ABCD

Statistical and Epidemiological Analysis Plan

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BMI	Body Mass Index
CBV	Centraal Beheer Verrichtingenbestand (Dutch) [Central File Management Operations]
COPD	Chronic Obstructive Pulmonary Disease
DDD	Defined Daily Dose
EMA	European Medicines Agency
EphMRA	European Pharmaceutical Market Research Association
FEV1	Forced Expiratory Volume in 1 Second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner or General Practice
ICD	International Classification of Diseases
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICD-9	International Classification of Diseases, 9th Revision
ICPC	International Classification of Primary Care
ICS	Inhaled Glucocorticosteroid
LABA	Long-Acting Beta2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LPD	Longitudinal Patient Database
NCSP	Nordic Medico-Statistical Committee Classification of Surgical Procedures
PASS	Postauthorisation Safety Study
PHARMO	Institute for Drug Outcomes Research (the Netherlands); also short for the PHARMO Database Network
PHARMO-GP	a data subset of PHARMO Database Network with information from GPs
RWE	Real-World Evidence
SABA	Short-Acting Beta2-Agonist
SAMA	Short-Acting Muscarinic Antagonist

Term	Definition / description
WHO	World Health Organization

3. INTRODUCTION

This statistical epidemiologic analysis plan (SEAP) provides a description of the plan for conducting the analyses for a drug utilisation study, qualified as a postauthorisation safety study (PASS), for Striverdi® (olodaterol).

The study primary objectives are to (1) quantify the frequency of off-label use of olodaterol among new users of this medication and (2) describe recorded baseline characteristics of new users of olodaterol. The study secondary objectives are to (1) quantify the frequency of off-label use of indacaterol among new users of this medication and (2) describe recorded baseline characteristics of new users of indacaterol.

Both olodaterol and indacaterol are indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD) [R16-2633, R16-2634]. The study will quantify frequency of off-label use in indications that are not COPD, e.g., asthma, and among populations not included in the label, e.g., children.

This is an observational cohort study using information collected in the following databases: (1) the PHARMO Database Network in the Netherlands (PHARMO), which includes the Out-patient Pharmacy Database, the General Practitioner (GP) Database, and the Hospitalisation Database; (2) the National Registers in Denmark, which are linkable through the centralised Civil Registration System and will include for this study the Danish National Patient Registry (inpatient hospital data and outpatient hospital clinic data) and the Danish National Health Services Prescription Database; and (3) the IMS Real-World Evidence (RWE) Longitudinal Patient Database (LPD) in France, an anonymised medical records database that includes a panel of 1,200 primary care physicians and a pulmonologist panel including 40 specialists. For additional details of the study data sources, see Table 2 and Table 3 in Section 5.

RTI Health Solutions serves as the coordinating centre and is responsible for leading development of the study protocol, SEAP, and study reports and for providing support and oversight to each of the research partners who will carry out the analysis within their own institutions.

The study period will start on the date of olodaterol launch in each country and will end on the latest date the data are available at the time of data extraction. Anticipated study periods for each data source at the time of data extraction and reporting milestones are shown in Table 1.

Table 1 Estimated study period in each study data source and reporting milestones

Event	**PHARMO, the Netherlands**	**National Registries, Denmark**	**IMS RWE LPD, France**
Olodaterol launch in country	March 2014	January 2014	October 2015
Data extraction for interim report	Q1 2017	Q1 2017	Q1 2017
Anticipated study period included in interim report[1]	March 2014 – Q4 2015	January 2014 – Q4 2015	October 2015 – Q4 2016
Interim report regulatory milestone	Q3 2017	Q3 2017	Q3 2017
Data extraction for final report	Q1 2018	Q1 2018	Q1 2018
Anticipated study period for final report	March 2014 – Q4 2016	January 2014 Q4 2016	October 2015 – Q4 2017
Final report regulatory milestone	Q3 2018	Q3 2018	Q3 2018

IMS = IMS Health Information Solutions; PHARMO = PHARMO Database Network; Q*n* = the quarter of the calendar year; RWE LPD = Real-World Evidence Longitudinal Patient Database.

1. Study periods of observation are estimated based on the following lag times in each data source: PHARMO, approximately 6 to 18 months, Danish registries, approximately 6 to 12 months; IMS RWE LPD, 2 to 7 months.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

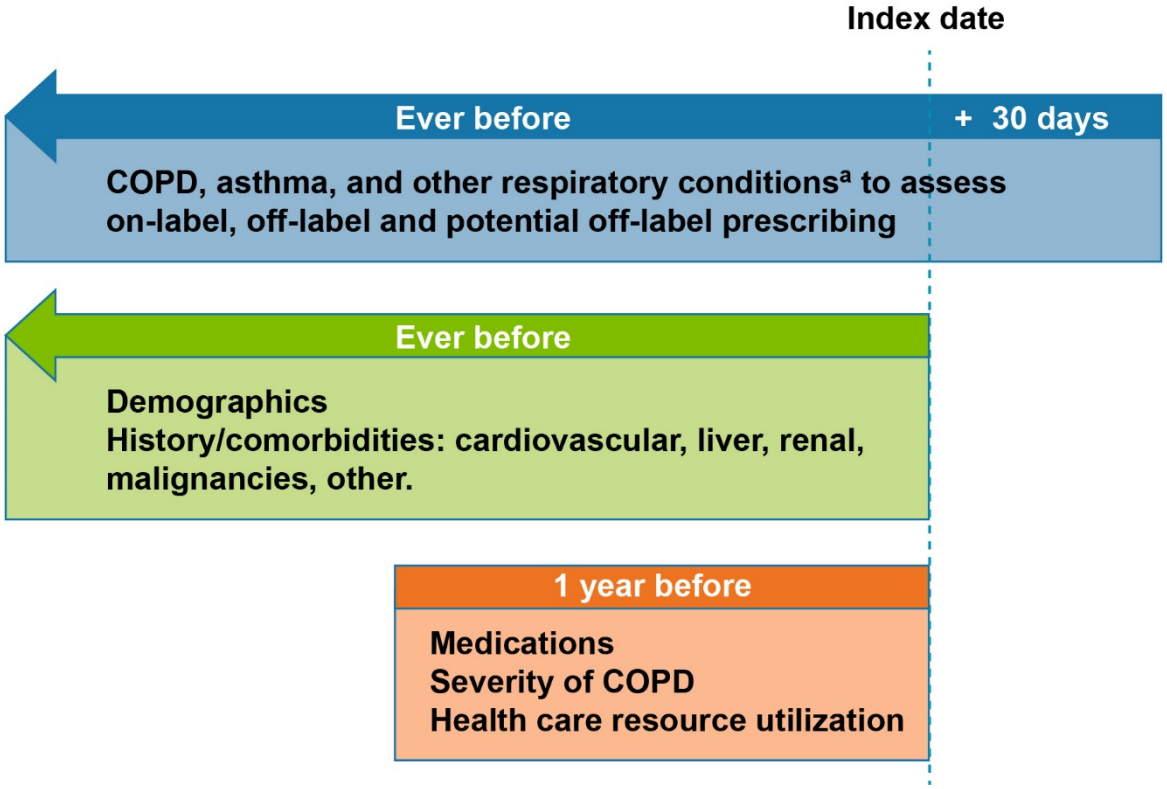
This section includes changes and clarifications in the planned analysis presented in the study protocol.

Number	Date	Section of SEAP	Update	Reason
1	16 Jan 2017	5.1	The time window used in the definition of COPD, asthma, and other respiratory diagnosis has been extended to include 30 days after index date	To take into account differences in recording practices and potential delay in data recording in each data source, e.g., the general practitioner may have recorded the COPD diagnosis a few days after hospital discharge
2	16 Jan 2017	5.1	Patients classified under potential off-label use (with no asthma and no COPD diagnosis) will be further characterised	To describe how many have "probable COPD" based on the use of medications and age, and how many have respiratory conditions other than COPD and asthma
3	16 Jan 2017	5.3	The definition of COPD severity has been modified	To update the algorithm and make it similar to current GOLD 2016 guidelines [P16-00121]
4	16 Jan 2017	5.3	COPD severity will be described among the patients with COPD aged 40 years or older and among patients with COPD aged 39 years or younger	Patients aged 40 years or older are the population most likely to have COPD; description by age groups will facilitate comparisons with published literature where patients with COPD are frequently selected if they are aged 40 or older

5. OUTCOMES

For each patient, the observation period will start at the index date and look retrospectively for all available historical data and prospectively for up to 30 days after the index date to identify potential off-label use (Figure 1). The index date is defined as the date of the first recorded dispensing/prescription of olodaterol or indacaterol during the study period in each data source (see Table 1). In each country, new users of olodaterol and indacaterol will be identified in the databases, which record information on the medications prescribed by the physicians or dispensed by pharmacies. Evaluation of off-label use and diagnosis of COPD, asthma, or other respiratory conditions will be assessed using all available information in the database before the index date (as far back in time as records in the data source are available)—i.e., 01 Jan 1994 in Denmark, 1998 in PHARMO (1998 for total patient set and 2006 for subset with GP data available), and 1994 in IMS RWE LPD (1994 for GP panel and 2007 for pulmonologist panel) and up to 30 days after index date. Characterisation of new users based on demographic and other non-respiratory comorbidities will be assessed using all available information in the database before the index date, unless otherwise specified. Medication use, severity of COPD, and health care resource utilisation will be assessed for the 1-year period before the index date. Database-specific specifications to define the variables of interest in each data source are included in Section 9.2.

Figure 1 Time periods for defining key study variables



[a] "Other respiratory conditions" are respiratory comorbidities other than COPD or asthma recorded at any time before or up to 30 days after index date and will be ascertained using the diseases and codes listed in Table 8. These will be described for the purpose of characterising the study population overall and the patients classified as potential off-label users.

The type of data available varies in each database and is summarised in Table 2.

Table 2 Selected characteristics of the study databases

Type of data	**PHARMO, the Netherlands**	**National Registers, Denmark**	**IMS RWE LPD, France**
Hospital inpatient discharge diagnoses	Yes	Yes	No
Hospital inpatient procedures	Yes	Yes	No
Hospital/clinic outpatient diagnoses	No	Yes	No
General practitioner outpatient diagnoses	Yes, in data subset PHARMO-GP[1]	No	Yes (a panel of 1,200 general practitioners)[2]
Specialist diagnoses	Yes, those in the hospital (no outpatient hospital or non-hospital clinics) or as communicated to and recorded by the GP in PHARMO-GP (primary care)	Yes, those in the hospital (inpatient diagnosis) and hospital outpatient clinics (outpatient diagnosis) (not outside the hospital)	Yes (a panel of 40 pulmonologists)[3]
Pharmacy-dispensed medications	Yes	Yes	No
Prescribed medications	Yes, in data subset PHARMO-GP[1]	No	Yes

GP = General Practitioner; IMS = IMS Health Information Solutions; PHARMO = PHARMO Database Network; RWE LPD = Real-World Evidence Longitudinal Patient Database.

1 For this study, data from the Out-patient Pharmacy Database and the Hospitalisation Database are available for the overall source population (approximately 4 million patients covered); the subcohort PHARMO-GP includes approximately 1 million patients with data in the Out-patient Pharmacy Database, the Hospitalisation Database, and the General Practitioner (GP) Database. The Out-patient Pharmacy Database will be used to identify medication use.

2 The GP panel covers a population of approximately 1.8 million active patients.

3 The pulmonologist panel covers a population of approximately 55,000 active patients.

The coding of diagnoses, procedures, and medications varies across databases (Table 3).

Table 3 Types of diagnosis, procedures, and medication codes in the study databases

Type of code	PHARMO, The Netherlands	National Registers, Denmark	IMS RWE LPD, France
Diagnoses	Hospital: ICD-10[1] Primary health care: ICPC[2]	ICD-10	Local in-house thesaurus that can be mapped to ICD-10
Procedures	CBV	NCSP version 1.16, 2012	Local in-house thesaurus that can be mapped to ICD-10
Medications	ATC	ATC	/ EphMRA mapped to ATC

ATC = Anatomical Therapeutic Chemical; CBV = Centraal Beheer Verrichtingenbestand (codes), Dutch Hospital Data Foundation–owned registration system for procedures, which links to the Dutch Healthcare Authority (NZa) declaration codes and the Dutch Classification of Procedures; EphMRA = European Pharmaceutical Market Research Association; ICD-9 = *International Classification of Diseases, 9th Revision*; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICPC = International Classification of Primary Care; IMS = IMS Health Information Solutions; NCSP = *Nordic Medico-Statistical Committee's Classification of Surgical Procedures*; PHARMO = PHARMO Database Network; RWE LPD = Real-World Evidence Longitudinal Patient Database.

1 Hospital codes in PHARMO before 2011 were ICD-9 and CBV. PHARMO will work with ICD-9 codes and map them to ICD-10 codes before conducting the analysis.

2 Available for PHARMO-GP, a data subset of PHARMO with information from GPs.

5.1 MAIN OUTCOMES

The main outcome of the study is the prevalence of off-label prescribing among new users of olodaterol. As a secondary outcome, the prevalence of off-label prescribing among new users of indacaterol will be assessed.

According to age and the presence of a recorded diagnosis of COPD and/or asthma, new users of olodaterol and new users of indacaterol will be classified into the following categories (Table 4):

- On-label prescribing: adults (aged ≥ 18 years at the index date) with a recorded diagnosis of COPD, with or without asthma
- Off-label prescribing:
  - Adults (aged ≥ 18 years at the index date) with a recorded diagnosis of asthma and without a recorded diagnosis of COPD, and
  - All children (aged < 18 years), irrespective of whether they have a recorded diagnosis of COPD (unlikely), asthma, or other respiratory disease
- Potential off-label prescribing: adults (aged ≥ 18 years) without a recorded diagnosis of COPD or asthma:
  - To further characterise these patients, recorded diagnosis of "other respiratory comorbidities" among these patients will be described (see conditions included in Section 5.3.4). The possibility of these patients having "probable COPD" will also be

explored. Probable COPD will be defined by the presence of at least two prescriptions of long-acting beta2-agonist (LABA), long-acting muscarinic antagonist (LAMA), or inhaled glucocorticosteroid (ICS) (or combination) after the age of 40 years but not before (see lists of medications in Annex Table 1-6).

Table 4 Classification of patients according to age and indication of olodaterol and indacaterol

Recorded diagnosis[1]	**Age**	**On-label prescribing: indication of COPD**	**Off-label prescribing**	**Potential off-label prescribing**
COPD	≥18	Yes		
COPD and asthma	≥18	Yes		
Children, irrespective of any recorded diagnosis	<18		Yes	
Asthma (no COPD)	≥18		Yes	
No COPD, no asthma[2]	≥18			Yes

COPD = Chronic Obstructive Pulmonary Disease.

1 Diagnosis recorded at any time before or on the index date and up to 30 days after the index date.

2 To further characterise adult patients with no COPD and no asthma, "potential COPD" and "other respiratory conditions" will be described among these patients.

A diagnosis of COPD or asthma will be defined as having one or more COPD or asthma diagnoses recorded in the database before the index date and up to 30 days following the index date. The *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) and International Classification of Primary Care (ICPC) codes to identify patients with COPD and asthma are detailed in Table 5.

Table 5 ICD-10 and ICPC diagnosis codes to identify patients with COPD and asthma

ICD-10 code description	**ICD-10 code**[1]	**ICPC code**[1]
COPD	J41-J44	R95
Chronic bronchitis[2]	J41-J42	R78, R91
Emphysema	J43	—
Other COPD	J44	—
Asthma	J45, J46	R96

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*;
ICPC = *International Classification of Primary Care*.

1. Data sources use different coding systems with different degrees of granularity; thus, subclassifications will be adapted to each database.

2. The use of ICD-10 code J40 "Bronchitis, not specified as acute or chronic" to define COPD will be assessed in the data source–specific definitions.

The indication for the prescribing of medications is not recorded in either the PHARMO databases or the Danish National Registries; indication is available but may be incomplete in the IMS RWE LPD. Therefore, when indication is not available, the indication of treatment and potential off-label use of olodaterol and indacaterol will be inferred from COPD and asthma diagnosis recorded at any time before or on the index date or up to 30 days after the index date and from the clinical review of information in computerised patient profiles. In addition, the time since first COPD diagnosis, i.e., time between the first recorded diagnosis of COPD in the database and the index date, will be ascertained for new users of olodaterol and indacaterol. Additional database-specific specifications on COPD, asthma, and on-label/off-label use are presented in Section 9.2.

A random sample, stratified by age (18-39 years, ≥ 40 years) and sex, of up to 100 patient profiles from new users of each medication before and up to 30 days after the first exposure to the respective drug will be reviewed to confirm that the algorithms and codes developed to identify COPD and asthma are correct, i.e., that no codes have been missed and that the time window proposed is appropriate for the specific data source. The 100 olodaterol and 100 indacaterol new users will be randomly selected among the following groups by sex and age: 25 females aged 18-39 years, 25 males aged 18-39, 25 females aged ≥ 40 years, and 25 males aged ≥ 40 years; if there are less than 25 patients in the younger age groups, the remaining patient profile reviews, up to 25, will be done in the older age groups). Patient profiles are chronological listings of the routinely recorded codes that represent clinical events recorded in the study databases for individual patients. These listings include general practitioner diagnoses (if available, depending on the data source), outpatient and hospital discharge diagnoses and procedures, and dispensings of medications. The clinical review of patient profiles will provide more accurate information for evaluation of the indication and potential off-label use of olodaterol and indacaterol than use of codes alone. This information will be useful for developing clinical algorithms that can be applied to the evaluation of all new users of olodaterol and indacaterol. Patient profile review will be performed after the initial application of the electronic algorithm; if needed, the algorithms will be modified. The algorithm developed after patient profile review will be used for all the analyses to be performed for the interim and final study reports.

5.3 OTHER VARIABLES

New users of olodaterol and indacaterol at the index date will be characterised according to demographic characteristics, available data on lifestyle habits, health care resource utilisation, comorbidities, and use of medications. Patients with a prior diagnosis of COPD will also be characterised based on their COPD severity.

For conditions and medications, if information on a particular binary covariate is available in the data, patients will be assumed to have the factor only if there is evidence for its presence (i.e., absence of any records with a diagnosis code for a condition will be taken to mean absence of the condition). The only exception to this principle will be when “missing” (or

other value, e.g., "unknown") is one of the possible values recorded for the variable in the data source, in which case the value as reported within the data source will be retained in the analysis as one of the possible values.

5.3.1 Demographic and lifestyle habits at the index date

The following demographic and lifestyle variables, as available in each data source, will be considered at the closest measure before and including the index date. Depending on the data source and the demographic or lifestyle variable, information may be restricted to a specific period before the index date (e.g., 1 year). The categories for these variables will depend on data source availability and will be described in the study report. The proposed categories and data availability by data source are presented in Table 6. Additional details on database-specific specifications for the definition of these variables in each data source are described in Section 9.2.

Table 6 Demographic and lifestyle variables: proposed definition, units, and categories, by data source

Variable	**Definition, units, and categories**	**PHARMO, the Netherlands**	**National Registers, Denmark**	**IMS RWE LPD, France**
Age	Years: year of the index date minus year of birth as a continuous variable and as a categorical variable of the following age groups: < 18, 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years			
Sex	Male, female			
Smoking status	Depending on data source and data availability	Ever use of smoking cessation medication (yes/no), and smoking status (current, former, never, and missing) in PHARMO-GP	N.A.	Smoker/non-smoker
Alcohol consumption	Yes/No	Alcohol-related disorder	Alcohol-related disorder	Alcohol-related disorder
Body mass index (kg/m^2)/obesity	Underweight (< 20), normal (20 to < 25), overweight (25 to < 30), obese (≥ 30), and missing	BMI and diagnosis of obesity or overweight	Diagnosis of obesity or overweight	BMI and categories
Socioeconomic status indicators or proxies	Depending on data source	Based on postal code	N.A.	Geographical location of physician
Duration of enrolment prior to index date	In years and defined as the year of the index date minus year of enrolment. Does not include the 30 days after the index date or the duration of follow-up after the index date			

BMI = Body Mass Index; N.A. = Not Available.

5.3.2 Health care resource utilisation

Health care resource utilisation will be evaluated within 12 months before cohort entry but not including the index date. The variables listed in Table 7 will be used to capture the utilisation of health care resources. Additional details on the definition of the variables in each data source are described in Section 9.2.

Table 7 Health care resource utilisation variables

Health care resource parameter	Definition and categories	Medications included
All dispensings	Number of dispensings for all medications; ordinal variable with 0, 1-9, 10-19, 20 or more	All medications included in Annex Table 1-6
Dispensings for respiratory medications[1]	Number of dispensings for respiratory medications; ordinal variable with 0, 1-4, 5-9, 10 or more	All medications included in the section on respiratory medications in Annex Table 1-6
Dispensings for systemic glucocorticosteroids	Number of dispensings for systemic glucocorticosteroids; ordinal variable with 0, 1-4, 5-9, 10 or more	ATC code H02AB
Dispensings for LABAs	Number of dispensings for LABAs; ordinal variable with 0, 1-4, 5-9, 10 or more	ATC codes R03AC012 (salmeterol) and R03AC013 (formoterol)
Hospitalisations	Number of hospitalisations for any cause; ordinal variable with 0, 1, 2, 3-4, 5 or more	To be determined by each data source
Hospitalisations for COPD	Number of hospitalisations with a primary discharge diagnosis of COPD; ordinal variable with 0, 1, 2, 3-4, 5 or more	ICD-10 codes for COPD: J41-J44, or as defined in Section 5.1 for each data source, but limited to inpatient codes
Hospitalisations for asthma	Number of hospitalisations with a primary discharge diagnosis of asthma; ordinal variable with 0, 1, 2, 3-4, 5 or more	ICD-10 codes for asthma: J45, J46, or as defined in Section 5.1 for each data source, but limited to inpatient codes

ATC = Anatomical Therapeutic Chemical; COPD = Chronic Obstructive Pulmonary Disease; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; LABA = Long-Acting Beta2-Agonist.

[1] Study medications will be counted (e.g., when describing the olodaterol cohort, the dispensings of indacaterol will be counted and vice versa).

5.3.3 Severity of COPD

Severity of COPD will be evaluated among new users of olodaterol and indacaterol that are aged 40 years or older and have a recorded diagnosis of COPD (with or without a diagnosis of asthma) ever before or up 30 days after the index date. The population aged 40 years or older is considered the most likely to have COPD and is frequently selected in studies to evaluate medication use among patients with COPD [P07-07347, P11-13226, P07-09136]. Patients aged 39 years or younger with a diagnosis of COPD will still be considered as

having COPD and described separately if there are at least 5 patients in each COPD severity category. Definitions shown in Table 8 will be adapted to the characteristics and data availability in each data source; database-specific specifications have been described in Section 9.2. The four severity categories will be mutually exclusive, and patients that fulfil criteria for more than one category will be classified as being in the more severe category.

Table 8 Definition criteria of COPD severity (adapted primarily from Verhamme et al., 2012 [P11-13226])

Severity of COPD	Definition
Mild	Less than two prescriptions/dispensings of drugs for obstructive airways disease of the same class in any 6-month interval in the 12 months before the index date (i.e., 0 or 1 prescriptions/dispensings of the same COPD drug class in the 12 months before the index date, or if ≥ 2 prescriptions/dispensings, these have to be more than 6 months apart)
Moderate	Regular bronchodilator treatment, defined as having at least two prescriptions/ dispensings of the same COPD drug class with an interval of ≤ 6 months in the 12 months before the index date[1,2]

Severe	Occurrence of at least one of the following events in the 12 months before the index date:
	• Hospitalisation for COPD exacerbation[1]
	• At least two COPD exacerbations without hospitalisation, where COPD exacerbation is defined by any of the following[3]:
	  • A course of antibiotics for lower respiratory tract infection (acute bronchitis or pneumonia)[1]
	  • A course of systemic corticosteroids for the treatment of COPD exacerbation[1]
	  • A diagnoses of COPD exacerbation without hospitalisation

Very severe	Occurrence of at least one of the following events in the 12 months before the index date unless another time period is specified: • Dispensed oxygen therapy[1,2] • Dispensed nebuliser therapy[1,2] • Diagnosis of emphysema at any time before the index date[1]

COPD = Chronic Obstructive Pulmonary Disease.

1 Severity criteria also included in definition from Curkendall et al., 2006 [P07-09136].

2 Severity criteria also included in definition from Soriano et al., 2001 [R08-1492].

3 Severity criteria modified to align with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 definition for severity categories C and D [P16-00121]. If two or more of these criteria occur within a 21-day time period, they will be considered part of the same exacerbation episode and counted only once. If one or more of these criteria occur within a 21-day period of a hospitalisation for COPD, this will be considered part of the same "COPD exacerbation with hospitalisation" episode.

Sources: modified from Verhamme et al., 2012 [P11-13226]; Soriano et al., 2001 [R08-1492]; Curkendall et al., 2006 [P07-09136]; and GOLD, 2016 [P16-00121].

Because data on hospitalisations are not available in the IMS RWE LPD database, COPD severity will not be described in this database.

The proposed operational definitions to be applied when assessing the severity of COPD are as follows:

- Same-class "drugs for obstructive airways disease": medications listed in Annex Table 1-6 will be identified through prescriptions/dispensings for the list of medications of interest recorded in the database within 12 months before or on the index date and classified into one of the following drug classes:
  - Bronchodilators: inhaled short-acting muscarinic antagonists (SAMAs), inhaled LAMAs, inhaled short-acting beta2-agonists (SABAs), inhaled LABAs, and fixed combinations of SABAs and SAMAs
  - Inhaled glucocorticosteroids: ICS alone, fixed combinations of SABAs and ICSs, and fixed combinations of LABAs and ICSs
  - Systemic glucocorticosteroids
  - Systemic beta2-agonists
  - Xanthines
  - Roflumilast
- Hospitalisation for COPD exacerbation: an inpatient (primary or secondary discharge) code for COPD (ICD-10 codes: J41-J44), acute bronchitis (ICD-10 codes: J20, J21, J22, J40), or pneumonia (ICD-10 codes J09, J18) within 12 months before or on the index date.
- At least two COPD exacerbations without hospitalisation, where COPD exacerbation is defined by any of the following: a course of antibiotics, a course of systemic glucocorticosteroids, or a diagnosis of COPD exacerbation (including COPD exacerbation diagnosis *per se*, acute bronchitis, or pneumonia) during the 12 months before or on the index date. To identify exacerbation episodes, a 21-day time period will be used [R16-1576]; consecutive prescriptions of antibiotics, systemic glucocorticosteroids, or diagnosis codes for COPD exacerbation within 21 days of the first record of each episode will be considered to be a single exacerbation. When there is a hospitalisation within 21 days of the COPD exacerbation, this will be counted as one "hospitalisation for COPD or COPD exacerbation with hospitalisation." The number of exacerbations without hospitalisation will be further categorised into 0 to 1 or ≥ 2.
- A course of antibiotics: all dispensings for country-specific antibiotics used to treat lower respiratory tract infections (acute bronchitis or pneumonia) during the 12 months before or on the index date will be identified (a list of Anatomical Therapeutic Chemical [ATC] codes will be developed in each data source and will include those that are specific to treat the disease in each country). A course of antibiotics will be defined as treatment involving consecutive dispensings of antibiotics with less than 7 days between the end of days of supply of one dispensing and the date of the next dispensing. The variable "second course of antibiotics" will be categorised as "no" if the patient had 0 or 1 course of antibiotics during the 12 months before or on the index date, or "yes" if the patient had at least two courses of antibiotics during the 12 months before or on the index date.
- A course of systemic glucocorticosteroids: all dispensings for country-specific systemic glucocorticosteroids used to treat COPD, such as prednisolone and prednisone, during the 12 months before or on the index date will be identified (a list of ATC codes will be developed in each data source and will include those that are specific to treat the disease

in each country). A course of systemic glucocorticosteroids will be defined as treatment involving consecutive dispensings of systemic glucocorticosteroids with less than 7 days between the end of days of supply of one dispensing and the date of the next dispensing. The variable "second course of systemic glucocorticosteroids" will be categorised as "no" if the patient had 0 or 1 course of systemic glucocorticosteroids during the 12 months before or on the index date or "yes" if the patient had at least two courses of systemic glucocorticosteroids during the 12 months before or on the index date.

- Diagnosis of COPD exacerbation without hospitalisation: an outpatient (GP, outpatient hospital clinic, or pulmonologist) ICD-10 code or ICPC code for COPD exacerbation (ICD-10 code: J44.1; free-text search in the PHARMO-GP), acute bronchitis (ICD-10 codes: J20, J21, J22, J40; ICPC code: R78), or pneumonia (ICD-10 codes: J09-J18; ICPC code: R81) within 12 months before or on the index date.
- Oxygen therapy: a prescription or dispensing for oxygen therapy (ATC code: V03AN01) within 12 months before or on the index date.
- Nebuliser therapy (to be identified in each data source using national drug codes).
- Emphysema: an outpatient or inpatient (primary or secondary hospital discharge or outpatient hospital clinics) code for emphysema at any time before or on the index date (ICD-10: J43; free-text search in the PHARMO-GP).

5.3.4 Respiratory comorbidity and allergies

Respiratory comorbidities other than COPD or asthma will be conditions recorded at any time before or up to 30 days after index date and will be ascertained using the diseases and codes listed in Table 9. These will be described for the purpose of characterising the study population overall and the subgroup of patients classified as potential off-label users, but do not constitute "suspected off-label indications."

Table 9 Respiratory comorbidity and allergies

Disease description[1]	**ICD-10 code**	**ICPC code**
Pneumonia	J09-J18	R81
Allergic rhinitis	J30	R97
Bronchiectasis	J47	—
Lung diseases due to external agents	J60-J69	—
Acute bronchitis or bronchiolitis[2]	J20, J21, J22, J40	R78
Other respiratory conditions	J80-J99	R99

COPD = Chronic Obstructive Pulmonary Disease; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICPC = *International Classification of Primary Care*.

[1] Other respiratory comorbidities of interest may be described depending on data availability.

[2] The use of ICD-10 code J40 "Bronchitis, not specified as acute or chronic" will be assessed in the data source–specific definitions.

5.3.5 Other comorbidities

Characterisation of the patient population will include a description of the medical history of comorbidities listed in Annex Table 1-5, which will be identified through recorded diagnosis at any time before or on the index date. Additional details on database-specific specifications are described in Section 9.2.

5.3.6 Comedications

Characterisation of the patient population will include a description of the prescriptions or dispensings for comedications of interest listed in Annex Table 1-6 that are recorded within 12 months before or on the index date.

6. GENERAL ANALYSIS DEFINITIONS

6.1 EXPOSURE

The main study exposures of interest are olodaterol and indacaterol. New users of olodaterol and indacaterol will be identified at the first record of a prescription/dispensing for the relevant medication code specific to each database within the study period (see Table 1 for study periods in each data source).

For these medications, the following characteristics will be described:

- *Daily dose at the index date* (µg): the dose prescribed by the physician at the index date, when available, or ascertained by the dispensed defined daily dose (DDD) and the estimation of the daily dose at index date. The estimated daily dose dispensed at the index date will be calculated using the recorded information on strength and quantity dispensed and the days of supply of the first prescription for olodaterol and indacaterol. Missing values for dose are expected and will be described.
- *Number of packages at the index date:* the number of packages prescribed by the physician, when available, or ascertained by the dispensed DDD. The estimated number of packages dispensed at the index date will be calculated using the recorded information on quantity dispensed and/or the days of supply of the first prescription for olodaterol and indacaterol. Missing values for dose are expected and will be described.

Information of interest to identify the drugs of interest and the daily dose and the number of packages at the index date is described in Table 10.

Table 10 Information on olodaterol and indacaterol

Descriptor	**Indacaterol**	**Olodaterol**
Brand name	Onbrez Breezhaler (Hirobriz Breezhaler and Oslif Breezhaler in The Netherlands)	Striverdi Respimat
ATC	R03AC18	R03AC19
Formulation	Inhalation powder	Solution for inhalation
Presentation	Capsules	Cartridges
Strengths	150 mcg and 300 mcg	2.5 mcg
Package size	30 capsules	60 cartridges
DDD	150 mcg	5 mcg
Recommended dose	150 mcg once a day	2 puffs of 2.5 mcg once a day
Maximum dose	300 mcg once a day	5 mcg once a day

ATC = Anatomical Therapeutic Chemical; DDD = Defined Daily Dose.

Source: Onbrez Summary of Product Characteristics [R16-2634]; Striverdi Summary of Product Characteristics [R16-2633]; WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015. Available at: https://www.whocc.no/atc_ddd_index/.

Additional details on the database-specific definitions of the exposure variables in each data source are described in Section 9.2.

6.2 IMPORTANT PROTOCOL VIOLATIONS

None.

6.3 PATIENT SETS ANALYSED

Patients in the study will be required to meet the following criteria, as ascertained from each of the data sources:

- Receive a first dispensing for single-agent formulations of olodaterol or indacaterol during the study period with no prescriptions/dispensings ever before (see study period in Table 1)
- Have at least 1 year of continuous enrolment in the data source immediately preceding the index date
- Have available data and no implausible values for age (< 0 years and > 120 years) or sex

Two study medication groups will be created: (1) a group of new users of olodaterol and (2) a group of new users of indacaterol. Inclusion in the study cohort as a new user in one of the two groups does not preclude the patient from being included as a new user in the other group if the inclusion criteria are met. The number of patients included in both groups will be reported.

6.5 HANDLING OF MISSING DATA AND OUTLIERS

The extent of missing data will be evaluated and described. Due to the nature of this study, no imputation of missing data is planned. Missing values are expected in some sociodemographic variables depending on the definition used and in variables related to exposure characterisations such as strength or daily dose. Degree of missingness will depend on the database, and some data sources will have variables that are not available, such as oxygen therapy in PHARMO and hospitalisations in IMS RWE LPD. Diagnoses, prescriptions, and dispensings can be identified in the databases only if they are recorded. Thus, all patients with a certain diagnosis/dispensing in the database will be coded as having

the respective condition/exposure to the respective drug. All others will be coded as not having the disease/not being exposed to the drug. Therefore, uncoded diagnoses/dispensings may result in misclassification and not in missing values.

6.6 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

The baseline or maximum lookback time period is defined as the period of continuous registration from enrolment up to the index date. Definition of the baseline period overall and the study period in each data source have been provided in Table 1.

The analyses performed in this study will describe off-label use and patient characteristics based on information at baseline; no exposure time windows of risk after the index date will be defined in this study.

Due to the observational and retrospective nature of this study, no mandated visits of patients to health care practitioners are required. Therefore, calculated study visits are not applicable.

7. PLANNED ANALYSIS

The different research centres will use the core final study protocol and SEAP to conduct analyses in the respective data sources and generate output that will be provided to the coordinating centre (RTI Health Solutions), which will generate the study reports.

All the analyses will be conducted separately for olodaterol and indacaterol new users and further stratified by LABA-naïve patients and switchers. Analysis for each report (i.e., interim and final) will include data on all patients starting treatment with olodaterol or indacaterol from the start of such treatment during the study period up to the latest available data (see anticipated study periods for interim and final reports in Table 1). The interim analysis will include all the analyses described in the present section.

Tables and figure shells describing all planned analyses have been developed (see separate Word file) and will be adapted to each data source. For each data source, an attrition table will be generated to describe the impact on the study size at each step of applying the study inclusion and exclusion criteria (Figure Shell 1).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1.1 Demographic and lifestyle characteristics of new users at the index date

The absolute and relative frequency (i.e., count and percentage) of new users of olodaterol and indacaterol will be presented overall and by calendar year (Shell Table 1); mean, standard deviation, and median and interquartile range of duration of prior enrolment before the index date, daily doses and number of packages of the index prescription (if available) will also be provided.

Distribution of new users by age and sex, overall and by calendar year, for the study medications will be presented. Absolute and relative frequencies, mean, standard deviation, and median and interquartile range will be provided (Shell Table 2.1-2.5).

Lifestyle characteristics, as defined in Section 5.1, will be presented by each index medication for the overall population (Shell Table 3.1), for adults (Shell Table 3.2), and for those patients aged 40 years or older with a diagnosis of COPD (Shell Table 3.3). Frequencies will be reported for categorical variables, and mean, standard deviation, median, interquartile range, and minimum and maximum will be reported for continuous variables. The specific characteristics reported within this table (e.g., smoking history and obesity or weight or body mass index) will depend on data availability in each data source.

7.1.2 Health care resource utilisation

A description of health care resource utilisation variables for new users of the study medications will be presented as mean, standard deviation, median, interquartile range, and absolute and relative frequencies. The results will be presented for the overall population (Shell Table 4.1), for adults (Shell Table 4.2), and for those patients aged 40 years or older with a diagnosis of COPD (Shell Table 4.3). The variables and their definitions are listed in Section 5.3.2.

7.1.3 Severity of COPD

Severity of COPD will be described among patients aged 40 years or older with a diagnosis of COPD with or without a recorded diagnosis of asthma, as described in Section 5.1. Severity of COPD will also be described among patients aged 39 years or younger if there are more than 5 patients in each severity category. The definition of COPD severity is included in Section 5.3.4. Criteria used to define COPD severity in each data source will be also described. For each data source, the absolute and relative frequency of patients in each category of COPD severity, and criteria within each category of COPD severity, will be presented by study medication (Shell Table 9).

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency of history of specific diseases and conditions of interest at any time before the index date will be assessed for each exposure group in each data source within the overall study population (Shell Table 5.1 and Shell Table 6.1). The same analysis will be repeated for adults (Shell Table 5.2 and Shell Table 6.2) and for those patients aged 40 years or older with a diagnosis of COPD (Shell Table 5.3 and Shell Table 6.3). Diagnosis of COPD, asthma, and other respiratory comorbidities and time since first COPD diagnosis will be included as part of the description of medical history. In this table, COPD, asthma, and respiratory comorbidities will not be mutually exclusive, and a patient will be allowed to be in more than one group. The comorbidities to be considered are listed in Sections 5.3.4 and 5.3.5, and a complete list of codes is included in Annex Table 1-5.

The number and percentage of patients with a prescription or dispensing for a specific medication within the year before the index date will be described in each exposure group for the overall population (Shell Table 7.1 and Shell Table 8.1), for all adults (Shell Table 7.2 and Shell Table 8.2), and for those patients aged 40 years or older with a diagnosis of COPD (Shell Table 7.3 and Shell Table 8.3). A description of the medications considered is detailed in Section 5.3.6, and the list of codes is presented in Annex Table 1-6.

7.3 METHODS ADDRESSING BIAS

The exclusive use of hospital outpatient and/or inpatient discharge diagnoses can overestimate potential off-label prescribing because many patients with COPD may have never been hospitalised, and COPD is a disease that is mainly managed in the primary care setting. For this reason, to maximise the sensitivity and specificity of the algorithms, the algorithms to identify patients with COPD and asthma will be adapted to each data source (e.g., using inpatient records only or outpatient and inpatient records or using ICD-10 or thesaurus coding) and based on available data and prior experience in designing studies evaluating COPD and other diseases. “Potential COPD” and “other respiratory conditions” will be characterised to provide a description of “other potential uses” of olodaterol and indacaterol among those with no diagnosis of COPD or asthma. However, it is acknowledged that none of these other respiratory conditions is an approved indication for olodaterol or indacaterol, and that indication of the prescription will be unknown for a certain portion of patients.

7.4 METHODS ADDRESSING CONFOUNDING/EFFECT MEASURE MODIFICATION

Not applicable.

7.5 MAIN ANALYSES

7.5.1 Clinical indication and evaluation of off-label and potential off-label use

A detailed description of the definition of COPD indication and on-label and off-label use is presented in Section 5.1. The prevalence of on-label and off-label new users and 95% confidence interval will be presented for olodaterol and indacaterol. Confidence intervals will be calculated using the Clopper-Pearson method for the binomial distribution [R06-1080]. Patients will be classified hierarchically:

- 1. All children will be classified as off-label, irrespective of their diagnosis.
- 2. All adult patients with a diagnosis of COPD will be considered on-label irrespective of whether they have a diagnosis of asthma or any other respiratory condition.
- 3. All adults without a COPD diagnosis and with a diagnosis of asthma will be classified under the group of "asthma only," irrespective of whether they have any other respiratory condition. These patients will be classified as off-label.
- 4. All adults with no COPD and no asthma diagnosis will be classified as potential off-label. Among these patients, "probable COPD" and "other respiratory conditions" will be described. These will not be mutually exclusive, patients can have one or more of the respiratory conditions listed and "probable COPD." Patients with no "other respiratory conditions" and no "probable COPD" will be classified under "No history of recorded respiratory conditions and no probable COPD."

Results for the main analysis will be presented overall (Shell Table 10.1) and separated by age group (< 18, 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+ years; Shell Tables 10.2 through 10.9).

7.5.2 Patient profile review to evaluate COPD and asthma algorithms

A description of the patient profile review process is presented in Section 5.1. Patient profiles will be created on a random sample, stratified by age (18-39 years, ≥ 40 years) and sex, of 100 new users of each study drug olodaterol and indacaterol. Results of the manual review of the patient profiles will be described and compared with the treatment indications identified through the electronic algorithms based on medical codes. These results will be described in the study report. Results reporting COPD, asthma, and "no COPD no asthma" as identified by the electronic algorithm and after patient profile review will be presented (Shell Table 11).

7.7 EXPOSURE TIME

Not applicable.

7.8 SAFETY ANALYSIS

Not applicable.

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ANNEX 1. CODES FOR COMORBIDITIES AND OTHER COMEDICATIONS

Annex Table 1-1 ICD-10 codes for alcohol-related disorders

ICD-10 codes	Description
85.9 in ICD-10, and I85.00 in ICD-10-CM	Oesophageal varices without mention of bleeding
E24.4	Alcohol induced pseudo-Cushing's syndrome
F10.1-F10.9	Alcohol dependence syndrome/Mental and behavioural disorders due to use of alcohol: dependence syndrome
G31.2	Degeneration of nervous system due to alcohol
G62.1	Alcoholic polyneuropathy
G72.1	Alcoholic myopathy
I42.6	Alcoholic cardiomyopathy
I85.0 in ICD-10 and I85.01 in ICD-10 CM	Oesophageal varices with bleeding
I85.0 in ICD-10-CM	Oesophageal varices in diseases classified elsewhere/Secondary oesophageal varices with bleeding
K29.2	Alcoholic gastritis
K29.20	Alcoholic gastritis without mention of haemorrhage/Alcoholic gastritis
K29.21	Alcoholic gastritis with haemorrhage/Alcoholic gastritis
K70.x	Alcoholic liver disease
K85.2	Alcohol induced acute pancreatitis
K86.0	Alcohol induced chronic pancreatitis
Z50.2	Alcohol rehabilitation
Z71.4	Alcohol abuse counselling and surveillance
Z72.1	Alcohol use

Annex Table 1-2 ICPC codes for alcohol-related disorders

ICPC codes	Description
P15	Chronic alcohol abuse
P16	Acute alcohol abuse

Annex Table 1-3 ICD-10 codes for overweight and obesity

ICD-10	**Description**
E66	Obesity
E68	Sequelae of hyperalimentation
Z68.25*	Body mass index (BMI) 25.0-25.9, adult
Z68.26*	Body mass index (BMI) 26.0-26.9, adult
Z68.27*	Body mass index (BMI) 27.0-27.9, adult
Z68.28*	Body mass index (BMI) 28.0-28.9, adult
Z68.29*	Body mass index (BMI) 29.0-29.9, adult
Z68.3*	Body mass index (BMI) 30-39, adult
Z68.4*	Body mass index (BMI) 40 or greater, adult

* To be used if coding is based on ICD-10-CM.

Annex Table 1-4 ICPC codes for overweight and obesity

ICPC	**Description**
T82	Obesity
T83	Overweight

Annex Table 1-5 Other comorbidity

Disease description	ICD-10 code	ICPC code
Cardiovascular diseases	I00-I99	K73-K99
Ischaemic heart disease	I20-I25 or coronary reperfusion surgery and procedures	
Stable angina pectoris	I20.1, I20.8, I20.9	K74.02 Stable angina pectoris
Unstable angina pectoris	I20.0	K74.01 Unstable angina pectoris
Acute myocardial infarction	I21	K75 Acute myocardial infarction
Other acute or subacute ischaemic heart disease	I22-I24	K76 Ischaemic heart disease w/o angina
Chronic ischaemic heart disease	I25	No specific code
Coronary reperfusion surgery and procedures	List of codes to be developed according to each database dictionary	List of codes to be developed according to each database dictionary
Arrhythmias	I47-I49	K78-K80
Paroxysmal tachycardia	I47	K79 Paroxysmal tachycardia
Ventricular tachycardia	I47.0, I47.2	No specific code
Supraventricular tachycardia and unspecified	I47.1, I47.9	No specific code
Atrial fibrillation and flutter	I48	K78 Atrial fibrillation/flutter
Other cardiac arrhythmias	I49	K80 Ectopic beats all types
Ventricular fibrillation and flutter	I49.0	No specific code
Other cardiac arrhythmias	I49.1-I49.9	No specific code
Conduction disorders	I44-I45	K84 Heart disease other
Cardiac arrest	I46	No specific code
Heart failure	I50	K77 Heart failure
Cerebrovascular disease	I60-I69, G45	K89-K90
Cerebral haemorrhage (subarachnoid, intracerebral, other non-traumatic)	I60-I62	K89 Transient cerebral ischaemia
Cerebral infarction and stroke	I63, I64, G46.5	K90 Stroke/cerebrovascular accident
Transient ischaemic attack	G45	K89 Transient cerebral ischaemia
Other cerebrovascular disease and sequelae of cerebrovascular disease	I65-I69	No specific code

Annex Table 1-5 (cont'd) Other comorbidity

Disease description	ICD-10 code	ICPC code
Hypertension and hypertensive heart disease	I10-I15	K85 Elevated blood pressure (excl. K86-K87) K86 Hypertension without organ damage K87 Hypertension with organ damage
Diseases of arteries, arterioles, and capillaries	I70-I79, and peripheral arterial revascularisation procedures	K91 Atherosclerosis (excl. K76, K90) K92 Atherosclerosis/PVD
Peripheral arterial revascularisation procedures	List of codes to be developed according to each database dictionary	List of codes to be developed according to each database dictionary
Other form of heart diseases	I00-I09, I30-I43, I80-I99	K73 Congenital anomaly cardiovascular K81 Heart/arterial murmur NOS K82 Pulmonary heart disease K83 Heart valve disease NOS K94 Phlebitis/thrombophlebitis K95 Varicose veins of leg K96 Haemorrhoids K99 Cardiovascular disease other
Hyperlipidaemia	E78	T93 Lipid disorder
Diabetes mellitus	E10-E14	T90 Diabetes mellitus
Renal disease	N00-N39	U99 Urinary disease, other
Chronic kidney disease	N18	U99.01 Kidney insufficiency
Other renal disorders	N00-N17, N19, N25-N39	U99 (excl. U99.01)
Anaemias	D50-D64	B78-B83
Peptic ulcer disease	K25-K28	D85 Duodenal ulcer D86 Peptic ulcer other
Liver disease	K70-K77	D97 Liver disease NOS
Osteoporosis	M80-M82	L95 Osteoporosis
Rheumatoid arthritis and other inflammatory arthropathies	M05-M14	L88 Rheumatoid/seropositive arthritis
Systemic connective tissue diseases	M30-M36	No code

Annex Table 1-5 (cont'd) Other comorbidity

Disease description	ICD-10 code	ICPC code
Malignancy	C00-C97	A79 Malignancy NOS B72 Hodgkin's disease/lymphoma B73 Leukaemia B74 Malignant neoplasm blood other D74 Malignant neoplasm stomach D75 Malignant neoplasm colon/rectum D76 Malignant neoplasm pancreas D77 Malig. neoplasm digest other/NOS F74 Neoplasm of eye/adnexa H75 Neoplasm of ear K72 Neoplasm cardiovascular N74 Malignant neoplasm nervous system R84 Malignant neoplasm bronchus/lung R85 Malignant neoplasm respiratory, other S77 Malignant neoplasm of skin T71 Malignant neoplasm thyroid U75 Malignant neoplasm of kidney U76 Malignant neoplasm of bladder
Malignancy (cont'd)		U77 Malignant neoplasm urinary other W72 Malignant neoplasm relate to preg. X75 Malignant neoplasm cervix X76 Malignant neoplasm breast female X77 Malignant neoplasm genital other (f) Y77 Malignant neoplasm prostate Y78 Malign neoplasm male genital other
Depressive disorders	F32-F33	P76 Depressive disorder
Pregnancy (at the index date)	O00-O48	W78 Pregnancy W79 Unwanted pregnancy

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*;
ICPC = *International Classification of Primary Care.*

Annex Table 1-6 Anatomical Therapeutic Chemical codes for comedications

Medication description	**ATC code**
Respiratory medications	
Inhaled SAMAs	
Ipratropium bromide	R03BB01
Oxitropium bromide	R03BB02
Inhaled LAMAs	
Tiotropium bromide	R03BB04
Aclidinium bromide	R03BB05
Glycopyrronium bromide	R03BB06
Inhaled SABAs	
Salbutamol	R03AC02
Terbutaline	R03AC03
Fenoterol	R03AC04
Rimiterol	R03AC05
Hexoprenaline	R03AC06
Isoetarine	R03AC07
Pirbuterol	R03AC08
Tretoquinol	R03AC09
Carbuterol	R03AC10
Tulobuterol	R03AC11
Clenbuterol	R03AC14
Reproterol	R03AC15
Procaterol	R03AC16
Bitolterol	R03AC17
Indacaterol	R03AC18
Inhaled LABAs	
Salmeterol	R03AC12
Formoterol	R03AC13

Annex Table 1-6 (cont'd) Anatomical Therapeutic Chemical codes for comedications

Medication description	**ATC code**
Respiratory medications (cont'd)	
Inhaled LABA/ICS	
Salmeterol and fluticasone	R03AK06
Formoterol and budesonide	R03AK07
Formoterol and beclometasone	R03AK08
Formoterol and mometasone	R03AK09
Vilanterol and fluticasone furoate	R03AK10
Formoterol and fluticasone	R03AK11
Salmeterol and budesonide	R03AK12
Inhaled glucocorticosteroid	
Beclometasone	R03BA01
Budesonide	R03BA02
Flunisolide	R03BA03
Betamethasone	R03BA04
Fluticasone	R03BA05
Triamcinolone	R03BA06
Mometasone	R03BA07
Ciclesonide	R03BA08
Fixed combinations of SABAs and SAMAs	ATC codes not available[1]
Fixed combinations of SABAs and ICSs	ATC codes not available[1]
Fixed combinations of LABAs and ICSs	ATC codes not available[1]
Systemic glucocorticosteroids	H02AB
Systemic beta2-agonists	R03CC
Xanthines and fixed dose combinations of xanthines with adrenergics	R03DA, R03DB
Roflumilast	R03DX07
Nasal glucocorticosteroids	R01AD
Omalizumab	R03DX05
Leukotriene receptor antagonists	R03DC
Cromoglicic acid	R03BC01
Nedocromil	R03BC03

Annex Table 1-6 (cont'd) Anatomical Therapeutic Chemical codes for comedications

Medication description	**ATC code**
Respiratory medications (cont'd)	
Oxygen therapy	V03AN01
Nebuliser therapy	ATC codes not available[1]
Cardiovascular medications	**All codes listed below in section Cardiovascular medications**
Cardiac glycosides and antiarrhythmics, Classes I and III	C01A, C01B
Vasodilators used in cardiac diseases	C01D
Other cardiac preparations	C01B, C01C
Diuretics	C03
Peripheral vasodilators	C04
Beta blocking agents	C07
Calcium channel blockers	C08
Antihypertensives	C02
Agents acting on the renin-angiotensin system	C09
Angiotensin-converting-enzyme inhibitors	C09A, C09B
Angiotensin II receptor antagonists	C09C, C09D
Renin-inhibitors	C09X
Lipid-modifying agents	C10
HMG CoA reductase inhibitors (statins)	C10AA
Other lipid-modifying agents	C10AB, C10AC, C10AD, C10AX
HMG CoA reductase inhibitors (statins), other combination	C10BX
Antithrombotic agents	**B01**
Platelet aggregation inhibitors	B01AC
Systemic antibacterials	**J01**
Iron preparations	**B03A**
Proton pump inhibitors	**A02BC**
Drugs used in diabetes	**A10**

Annex Table 1-6 (cont'd) Anatomical Therapeutic Chemical codes for comedications

Medication description	ATC code
Drugs for musculoskeletal system	**M01A, N02BA, M01B, M01C**
Antidepressants	**N06A**
Antineoplastic agents	**L01**
Immunosuppressants	**L04**
Antivirals for systemic use	**J05**
Hormone-replacement therapy: Estrogens, progestogens, and estrogens in combination	**G03C, G03D, G03F**
Drugs used in nicotine dependence	**N07BA**

ATC = Anatomical Therapeutic Chemical; ICS = Inhaled Glucocorticosteroid; LABA = Long-Acting Beta2-Agonist; LAMA = Long-Acting Muscarinic Antagonist; SABA = Short-Acting Beta2-Agonist; SAMA = Short-Acting Muscarinic Antagonist.

1 The national drug code of each database country will be used to identify medications without an individual ATC code.

Source: WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2013. Updated 20 December 2012. Available at: website: whocc.no/atc_ddd_index/. Accessed 21 January 2013.

Annex Table 1-7 Database-specific codes for nebulisers in PHARMO

Devices	**code**
RESPIFLO VERNEVEL ADAPTER	14057816
VERNEVELAAR	14684217
MEDICIJN VERNEVELSET KENDALL MET AER MASKER KIND	14824256
MEDICIJN VERNEVELSET KENDALL MET AER MASKER VOLWAS	14824264
MONDSTUK VERNEVELAAR KENDALL LOS	14825678
MEDICIJN VERNEVELAAR KENDALL LOS	14825686
MEDICIJN VERNEVELSET KENDALL MET MONDSTUK	14825694
RESPIFLO CUP VOOR UN VERNEVELAAR 145ML	14826836
HUDSON ISONEB VERNEVELAAR	15136620
OMRON COMP AIR COMPRESSORVERNEVELAAR	15214508
OMRON COMP AIR ELITE COMPRESSORVERNEVELAAR	15214532
OMRON COMP AIR PRO COMPRESSORVERNEVELAAR	15214540
PARI EFLOW OPBERGZAK TBV VERNEVELAAR	15502155
PARI EFLOW VERBINDINGSKABEL NAAR VERNEVELAAR	15502198
PARI EFLOW VERNEVELSET INCLUSIEF MESH	15502201
PARI SINUS VERNEVELAAR COMPLEET	15502309
PARI TURBOBOY N MEDICATIE VERNEVELAAR COMPLEET	15502333
PARI LC PLUS VERNEVELAAR	15559025
PARI LC SPRINT VERNEVELAAR	15559033
OMRON COMP AIR COMPRESSORVERN COMPACT GEEL KIND	15910253
OMRON COMP AIR COMPRESSORVERNEVELAAR COMPACT WIT	15910261
VERNEVELSET INTERSURGICAL INCL FILTER Z FLOWMETER	16135067
CIRRUS 2 VERNEVELAAR	16135091
CIRRUS 2 VERNEVELAAR + KINDERMASKER + SLANG	16135105
CIRRUS 2 VERNEVELAAR + MONDSTUK + SLANG	16135113
VERNEVELMASKER INTERSURGICAL ECO KIND	16135121
T-STUK INTERSURGICAL MET VEER VOOR VERNEVELING	16135199

Annex Table 1-8 Codes for nebulisers in Denmark

Respiratory medications	ATC code	Nordic article number*
Inhaled SAMAs		
Ipratropium bromide	R03BB01	009502, 023940, 129817, 129817, 139883, 526137, 530337
Inhaled SABAs		
Salbutamol	R03AC02	023973, 031085, 059378, 085407, 184887, 475202, 475210, 536896, 555561
Terbutaline	R03AC03	567685
Inhaled glucocorticosteroid		
Budesonide	R03BA02	017895, 017900, 023896, 023907, 083744, 085169, 108925, 132244, 136473, 379032, 428271, 485408, 491688, 491704, 498797, 507908, 528916

11. HISTORY TABLE

Version No.	Date (dd Mmm yyyy)	Author	Sections changed	Brief description of change