PASS information

DKP-TRAM

Title	**Drug Utilization Study (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen (DKP-TRAM)**
Protocol version identifier	v03
Date of last version of protocol	v02 26th September 2018
EU PAS register number	EUPAS24858
Active substance	Dexketoprofen and tramadol hydrochloride (DKP-TRAM) (ATC: N02AJ14)
Medicinal product	Dextradol®, Lenizak® for Italy Enanplus®, Takudex® for Spain
Product reference	DKP-TRAM
Marketing authorisation holder(s)	Menarini International Operations Luxembourg SA (MIOL) - Laboratorios Menarini S.A. - Guidotti Farma S.L.U
Joint PASS	No
Research question and objectives	To evaluate pattern of prescriptions of DKP-TRAM. To assess the risk of adverse events (nausea, vomiting, diarrhoea, vertigo, constipation) in DKP-TRAM versus tramadol monotherapy and tramadol-paracetamol combinations. To evaluate the effect modification exerted by age (75 or older vs. 74 or younger) on the risk of adverse events in DKP-TRAM versus tramadol monotherapy and tramadol-paracetamol combinations users. To evaluate the effect modification exerted by frailty (mild, moderate or severe) on the risk of adverse events in DKP-TRAM versus tramadol monotherapy and tramadol-paracetamol combinations users aged 65 years or older.
Country(-ies) of study	Italy and Spain
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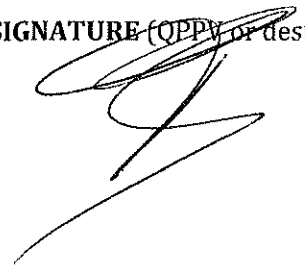

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2. LIST OF ABBREVIATIONS

AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
COX	Cyclooxygenase
CUI	Concept Unique Identifier
DDD	Defined Daily Doses
DKP-TRAM	Dexketoprofen trometamol - tramadol hydrochloride
DUS	Drug Utilization Study
eFI	electronic Frailty Index
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practice
HR	Hazard Ratio
HSD	Health Search Database
ICD-10-CM	International Classification of Diseases, 10th rev., Clinical Modification
ICD-9-CM	International Classification of Diseases, 9th rev., Clinical Modification
IR	Incidence rate
NHS	National Health System
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds Ratio
PASS	Post Authorization Safety Study
PDD	Prescribed daily doses
RCT	Randomized clinical trial
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCA	Tricyclic antidepressant
USA	United States of America
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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Scientific advisory committee	Not applicable

4. ABSTRACT

Title	Drug Utilization Study (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen (DKP-TRAM)
Rationale and background	DKP-TRAM is a pharmacological fixed association with analgesic activity, which has been registered for treatment of acute pain in 2017 in several European Countries. In Spain and Italy, the product has been launched in January 2017 and March 2017, respectively. The safety and efficacy of DKP-TRAM (25 mg – 75 mg) combination has been extensively demonstrated in the clinical development program in more than 1800 patients, especially from randomized clinical trials (RCTs) in post-operative pain. However, there is limited evidence in the real-life use of the product in the primary care settings particularly in elderly patients where the use of the 75 mg dose (with no possibility of dose titration) of tramadol contained in the combination could be a source of safety concerns for the prescribers. In the light of this background, the evaluation of the patterns of use and the safety profile of DKP-TRAM combination will be investigated through a real-world study involving an Italian and a Spanish database. Furthermore, we will test the potential effect modification exerted by age (75 years or older vs. younger patient) or frailty (mild, moderate, severe) among elderly patients (aged 65 or older) on the risk of adverse events (AEs) likely due to DKP-TRAM.
Research question and objectives	**Primary objectives:** To evaluate pattern of drug use (i.e. indication, dosage, and duration) of DKP-TRAM. **Secondary objectives:** • To assess the risk of AEs (nausea, vomiting, diarrhoea, vertigo, hallucinations, somnolence, and constipation) in incident users of DKP-TRAM vs. incident users of tramadol as monotherapy and fixed combination tramadol-paracetamol. • To evaluate the effect modification exerted by age (75 or older vs. 74 or younger) on the risk of adverse events in DKP-TRAM vs. tramadol monotherapy and tramadol-paracetamol combinations users. • To evaluate the effect modification exerted by frailty (mild, moderate or severe) on the risk of adverse events in DKP-TRAM vs. tramadol monotherapy and tramadol-paracetamol combinations users aged 65 years or older.
Study design	A bi-national database cohort study will be conducted. These data will be derived from two electronic health

	care databases from two European countries: Italy and Spain.
Population	**Primary objective (drug utilisation):** All patients, aged 18 years or older, prescribed with DKP-TRAM from January 1, 2017 up to December 31, 2018, will be included in the study. **Secondary objective (comparative safety):** All patients, aged 18 years or older, prescribed for the first time with DKP-TRAM and/or tramadol monotherapy or tramadol-paracetamol combinations from January 1, 2017 and with at least 1-year of database history will be included in the study. To evaluate the effect modification due to frailty, all patients, aged 65 years or older, prescribed for the first time with DKP-TRAM and/or tramadol monotherapy or tramadol-paracetamol combinations from January 1, 2017 and with at least 1-year of database history will be included in the study.
Variables	Indication, duration and dosage of medications use, demographic factors, life style factors, comorbidities, co-medications and prescriber type (GP or specialist). Adverse Events: nausea, vomiting, diarrhoea, vertigo, hallucinations, somnolence, and constipation.
Data sources	The Health Search Database (HSD) from Italy and the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain.
Study size	From preliminary counts, 2763 and 7945 patients have been prescribed with this medication in 2017 in HSD and SIDIAP, respectively. Thus, assuming an estimated yearly incidence rate of medication use of almost 0.2 and 1% in HSD and SIDIAP, respectively, these numbers of users would be large enough to assume a 0.01 precision with 95% Confidence Intervals (CI). Given that HSD currently includes almost 1 million patients and SIDIAP almost 7,6 million, these numbers should ensure stable estimates. For what concerns the safety study, the occurrence of opioid-related AEs is observed in greater than 20% of users. Such a prevalence would allow to estimate of Hazard Ratio (HR)=1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. Tramadol (including tramadol-paracetamol). Still, from preliminary evaluation, the number of DKP-TRAM users aged 75 years or older resulted 705 and 949 for HSD and SIDIAP, respectively. Indeed, still assuming an occurrence of opioid-related AEs greater than 20% (likely higher among patients aged 75 or older), a minimum OR equal 1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. tramadol (or tramadol-paracetamol) is estimable among this patients' category as well.
Data analysis	**Primary objectives:** Crude, age- and sex-standardised

	incidence rate (IR) of DKP-TRAM use will be computed, along with descriptive analysis concerning indication, duration and dosage. Continuous variables will be described as means with standard deviations or median with interquartile range. Categorical variables will be described as N and percentages. Duration of DKP-TRAM use will be evaluated by means of Kaplan-Meier method as well, by following DKP-TRAM users up to the fifth day of follow-up, namely the maximum length of use be allowed by the SmPC. **Secondary objectives:** The risk of AEs in users of DKP-TRAM will be compared with the risk of AEs in users of tramadol as monotherapy and as tramadol-paracetamol combinations by estimating HR with related 95% CI trough Cox regression model. Tramadol monotherapy (and/or tramadol/paracetamol combinations) users will be the reference category. The risk of AEs in users of different dosages and durations of DKP-TRAM will be compared with the risk of AEs in users of tramadol (or tramadol-paracetamol) different dosages and durations by estimating Odds Ratio (OR) with related 95% CI, according to a nested case-control analysis, trough conditional logistic regression model. Such a model will be adopted to evaluate the presence of effect modifications due to age or frailty on the risk of AEs. All these analyses will be updated with information on data entering the databases in 2018.
Milestones	Start of data collection, 1st January 2017 End of data collection, 31st December 2018 Study progress report, 28th February 2020 Interim report, 31st January 2021 Registration in the EU PAS register, 17th July 2018 Final report of study results, 29th February 2021

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	March 11, 2019	7. Rationale and background	In the Italian market there are other products containing ("high" dose)) 75 mg of tramadol (i.e. tramadol-paracetamol combinations. In particular, tramadol-paracetamol combinations is featured by a place in therapy similar to DKP-TRAM, with the same suggested dosage for tramadol (i.e. 75 mg) according to SmPC. Nevertheless, given that tramadol-paracetamol formulation contains tablets of 37,5 mg of tramadol, clinicians are able to titrate the dosage on the bases of patient's response.	Further information on the reason why the PASS has been requested.
2	March 11, 2019	7. Rationale and background	Certain sales have been reached also in France. the available French claims database (SNIIRAM and EGB) is able to track reimbursed medications only. Nevertheless, the DKP-TRAM has been approved for reimbursement by the French national HTA authority (HAS) in March 2018, but it has not appeared yet in the reimbursement database, as of August, 2018. The inclusion of this data source, with information until December 2018 should be therefore underpowered.	Information on the potential inclusion of French database has been requested.
3	March 11, 2019	9.3.1 Primary objective Duration of treatment	In HSD, the duration of treatment with DKP-TRAM will be evaluated, for the first prescription, as longer or shorter than	The Kaplan-Meier analysis on treatment duration with DKP-TRAM

			5 days, namely the maximum durations allowed by the SmPC [1], along with describing the different treatment courses (i.e., number of courses, related durations and 5-day courses) being identified and cumulated during follow-up. The length of follow-up will be set on three, six or twelve months. Thus, we will compare durations (and related number of 5-day courses) of DKP-TRAM being calculated using PDD or dosage reported in the SmPC for different period of follow-up. With this approach, given that PDD is the actual dosage indicated by GPs, we will identify potential inconsistencies in using the SmPC dosage. Furthermore, duration of prescriptions with DKP-TRAM will be investigated according to Kaplan-Meier methods (using both SIDIAP and HSD databases) in an attempt to clarify the burden of drug discontinuation, namely those DKP-TRAM users who will stop DKP-TRAM or switch to another therapy. Stopping will be defined as the occurrence of any AEs (see 9.3.2 SECONDARY OBJECTIVES: Outcome), end of registration of patient' data, death, the fifth day of follow-up, whichever will come first. In the light of the GP's delay for AEs registration, the longest durations of follow-up (i.e. censoring criteria)	was revised.

			will be varied from the 5th to the 15th, or the 30th day of follow-up.	
4	March 11, 2019	9.3.2 Secondary objectives Outcomes	Constipation was added to the potential AEs under study (see Table 3).	We extended the event definition to other types of AEs.
5	March 11, 2019	9.5 Study size	Still from preliminary evaluation, the number of DKP-TRAM users aged 75 years or older resulted 705 and 949 for HSD and SIDIAP, respectively. These numbers would ensure stable estimates to test the presence of effect modifications due to age on the risk of AEs. Indeed, still assuming an occurrence of opioid-related AEs greater than 20% (likely higher among patients aged 75 or older), a minimum OR equal 1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. tramadol (or tramadol-paracetamol) is estimable among this patients' category as well.	We reported the evaluation on the study size for what concerns the DKP-TRAM users aged 75 years or older.
6	March 11, 2019	9.7 Data analysis	The duration of prescriptions of DKP-TRAM will be investigated according to Kaplan-Meier methods (using both SIDIAP and HSD databases) in an attempt to clarify the burden of drug discontinuation, namely those DKP-TRAM users who will stop DKP-TRAM and/or switch to another therapy. Stopping will be defined as the occurrence of any AEs (see 9.3.2 SECONDARY OBJECTIVES: Outcome), end of registration of patient' data, death, the fifth day of follow-up,	Data analysis using Kaplan-Meier method needed to be revised given the use absence of actual daily dose in Spain data.

			whichever will come first. In the light of the GP's delay for AEs registration, the longest durations of follow-up (i.e. censoring criteria) will be varied from the 5th to the 15th, or the 30th day of follow-up.	

6. MILESTONES

Milestone Planned date	
Start of data collection	1st January 2017
End of data collection	31st December 2018
Study progress report	28th February 2020
Interim report	31st January 2021
Registration in the EU PAS register	17th July 2018
Final report of study results	29th February 2021

7. RATIONALE AND BACKGROUND

This study was imposed as a condition of the marketing authorisation during the procedure ES/H/0317-0318/001/DC to address concerns regarding the safety and tolerability of this high fixed tramadol and dexketoprofen dose in the general population including frail-elderly and very elderly patients in the approved indication. This PASS is part of the currently approved Risk Management Plan (RMP) v.2.2 (dated 21 December 2017) with the following title:

- **Category 1** (imposed): TBD Drug utilization Study (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen. Cohort, population-based, study.

Acute and chronic pain represent one of the most relevant public health concerns, with socioeconomic impact in both Europe [2] and USA [3]. Furthermore, a poor pain control may result in reduced patients' quality of life, increasing risk of developing chronic pain and other medical complications [4].In 1986 the World Health Organization (WHO) has proposed an analgesic ladder to treat patients with pain. This scale suggests a first treatment with a non-opioid analgesic drug and an eventual add-on therapy with and/or switch to opioids if pain has not adequately controlled. This scale includes nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol with or without adjuvants at the first step; weak opioids for mild-moderate pain +/- non opioids +/- adjuvants at the second step; therapy with strong opioids for moderate-severe pain +/- non opioids +/-adjuvants at the last step [5].

In patients with moderate and severe acute pain, it is difficult to obtain a pain relief with a single drug therapy and, at the same time, the increase of dosage needs to be accurately evaluated because of the risk of adverse events (AEs) [6]. Therefore, the optimal strategy is combining different analgesic drugs with results in potential benefits such as wider spectrum of action, better compliance and greater efficacy and safety [6,7].
Dexketoprofen trometamol plus tramadol hydrochloride (25 mg – 75 mg) (DKP-TRAM) is a new pharmacological fixed-dose combination with analgesic activity and is indicated in the symptomatic short-term treatment of moderate to severe acute pain in adult patients. DKP-TRAM has been registered in 2017 in 31 European countries, including Italy and Spain.
From when the product was launched on the market (i.e. from December 31, 2016 to March 31, 2017) to June 2018, Italy and Spain are the European countries with the highest sales, reporting 746,553 and 1,271,703 dispensed packs (internal sales data), respectively, along with Poland, France, and Portugal with 1,039,551, 214,083, and 267,546 dispensed packs (internal sales data), respectively. Spain is the only European country in which DKP-TRAM is partially reimbursed (almost 40%) by the public health system.

Tramadol is a weak opioid with central analgesic activity and long-lasting effect [9]. It is featured by a double mechanism of action including partial agonism on the μ-opioid receptor and inhibition of serotonin and noradrenaline reuptake [9,10]. Dexketoprofen trometamol is a NSAID, in particular is the S(+)-enantiomer of ketoprofen, with a quick onset of action and demonstrated effectiveness on acute pain relief [12], [13]. The pharmacological properties of dexketoprofen consists of strong inhibition of COX-1 along with moderate inhibition of COX-2, so allowing the drug to have anti-inflammatory effects in both the peripheral tissue and in spinal cord.
Tramadol is generally considered safer than other opioids. Namely, the most important tramadol-related AEs include nausea (ranging 11.3-53,7%), dizziness (5.3-36.7%), vomiting (4.3-19%), headache (2.1-22%), constipation (3.4-45%) and somnolence (6.7-37.2%) [14].

Given the dose-related risk of AE due to tramadol, which lead to drug discontinuation in 20% of users [14], the choice of initial dosage is usually the lowest one (50 mg) with a subsequent increase according to patient's response in terms of drug efficacy and tolerability. This concern is of particular relevance in special populations, such as in older patients, who are the most frequent users of this therapy and are more prone to AEs because of age-related factors including the growing frailty.

DKP-TRAM represents one of the first combinations of a new pharmacological class, in which the opioid centrally-acting analgesic has been combined with a drug with peripheral and central (spinal) anti-inflammatory activity [15]. Such a combination allows a rapid onset, long duration of action and a reduction in tramadol dosage, potentially minimizing the risk of AEs [16]. Indeed, the safety and efficacy of DKP-TRAM (25 mg – 75 mg) combination has been extensively demonstrated in the clinical development program in more than 1800 patients, especially from randomized clinical trials (RCTs) in post-operative pain [17], [18]. However, there is limited evidence in the real-life use of the product in the primary care settings in which it could be prescribed for several and frequent pain conditions such as low back pain and other musculoskeletal disorders.

Indeed, the initial exposure to 75 mg of tramadol, with no possibility of titration could be a cause of AEs leading to drug discontinuation, especially for incident users (i.e.: those previously unexposed to other tramadol-containing formulations). Furthermore, this is particularly relevant among elderly and frail patients who, as mentioned above, are featured by a greater risk of AEs than younger patients.

Currently, there are other pharmacological fixed combinations to treat pain including weak (e.g., codeine, tramadol) or strong (e.g., oxycodone) opioids combined with paracetamol, a medication with negligible peripheral anti-inflammatory activity. In particular, tramadol-paracetamol combinations is featured by a place in therapy similar to DKP-TRAM, with the same suggested dosage for tramadol (i.e. 75 mg) according to SmPC even iftramadol-paracetamol formulation contains tablets of 37,5 mg of tramadol.

In the light of this background, the evaluation of the patterns of use and safety profile of DKP-TRAM combination will be investigated in a real-world setting with particular relevance in special populations, such as older (75+ years of age) and/or frail patients, who may be more prone to AEs or drug discontinuation because of gastrointestinal and central AEs when compared with younger patients [19]. To answer these research questions, we will conduct an observational study in Italy and Spain given the fact that, within the territories where the product has been launched, only these two countries have a relevant consumption of DKT-TRAM along with two research databases fully validated and already used for several observational, population-based, multi-country investigations [20]–[22]. Indeed, certain sales have been reached also in France. The available French claims database (SNIIRAM and EGB) is able to track reimbursed medications only [23]. Nevertheless, the DKP-TRAM has been approved for reimbursement by the French national HTA authority (HAS) in March 2018, but it has not appeared yet in the reimbursement database, as of August, 2018. The inclusion of this data source, with information until December 2018 should be therefore underpowered.
High sales have been revealed in Portugal and Poland as well, but these countries don't have a reliable database (so far) to provide adequate information, as per study requirement.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of the present project is to evaluate the pattern/s of drug use of DKP-TRAM, and to assess the risk of AEs among users of DKP-TRAM vs. those using tramadol as monotherapy (or tramadol-paracetamol combination), in real-world primary care data from Italy and Spain.

Primary Objectives: To describe the pattern of drug use of DKP-TRAM in primary care in Italy and Spain in 2017 and 2018.

Specific aims:

- To estimate the population-based yearly incidence rate (IR) of DKP-TRAM use in patients aged 18 years or older.

- To describe the demographic, clinical characteristics, and prescriber type (GP-General Practitioners or specialist) for patients aged 18 years or older and prescribed with DKP-TRAM.
- To describe the indications for which DKP-TRAM is prescribed.
- To describe the prescribed daily doses (PDD) and durations of treatment with DKP-TRAM.

Secondary Objectives: To assess the risk of AEs in patients aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations tramadol-paracetamol), and to evaluate the presence of effect modification exerted by age (75 or older) or frailty (mild, moderate, severe) on the risk of AEs in 2017 and 2018.

Specific aims:

- To calculate the IR of AEs occurring during the first 3 months of follow-up among patients aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations tramadol-paracetamol).
- To estimate the hazard ratios (HR) of AEs in patient aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations tramadol-paracetamol).
- To evaluate the presence of effect modification exerted by age (75 years or older vs. 74 or younger) on the risk of AEs in patients aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations tramadol-paracetamol).
- To evaluate the presence of effect modification exerted by frailty (mild, moderate, severe) on the risk of AEs in patients aged 65 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations tramadol-paracetamol).

9. RESEARCH METHODS

9.1. STUDY DESIGN

This is a post-authorization, bi-national, multi-database, non-interventional, retrospective, population-based cohort study.
A retrospective cohort study was deemed the best design to characterize the use of DKP-TRAM in terms of patients' features, prescriber type (i.e. GP or specialist), indication of use, dosages, and duration of treatment.
Furthermore, this study will assess the safety profile of DKP-TRAM compared to monotherapy with tramadol (and tramadol-paracetamol combinations) for what concerns the risk of AEs.
When the dosage and duration of use will be modelled as exposure variable, a nested case-control analysis will be adopted. Each case will be matched up to ten controls (i.e. person-times) according to age (+/- 5 years), gender and GP. The date of cases will be the index date and assigned to the respective controls. This same nested case-control dataset will be adopted to investigate the presence of effect modification due to age on the risk of AEs,

and it will be limited to patients aged 65 years or older when frailty will be evaluated as effect modification on the risk of AEs.

9.2. SETTING

9.2.1 STUDY POPULATION

This study will be conducted on data collected in 2 European electronic health care databases, namely the Health Search Database (HSD) for Italy, and the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), for Spain.
All patients aged 18 years or older being registered in the databases between January 1, 2017 and December 31, 2018.

9.2.2 STUDY PERIOD

This study will contain patients' data from the first launch of DKP-TRAM in Italy (March 2017) and Spain (January 2017). The end of the study will be December 31, 2018.

9.2.3 IN- AND EXCLUSION CRITERIA

Inclusion criteria

Primary objectives (drug utilisation): all patients aged 18 years or older with at 1-year medical history in the database and prescribed with DKP-TRAM coded via the Anatomical Therapeutic Chemical (ATC) classification system (ATC: N02AJ14) will be identified. For each patient, the date of the first prescription of DKP-TRAM being registered in the study period will be the index date.

Secondary objectives (comparative safety): all patients aged 18 years or older and newly prescribed with DKP-TRAM (ATC: N02AJ14) or tramadol (ATC: N02AX02) or tramadol-paracetamol (ATC: N02AJ13) will be identified. For each patient, the date of the first DKP-TRAM or tramadol (including tramadol-paracetamol) prescription in the study period will be the index date.

Exclusion criteria

Primary objectives (drug utilisation): Patients 1) with missing data on age or gender, 2) with less than 1-year medical history in the database, 3) aged 17 years or younger.

Secondary objectives (comparative safety): Patients 1) with missing data on age or gender, 2) with less than 1-year medical history in the database, 3) aged 17 years or younger, 4) being prescribed with tramadol (or tramadol-paracetamol) in the entire period (up to 1998 and 2010 for HSD and SIDIAP, respectively) preceding the index date.

9.2.4 FOLLOW-UP

Primary objectives (drug utilisation): Eligible patients will be followed up from the index date until the occurrence of these events whichever will come first: i) patient's exit from the database, ii) patient's death, iii) end of data availability (December 31st, 2018).

Secondary objectives (comparative safety): Eligible patients will be followed up from the index date until the occurrence of these events whichever will come first: i) occurrence of one of the AEs under study (event date), ii) third month of follow-up), iii) patient's exit from the database, iv) patient's death, v) end of data availability (December 31st, 2018). We will end the follow-up at the 3rd month of observation in an attempt to consider

titration for tramadol (including tramadol-paracetamol), the expected short-time of onset for these AEs as well as the GP's delay for AEs registration.

9.3. VARIABLES

9.3.1 PRIMARY OBJECTIVE

Exposure

The drug of interest is DKP-TRAM (ATC: N02AJ14). HSD contains information on primary care prescriptions, while SIDIAP contains information on drug dispensing.

Indication

DKP-TRAM is indicated in symptomatic short-term treatment of moderate-severe acute pain in adult patients whose symptomatology is considered to require a combination therapy [1].

All diagnoses associated to prescriptions of DKP-TRAM will be identified and classified according to ICD9CM (International Classification of Diseases, 9th rev., Clinical Modification) and ICD-10 International Classification of Diseases, 10th rev., Clinical Modification). While HSD is able to identify the actual indication of use (i.e. every prescription has to be coupled with diagnosis by GP), in SIDIAP all diagnoses registered in 1 week before or after the index date will be captured. The selected indications will be manually reviewed in HSD to minimize the burden of miscoding.

Dosage

The distribution of the PDD will be described for all users of DKP-TRAM. The PDD and dosing instructions are recorded in HSD only, so this analysis will be limited to Italian data.

Considering that daily dose should not exceed three tablets per day (corresponding to 225 mg of tramadol and 75 mg of dexketoprofen), we will evaluate cases with a PDD higher vs. lower than 225 mg of tramadol and 75 mg of dexketoprofen. We will evaluate the PDD related to the initial prescriptions and those registered during follow-up. For this analysis, the length of follow-up will be set on three, six or twelve months.

Duration of treatment

The duration of treatment with DKP-TRAM will be calculated using:

- Total units*Strength/PDD value (in HSD).
- Total number of daily doses being prescribed/dispensed, calculated as total Units*Strength/ daily dose as indicated in the Summary of Product Characteristics (SPC; in HSD and SIDIAP).

In HSD, the duration of treatment with DKP-TRAM will be evaluated, for the first prescription, as longer or shorter than 5 days, namely the maximum durations allowed by the SmPC [1], along with describing the different treatment courses (i.e., number of courses, related durations and 5-day courses) being identified and cumulated during follow-up. The length of follow-up will be set on three, six or twelve months. Thus, we will compare durations (and related number of 5-day courses) of DKP-TRAM being calculated using PDD or dosage reported in the SmPC for different period of follow-up. With this

approach, given that PDD is the actual dosage indicated by GPs, we will identify potential inconsistencies in using the SmPC dosage.

Furthermore, duration of prescriptions with DKP-TRAM will be investigated according to Kaplan-Meier methods (using both SIDIAP and HSD databases) in an attempt to clarify the burden of drug discontinuation, namely those DKP-TRAM users who will stop DKP-TRAM or switch to another therapy. Stopping will be defined as the occurrence of any AEs (see 9.3.2 SECONDARY OBJECTIVES: Outcome), end of registration of patient' data, death, the fifth day of follow-up, whichever will come first. In the light of the GP's delay for AEs registration, the longest durations of follow-up (i.e. censoring criteria) will be varied from the 5th to the 15th, or the 30th day of follow-up.

Demographics and life style factors
Information on patients' age and sex will be retrieved on the index date. Furthermore, life style information will be captured on:

- Smoking status (if available); patients will be classified as "current smoker", "past smoker", "non-smoker" or "smoking status unknown" at the time of the index date.
- Obesity, also defined as body mass index (BMI) higher than 30 kg/m^2, considering the last BMI measurement before the index date.
- Alcohol abuse and/or alcohol-related disorders, considering the last assessment before the index date.

Comorbidities and co-medications
Comorbidities and co-medications will be assessed through codes registered in the databases. Operationally, diagnoses and medications will be defined in the overall period and 1 year preceding and/or on the index date, respectively (see Table 1-2 and Annex 3). After defining ICD9CM codes, ICD10 will be identified using the CodeMapper system and then harmonized with the related ICD9CM codes through manual revision [24].
Previous and subsequent use of tramadol (or tramadol-paracetamol) will be investigated in terms of dosage according to the criteria indicated below.

Prescriber type
Pattern of DKP-TRAM use (i.e. prevalence and IR of use, dosage and duration) will be evaluated according to the prescriber type. Namely, prescriptions of DKP-TRAM will be differentiated whether they will be made by GPs or specialists. This distinction will be directly obtained in SIDIAP in which the prescriber type is codified. Given that in HSD we can capture prescriptions filled by GP only, we will identify every specialist referral being registered by GP in the month preceding the index date. As such, we will be able to hypothesize whether the prescriptions of DKP-TRAM might be started by specialist, nominally internist, geriatrician, rheumatologist, and anaesthesiologist.

Table 1. List of ICD9CM codes defining comorbidities.

Comorbidities	ICD9CM
Hepatic impairment	570*, 573.3*, 794.8*, 572.2*
Kidney disease	580*-589*, 250.4*, 403.0*, 403.1*, 403.9*, 404*, 274.10, 440.1, 442.1, 453.3, 593*, 753.0, 753.3, 866*, 585, 250.4, 581.1, 581.8, 791.0

	V45.1, V56.0, V56.8 V42.0, 996.81
Depression	296.2, 296.3, 311*,
Chronic obstructive pulmonary disease and allied conditions and Asthma	493, 493.90, 493.1, 493.0, 493.02, 493.12, 493.91, 493.01, 493.10, 493.11, 493.2, 493.8 490-496.99 (excluding 493*)
Epilepsy	345*
Chronic dyspepsia	536.8
Alcohol abuse and/or alcohol-related diseases	303*, 305.0, 357.5, 425.5, 535.3, 571.0-3, 790.3, V11.3,
Drug abuse or dependence	304* 305.2- 305.9.
Mental health diagnoses and personal history of mental disorder	293.0-301.9 (excluding 294.0, 296.2, 296.3) V11.0, V11.1, V11.2, V11.8, V11.9
Hallucinations	368.16; 780.1
Dementia and memory deficit	294.0, 310.1, 331.0, 290.0, 290.1, 290.2, 290.3, 290.4, 046.1, 046.3, 291.2, 292.82, 331.1, 331.2, 331.7, 331.8, 331.9, 332.0, 292.83, 780.9
Cognitive Impairment after trauma	907.0
Cerebro/cardiovascular disease	410*-414*, 428*, 402.91, 404.91, 402.01, 402.11, 404.01, 430-2*, 433.01, 433.11, 434.01, 434.11, 436*, 438*, V45.81
Gastrointestinal haemorrhages	531.00, 531.10, 532.00, 533.00, 535.01, 535.41, 535.51, 535.61, 578.0, 578.1, 578.9

Table 2. List of ATC codes defining co-medications.

Co-medications	**Anatomical Therapeutic Chemical (ATC)**
Tramadol	N02AX02
NSAIDs (nonsteroidal anti-inflammatory drugs)	M01A*
Anticoagulants or anti-platelet, anti-aggregation drugs	B01*
Carbamazepine	N03AF01
Cimetidine	A02BA01
Opioid drugs (excluding tramadol)	N02A*
Antidepressants (Selective serotonin reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs), Tricyclic antidepressants (TCA); Other seizure threshold-lowering medicinal product	N06A* (excluded N06AF*, N06AG, N04BD02, N04BD01, N04BD03, J01XX08)
Patients currently receiving (or received within the last 14 days) MAO inhibitors	N06AF, N06AG, N04BD02, N04BD01, N04BD03, J01XX08
Antipsychotics	N05A*
Anxiolytics	N05B*
Ondansetron	A04AA01
Ketoconazole	J02AB02
Erythromycin	D10AF02

9.3.2 SECONDARY OBJECTIVES

Outcomes

Adverse Events have been identified to define patients being intolerant to tramadol. We will capture all events which have been previously considered as leading cause of drug discontinuation [13].

Each event will be therefore identified in HSD and SIDIAP via ICD9CM and ICD-10 coding system, respectively (Table 3). After defining ICD9CM codes, ICD-10 will be identified using the CodeMapper system and then harmonized with the related ICD9CM codes through manual revision [24].

In HSD these events will be also identified through a specific electronic file coding medications intolerance. Eligible patients might experience two or more AEs at the same time.

Table 3. List of ICD9CM coding adverse events.

Terms	ICD9CM
Nausea, vomiting	563.2; 787.0*
Diarrhoea	787.91
Constipation	564.0
Hallucinations	368.16; 780.1/00
Vertigo	780.4
Somnolence	780.09

Exposure

The drugs of interest will be DKP-TRAM (ATC: N02AJ14) and tramadol (ATC: N02AX02) as monotherapy (and as tramadol-paracetamol combinations(ATC: N02AJ13)). We chose this comparator because it includes the most used tramadol formulations whose dose can be escalated. Furthermore, tramadol-paracetamol combinations will be helpful as comparator because the initial dosage (as indicated by SmPC) is equivalent to 75 mg of tramadol (i.e. two tablets of 37,5 mg tramadol). HSD contains information on primary care prescriptions, while SIDIAP contains information on drug dispensing.

Dosage

The PDD of DKP-TRAM and tramadol monotherapy will be evaluated in the period preceding and/or on the date of AEs registration. The PDD and dosing instructions are recorded in HSD only, so this analysis will be limited to Italian data. To account for the presence of different treatment courses during follow-up, we will categorise the exposure into two mutually exclusive subgroups according to the recency of use. Namely, patients exposed to DKP-TRAM, or the compared medications, in the month preceding or on the index date will be the current users. Those being excluded from this category will be the recent users. By doing so, the exposure categories will be modelled according to a time-dependent fashion. Operationally, we will therefore identify the cumulated dosage of tramadol (i.e., it is expected a multiple of 75 mgs for DKP-TRAM and more heterogeneous doses for the other formulations containing tramadol) being registered be the current users.

Given that this exposure will be modelled according to a nested case-control analysis, we will categorise the dosage (in mg) in terciles as it will be registered in the controls as reference for the general population. This approach will allow us to compare the

individual dosage categories being prescribed for DKP-TRAM users versus those being prescribed for tramadol (or tramadol-paracetamol combination) users.

Duration of treatment
The duration of treatment with DKP-TRAM and with tramadol as monotherapy (and as tramadol-paracetamol combinations) will be calculated using:

- Total units*Strength/PDD value (in HSD).
- Total number of daily doses being prescribed/dispensed, calculated as total Units*Strength/ daily dose as indicated in the Summary of Product Characteristics (SPC; in HSD and SIDIAP).

Given that this exposure will be modelled according to a nested case-control analysis, we will categorise the duration (in days) in terciles as it will be registered in the controls as reference of general population. To account for the presence of different treatment courses during follow-up, we will categorise the exposure into two mutually exclusive subgroups according to the recency of use. Namely, patients exposed to DKP-TRAM, or the compared medications, in the month preceding and/or on the index date will be the current users. Those being excluded from this category will be the recent users. By doing so, the exposure categories will be modelled according to a time-dependent fashion. Operationally, we will therefore identify the cumulated duration of tramadol (in days) being registered by the current users.
Given that this exposure will be modelled according to a nested case-control analysis, we will categorise the durations in terciles as it will be registered in the controls as reference of general population. Furthermore, we will check the presence of 5-day courses and related multipliers (e.g. 1=one course, 2=two courses etc…) of therapy among current users. This approach will allow us to compare the cumulative duration categories among DKP-TRAM versus tramadol (or tramadol-paracetamol combination) users. In addition, the reference category will be split into tramadol and tramadol-paracetamol.

Demographics
Information on patients' age and sex will be retrieved on the index date. Furthermore, life style information will be captured on:

- Smoking status (if available); patients will be classified as "current smoker", "past smoker", "non-smoker" or "smoking status unknown" at the time of the index date.
- Obesity, also defined as BMI higher than 30 kg/m2, considering the last BMI measurement before the index date.
- Alcohol abuse and/or alcohol-related disorders, considering the last assessment before the index date.

Comorbidities and co-medications (potential confounders)
Comorbidities and co-medications will be assessed through codes registered in the databases. Operationally, diagnoses and medications will be defined in the overall period and 1 year preceding and/or on the index date, respectively (see Table 1-2 (excluding previous use of tramadol)).

Frailty

A direct measure of frailty is not available in HSD and SIDIAP. Therefore, we will adopt the electronic Frailty Index (eFI) developed and validated by Clegg and co-workers [25], [26] using UK primary care data. We will recalibrate this Index in Italian and Spanish data using the Clegg's methodology on patients aged 65 or older. In brief, the criteria for variable inclusion in the FI will be: a) biological plausible; b) accumulates with age; c) do not saturate too early.

An expert frailty panel will select codes being biologically plausible in defining a range of deficits consistent with decline in multiple physiological system. The prevalence of candidate deficits will be plotted against age and linear regression coefficient and r^2 will be calculated. Only deficits with a population prevalence >0.5%, a positive regression coefficient and r^2 >30% will be included, excluding those that will reach 100% prevalence by age 65. The Index will be therefore categorised into quartiles (99^{th} centile will be the upper limit) staging for mild, moderate and severe frailty, and it will be evaluated in prediction of all-cause mortality in terms of discrimination and explained variance by calculation Area Under the Curve (AUC) and pseudo R^2, respectively. We will adopt a development and internal validation cohort for both HSD and SIDIAP.

Every deficit will be identified in HSD and SIDIAP via ICD9CM and ICD-10, respectively. After defining ICD9CM codes, ICD-10 will be identified using the CodeMapper system and then harmonized with the related ICD9CM codes through manual revision [24]. Nevertheless, every country-specific deficit will be maintained for the country-related FI.

9.4. DATA SOURCES

The database included in this study will be HSD (Italy) and SIDIAP (Spain). These two databases comply with European Union (EU) guidelines on the use of medical data for medical research and have been validated for pharmaco-epidemiological research [27], [28] and they are listed under the ENCePP resources database: (www.encepp.eu/encepp/resourcesDatabase.jsp).

Table 4. Overview of databases

	Italy	**Spain**
Name of the database	HSD	SIDIAP
Type of database	MR	MR
Number of patients, *millions*	1.5	5.1
Date in	Yes	Yes
Date out	Yes	Yes
Date of death	Yes	Yes
Cause of death	No	No
Updates	Twice a year: (30/06 and 31/12)	Yearly (April/May)
Outpatient Rx	Yes (specialist incomplete)	Yes (specialist incomplete)

	Italy	Spain
Coding of drugs	ATC	ATC
Dosing regimen	Yes	Yes (incomplete)
Hospitalisations	Yes (incomplete)	Yes
Outpatient diagnoses	Yes	Yes
Coding of disease	ICD-9 CM	ICD-10

ATC = Anatomical Therapeutic Chemical; ICD = International classification of disease, MR = Medical Records

HSD –Longitudinal Patient Database, Italy

The HSD is a general practice research database and it covers data from computer-based patient records covering a total of 1.5 million patients. HSD was established in 1998 by the Italian College of General Practitioners and Primary Care [29]. The database contains clinical (diagnoses, patient referrals, hospital admissions, clinical investigations' results and date of death), life style records (BMI, smoking and alcohol use) along with prescription data (drug name, prescription date, number of days' supply) for the drugs which are reimbursed by the National Health System (NHS). All prescription data were coded with ATC classification system while the ICD-9-CM for all medical records [30].
The GPs included in the study had to meet 'up-to-standard' quality criteria for epidemiological studies, in particular: levels of coding, prevalence of well-known diseases, and mortality rates. Furthermore, only GPs who provided data at least one year were included in the analysis [31].
HSD is a valid data source for scientific research and it is aligned to the European Union guidelines on the use of medical data for research. Representativeness of HSD has been previously demonstrated by compared distributions of patients' categories in age and sex with the National Institute of Statistics (https://www.healthsearch.it/). For these reasons, HSD has been used as data source in many studies and publications [32]–[36].
Approval for use of data was obtained from the Italian College of General Practitioners and Primary Care for the current study.

SIDIAP Database, Spain

General Practitioners play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. SIDIAP Database comprises of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.9 million patients (about 80% of the total of 7.5 million population of Catalonia) from 279 primary care practices with 3,414 participating GPs. The size of the SIDIAP base populations currently higher than 5 million, so covering over 80% of the population of Catalonia. The SIDIAP has been shown to be highly representative of the regional population, both in terms of socio-demographics as well as in terms of burden of long-term disease [37]. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff

in electronic medical records, comprehensive demographic information, reimbursed prescription/s and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes.
Health professionals gather this information using ICD-10 codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, BMI, tobacco and alcohol use, blood pressure measurements, blood, and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP. Recent reports have shown the SIDIAP data to be useful for epidemiological research [37].
Approval for the current study was obtained from both the SIDIAP Scientific and the IDIAP (Institut d'Investigació en Atenció Primària) Jordi Gol primary care research Ethics Committee.

A direct measure of frailty is not available in HSD and SIDIAP. Therefore, we will implement in HSD and SIDIAP the eFI developed and validated by Clegg and co-workers [25], [26] using UK primary care data (see section 9.3.2 on "Frailty").

Italy and Spain are at this time the only 2 countries included in this study since they have a reliable database for clinical research able to track information about reimbursed and non-reimbursed medication. medications [38].

9.5. STUDY SIZE

DKP-TRAM -containing medications have been launched in Italy and Spain in January 2017 and March 2017, respectively. From preliminary counts, 2763 and 7945 patients have been prescribed with this medication in 2017 in HSD and SIDIAP, respectively. Thus, assuming an estimated yearly incidence rate of medication use of almost 0.2 and 1% in HSD and SIDIAP, respectively, these numbers of users would be large enough to assume a 0.01 precision with 95% Confidence Intervals (CI). Given that HSD currently includes almost 1 million patients and SIDIAP almost 7,6 million, these numbers should ensure the study power.
For what concerns the safety study, the occurrence of opioid-related AEs is observed in greater than 20% of users, which is the proportion of users incurring in opioids discontinuation [14]. Such a prevalence would allow to estimate of HR=1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. tramadol (or tramadol-paracetamol). Still from preliminary evaluation, the number of DKP-TRAM users aged 75 years or older resulted 705 and 949 for HSD and SIDIAP, respectively. These numbers would ensure stable estimates to test the presence of effect modifications due to age on the risk of AEs. Indeed, still assuming an occurrence of opioid-related AEs greater than 20% (likely higher among patients aged 75 or older), a minimum OR equal 1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. tramadol (or tramadol-paracetamol) is estimable among this patients' category as well.

9.6. DATA MANAGEMENT

Data from the two different databases will be pooled after local extraction, validation and data-cleaning, and not with single data extraction algorithm for all the databases. The reason for this is that these databases use different coding schemes (e.g. ICD9CM and

ICD10) and their content comes from different data sources (e.g., general practitioners' records, and hospital discharge diagnoses).
To reunite differences across coding system, all variables will be defined according to a multi-step and iterative process for the harmonization of event data.

9.6.1 DEFINITION OF DATA EXTRACTION ALGORITHM

Based on the relevant diagnostic codes and key words (for free-text search), a data extraction algorithm will be constructed for each event based on the consensus of the data providers. This data extraction algorithm will then be implemented in HSD and SIDIAP. Every extraction will be validated by data providers according to pre-specified criteria. Expected frequency of diagnoses and medications use and correctness of variables categorization (e.g. smoking categories) will be checked including the burden of missing data.

9.7. DATA ANALYSIS

9.7.1 PRIMARY OBJECTIVES

Incidence rate of DKP-TRAM use

The crude IR of use of DKP-TRAM will be calculated considering patients prescribed with DKP-TRAM during the year (numerator) on the total number of patients being active (alive and currently registered with their GPs) in the database on December 31, 2017. This calculation will be repeated for 2018 by excluding patients prescribed with DKP-TRAM in the year prior. The crude IR will be calculated considering patient's person-times as denominator as well. Age and sex-standardized IR will be calculated according to indirect method.
Concerning the other events under study, continuous variables will be described as absolute numbers (considering both valid and missing cases), means with standard deviations and/or median values with interquartile range, according to the shape of data distribution.
Categorical variables will be described as percentages. Missing data will be quantified and used as specific categories in the analysis [39], [40].
To characterize patterns of use for DKP-TRAM, we will calculate the crude IR using the total number of patients exposed to DKP-TRAM (numerator), and the total number of person-years cumulated during follow-up by the whole source population (denominator) stratified by age, gender, study period, country/database, comorbidities and co-medications. The 95% CI will be derived for IR using Poisson distribution.
The duration of prescriptions of DKP-TRAM will be investigated according to Kaplan-Meier methods (using both SIDIAP and HSD databases) in an attempt to clarify the burden of drug discontinuation, namely those DKP-TRAM users who will stop DKP-TRAM and/or switch to another therapy. Stopping will be defined as the occurrence of any AEs (see 9.3.2 SECONDARY OBJECTIVES: Outcome), end of registration of patient' data, death, the fifth day of follow-up, whichever will come first. In the light of the GP's delay for AEs registration, the longest durations of follow-up (i.e. censoring criteria) will be varied from the 5th to the 15th,or the 30th day of follow-up.

9.7.2 SECONDARY OBJECTIVES

For this objective, both descriptive and inferential analysis will be performed.
Continuous variables will be described as absolute numbers, and as means with standard

deviations or median values with interquartile range, according to the shape of data distribution. Mean or median values will be performed using the t-Student or Mann-Whitney test, respectively. Categorical variables will be described as percentages, and they will be compared among different categories of covariates, using Chi-square test. Missing data will be described and included in the analyses using a specific category. Patients exposed to DKP-TRAM will be compared to those exposed to tramadol (or tramadol-paracetamol). When the nested case-control analysis will be adopted, the same analyses will be conducted to compare cases and respective controls.

Incidence rates of acute AEs

We will calculate the IR for each AEs using the total number of patients incurred in an AE (numerator), and the total person-years cumulated during follow-up by the exposed population (denominator) stratified by new users of DKP-TRAM and new users of tramadol as monotherapy (and as tramadol-paracetamol combinations). The person-times of exposure will be split according to a time-dependent approach. The 95% CI will be derived for IR using Poisson distribution. IR will only be estimated in case of at least 5 events per exposure category.

We will estimate the HR, and related 95% CI, for AEs occurred in new users of DKP-TRAM vs. new users of tramadol as monotherapy (or as tramadol-paracetamol combinations), using Cox regression time-dependent models. HRs will only be estimated in case of at least 5 events per exposure category. The reference category will be the use of tramadol as monotherapy (including tramadol-paracetamol as well). To control for potential confounding, the following covariates (all measured at the index date) will be included in the final model (see Table 1-2):

- Age
- Gender
- Comorbidity
- Concomitant drug use

We will estimate conditional logistic regression in case of nested case-control analysis, which will provide Odds Ratio (OR) and related 95% CI. The exposure will be categorized according to dose and duration of use in DKP-TRAM users, defining mixed users of tramadol and DKP-TRAM as a separated category.

To account for the presence of different treatment courses during follow-up, we will categorise the exposure into two mutually exclusive subgroups according to the recency of use. Namely, patients exposed to DKP-TRAM, or to the compared medications, in the month preceding and/or on the index date will be the current users. Those being excluded from this category will be the recent users. By doing so, the exposure categories will be modelled according to a time-dependent fashion. In addition, we will identify “new” current users (i.e. those who will not exposed to treatment in the recent time-window but in the current time-window only) and “old” current users (i.e. those who will be exposed to treatment in the current and recent time-window).

Operationally, we will therefore identify the cumulated dosages or duration of tramadol (in days) being registered by the current users. We will categorise the durations in terciles as it will be registered in the controls as the reference of general population. This approach will allow us to compare the cumulative dosage and duration categories among

DKP-TRAM users versus those cumulated by tramadol (or tramadol-paracetamol combination) users.

9.7.3 SECONDARY ANALYSES

The prescription of DKP-TRAM is likely influenced by previous prescription of tramadol (or tramadol-paracetamol combination), especially in terms of AEs already experienced by patients. Indeed, we will exclude previous use of tramadol preceding the index date to minimize selection bias. However, the knowledge of how GPs select patients to use DKP-TRAM and the how this behaviour acts on the risk of AEs might be informative. The Cox regression model comparing the risk of AEs among DKP-TRAM users vs. tramadol users (or tramadol-paracetamol combinations), will be therefore re-run including in the cohort previous users of tramadol as well. In addition, given that older patients are more prone to incur in such AEs [1], the analyses concerning the risk of AEs among DKP-TRAM users will be re-run limiting the cohort to patients aged 75 years or older.

Sensitivity analyses

In the sensitivity analysis we will change the follow-up for the evaluation of acute AEs. We will therefore change the duration of follow-up from 90 to 30, 60, 120 days, and the entire available follow-up. Then, we will re-run the primary model by imputing missing data for smoking and BMI according to multiple imputation methods [41]. Finally, given the potential difference in terms of indication and severity of pain among DKP-TRAM users vs. tramadol users, we will re-run the primary model by adjusting the analysis for propensity score. The covariates reported in Table 1-2 (except for previous use of tramadol) will be used in a logistic regression model to estimate the propensity score to be prescribed with DKP-TRAM instead or tramadol as monotherapy [42]. Finally, the primary model will be rerun by recoding the exposure into three categories: DKP-TRAM, tramadol and tramadol-paracetamol combination.

9.8. QUALITY CONTROL

The study will be conducted according to the guidelines for Good Pharmaco-epidemiology Practice (GPP) [43].

The two databases have experience in conducting pharmaco-epidemiological research and research is done by researchers trained in pharmaco-epidemiology. In addition; the databases are representative of the respective countries and database specific disease prevalence rates are in line with what has been published before.

All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement. Only validated software (SAS version 9.2, SAS Institute Inc., Cary, NC) will be used for statistical analyses.

9.9. LIMITATIONS OF THE RESEARCH METHODS

The limitations of this study will be related to the availability and level of detail of data. In fact, not all potential confounders (e.g. life style factors such as smoking, BMI, race) are contained in databases and not all variables contain the information in desired detail. Both databases have information on prescriptions or on dispensing and not on actual drug intake. However, the risk of misclassification of exposure is lower in a new-user design study, because it is known that adherence to drugs is higher at initiation of therapy.

Misclassification of endpoints as well as confounders is possible, especially because the information on underlying diseases is based on disease codes. For this reason, comparison of IRs of endpoints between databases will allow checking for internal and external validity. Furthermore, the primary objective of data collection of these databases is the management of patients and not medical research. For this reason, only relevant events related to the patient's care are collected in the databases. Finally, we included only two European data sources and the results may suffer from limitations that they will not be fully representative.

10. PROTECTION OF HUMAN SUBJECTS

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All of the databases used in this study are currently already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

The protocols will be reviewed by the Institutional Review Boards of the respective databases. As this is a non-interventional observational study, there is no need for ethical approval in Italy.

For SIDIAP (Spain), both the scientific committee for SIDIAP studies and the local ethics committee will evaluate the protocol before the study can be carried out.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology [43], the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [44], and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' [45].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the new guideline on good pharmacovigilance practice (EMA/873138/2011) there is no requirement for reporting of adverse drug reactions from secondary use of data (such as electronic health care databases). Reports of adverse events/reactions will not be provided on an individual case level; only aggregated safety results, i.e. the overall association between an exposure and an outcome will be reported in the final study report.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As the study progresses, Menarini will submit the progress/interim reports and final study report to EMA. The study progress and interim results will be reported in yearly intervals following first launch of DKP-TRAM in Europe.

Dissemination activities to be undertaken will have mainly, although not exclusively, a scientific nature (articles, presentations at conferences, etc.). In order to allow EMA to review in advance the results and interpretations to be published, Menarini will communicate to the EMA the final manuscript of an article within two weeks after first acceptance for publication.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
Annex 2	v01	26 March 2018	ENCePP checklist for study protocols
Annex 3	v01	26 March 2018	Additional information
Annex 3.1	v01	26 March 2018	Co-morbidity definition

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 (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen (DKP-TRAM)

Study reference number:

EUPAS24858

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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☐	☒	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

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)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

Section 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)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3, 9.7
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)	☒	☐	☐	9.7
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)	☐	☒	☐	

Comments:

This is the case of primary data collection. Thus, adverse Events will not be collected.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:	☒	☐	☐	9.2.2
4.2.1 Study time period?	☒	☐	☐	9.2.3
4.2.2 Age and sex?	☒	☐	☐	9.4
4.2.3 Country of origin?	☒	☐	☐	9.3
4.2.4 Disease/indication?	☒	☐	☐	9.2.4
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)	☒	☐	☐	9.2.3

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)	☒	☐	☐	9.3.1, 9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1, 9.3.2
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.7
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2.4

Comments:

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?	☒	☐	☐	9.3.1, 9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1, 9.3.2
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)	☒	☐	☐	9.7
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment?				

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
(e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Several sensitivity analyses will be conducted to verify the robustness of the results.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.3.1, 9.3.2, 9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.3
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)				
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.7.3, 9.9
	☒	☐	☐	9.7.3, 9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.7.3

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:

The analysis will be re-run among patients aged 75 or older given their higher risk of incurring in the events under study.

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, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7.3
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.3
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

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)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
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:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias?	☒	☐	☐	9.7.3, 9.9
12.1.2 Information bias?	☒	☐	☐	9.7.3, 9.9
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)	☒	☐	☐	9.7.3, 9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

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?	☒	☐	☐	5

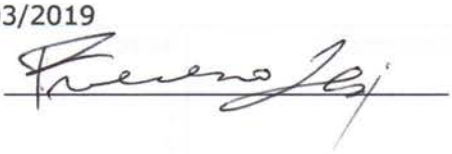
Comments:

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Francesco Lapi

Date: 11/03/2019

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Annex 3.1 Co-morbidity definition

Hepatic impairment

All codes (ICD9CM and ICD10) reported in databases ever before the period preceding or on the index date and the **ALT>40 UI/l; AST >35 UI/l; AP>140 UI/l; 7**

Furthermore, mild to moderate hepatic dysfunction or severe hepatic dysfunction were codified with Child-Pugh classification.

- **Mild to moderate hepatic dysfunction** (Score 5-6, 7-9)
- **Severe hepatic dysfunction** (score 10-15)

The Child-Pugh classification

Assessment	Degree of abnormality	Score
Encephalopathy	None Moderate Severe	1 2 3
Ascites	Absent Slight Moderate	1 2 3
Bilirubin (mg/dL)	<2 2.1-3 >3	1 2 3
Albumin (g/dL)	>3.5 2.8-3.5 <2.8	1 2 3
Prothrombin Time (seconds > control)	0-3.9 4-6 >6	1 2 3

Total Score	Group	Severity
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe

Terms	ICD9CM
Acute and subacute necrosis of liver, acute and subacute yellow atrophy of the liver, parenchymatous degeneration of liver, Acute or subacute non-viral hepatitis, acute liver failure	570*
Hepatitis	573.3*
Abnormal results of liver function studies	794.8*
Hepatic coma	572.2*

Kidney disease

All codes (ICD9CM or ICD10) or free text "dialysis" or "renal transplant" (including the presence in a waiting list for renal transplantation), ever before the period preceding or on the entry date.

Patients renal function was codified as:

- **Mild** (glomerular filtration rate ≥60 ml/min/1.73 m2),
- **Moderate** (glomerular filtration rate of 30 to 59 mL/min/1.73 m2),
- **Severe** (glomerular filtration rate 15 to 29 mL/min/1.73 m2),
- **Kidney failure** (glomerular filtration rate less than 15 mL/min/1.73 m2)

Terms	ICD9CM
Acute glomerulonephritis (included acute nephritis)	580*
Small kidney of unknown cause	589*
Diabetes with renal manifestations	250.4*
Malignant Hypertensive nephropathy	403.0*
Benign hypertensive nephropathy	403.1*
hypertensive Nephropathy (non-specific)	403.9*
Hypertensive heart and renal disease	404*
Gouty Nephropathy	274.10
Stenosis of renal artery	440.1
Renal artery aneurysm	442.1
Renal vein thrombosis and embolism	453.3
Other disorders of kidney and ureter	593*
Renal agenesis and dysgenesis	753.0
Other specified anomalies of kidney	753.3
Injury of kidney	866*
Chronic kidney disease	585
Diabetes with renal manifestations	250.4
Nephrotic syndrome with lesion of membranous glomerulonephritis	581.1
Nephrotic syndrome with other specified pathological lesion in kidney	581.8
Proteinuria	791.0
Postsurgical renal dialysis status	V45.1
Encounter for extracorporeal dialysis	V56.0

Encounter for other dialysis	V56.8
Kidney replaced by transplant	V42.0
Complications of transplanted kidney	996.81

Depression

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	**ICD9CM**
Major depressive disorder single episode	296.2
Major depressive disorder recurrent episode	296.3
Depressive disorder, not elsewhere classified	311*

Chronic obstructive pulmonary disease and allied conditions and Asthma

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	**ICD9CM**
Asthma	493
Asthma, unspecified	493.90
Nonallergic asthma Intrinsic asthma	493.1
Mixed asthma	
Atopic asthma	
extrinsic allergic asthma	493.0
Predominantly allergic asthma	
Extrinsic asthma with asthma attack	493.02
Intrinsic asthma + attack	493.12
Status asthmaticus	493.91
Extrinsic asthma with status asthmaticus	493.01
Intrinsic asthma NOS	493.10
Intrinsic asthma with status asthmaticus	493.11
chronic obstructive asthma	493.2
Other forms of asthma	493.8
Bronchitis, not specified as acute or chronic	490
Chronic bronchitis	491
Emphysema	493
Bronchiectasis	494
Extrinsic allergic alveolitis	495
Chronic airway obstruction, not elsewhere classified	496

Epilepsy

Code (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Epilepsy	345*

Chronic dyspepsia

Code (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Chronic dyspepsia	536.8

Alcohol abuse and/or alcohol-related diseases

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Alcohol dependence syndrome	303*
Alcohol abuse	305.0
Alcoholic polyneuropathy	357.5
Alcoholic cardiomyopathy	425.5
Alcoholic gastritis	535.3
Alcoholic fatty liver	571.0
Acute alcoholic hepatitis	571.1
Alcoholic cirrhosis of liver	571.2
Alcoholic liver damage, unspecified	571.3
Excessive blood level of alcohol	790.3
Personal history of alcoholism	V11.3

Drug abuse or dependence

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Drug dependence	304*
Nondependent cannabis abuse	305.2
Nondependent hallucinogen abuse	305.3
Nondependent sedative, hypnotic or anxiolytic abuse	305.4
Nondependent opioid abuse	305.5
Nondependent cocaine abuse	305.6
Nondependent amphetamine or related acting sympathomimetic abuse	305.7
Nondependent antidepressant type abuse	305.8
Nondependent other mixed or unspecified drug abuse	305.9

Mental health diagnoses and personal history of mental disorder

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Transient mental disorders	293*
Persistent mental disorders	294* (excluding 294.0, 294.1)
Schizophrenic disorders	295*
Episodic mood disorders	296* (excluding 296.2, 296.3)
Delusional disorders	297*
Other nonorganic psychoses	298*
Pervasive developmental disorders	299*
Anxiety, dissociative and somatoform disorders	300*
Personality disorders	301*
Personal history of schizophrenia	V11.0
Personal history of affective disorders	V11.1
Personal history of neurosis	V11.2
Personal history of other mental disorders	V11.8
Personal history of unspecified mental disorder	V11.9

Hallucinations

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Psychophysical visual disturbances	368.16
Hallucinations	780.1

Dementia and memory deficit

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Amnestic disorder	294.0
Personality change due to conditions classified elsewhere	310.1
Alzheimer's disease	331.0
Senile dementia, uncomplicated	290.0
Presenile dementia	290.1
Senile dementia with delusional features	290.2
Senile dementia with delirium	290.3
Vascular dementia	290.4
Jakob-Creutzfeldt disease	046.1
Progressive multifocal leukoencephalopathy	046.3
Other alcoholic dementia	291.2
Drug-induced dementia	292.82
Pick's disease	331.1
Senile degeneration of brain	331.2
Cerebral degeneration in diseases classified elsewhere	331.7
Other cerebral degeneration	331.8
Cerebral degeneration, unspecified	331.9
Parkinson's disease	332.0
Drug-induced persistent amnestic disorder	292.83
Amnesia (retrograde)	780.9

Cognitive Impairment after trauma

Codes (ICD9CM) ever before the period preceding or on the index date

Terms	ICD9CM
Late effect of intracranial injury without mention of skull fracture	907.0