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Drug Utilisation Study – Evaluation of the Use of Nepafenac in Selected European Populations

Study Core Protocol Summary

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ABSTRACT

Title

Evaluation of the Use of Nepafenac in Selected European Populations

Rationale and Background

Nepafenac (Nevanac) is an ophthalmic non-steroidal agent that has been available for some time for the prevention and treatment of postoperative pain and inflammation after cataract surgery. It is prescribed in hospitals or ophthalmology clinics. In December 2011, the European Commission approved a new indication: to reduce the risk of macular oedema after cataract surgery in patients with diabetes. Launch in Europe is anticipated in 2012. For this indication, nepafenac is to be prescribed by ophthalmologists in an outpatient setting for a treatment duration up to 60 days.

The European Medicines Agency (EMA) is concerned about potential off-label use of nepafenac, and Alcon has agreed with the EMA to conduct a drug utilisation study to characterise off-label use. Other selected ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs), such as bromfenac, will be included in the study to contextualize findings.

Research Question and Objectives

- To describe the characteristics of nepafenac users (e.g., demographics, medical history including concurrent ocular and systemic diseases, and use of other medications pre and post nepafenac start)
- To characterise off-label nepafenac use
  - Use not associated with cataract surgery (patients with and without diabetes)
  - Use associated with cataract surgery longer than 21 days in patients without diabetes or longer than 60 days per eye in patients with diabetes
  - Use in individuals aged less than 19 years
- In a similar manner, to describe the characteristics of users of other selected individual ophthalmic NSAIDs, such as bromfenac, and the use of those drugs

Study Design

This will be a cohort study of users of nepafenac and users of other selected ophthalmic NSAIDs.

Population

The study will be conducted in the network of databases from the National Health Databases in Denmark and the PHARMO Record Linkage System database (PHARMO-RLS) of the PHARMO Institute for Drug Outcomes Research in the Netherlands.

The study cohort will consist of new users of nepafenac and new users of other selected ophthalmic NSAIDs with at least 6 months of previous enrolment in the database. No exclusion criteria will be applied. Each member of the study cohort will be followed from the cohort entry date to the earliest of the following dates:

- 60 days after the last prescription of a drug of interest
- End of the study period
- Death
- Disenrolment from the database

Variables

Exposure will be based on dispensed prescriptions. Whenever available, the duration of exposure will be based on days of supply; otherwise, it will be estimated as up to 30 days per bottle, based on the volume of the vial and the recommended dosage. Drugs will be assessed individually.

The *medical condition associated* with nepafenac or other ophthalmic NSAIDs will be derived from diagnoses and procedures around the prescription dispensing date.

Patient characteristics of interest are age, sex, selected comorbidities, and concomitant medications.

Data Sources

National Health Databases, Denmark

The centralised Civil Registration System in Denmark enables identification of each person in the entire Danish population and the possibility of linkage to all Danish registries containing civil registration numbers, such as the Danish National Registry of Patients, Danish National Prescription Database, Prescription Databases of the Central Denmark Region, and the Danish Registry of Causes of Death.

PHARMO, the Netherlands

The PHARMO Institute for Drug Outcomes Research has a network of databases that includes complete patient-level information on patient demographics, mortality, in-hospital and ambulatory drug dispensing, hospital morbidity, clinical laboratory test results, pathology reports, and general practitioner for 3.2 million community-dwelling inhabitants.

Data Analysis

The analysis will be descriptive.

Baseline Analysis

- At the cohort entry date, characteristics of users of nepafenac and users of other selected ophthalmic NSAIDs will be assessed based on review of data from 6 months prior to that date.
- Medical condition associated with use of nepafenac or other selected ophthalmic NSAIDs will be assessed.

Treatment Period Analysis

- Evaluation of patterns of duration of prescriptions for nepafenac or other ophthalmic NSAIDs, focusing on (1) use longer than 3 weeks among patients without diabetes and with recent cataract surgery or (2) use longer than 60 days among patients with diabetes with recent cataract surgery
- Evaluation of patterns of duration of prescriptions for nepafenac or other ophthalmic NSAIDs in patients without previous cataract surgery
- Evaluation of the proportion of patients using specific medications during treatment with nepafenac or other ophthalmic NSAIDs.

AMENDMENTS AND UPDATES

Not applicable.

1 RATIONALE AND BACKGROUND

Nepafenac is a topical ophthalmic non-steroidal anti-inflammatory pro-drug that is converted in the eye to the non-steroidal anti-inflammatory drug (NSAID) amfenac. In Europe, it has been approved for (1) prevention and treatment of postoperative pain and inflammation associated with cataract surgery in adults—to be used from the day prior to surgery to up to 21 days after the surgery (approval in December 2007)—and (2) reduction in the risk of postoperative macular oedema associated with cataract surgery in adult patients with diabetes—to be used from the day prior to the surgery to up to 60 days after the surgery (approval in December 2011). With the approval of the second indication, the European Medicines Agency (EMA) requested Alcon to conduct a drug utilisation study, this goal of which is to describe the off-label use of nepafenac. After systematic assessment of availability of information and the use of nepafenac in candidate databases, it is recommended that the drug utilisation study be conducted using the Danish National Registry of Patients (Denmark) and PHARMO medical record linkage system (the Netherlands).

This protocol describes the proposed drug utilisation study in Denmark and the Netherlands. Other selected individual ophthalmic NSAIDs, such as bromfenac, will be included in the study to provide context to the assessment of nepafenac off-label use.

2 RESEARCH QUESTION AND OBJECTIVES

- To describe the characteristics of nepafenac users (e.g., demographics, medical history including concurrent ocular and systemic diseases, and use of other medications pre and post nepafenac start)
- To characterise off-label nepafenac use
  - Use not associated with cataract surgery (patients with and without diabetes)
  - Use associated with cataract surgery longer than 21 days in patients without diabetes or longer than 60 days per eye in patients with diabetes
  - Use in individuals aged less than 19 years
- In a similar manner, to describe the characteristics of users of other selected individual ophthalmic NSAIDs, such as bromfenac, and the use of those drugs

3 RESEARCH METHODS

3.1 Study Design

This will be an observational cohort study of users of nepafenac and users of other selected ophthalmic NSAIDs, such as bromfenac.

3.2 Setting

The study will be conducted in the network of databases from the National Health Databases in Denmark and the PHARMO Record Linkage System database (PHARMO-RLS) of the PHARMO Institute for Drug Outcomes Research in the Netherlands.

Patients will become eligible for cohort entry after 6 months of enrolment in the databases. New use of a drug of interest will be defined as the first prescription for the drug after 6 months free of prescriptions for the specific drug. Follow-up will start with the first new prescription (cohort entry date) and will continue until the earliest of the following dates:

- 60 days after the last prescription for a drug of interest
- End of the study period (estimated to be 15 months after launch for the new indication)
- Death
- Disenrolment from the database

The 6 months prior to the cohort entry date will be the baseline period; baseline characteristics will be assessed during this interval.

3.3 Variables

3.3.1 Therapy Episodes

The drugs of interest will be identified through their Anatomical Therapeutic Classification (ATC) code.

Exposure will be assumed to start on the prescription date, which is the date of the drug dispensing in both data sources. Duration of treatment will be ascertained from days supply information in the prescription data, when this information is available in the database; the exposure episode associated with the prescription will be assumed to finish the last day of the days supply. In the Danish data, no information on days supply is available. In this situation, the duration of treatment will be estimated from the content of the bottle and the posology of the medication.

3.3.2 Medical Condition Associated With Each Therapy Episode

This condition will be derived from diagnoses and procedures dated within 30 days before or procedures dated within 30 days after the prescription dispensing date:

- Scenario 1: the condition (diagnosis or procedure) is dated before the prescription. The patient visits his or her physician, who records the reason for the visit (which will be used as the medical condition associated with the therapy episode) and issues a prescription. The prescription is filled (and dated) a few days later.

- Scenario 2: the procedure is dated after the prescription. An ophthalmic surgery or procedure is planned. The patient goes to the clinic for his or her preoperative visit, and the physician issues the prescription. The patient fills the prescription; the procedure (which will be used as the condition associated with the therapy episode) takes place (and is dated) a few days later.

Target conditions for this evaluation are cataract surgery, refractive procedures (photorefractive keratotomy, laser in situ keratotomy, non-specified or other refractive procedures), other ophthalmic procedures, two or more ophthalmic surgeries or procedures, dry eye/Sjögren syndrome, uveitis/iritis, ophthalmic manifestations of allergy, ocular pain, macular oedema, vitreous-related disorders.

If codes for more than one condition are found, including cataract surgery, it will be assumed that the condition associated with the therapy episode was cataract surgery. If there are codes for more than one condition, not including cataract surgery, we will assume the condition associated with the therapy episode is the one closest to the prescription date.

3.3.3 Identification of Cataract Surgery, Other Potential Conditions Associated With Therapy Episodes, and Diabetes

Cataract surgeries will be identified from diagnostic and procedure codes. In the Danish registries, cataract surgeries will be captured from hospital discharge records. In the PHARMO-RLS, cataract surgeries will be identified primarily from procedure codes in hospital data. Procedures performed in specialist clinics are not recorded; however, referrals for the surgery and related codes are recorded. To ensure that data capture is complete, in the PHARMO-RLS we will also identify cataract surgeries reported in the outpatient files as referrals and related codes, and through free-text search.

In the present study, it is important to determine whether each enrolled individual had one or both eyes operated and the date of each surgery. When more than one code for cataract surgery per person is present, we will apply the following considerations:

- When codes specify surgery in both eyes, we will assume that both eyes have undergone surgery.
- Because it is atypical to have both eyes operated the same day, we will assume that all codes for cataract surgery with the same date correspond to a single surgery, unless codes specify surgeries on both eyes.
- When codes for two different dates are identified, we will assume two different surgeries occurred, one on each date (regardless of the number of codes for cataract surgery per day).

Diabetes status will be ascertained from outpatient and inpatient diagnostic codes for diabetes, diagnostic codes for diabetes complications (e.g., diabetic nephropathy, diabetic retinopathy, diabetic foot), procedural codes for the treatment of such complications (e.g., photocoagulation for diabetic retinopathy), and prescriptions for antidiabetic drugs.

3.3.4 Baseline Ophthalmic and Systemic Conditions and Baseline Use Of Medications

The presence of baseline ophthalmic and systemic conditions will be ascertained from diagnostic or procedural codes during the 6-month baseline period. The characteristics of interest are age, proportion of patients aged ≥ 19 years, sex, ophthalmic conditions and procedures, bleeding disorders, and autoimmune disorders (rheumatoid arthritis, ankylosing spondylitis, Behçet's disease, Sjögren syndrome, systemic lupus erythematosus).

Baseline medication use will be ascertained from pharmacy data.

3.3.5 Concomitant Medications

Ophthalmic and systemic medications of interest will be ascertained. Two or more drugs will be considered to be used concomitantly if the therapy episodes overlap.

3.4 Data Sources

3.4.1 Danish National Registry of Patients, Denmark

The Danish health care system provides universal coverage to all Danish residents (5.5 million inhabitants; http://www.si-folkesundhed.dk/Forskning.aspx). Health care coverage includes visits to general practitioners and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health care system. The centralised Civil Registration System in Denmark allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registries containing civil registration numbers such as the Danish National Registry of Patients, Danish National Prescription Database, Prescription Databases of the Central Denmark Region, and the Danish Registry of Causes of Death. Data collected in these registries are available for research purposes. This database has been widely used to study ophthalmic conditions. The conduct of research includes collaboration with a local university or investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle data (Danish Data Protection Agency, 2011; Danish National Board of Health, 2011). All applications have to be submitted in Danish.

The Danish National Registry of Patients provides data on all admissions to hospitals since January 1, 1977, and on visits to outpatient clinics and emergency departments since 1995. Diagnosis codes are registered by the discharging physician at the time of the hospital discharge. Hospital discharge diagnoses are currently recorded using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes. Data on surgical procedures, including cataract extractions, are also recorded.

The Danish National Prescription Database provides patient-level data and contains data on drug prescriptions dispensed by pharmacies to individuals receiving ambulatory care since

1994. Denmark also has two regional prescription databases (Odense and Aarhus) established for research purposes. The national and regional prescription databases collect data on reimbursed drugs. In addition, the Danish National Prescription Database collects data on unreimbursed drugs. The Danish National Prescription Database has the ability to capture nepafenac use: as of 31 December 2010, 30,000 prescriptions have been issued for an estimated 14,607 patients (Danish Medicines Agency, 2011).

Regarding use of concomitant medications, the Danish National Prescription Database includes prescriptions for ophthalmic drugs (e.g., ophthalmic diclofenac, ophthalmic flurbiprofen) and non-ophthalmic drugs, topical or systemic, used in the primary care setting. Dose and duration of prescription use are not available, but can be derived from the number of prescriptions and the dispensed strength. The Danish National Prescription Database has been used to study selected ocular endpoints, including cataracts, in many occasions (Haargaard et al., 2004; Rasmusen et al., 2011).

3.4.2 PHARMO Medical Record Linkage System, the Netherlands

The PHARMO medical record linkage system is a population-based data tracking system that includes complete patient-level information on patient demographics, mortality, in-hospital and ambulatory drug dispensing, hospital morbidity, clinical laboratory test results, pathology reports, and general practitioner information for 3.2 million community-dwelling inhabitants of 65 municipal areas in the Netherlands (http://www.pharmo.nl/).

Hospital morbidity data are available in the Dutch National Medical Register. Hospital discharge diagnoses are recorded using ICD-9-CM[1] codes. The drug exposure inpatient database comprises hospital pharmacy data collected in a growing number of hospitals in the Netherlands. Currently, hospital data are collected at the patient level for more than 1 million patients. The hospital pharmacy database consists of a representative sample of hospital pharmacies scattered over the Netherlands. The inpatient database includes data on inpatient medication orders (type of drug, dose, time of administration, and duration of use), reasons for hospitalisation (discharge diagnoses), duration of hospitalisation, and procedures.

For the study on nepafenac use, a combination of hospital and ambulatory drug dispensing, hospital morbidity, and general practitioner databases is needed. Information on nepafenac is captured in the drug exposure inpatient database and the outpatient pharmacy database. Information on cataract extraction is available in hospital morbidity data, except for procedures performed in specialist clinics. For those procedures, general practitioner data will be used to identify referral to a specialist for extraction of the cataract or the presence of cataract as a disease. Medical records could be reviewed.

The PHARMO medical record linkage system has been used to study diabetic cataract (Van der Linden et al., 2009).

[1] International Classification of Diseases, Ninth Revision, Clinical Modification.

3.4.3 Suitability of the Data Sources for this Research

To evaluate the potential of these and other data sources for this research effort, we have conducted a feasibility evaluation. We selected 5 European countries and assessed the potential of their databases for the current drug utilisation study. The selection of the candidate countries/databases was based on the 2012 expected sales for nepafenac (provided by Alcon), expected launch date or date of price change (provided by Alcon), nepafenac reimbursement status, and availability of data suitable for a drug utilisation study. The evaluation of the candidate databases was based on their ability to capture nepafenac use (current use, which reflects use under the first indication, and expected use), characteristics of nepafenac users, concomitant use of other medications, and published literature on related outcomes using each database. We proposed that the drug utilisation study be conducted using the Danish National Registry of Patients (Denmark) and PHARMO medical record linkage system (the Netherlands). The Clinical Practice Research Datalink (CPRD; United Kingdom) and the Swedish National Registers will be considered backup data sources.

3.5 Data Management

Data will be managed and analyses will be implemented by the database custodians according to protocols developed in collaboration with RTI Health Solutions (RTI-HS) and the research institutions that maintain the databases.

3.6 Data Analysis

The analysis will be descriptive (i.e., no statistical tests will be conducted). The analysis will be performed separately for each country and each individual drug of interest.

3.6.1 Baseline Analysis

Baseline characteristics of users of nepafenac and users of other selected ophthalmic NSAIDs in each population will be displayed in a tabular format. The characteristics of interest are age (mean age, proportion of patients aged ≥ 19 years, mean age among patients aged ≥ 19 years, proportion of patients aged ≤ 18 years, mean age among patients aged ≤ 18 years); sex; and systemic conditions including autoimmune disorders, bleeding disorders, and diabetes mellitus.

The distribution of conditions associated with drug use by age will be presented as a table. Potential conditions considered are cataract surgery, refractive procedures (photorefractive keratotomy, laser in situ keratotomy, and non-specified or other refractive procedures), other ophthalmic procedures, two or more ophthalmic surgeries or procedures, dry eye/Sjögren syndrome, uveitis/iritis, ophthalmic manifestations of allergy, ocular pain, macular oedema, and vitreous-related disorders.

In patients with cataract surgery associated with use of nepafenac or other selected ophthalmic NSAIDs, we will also assess the presence of previous ophthalmic conditions and procedures, e.g., previous cataract surgery, refractive procedures (photorefractive keratotomy, laser in situ keratotomy, non-specified or other refractive procedures), other ophthalmic procedures, two or more ophthalmic surgeries or procedures, dry eye/Sjögren syndrome, uveitis/iritis, ophthalmic manifestations of allergy, ocular pain, macular oedema, and vitreous-related disorders.

3.6.2 Drug Utilisation Analysis

The drug utilisation analysis will involve the calculation of proportions of use stratified by age, medical conditions associated with nepafenac or other selected ophthalmic NSAID therapy episodes, duration, and presence of comorbidities or comedications. The following proportions of use are of special interest:

- Use associated with cataract surgery for longer than 21 days in adult patients without diabetes
- Use associated with cataract surgery for longer than 60 days in adult patients with diabetes
- Concomitant use of other medications in patients with or without surgery.
- Concurrent use of medications that may delay healing (e.g., other ophthalmic NSAIDs, systemic or ophthalmic steroids)
- Concurrent use of medications that may increase bleeding time (e.g., ophthalmic NSAIDs, antiplatelets, anticoagulants)

Results will be displayed in a tabular format for each country.

3.7 Quality Control

Standard operating procedures at each research centre will guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

At RTI-HS an independent Office of Quality Assurance will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry, data transfer, and institutional review board documentation. Such audits would be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

A quality-assurance audit of this study may be conducted by the sponsor or the sponsor’s designees.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM and DVD), with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

3.8 Limitations and Strengths of the Research Methods

Neither the National databases in Denmark nor the PHARMO database have direct information on indication. Although the study design intends to capture all conditions and procedures around the dispensing date, errors could be made when assigning the medical condition or procedures as indications. However, cataract surgeries are less likely to be missed than the other ophthalmic conditions.

In PHARMO, information on cataract extraction is available in hospital morbidity data, except for procedures performed in specialist clinics. For those procedures, general practitioner data will be used to identify referral to the specialist for extraction of the cataract or the presence of cataract as a disease, or specialist letters or reports. Medical records can be reviewed. However, if this process does not enable identification of 100% of the cataract surgeries, some nepafenac use could be misclassified as off-label.

As in any study on off-label medication utilisation, we cannot ignore that clinicians might record diagnoses aligned with approved indications, which would lead to an underestimation of off-label use. However, because in this study the condition associated with nepafenac use will be retrieved from medical information contemporary to the dispensing, rather than from pharmacy data, we do not expect this potential concern to be a problem. In a prospective study with data specifically collected to assess off-label use, clinicians may be more inclined to align diagnoses with approved indications than when working in their day-to-day clinical care setting.

4 PROTECTION OF HUMAN SUBJECTS

Institutional review board approval and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations.

In Denmark, the study will require notification of or approval by the ethics committee (Danish Data Protection Agency, 2011; Danish National Board of Health, 2011). PHARMO is not allowed to disclose any information that may be traced back to identifiable persons. Therefore, no approval of ethics committees will be needed in the Netherlands.

5 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the new *Guideline on Good Pharmacovigilance Practices (GPV), Module VI* (EMA and Heads of Medicines Agencies, 2012),

> *"For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarised in the final study report."*

For studies in which the research team uses data from automated health care databases only, according to the International Society for Pharmacoepidemiology (2007) *Guidelines for Good Pharmacoepidemiology Practices (GPP),*

> *"Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines."*

6 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, study status, and reports will be included in regulatory communications in line with the risk management plan and other regulatory milestones and requirements.

When reporting results of this study, the checklist entitled Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (2007) will be followed.

7 OTHER GOOD RESEARCH PRACTICE

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (2007) *Guidelines for Good Pharmacoepidemiology Practices (GPP)*, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2011a).

The ENCePP *Checklist for Study Protocols* (ENCePP, 2011b) will be completed, and the study will be registered in the ENCePP study registry (ENCePP, 2010).

8 REFERENCES

Danish Data Protection Agency. Introduction to the Danish Data Protection Agency. Updated April 14, 2011. Available at: http://www.datatilsynet.dk/english/. Accessed 8 March 2012.

Danish Medicines Agency. Medicine sales in Denmark. 2011. Available at: http://www.medstat.dk/en. Accessed 3 April 2012.

Danish National Board of Health. Web site. 2011. Available at: http://www.sst.dk/English.aspx. Accessed 8 March 2012.

European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP). Module VI – management and reporting of adverse reactions to medicinal products (EMA/873138/2011). 20 February 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123203.pdf. Accessed 24 May 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Electronic register of studies. Version 3.0.46. 2010. Available at: http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed 8 March 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP checklist for study protocols (revision 1). July 25, 2011b. Available at: http://www.encepp.eu/standards_and_guidances/index.html. Accessed 8 March 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology. May 13, 2011a. Available at: http://www.encepp.eu/standards_and_guidances/index.html. Accessed 8 March 2012.

Haargaard B, Wohlfahrt J, Fledelius HC, Rosenberg T, Melbye M. Incidence and cumulative risk of childhood cataract in a cohort of 2.6 million Danish children. Invest Ophthalmol Vis Sci. 2004 May;45(5):1316-20.

International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Updated Apr 2010. Available at: http://www.icmje.org/urm_main.html. Accessed 8 March 2012.

International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Apr 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed 8 March 2012.

Lafuma A, Salmon JF, Robert J, Berdeaux G. Treatment persistence and cost-effectiveness of latanoprost/latanoprost-timolol, bimatoprost/bimatoprost-timolol, and travoprost/travoprost-timolol in glaucoma: an analysis based on the United Kingdom General Practitioner Research Database. Clin Ophthalmol. 2011;5:361-7.

Rasmussen LD, Kessel L, Molander LD, Pedersen C, Gerstoft J, Kronborg G, et al. Risk of cataract surgery in HIV-infected individuals: a Danish Nationwide Population-based cohort study. Clin Infect Dis. 2011 Dec;53(11):1156-63.

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. STROBE checklists. 2007. Available at: http://www.strobe-statement.org/index.php?id=available-checklists. Accessed 8 March 2012.

van der Linden MW, Plat AW, Erkens JA, Emneus M, Herings RM. Large impact of antidiabetic drug treatment and hospitalizations on economic burden of diabetes mellitus in The Netherlands during 2000 to 2004. Value Health. 2009 Sep;12(6):909-14.

Annex I. ENCePP Checklist

ENCePP Checklist for Study Protocols (Revision 2)

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

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

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

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	11
1.1.2 End of data collection[2]	☒	☐	☐	11
1.1.3 Study progress report(s)	☒	☐	☐	11
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	22
1.1.6 Final report of study results	☒	☐	☐	11

Comments:

The protocol specifies that the study will be registered in the EU PAS register, but the protocol does not specify it as a milestone.

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

[2] Date from which the analytical dataset is completely available.

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

Comments:

This is a drug utilization study, and there are no hypothesis under study.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12-15
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15-17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12-13
4.2.2 Age and sex?	☒	☐	☐	12-13
4.2.3 Country of origin?	☒	☐	☐	12-13
4.2.4 Disease/indication?	☒	☐	☐	12-13
4.2.5 Co-morbidity?	☒	☐	☐	12-13
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	13

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	13
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	13, 19
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	13
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	13
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Only current exposure is of interest.

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

Comments:

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

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	13, 15-17
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☒	☐	☐	13-17

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	13, 15-17
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	13-17
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	15-17
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	15-17

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	17

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	18, 19
10.3 Are descriptive analyses included?	☒	☐	☐	18
10.4 Are stratified analyses included?	☒	☐	☐	18, 19
10.5 Does the plan describe the methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	19
11.3 Are methods of quality assurance described?	☒	☐	☐	19

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	19-20
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	20-21

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	19-20
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	17
12.3 Does the protocol address other limitations?	☒	☐	☐	19-20

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	20
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☒	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	21
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	21

Comments:

Name of the main author of the protocol: Alejandro Arana

Date: 12 / Oct / 2013

Signature: