AB05	Diclofenac	II
Bullous eruptions	N03AF01	Carbamazepine	II
	J01EE01	Sulfamethoxazole and trimethoprim	II
	N03AX09	Lamotrigine	II
	M04AA01	Allopurinol	II
	C03CA01	Furosemide	II
Cardiac valve fibrosis	No drug with sufficient exposure that satisfies criteria for True Positive		
Neutropenia/agranulocytosis	H03BB02	Thiamazole	II
	B01AC05	Ticlopidine	II
	C09AA01	Captopril	II
	N03AF01	Carbamazepine	II
	N03AG01	Valproic acid	II
Aplastic anaemia/pancytopenia	B01AC05	Ticlopidine	II
	N03AF01	Carbamazepine	II
	H03BB02	Thiamazole	II
	M04AA01	Allopurinol	II
	C09AA01	Captopril	II
Rhabdomyolysis	C10AA07	Rosuvastatin	I
	C10AA05	Atorvastatin	I
	C10AA03	Pravastatin	I
	C10AA01	Simvastatin	I
Upper gastrointestinal bleeding	N02BA01/B01AC06	Aspirin	I
	M01AB01	Indometacin	I
	B01AB01	Heparin	I
	H02AB06	Prednisolone	II
	M01AE01	Ibuprofen	I

ATC Anatomical Therapeutic Chemical

Table 5 'Negative control' associations

Event	ATC code	Name
Acute liver injury	R03AC13	Formoterol
	S01ED05	Carteolol
	G04CA03	Terazosin
	N04BA02	Levodopa and decarboxylase inhibitor
	C01DA02	Glyceryl trinitrate
Acute myocardial infarction	A10AD01	Insulin (human)
	B03AA07	Ferrous sulfate
	J01CR02	Amoxicillin and clavulanic acid
	J05AB11	Valaciclovir
	C10AB04	Gemfibrozil
Acute renal failure	R01AD09	Mometasone
	H03AA01	Levothyroxine sodium
	R06AX26	Fexofenadine
	N04BA02	Levodopa and decarboxylase inhibitor
	B03AA07	Ferrous sulfate
Anaphylactic shock	N06AX11	Mirtazapine
	H03AA01	Levothyroxine sodium
	C02AC01	Clonidine
	C02CA04	Doxazosin
	N05BA04	Oxazepam
Bullous eruptions	C01BC03	Propafenone
	C07AB03	Atenolol
	R03BB01	Ipratropium bromide
	R03BB04	Tiotropium bromide
	C08CA02	Felodipine
Cardiac valve fibrosis	N06AB08	Fluvoxamine
	L04AX03	Methotrexate
	C09CA04	Irbesartan
	C03CA01	Furosemide
	G03CA03	Estradiol
Neutropenia/agranulocytosis	C07AA07	Sotalol
	H03AA01	Levothyroxine sodium
	C10AA05	Atorvastatin
	C01DA14	Isosorbide mononitrate
	G04CA02	Tamsulosin
Aplastic anaemia/pancytopenia	C09CA04	Irbesartan
	C10AA04	Fluvastatin
	S01EE01	Latanoprost
	S01ED01	Timolol
	R06AX27	Desloratadine
Rhabdomyolysis	G03CA03	Estradiol
	C02CA04	Doxazosin
	A10BB12	Glimepiride
	S01ED01	Timolol
	C01DA02	Glyceryl trinitrate
Upper gastrointestinal bleeding	R06AX26	Fexofenadine
	C10AA01	Simvastatin
	S01EC03	Dorzolamide
	L02AE03	Goserelin
	N05CF01	Zopiclone

ATC Anatomical Therapeutic Chemical

12 Discussion

In this study we present a novel approach to identify a surrogate 'gold standard' for drug safety signal detection using a systematic and rigorous methodology, applied across various data sources and which could be extended to examine other drug-event associations. We put together a list of drug-adverse event associations known to be true and drug-event associations considered to be unlikely based on current published scientific literature, drug product labels, spontaneous ADR reports and expert opinion. Although the rationale for creating this reference standard is to have one single index against which signal detection methods (as applied to EHR data) can be tested, this reference standard can be re-evaluated and adapted to different settings as needed.

In evaluating the evidence from the literature we only considered associations that were reported with use of the drug in therapeutic doses, which is consistent with the definition of an ADR [19]. For aspirin, citations referring to both cardiovascular prophylactic (low dose) and analgesic doses were considered. We considered, aside from case reports that described the clinical characteristics leading to suspicion of an ADR, publications that proposed (or elucidated) biological mechanisms for the associations. Such publications came in the form of both narrative reviews and systematic reviews. We likewise considered associations that were described in the context of drug-drug interactions (e.g. aplastic anaemia resulting from the synergistic interaction between azathioprine and allopurinol) [20]. For the event acute renal failure, we disregarded associations that arose from rhabdomyolysis leading to renal failure, but considered the reverse situation (i.e. associations for rhabdomyolysis that resulted in renal failure). While randomized controlled trials (RCTS) and meta-analyses are considered supreme with respect to level of evidence, this is more true for evidence regarding efficacy, not so much safety, of interventions [21–24]. This is apparent in Table 4, where most of the evidence pertaining to the positive associations came from observational studies and case reports (or reviews). The associations with Level I evidence are those that are well known (e.g. association of the NSAIDs and heparin with upper gastrointestinal bleeding) or well investigated, either because of controversy or public health impact (e.g. the association of the statins with rhabdomyolysis, and the association of coxibs and rosiglitazone with acute myocardial infarction). Interestingly, but perhaps not surprisingly, the most widely-investigated association was that between aspirin and upper gastrointestinal bleeding (259 MEDLINE citations overall, see Appendix [Online Resource 1]). Most of the publications related to this association, including clinical trials, described the drug as a comparator to other drugs that are presumed (and proven) to confer a lower risk of the event.

There have been previous attempts to develop a reference standard with which data mining methods for safety signal detection can be evaluated, 'rules of evidence' being devised ad hoc [25–27]. In the creation of this reference standard we employed a systematic approach incorporating various sources of drug safety information, the process designed to be transparent and reproducible, thus also making it easier to update. Different sources have varying comprehensiveness and accuracy with regards to documenting drug-adverse event associations. Because RCTs may be restricted to specific populations and lack statistical power to detect rare events, they must be supplemented by non-experimental studies and other types of evidence, including case reports [21–24]. Rare or idiosyncratic events (e.g. bullous eruption such as Stevens-Johnson syndrome) and events occurring after chronic exposure (e.g. cardiac valvulopathy) are unlikely to be identified in clinical trials, but rather in case reports or observational studies.

There was only one disagreement between evaluators in the final list of positive associations ('undetermined' vs 'positive' for the association paracetamol-anaphylactic shock; arbitration resulted in positive association). There was no disagreement between evaluators in the final list of 'negative control' associations. Although this high overall agreement between evaluators indicates that the resulting reference standard fulfills the pre-determined criteria, as the definitions of positive associations and 'negative controls' are based on existing knowledge at the time of this review, these associations (especially the 'negative controls') may be refuted as new data come along [28]. Hence, this reference standard should be considered dynamic and will need periodic re-evaluation. Adoption of this reference standard for use by other investigators can validate its applicability in other settings and will facilitate its further improvement.

While a reference standard, however rigorously constructed, may be able to permit evaluation and comparison of methods for signal detection, a method shown to successfully detect known drug-adverse events associations is not a guarantee that such method will also be able to detect signals, i.e. new, currently unknown drug-event associations (problem of contemporary comparison) [29].

13 Limitations

Since the selection of drugs for the reference standard was dependent on the presence of adequate exposure to detect an association within the EU-ADR network (i.e. drugs that are more frequently used in the population were more

likely to be chosen), this reference standard may not be as useful for evaluation in situations where the drug use patterns are expected to be different. In particular, the EU-ADR database network is unable to capture information on drugs that are primarily used in hospitals or specialist centres (e.g. anti-cancer drugs), and for this reason such drugs have not been included in the reference standard. This criterion also precluded the inclusion of known associations with drugs that have been withdrawn from the market for a long time before the accrual of healthcare data in the databases. Because of this there was no drug that could be used as a positive reference for the event cardiac valve fibrosis; the use of the appetite suppressants fenfluramine and phentermine, as well as the dopamine agonists pergolide and cabergoline, were inadequately documented or no longer captured in the databases because of the decline in use (or eradication in practice) of these drugs [30]. The choice as to which drug-event pairs can be considered for the positive associations was primarily established on the basis of the number of publications (i.e. number of MEDLINE citations with co-occurrence of the drug and the event of interest). This meant that drugs that have been on the market longer—or were involved in high-profile or controversial issues—had a higher chance of being included in the reference standard.

Finally, the availability of a surrogate 'gold standard' is only one component of the evaluation process for signal detection methodologies [3, 31]. Other issues that need to be considered in performance evaluation of these methods include standardization of event definitions, establishment of reliable and consistent criteria for adjudicating causality and expectedness of adverse events, as well as understanding variations in database content and quality.

14 Conclusions

A unique strategy for the construction of a reference standard to evaluate drug safety signal detection methodologies using EHR has been proposed. This reference standard should be considered dynamic, and as knowledge on drug safety evolves over time and new issues in drug safety arise, this reference standard can be periodically re-evaluated. Our proposed strategy represents a novel contribution to pharmacovigilance, with opportunities for adaptation to evaluate harms and benefits for other suspected ADRs.

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ages ranged from 0.83% to 2% respectively. All-cause healthcare Per Patient Per Year costs were approximately $13,200 in each database. **CONCLUSIONS:** Creation of a database using a CDM approach allows for simultaneous examination of standardized claims across databases, thus broadening the efficiency and generalizability of retrospective claims analyses. The diverseness of comorbidities among HCV patients combined with the evolving treatment landscape makes it an ideal candidate for this type of research.

PRM45

BIG DATA IN EMERGENCY DEPARTMENT CARE DELIVERY: BENEFITS OF RADIO FREQUENCY IDENTIFICATION

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OBJECTIVES: Lack of a coordinated primary care system is forcing individuals to seek emergency departments (EDs) as gateway into the health system. As volumes increase and cases become more complex, combined with inadequate downstream capacity lead to boarding, bottlenecks and wait times. The goal was to review benefits of Radio Frequency identification (RFID) demonstrated in the literature in the ED. **METHODS:** Article searches were conducted and they were categorized based on benefits in three areas: patients, staff, assets. **RESULTS:** Evidence of use of RFID in ED went as far back as 2006 with both domestic and international applications mostly using active technology. Majority of the articles demonstrated reducing wait times in the ED. One of the articles in turn demonstrated impact on patient satisfaction. Reduction in wait times were demonstrated when admitting patients into ICU from the emergency setting. In case of staff, use of RFID demonstrated increased satisfaction in a pediatric emergency setting. Evidence also exists in better tracking of assets and equipment in the ED. Very little evidence of use of RFID in simulation and analytical models exist. Most of the studies were retrospective in nature. Wait times and asset tracking are tangible benefits with direct impact on return-on-investment. **CONCLUSIONS:** RFID has been used is various settings in healthcare and quality benefits have been demonstrated. Lesser evidence of RFID use in the ED exists. RFID benefits have primarily been demonstrated with regard to wait times and asset tracking and management. Patient and staff satisfaction are more intangible benefits. As EDs start to reap benefits with wait times, use in simulation and advanced analytical models could potentially inform workload, team configuration and team dynamics studies. As healthcare moves into the era of big data, live streaming RFID data can be tapped for real-time decision making.

PRM46

WHY PEER-REVIEW JOURNALS REJECT REAL-WORLD AND HEALTH-ECONOMIC PAPERS

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OBJECTIVES: To evaluate the most common reasons provided by peer-reviewed journals to reject manuscripts describing data derived from real-world or health-economic (RW/HE) studies. **METHODS:** Our company project administration records from the last 10 years were reviewed for manuscripts describing HE studies, RW/observational studies (including retrospective database analyses), and patient or disease registries. Reasons for rejection were collected and stratified into "categories". If more than one reason was provided by the journal, then all reasons were counted. Our analysis was based on industry-sponsored manuscripts for which a complete submission history was available. **RESULTS:** Rejection letters were collected for 78 manuscripts. Of these, 12 did not specify a reason for rejection. The remaining records revealed a total of 100 rejection counts. The most common reasons were 'priority rating not high enough' (33%), 'concerns about the methodology' (18%), and 'information not sufficiently novel' (15%). Other reasons for rejection included 'topic not appropriate for the journal' (7%), 'manuscript is biased/conclusions are too strong' (5%), 'industry involvement not sufficiently disclosed' (2%), and referral to a sister journal instead (2%). **CONCLUSIONS:** These common reasons for rejection could provide authors with some guidance on which factors are particularly important to focus on during the development of a RW/HE manuscript to help improve the chances of acceptance by peer-reviewed journals.

PRM47

UTILIZING ELECTRONIC MEDICAL RECORD NETWORKS FOR IDENTIFYING PATIENTS FOR CLINICAL TRIAL RECRUITMENT

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OBJECTIVES: Much of the increase in health-care expenses in the U.S. can be traced to the development of new drug therapies; with the average discovery and development process costing over $1.4 billion per drug. This motivates the need to reduce drug costs through more efficient drug development and testing, specifically, by streamlining clinical trials. The current study aims to implement and evaluate a process, using a data driven approach, to recruit patients for a clinical trial for an asthma treatment. Our hypothesis is that recruitment could be improved and accelerated with the support of an EMR network to identify patients. **METHODS:** All trial protocol eligibility criteria were reviewed in the context of EMR data availability, as well as protocol-specific procedures. We then queried our EMR network to identify sites with high patient concentrations. Four sites were recommended to the team by partners in this network and selected, with one site opting not to participate in the study after being selected. **RESULTS:** EMR queries identified over 300 potentially eligible patients at three different sites. Of identified patients who were contacted, and for whom information was available, 84% responded to outreach efforts, which represents a very substantial increase over the 10% that is typical in the industry. Among respondents, enrollment rates ranged from 14% to 40%. **CONCLUSIONS:** For all participating sites, querying EHR data proved to be an effective means of identifying eligible patients. Furthermore, once candidates were identified, all recruitment efforts could be directly targeted to specific patients as opposed to advertising to a large, undefined population or relying on physician referral. This resulted in improved patient response rates, which could conceivably be improved further with the creation of more targeted recruitment materials developed by patient demographic profiles generated from EMR data.

PRM48

COMPARATIVE LANDSCAPE ASSESSMENT OF US HEALTHCARE DATABASES FOR USE IN HEALTH ECONOMICS MODELING

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OBJECTIVES: Real world evidence (RWE)-based tools are important to fill data gaps and capture real world cost and treatment patterns in economic modeling. The objective of this study was to assess the capabilities of US-based longitudinal, retrospective data assets to inform health economic models in diabetes and oncology. **METHODS:** To illustrate the availability of RWE data for modeling, several IMS data assets were compared in a landscape assessment, including Pharmetrics Plus (PMTX+), Oncology Electronic Medical Record (EMR), Ambulatory EMR, Charge Data Master (CDM), Pharmacy (LRx), Office Based Medical Claims Data (Dx), and Laboratory Data (Labs). Diabetes and oncology were chosen to illustrate the range of needed inputs across commonly modeled diseases. Data availability was assessed in a matrix framework across core categories of model inputs including: treatment patterns, epidemiology, adverse events (AEs), patient health metrics (i.e., BMI), costs, resource use, and disease status. **RESULTS:** For oncology, inputs for treatment patterns (PMTX+, Oncology EMR), epidemiology (PMTX+, Oncology EMR, CDM), AEs (PMTX+, Oncology EMR, CDM), and resource use (PMTX+, Oncology EMR) are available in several data assets but information on patient health metrics and disease status may require leveraging the Oncology EMR database to capture sufficient detail. For diabetes, availability of data for populating models is more robust increasing information on treatment patterns (PMTX+, LRx linked to Dx), epidemiology (PMTX+, Ambulatory EMR, CDM), resource use (PMTX+, Labs, Dx), AEs (PMTX+, Ambulatory EMR, CDM, Dx), and patient health metrics (Ambulatory EMR, CDM). While several databases report cost outcomes, the most relevant costs for modeling are found in PMTX+. **CONCLUSIONS:** Core concepts for economic modeling can be populated with RWE assets in the US though no single database is likely to cover all inputs. The choice of data should be informed by the research question, patient counts and the ability to link databases.

PRM49

VALIDITY AND LIMITATIONS OF THE LONGITUDINAL PATIENT DATABASE FRANCE FOR USE IN PHARMACOEPIDEMIOLOGICAL AND PHARMACOECONOMICS STUDIES

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OBJECTIVES: Longitudinal Patients Database (LPD) is a primary care database of anonymized electronic medical records (EMR) from about 4 % of the French population. Diagnosis and prescription data are routinely collected from proprietary practice management software used by physicians (primary care and specialists) to maintain EMR of their patients. Although LPD has been extensively validated by numerous publications and its use by French National Health Authorities, this is the first time that its representativeness and validity is systematically examined. **METHODS:** The distribution of several variables were analyzed and compared to available literature. Part of these variables refers to physician's practices participating to the database while others refer to patients in these practices. Data about prevalence, treatments, and patients profile were retrieved from published French Health Authorities studies based on LPD data and compared to other published sources. **RESULTS:** The sampling methods for the physician's selection practices were shown to provide a good representativeness of the physician panel. Analyze of the patients population showed that LPD included all the subsets of the French general population, although pediatrics were underrepresented. Prevalences of several illnesses (diabetes, asthma, atrial fibrillation, aortic aneurism), treatments (dyslipidemia, diabetes), patients' profiles (dyslipidemia, atrial fibrillation, venous disease) were in agreement to those encountered in literature. However, smoking status, hospitalizations, referral to specialists were only partially reported and no information was available about sociodemographic status or death of patients. The availability of missing information through the use of questionnaires/pop up screens for physicians and patients, and the linkage of the EMR database to a claims database (HEAD) is also documented. **CONCLUSIONS:** We found no indications of lack of representativeness or validity of the LPD. While presenting some flaws associated with its naturalistic nature, LPD is a good support for pharmacoepidemiological and pharmacoeconomics studies.

PRM50

LACK OF ADHERENCE TO IMMUNOSUPPRESSIVE TREATMENT IN KIDNEY TRANSPLANT PATIENTS: COMPUTER ASSISTED QUALITATIVE DATA ANALYSIS (CAQDAS) OF AN EXPERT PANEL

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OBJECTIVES: To investigate the risk of Chronic Humoral Rejection (CHR) due to Lack of Adherence to Immunosuppressive Treatment (LAIT) in Kidney Transplant (KT) patients using Computer Assisted Qualitative Data Analysis (CAQDAS). **METHODS:** A systematic literature review was conducted using Medline, Psycinfo and BVS to identify studies published between 2009 and 2013 on CHR due to LAIT in KT patients. Based on this review a questionnaire was developed focussing on the information gaps identified. Six physicians from major Spanish Transplant centres then com-

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Original Full Length Article

Assessing 5-year incidence rates and determinants of osteoporotic fractures in primary care

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ABSTRACT

Purpose: To assess the gender and age-related 5-year incidence rates of osteoporotic fractures, and their related predictors, in a primary care setting.
Methods: We obtained information from the Health Search–CSD Longitudinal Patients Database (HSD). This is an Italian General Practice data repository which comprises information given by computer-based patient records of a selected group of over 900 Primary Care Physicians (PCPs).
We selected all patients aged 50 to 85 years, who were actively included into the PCP's list at the beginning of the enrolment period (1st January 2002–31st December 2003). We excluded individuals who were registered in the PCPs' list for less than 1 year before the entry date (Index date) into the cohort, as well as those who were diagnosed with Paget disease or malignant neoplasm. Participants were followed up until the occurrence of osteoporotic fracture, one of the exclusion criteria, or the end of the study period.
Results: The 5-year rates (per 1000 person-years) of any osteoporotic fracture were 11.56 (95% C.I. 11.33 to 11.77) among females, and 4.91 (95% C.I. 4.75 to 5.07) among males. For hip fractures, the overall incidence rates were 3.23 (95% C.I. 3.11 to 3.34) among females and 1.21 (95% C.I. 1.12 to 1.28) among males, respectively. Advanced age, history of fracture, use of corticosteroids, rheumatoid arthritis, BMI<=20, presence of osteoporosis, gastrointestinal and chronic hepatic disease, depression, chronic obstructive pulmonary disease, use of anticonvulsants and a higher number of co-medications, increased the risk of any osteoporotic fractures.
Conclusions: The use of primary care data confirms a higher incidence of osteoporotic fractures among females vs. males as well as in older individuals. Predictors of osteoporotic fractures were consistent with FRAX® algorithm. Given the clinical utility of a simple score for the assessment of absolute fracture risk among osteoporotic patients, its assessment and validation in the Italian HSD could potentially provide an applicable prediction tool.

Introduction

Osteoporosis is a systemic condition characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and, consequently, an increased risk of fracture. Osteoporotic fractures represent an increasing cause of morbidity in the older populations and a considerable burden to health services in many regions of the world [1–4].

Hence, there is the need to improve methods for accurate identification of individuals at high risk of fractures, who might benefit from a preventive or therapeutic intervention. Indeed, although Bone Mass Density (BMD) measurement at the femoral neck with Dual energy X-ray Absorptiometry (DXA) is a strong predictor of the osteoporotic fracture risk [5], there have been several issues associated with its use as a clinical diagnostic test, because of its relevant cost and low sensitivity [6]. Several fractures occur in women with normal BMD [7], and the evidence suggests that risk prediction algorithms that do not include BMD, seem to possess an equal effectiveness [8]. Along this line, less expensive and more practical methods for identifying those individuals at high risk of osteoporotic fractures is a healthcare requirement. These methods should ideally be based on models which have developed similar questions in diverse populations, which are representative of the specific healthcare setting.

Recently, computer-based algorithms (FRAX®) have been developed (www.shef.ac.uk/FRAX®) under the auspices of the World Health Organization (WHO). This algorithm provides 10-year probabilities of hip fracture and other major osteoporotic fractures (i.e., spine and

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forearm). This prediction tool seems to possess a higher sensitivity to detect those at high risk of fracture [9], besides suggesting which intervention threshold should be developed [10]. However, a necessary prerequisite for the implementation of prediction score are data on the epidemiology of fragility fractures and the potential risk factors which underlie this risk. To this purpose, little is known on the general practice setting.

Furthermore, since the incidence of fracture and the prevalence of associated risk factors will change over time, the methods to derive the risk prediction algorithms need to be dynamic, so that they can be modeled over time. Longitudinal primary care databases have the advantage of having large and broadly representative populations with historical data, constantly updated and retrospectively traced to a decade in the majority of practices. In this context, they have been demonstrated to provide complete and reliable information aimed at developing and validating clinical risk score of fractures [11].

Thus, the aim of this study was to assess – in a primary care setting – the 5-year gender and age specific absolute risk of osteoporotic fractures (hip, vertebral and others) taken as a whole, only those of hip, and the related predictors.

Methods

Data source

We obtained information from the Health Search–CSD Longitudinal Patients Database (HSD), an Italian General Practice (GP) database that comprises data given by computer-based patient records of a selected group of over 900 Primary Care Physicians (PCPs). PCPs voluntarily agreed to collect patient information and to attend specific training courses for data entry. The HSD contains patients' demographic details that are linked through the use of an encrypted code with clinical records (diagnoses, referrals, and tests results), drug prescriptions (drug name, date of the filled prescription, and number of days' supply), prevention records, hospital admissions, and the date of death. To be considered for participation in epidemiological studies, PCPs should meet "up-to-standard" quality criteria pertaining to the levels of coding, prevalence of well-known diseases, mortality rates, years of recording and the evaluation of missing values [12].

A number of studies have been published confirming the research validity of the HSD information in conducting epidemiological research [13–15].

When this study was initiated, 500 PCPs homogeneously distributed across all Italian areas, covering a patient population of 1,088,229 individuals, fitted the up-to-standard quality criteria.

Study cohort

We enrolled all patients who were actively included into the PCPs list at the beginning of the enrolment period (1st January 2002–31st December 2003). To be eligible patients had to be registered with one of the participating PCPs for at least 1 year before the entry (Index date) into the study cohort, and to be aged between 50 and 85 years.

To estimate the osteoporotic-related fractures, we excluded patients who had been diagnosed with alternative causes of bone fragility, such as Paget disease (International Classification Disease, 9th revision, Clinical Modification-ICD9CM-code: 731.x) or malignant neoplasm (ICD9CM: 140–208.x), before the Index date. Subjects were followed up from the Index date until the occurrence of these events, whichever came first: osteoporotic fracture, diagnosis of tumor and/or Paget disease, death, PCP's change, and end of the study period.

According to data availability, participants' mean age (major than 60 years), and medical literature [4,16–18] patients were followed up to 5 years.

Outcomes

Osteoporotic fractures were ascertained through the physician's coded diagnosis [4,16,17,19] during follow-up and were defined as an incident event of hip (ICD9CM: 733.14, 820.x, 821.0 and 821.2), vertebral (733.13, 805.x) and other fractures such as humerus (733.11, 812.x), radius and ulna (733.12, 813.x), shinbone and fibula (733.16, 823.x), and pelvis (808.x).

Covariates

In our analysis we examined a series of explanatory variables. All of them are known to affect the risk of fracture [6,9,20] according to FRAX® score. They comprise history osteoporotic fractures, chronic use of corticosteroids (ATC H02* and at least 120 Defined Daily Dose (DDD) within one year before the Index date), rheumatoid arthritis (ICD9CM 714.x and 720.0 or at least two prescriptions of antirheumatic drugs [ATC M01C*, L04AA*, L01BA01] six months before the Index date), Body Mass Index (BMI) and current smoking.

We have also included additional features potentially associated with fracture risk, such as doctor-diagnosis of osteoporosis (733.0x), hypogonadism (257.2x), neurologic diseases (340.x, 335.2x, 356.x, 359.x, 271.x, 358.x and 740 through 759.x), organ transplant (V42.x), type 1 diabetes (250.x1 and 250x3), hyperthyroidism (242.0, 242.1, 242.8 and 242.9), gastrointestinal diseases (530.x through 534.x), chronic hepatic diseases (571.x), Chronic Pulmonary Obstructive Disease (COPD: 491.2x and 496.x), asthma (493.x) and depression (311.x, 296.2x and 296.3x) [2,11,18,21–26].

Finally, we have also included certain medications as covariates likely related to fracture risk: they comprised use of anticonvulsants (N03A*) and the number of distinct drugs being prescribed six months before the Index date.

Data analysis

On the basis of the study outcomes, we adopted two different cohorts.

In the first one, we also excluded patients with previous osteoporotic fractures before the Index date from the aforementioned *"Study cohort"*. Herein, we provided age and sex-specific incidence rates of 5-year overall osteoporotic fractures, and solely those of hip, as cases per 1000 person-years.

In the second one, to investigate the possible risk factors, we maintained the overall *"Study cohort"*.

The prevalence of any predictor and the demographic characteristics of the study cohort were then evaluated according to a descriptive analysis for man and women, separately. We used the chi-square test to evaluate the potentially significant differences in baseline characteristics between genders.

Multivariable Poisson regression models, adjusting for selected baseline factors, were constructed to derive continuous hazard functions. Separate models have been carried out for women and men. The outputs were the estimated 5-year risk of fractures combination (vertebral, hip and others) and only for hip fractures. Any covariate was selected according to statistical and/or clinical meaning as shown by univariate analysis and current medical literature, respectively. In particular, any feature apt to identify patient's chronic status at baseline was investigated. Hence, the final models retained age categories, history of fracture, BMI (<=20 vs. higher), rheumatoid arthritis, current smoking (as per FRAX® score), osteoporosis diagnosis, neurologic disease, hyperthyroidism, gastrointestinal and chronic hepatic disease, depression, asthma, COPD, number of co-medications and use of anticonvulsants. We performed a goodness-of-fit test to assess the appropriateness of the Poisson regression.

Statistical significance was defined as a 2-tailed value of $p<0.05$. Estimates of incidence rate ratio, 95% Confidence Intervals (CIs), and

probability values were generated with STATA software, version 10.1 (STATA Corp, College Station, Tex).

Results

Characteristics of the study cohort

After applying the inclusion and exclusion criteria, 271,121 subjects (122,553 males and 148,568 females) entered the analysis.

Baseline demographic and clinical features of the study population are shown in Table 1. Significant differences have been observed between males and females with regard to several characteristics. Among females, a significantly higher prevalence of previous fractures was reported when compared with males (2.42% vs. 1.21%; $p<0.0001$).

Consistently, females showed a higher prevalence for all other FRAX® items, except for current smoking (males: 6.62% vs. females: 3.86%; %; $p<0.0001$).

Concerning the other potential risk factors, presence of osteoporosis, hyperthyroidism, depression, asthma, as well as the use of anticonvulsants showed a greater prevalence among females than males. No significant differences between males and females have been observed about the prevalence of neurologic disease and type 1 diabetes.

Incidence rates

The 5-year incidence rates (per 1000 person-years) of any osteoporotic fracture stratified by age group and gender are depicted in Fig. 1. Overall, we have found estimates ranging from 4.91 (95% C.I. 4.75 to 5.07) among males to 11.56 (95% C.I. 11.33 to 11.77) among females. Although the incidence appeared higher among women across all age groups, an increased gap has been observed from the age group 65–69 years and forward.

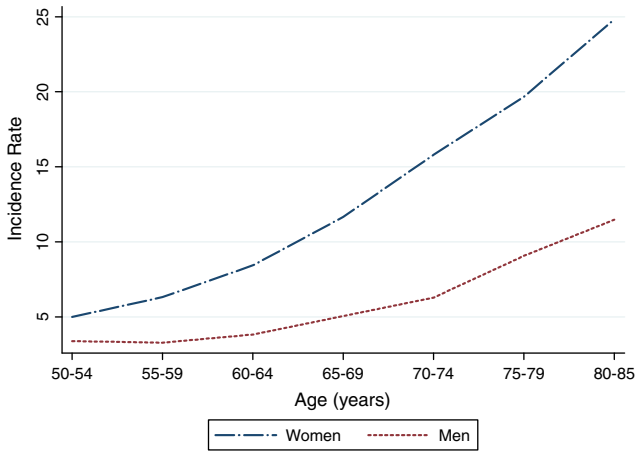

Fig. 1. Age and gender-specific 5-year incidence rates of any osteoporotic fracture (per 1000 person-years).

Concerning hip fractures (Fig. 2), the overall incidence rates were 3.23 (95% C.I. 3.11 to 3.34) and 1.21 (95% C.I. 1.12 to 1.28) among females and males, respectively. We have observed similar incidence up to 60 years between genders, whereas a sharp increase among older females was revealed until the age group 80–85.

Table 1
Baseline characteristics of the study cohort according to gender.

	Men N = 122,553	Women N = 148,568	P value
Demographic characteristics			
Mean age (year)	63.4 (9.74)	65.2 (9.22)	<0.0001
Age strata			<0.0001
<=60	48,948 (39.94%)	50,482 (33.98%)	
65–69	39,727 (32.42%)	45,325 (30.51%)	
>=70	33,878 (27.64%)	52,761 (35.51%)	
FRAX® factors			
Fracture history	1489 (1.21%)	3592 (2.42%)	<0.0001
Hip fracture	318 (0.26%)	951 (0.64%)	<0.0001
Vertebral fracture	429 (0.35%)	784 (0.53%)	<0.0001
Other fractures	772 (0.63%)	1965 (1.32%)	<0.0001
Use of corticosteroids	627 (0.51%)	936 (0.63%)	<0.0001
Rheumatoid arthritis	556 (0.45%)	1595 (1.07%)	<0.0001
BMI<=20[a]	483 (0.39%)	1770 (1.19%)	<0.0001
Current smoking	8115 (6.62%)	5739 (3.86%)	<0.0001
Other possible risk factors			
Osteoporotic diagnosis	1009 (0.82%)	17,382 (11.70%)	<0.0001
Hypogonadism	10 (0.01%)	0 (0%)	–
Neurologic disease	1176 (0.96%)	1455 (0.98%)	=0.601
Organ transplant	178 (0.15%)	101 (0.07%)	<0.0001
Type 1 diabetes	135 (0.11%)	153 (0.10%)	=0.568
Hyperthyroidism	377 (0.31%)	1344 (0.90%)	<0.0001
Gastrointestinal disease	9750 (7.96%)	10,087 (6.79%)	<0.0001
Chronic hepatic disease	3796 (3.10%)	3277 (2.21%)	<0.0001
Depression	2225 (1.82%)	6160 (4.15%)	<0.0001
Asthma	2268 (1.85%)	4177 (2.81%)	<0.0001
COPD	6457 (5.27%)	3785 (2.55%)	<0.0001
Pharmacotherapy			
Anticonvulsants	1608 (1.31%)	2108 (1.42%)	=0.017
Number of concurrent medications			<0.0001
0	47,670 (38.90%)	46,804 (31.50%)	
1	36,800 (30.03%)	52,833 (35.56%)	
2+	38,083 (31.07%)	48,931 (32.94%)	

Each feature is reported as n (%).
COPD: Chronic Obstructive Pulmonary Diseases, BMI: Body Mass Index.
[a] BMI: patients with a BMI measurement within 3 years before the Index date.

Risk factors

The result of the multivariate Poisson regression analysis, in terms of 5-year absolute risk for any osteoporotic fracture and only for hip fractures, is shown in Table 2. As a whole, 14,225 osteoporotic fractures occurred in the study cohort, 10,542 (74.1%) among females and 3683 (25.9%) among males.

For female gender, advanced age, history of fracture, use of corticosteroids, rheumatoid arthritis, BMI<=20, a diagnosis of osteoporosis, gastrointestinal and chronic hepatic diseases, depression, COPD, use of anticonvulsants and a higher number of medications, significantly increased the risk of any osteoporotic fractures. Concerning hip fractures, we gathered a 13.27-fold higher risk among patients

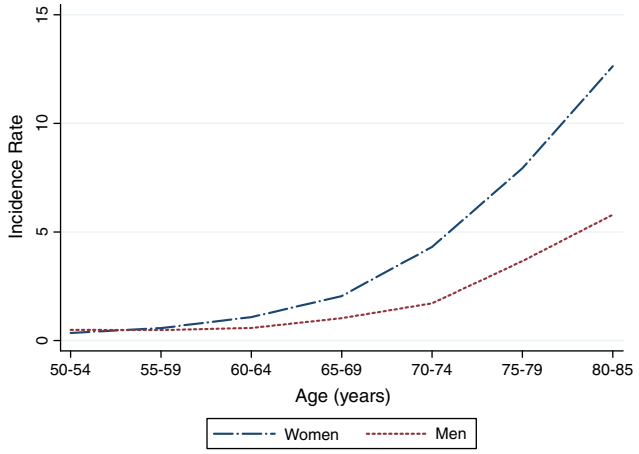

Fig. 2. Age and gender-specific 5-year incidence rates of hip osteoporotic fracture (per 1000 person-years).

Table 2
Multivariable Poisson regression of the association[a] between baseline clinical characteristics and 5-year fracture risk.

	All fractures (N = 14,225)		Hip fractures (N = 3929)	
	Males (N = 3683)	Females (N = 10,542)	Males (N = 914)	Females (N = 3015)
Demographic characteristics				
Age strata				
<=60	1	1	1	1
65–69	1.26 (1.16–1.38)	1.68 (1.58–1.78)	2.06 (1.64–2.6)	2.77 (2.32–3.30)
>=70	2.31 (2.13–2.50)	3.19 (3.02–3.37)	8.06 (6.58–9.87)	13.27 (11.37–15.5)
FRAX® factors				
History of fracture	2.39 (1.99–2.89)	1.9 (1.75–2.06)	1.99 (1.36–2.91)	2.21 (1.93–2.52)
Use of corticosteroids	1.39 (0.98–1.97)	1.69 (1.42–2.01)	1.57 (0.86–2.88)	1.80 (1.34–2.43)
Rheumatoid arthritis	1.41 (0.97–2.05)	1.25 (1.07–1.46)	1.11 (0.49–2.50)	1.28 (0.97–1.69)
BMI<= 20[b]	1.69 (1.18–2.43)	1.42 (1.23–1.63)	1.67 (0.86–3.25)	2.01 (1.61–2.50)
Current smoking	1.06 (0.93–1.20)	1.08 (0.97–1.20)	1.13 (0.87–1.47)	1.13 (0.91–1.39)
Other possible risk factors				
Osteoporotic diagnosis	1.57 (1.23–2.00)	1.42 (1.35–1.49)	2.09 (1.43–3.05)	1.30 (1.19–1.43)
Neurologic disease	1.33 (1.02–1.74)	1.15 (0.97–1.37)	1.66 (1.04–2.66)	1.23 (0.91–1.67)
Hyperthyroidism	1.00 (0.58–1.72)	0.89 (0.72–1.10)	1.69 (0.76–3.78)	1.21 (0.87–1.69)
Gastrointestinal disease	1.13 (1.02–1.27)	1.17 (1.10–1.25)	1.11 (0.89–1.38)	1.13 (1.00–1.29)
Chronic hepatic disease	1.49 (1.27–1.73)	1.33 (1.19–1.48)	1.92 (1.45–2.54)	1.38 (1.13–1.68)
Depression	1.17 (0.95–1.44)	1.24 (1.14–1.35)	1.51 (1.05–2.16)	1.36 (1.17–1.57)
Asthma	1.09 (0.87–1.37)	1.08 (0.96–1.20)	0.82 (0.48–1.39)	1.13 (0.92–1.39)
COPD	1.24 (1.09–1.40)	1.22 (1.10–1.34)	1.19 (0.96–1.49)	1.24 (1.04–1.46)
Pharmacotherapy				
Anticonvulsants	1.57 (1.27–1.95)	1.49 (1.32–1.70)	2.07 (1.45–2.96)	1.61 (1.28–2.01)
Number of concurrent medications				
0	1	1	1	1
1	1.22 (1.12–1.33)	1.22 (1.16–1.29)	1.12 (0.94–1.33)	1.09 (0.99–1.21)
2+	1.23 (1.13–1.33)	1.18 (1.12–1.25)	1.25 (1.06–1.47)	1.15 (1.04–1.26)

COPD: Chronic Obstructive Pulmonary Diseases, BMI: Body Mass Index.
[a] Incidence rate ratio and 95% CI.
[b] BMI: patients with a BMI measurement within 3 years before the Index date.

aged 70 years than lower sixties. Furthermore, a significant increased risk was here reported for the same characteristics related to the overall fractures, with some exceptions. In fact, rheumatoid arthritis, a diagnosis of osteoporosis, depression and COPD did not show any association with hip fracture occurrence.

Instead, among men, the predictors significantly associated with any osteoporotic fracture comprised advanced age, history of fracture, BMI<=20, a diagnosis of osteoporosis, chronic hepatic disease and COPD as well as the use of anticonvulsants and the increasing number of coexistent medications. Increased age, previous fractures (FRAX® component), a diagnosis of osteoporosis, chronic hepatic disease, use of anticonvulsants and the increasing number of concurrent medications were significantly associated with the risk of hip fracture.

The concurrent prevalence of one or more risk factors significantly affected the results (Fig. 3). The risk of either overall or hip fracture ranged from 8.2 (95% C.I. 8.03 to 8.31) to 2.2 (95% C.I. 2.10. to 2.25) per 1000 person years among patients with no risk factor to 20.5 (95% C.I. 17.61 to 23.77) and 7.0 among patients (95% C.I. 5.47 to 9.03) with 2 or more risk factors, respectively.

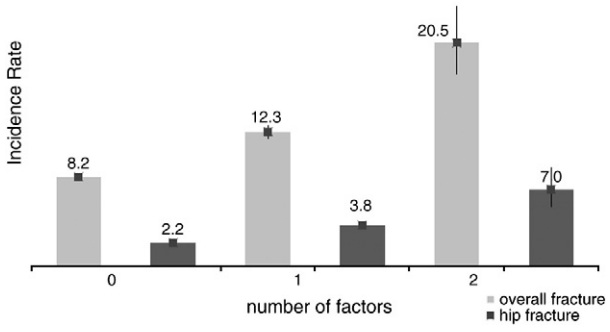

Fig. 3. Incidence rates of fracture (per 1000 person-years) according to the number of risk factors.

Discussion

The present study provides the basis for the assessment of 5-year probability fracture risk in men and women in a large specific Italian population. The use of primary care data, derived from the HSD, has allowed the examinations of the general relationship whit each predictor of osteoporotic fractures by gender and duration of follow-up. In general, a higher incidence of osteoporotic fractures was observed among females when compared with males, as well as in the older population strata. This result was confirmed when analysis was restricted to hip fractures. Additionally, we identified predictors which were those expected by FRAX® algorithm and identified in some previous surveys.

In keeping with current medical literature, females showed a higher incidence of osteoporotic fractures than males. When compared with ours, Hippisley-Cox and coworkers [11] reported analogue rates for both genders; Barrett-Connor et al. [27] retrieved a similar incidence of approximately 4 cases per 1000 person-years among male elders; Cooper and Cheng [28,29] showed secular and geographical trends of osteoporotic fractures, whose estimates were coherent with ours.

As expected, an increasing trend of fractures occurrence was positively related to the increasing patients' age. The rate appeared higher among females across all age groups, and a wider gap has been observed from the 65–69 years group and forward. Yet, our findings agree with other surveys [2,4,16,27–32], where the more evident difference was estimated after 60–65 years. As per Cummings [2], Hippisley-Cox [11] and Piscitelli et al. [4], hip and vertebral fractures should be mainly responsible of this trend.

Consistently, our estimates were reproducible with previous findings when the analysis was focused on the hip site [2,4,11]. A sharp increase was achieved among older males and females until the age group of 80–85 years. Between genders, as also reported by Piscitelli et al. [4], no relevant differences has been recorded up to 60–65 years of age, while they strictly diverge moving towards the older age groups. The plausible explanation to these results could be due to bone loss associated with menopause, which is generally more common after 55–60 years of age [2,28,29,31,32].

Also the other determinants of osteoporotic fractures here reported were somewhat in line with other studies [2,4,16,27,30]. Nevertheless, smoking habits and asthma were not supported by our results. Some explanations could address the differences. The fact that a 10-year cohort was adopted by some previous surveys [11,30] implies a higher number of cases, and an increased cumulative effect of risk factors over time [18]. Herein, some clinical features could be missed by our analysis. Furthermore, a study from UK [11] enrolled patients at 30 years of age, whereas we selected patients aged 50+ years to preserve a clinical plausibility between fractures and osteoporosis. Along this line, while asthma is a risk factor in previous investigations [11], the presence of COPD in our predictors could be suggestive of a related respiratory impairment which is more common among elderly than in younger asthmatic patients. Concerning smoking habits, although it was proportionally coherent with the participants' age and selection (oncologic patients were excluded) when compared with the general Italian population [33], its lacking association with fracture occurrence could be due to social desirable answers [34].

Rheumatoid arthritis did not result a risk factor as well. Such an explanation, it could be due to the fact that this disorder is self-reported by patients, who generally misclassify rheumatoid arthritis, osteoarthritis or arthralgia [18].

Concerning both overall and hip fractures, Hippisley-Cox et al. [11] reported the use of tricyclic antidepressants as a predictor. Partly in keeping with them but fully in agreement with other surveys [30], our data report depression as a risk factor. We examined the disease instead of its pharmacological treatment to overcome the possibility of confounding by indication [35]. On the contrary, anticonvulsants were expectedly associated to fracture occurrence also taking into account their indication of use [23,24,36].

In any case, although not-significant, most of the patient's features (e.g. use of steroids among males) inspected by us, were not so far to exclude unit from their CIs.

From a clinical perspective, the history and combination of one or more risk factors could be profitably adopted by the PCP to evaluate the predictability of osteoporotic fractures. FRAX® score is currently proposed by WHO and its use could be part of clinical activity to overcome BMD insensitivity. To this purpose, each predictor here discussed is part of FRAX® [37,38], so demonstrating its or certain variants usefulness for the PCPs [18].

This study has some limitations. Firstly, no validation study has been formally carried out to test the accuracy of the fractures diagnosis. However, the incidence rates here reported are consistently in line with current literature, either between genders or among age categories [2,4,11,16,17,19,27,31,32].

Secondly, absence of information on certain features (e.g. history of falls, alcohol intake, fracture family history [9,37]) could have missed other possible risk factors. Indeed, HSD database does not supply with accurate measures of some covariates. For instance, alcohol abuse it is difficult to measure because of social desirable answers albeit its causal association with osteoporotic fractures is not still exhaustively demonstrated [18]. In the same way, history of falls might be inaccurately recorded in the database, because the PCP does not collect radiographs for most patients [18]. Thus, it appears difficult to record severe falls that are plausibly related to fractures. Consistently, the fracture family history appeared not analytically usable when the PCPs' standard quality requirements [12] were verified.

Finally, the possibility of competing rates with mortality could partly explain the lacking association between some covariates, such as smoking habits, and the risk of fracture. Nevertheless, it is more plausible that a relatively short follow-up (5 years instead of 10) could not have permitted an exhaustive analysis of certain variables.

Conclusions

This survey provides a model for the assessment of 5-year probability fracture risk in men and women in a large specific Italian population. The use of primary care data confirms, in fact, a higher incidence of osteoporotic fractures among females when compared with males, as well as in the older population strata. In addition, predictors of osteoporotic fractures were those expected to be identified by the FRAX® algorithm in a general practice setting as well.

In the light of the clinical utility of a simple risk score for the assessment of absolute fracture risk among osteoporotic patients, its assessment and validation in the Italian HSD could potentially provide an applicable prediction tool in primary care.

Conflict of interest

No disclosures.

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