1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Striverdi, Respimat			
Name of active ingredient: Olodaterol, R03AC19			
Report date: 08 August 2018	**Study number:** 1222.53	**Version/Revision:** 1.0	**Version/Revision date:** 08 August 2018
Title of study:	Drug Utilisation Study for Olodaterol		
Keywords:	Olodaterol, indacaterol, off-label, drug utilisation study, COPD		
Rationale and background:	Boehringer Ingelheim GmbH developed olodaterol, an inhaled long-acting beta2-agonist (LABA), for the indication of chronic obstructive pulmonary disease (COPD). LABAs are used in COPD to relieve bronchial constriction and, consequently, to improve symptoms. Because the use of LABAs has been associated with increased morbidity and mortality in patients with asthma, within the "Decentralised Procedure for Striverdi Respimat" the health authorities of the European Union/European Economic Area Member States requested the conduct of a post-approval drug utilisation study to assess potential off-label use of olodaterol in asthma and to characterise the use of olodaterol in clinical practice.		
Research question and objectives:	This study aims to characterise the use of single-agent olodaterol and single-agent indacaterol, the only marketed LABAs authorised for COPD, but not for asthma, in clinical practice. Study objectives are as follows: Primary objectives: • Quantify the frequency of off-label use of olodaterol among new users of these medications (i.e., the proportion of new users who do not have COPD) • Describe the baseline characteristics of new users of olodaterol Secondary objective: • Quantify the frequency of off-label use of indacaterol (a LABA approved for COPD but not for asthma) among new users of these medications (i.e., the proportion of new users who do not have COPD), in order to put into perspective the results for olodaterol initiators • Describe the baseline characteristics of new users of indacaterol		
Study design:	This is the final report of a cross-sectional study using information collected in health care databases among new users of olodaterol or indacaterol in the Netherlands, Denmark, and France.		

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Setting:	The study was implemented using data collected from existing data sources, located in three European countries: • The PHARMO Institute for Drug Outcomes Research (PHARMO) Database Network in the Netherlands • The National Registers in Denmark • IMS Health Information Solutions Real-World Evidence Longitudinal Patient Database (IMS RWE LPD) in France		
Subjects and study size, including dropouts:	• The *source population* included all patients enrolled in the selected study databases at the date olodaterol became available in each database's country. • The *study population* included those patients from the source population who received a first dispensing for single-agent formulations of olodaterol (for the primary objective) or indacaterol (for the secondary objective) during the study period and had at least 12 months of continuous enrolment in the study databases prior to index date. • No sample size calculations were done given that no hypothesis testing was performed. • For this final report, the *study period* began on the date of olodaterol launch in each country and ended on the latest date the data were available at the time of each final data extraction: i.e., from 01 March 2014 to 31 December 2016 in PHARMO and the National Registers in Denmark, and from 01 October 2015 to 30 November 2017 in the IMS RWE LPD panels.		
Variables and data sources:	**Data Sources:** This study used data on drug prescriptions/dispensings and disease occurrence routinely collected on an ongoing basis for large, population-based, automated health care databases in the Netherlands, Denmark, and France. • The PHARMO Database Network in the Netherlands is a population-based network of health care databases. Data sources are linked on a patient level through validated algorithms. To address the objectives of the present study, the following PHARMO databases have been used: (1) Out-patient Pharmacy Database, (2), Hospitalisation Database, and (3) General Practitioner (GP) Database. All new users identified in (1) were linked to (2) and are hereafter referred as the PHARMO overall population. The subset of patients that in addition were linkable		

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to (3) are hereafter referred as the PHARMO-GP population.

- The Danish health care system provides tax-funded universal coverage to all Danish residents (5.6 million inhabitants). Health care coverage includes use of services provided by GPs and GP-triaged to non-emergency hospital admissions, as well as outpatient hospital clinics visits. The costs of medicines are partially covered by the Danish Health Service. The centralised Civil Registration System in Denmark has assigned a unique identifier to every resident and therefore enables linkage to all Danish registers. To address the objectives of the present study, the following Danish registers were used: the Danish National Patient Registry, the Danish National Health Services Prescription Database, and the Danish Civil Registration System. Relevant data from the three data sources linked for this study are referred to hereafter as the National Health Databases, Denmark.
- The French IMS RWE LPD is an anonymised medical records database. To address the objectives of the present study, the following IMS RWE LPD panels have been used: (1) the primary care panel (hereafter referred as the IMS RWE LPD GP panel) and (2) the pulmonologist panel (hereafter referred as the IMS RWE LPD pulmonologist panel). The IMS RWE LPD GP panel currently includes 1,200 primary care physicians covering 1.8 million patients. The IMS RWE LPD pulmonologist panel currently includes 40 pulmonologists covering 50,000 patients. The data contain events that physicians record during routine clinical practice, e.g., diagnoses, prescriptions, measurements, tests, and referrals.

Variables:

- *Indication and potential off-label use of olodaterol and indacaterol*: Patients were classified in three mutually exclusive groups based on their potential indication:
  1. *On-label*: patients with a recorded diagnosis of chronic bronchitis, emphysema, or a diagnosis of COPD (without specifying chronic bronchitis or emphysema) in the database at any time before the index date or up to 30 days after the index date. Because COPD can occur in association with asthma, patients with a recorded diagnosis for both COPD and asthma were considered on-label.
  2. *Off-label*: (1) patients with a recorded diagnosis of asthma but no recorded diagnosis of COPD at any time before or up to 30 days

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	after the index date, and (2) all patients aged 17 years or younger. 3. *Potential off-label*: patients with no COPD and no asthma diagnosis recorded in the database at any time before the index date or up to 30 days after the index date. To further characterise potential off-label patients: a. An alternative definition of COPD was applied to these patients to identify the subset of these patients that probably have COPD. Prior diagnosis of other respiratory diseases was also identified and described among them. *Probable COPD* was defined by the presence of at least two prescriptions of LABA, long-acting muscarinic antagonist (LAMA), or inhaled glucocorticosteroid (ICS) (or combination) after the age of 40 years but not before. b. Prior diagnosis of other respiratory diseases was also identified and described among these potential off-label patients. • Characterisation of new users of olodaterol and indacaterol by demographic variables, medical history, and use of other medications: New users of olodaterol and new users of indacaterol were characterised at the index date according to demographic variables, available data on lifestyle habits, comorbidity, and use of medications. Comorbidity was ascertained through diagnosis codes and procedures recorded at any time before the index date. Use of medications was ascertained for the 12 months before the index date.
Results:	There were 4,158 new users of olodaterol and 9,966 new users of indacaterol identified during the study period of this final report. **Frequency of off-label use of olodaterol:** • The proportion of patients with off-label prescription/dispensing of olodaterol, i.e., patients aged 17 years or younger, or patients with prior diagnosis of asthma but no prior diagnosis of COPD, ranged from 3.5% in PHARMO overall to 12.4% in the IMS RWE LPD GP panel. • The proportion of new users of olodaterol classified as on-label (based on the presence of a COPD diagnosis code) ranged from 47.8% in PHARMO overall to 77.7% in the IMS RWE LPD pulmonologist panel. • The proportion of new users of olodaterol who were classified as

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potential off-label (with no COPD diagnosis and no asthma diagnosis) ranged from 17.3% in the IMS RWE LPD pulmonologist panel to 48.6% in PHARMO overall. Among these patients, the overall proportion of new users of olodaterol who were classified as probable COPD (based on prescriptions of LABA, LAMA, or ICS after the age of 40 years but not before) ranged from 7.4% in the IMS RWE LPD pulmonologist panel to 37.1% in PHARMO overall.

Frequency of off-label use of indacaterol:

- The proportion of patients with off-label prescription/dispensing of indacaterol, i.e., patients aged 17 years or younger or patients with prior diagnosis of asthma but no prior diagnosis of COPD, ranged from 3.5% in PHARMO overall to 11.9% in the IMS RWE LPD GP panel.
- The proportion of new users of indacaterol classified as on-label (based on prior diagnosis of COPD) ranged from 28.7% in Denmark to 70.1% in the IMS RWE LDP pulmonologist panel.
- The proportion of new users of indacaterol classified as potential off-label (with no COPD diagnosis and no asthma diagnosis) ranged from 20.5% in the IMS RWE LPD pulmonologist panel to 66.6% in Denmark. Among these patients, the overall proportion of new users of indacaterol who were classified as probable COPD (based on prescriptions of LABA, LAMA, or ICS after the age of 40 years but not before) ranged from 4.7% in the IMS RWE LPD pulmonologist panel to 36.6% in PHARMO overall.

Baseline characteristics of new users of olodaterol and indacaterol:

- The median age ranged from 63.0 years in the IMS RWE LPD GP panel to 71.0 years in Denmark among new users of olodaterol and from 63.0 years in the IMS RWE LPD GP panel to 69.0 years in Denmark among new users of indacaterol. Approximately 50% of these users were males.
- Information on smoking, body mass index (BMI), overweight, obesity, alcohol use, and socioeconomic status was scarce in all data sources. Differences between the characteristics of olodaterol and indacaterol users within each data source were small, but there were greater differences between data sources.
- The proportion of patients with a diagnosis of COPD (i.e., a COPD diagnosis ever before the index date up to 30 days after) corresponded to the proportion of patients on-label described above. The median time

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	since first diagnosis of COPD ranged from 2.7 years to 4.8 years among new users of olodaterol and from 2.0 years to 3.6 years among new users of indacaterol, in all data sources. • The proportion of patients with medical history of asthma at any time before index date or up to 30 days after ranged from 12.0% to 31.3% among all new users of olodaterol and from 8.5% to 28.7% among all new users of indacaterol. • The most frequent non-respiratory disease (among those evaluated) ever before index date among new users of olodaterol and indacaterol was hypertension, which ranged from 18.8% to 43.8% among new users of olodaterol and from 13.4% to 42.8% among new users of indacaterol. Other frequently recorded non-respiratory diseases were ischaemic heart disease, other forms of heart disease, arrhythmia, hyperlipidaemia, renal disease, diabetes mellitus, and malignancies. • In general, the most frequently prescribed/dispensed respiratory medications in the year before index date among new users of olodaterol and/or indacaterol were LAMA (ranging from 42.5% to 78.5% among new users of olodaterol and from 17.7% to 64.6% among new users of indacaterol), followed by systemic glucocorticosteroids, LABA/ICS, SABA, nasal glucocorticosteroids, and LABA. • In general, the most frequently prescribed/dispensed non-respiratory medications in the year before index date among new users of olodaterol and/or indacaterol were cardiovascular medications (ranging from 59.5% to 72.7% among new users of olodaterol and from 54.3% to 66.9% among new users of indacaterol users, without including IMS LPW RWE pulmonologists panel, which had very few records for non-respiratory medications, e.g. only 1.6% to 3.0% had a record for a prescription of a cardiovascular medication) followed by systemic antibacterials, proton pump inhibitors, antithrombotic agents, and drugs for musculoskeletal system.		
Discussion:	• Off-label use was low, and no difference was observed between olodaterol and indacaterol. In all data sources, except in the IMS RWE LPD GP panel, off-label use ranged from 3.5% to 6.2% for olodaterol and from 3.5% to 9.4% for indacaterol. In the IMS RWE LPD GP panel, the prevalence of off-label use was higher than in other data sources (12.4% for olodaterol and 11.9% for indacaterol). • Some degree of overestimation of off-label use and underestimation of		

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	on-label use is possible in all data sources due to underrecording of COPD diagnoses. However, the results suggest that COPD diagnosis is more likely to be underrecorded in the PHARMO overall and in the IMS RWE LPD GP panel than in the other data sources. • Underrecording of COPD diagnosis in the IMS RWE LPD GP panel is likely to occur due to the nature of the database where only day-to-day diagnoses are recorded and there is no incentive to record all of the patient's comorbidities. This phenomenon is also supported by the fact that recording of a COPD diagnosis is the highest in the IMS RWE LPD pulmonologist panel, where day-to-day visits include a large proportion of COPD patients. • Underrecording in data sources such as PHARMO where only 25% have primary care data available—and in Denmark, which is 100% hospital based—is likely given that users of olodaterol and indacaterol were identified in the out-patient pharmacy databases, and that only hospital discharge diagnoses were available to evaluate COPD diagnosis in Denmark and for 75% of the patients in PHARMO overall. Consequently, it is likely that a high proportion of patients remained without a COPD diagnosis because they had never been hospitalised for COPD. This outcome is also supported by the fact that the proportion of patients classified as "probable COPD" is high in all data sources but higher in these hospital-based data sources. The proportion of patients with a diagnosis of COPD was lower in PHARMO overall than in Denmark. This result might be explained by the fact that, compared with PHARMO overall, in Denmark, patients for whom a diagnosis of COPD was identified through a hospital discharge diagnosis had more severe COPD than patients in the PHARMO overall where a subset of patients do have GP data. • Results from this study also indicate that the new users of olodaterol and indacaterol are elderly patients with a high prevalence of comorbidity and concurrent use of medications. • Differences across data sources may be due to true differences in the patterns of use of the medications in the different countries but more likely due to the type and completeness of data in each data source (see Section 9.5 for more details).		
Marketing Authorisation	Boehringer Ingelheim GmbH		

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Holder(s):			
Names and affiliations of principal investigators:	[redacted]		