PART VI SUMMARY OF THE RMP

Active substance	Olodaterol
Product concerned	Striverdi® Respimat®
Name of Marketing Authorisation Holder or Applicant	Boehringer Ingelheim International GmbH, Ingelheim, Germany
Data lock point for this module	31 Jan 2014
Version number of Risk Management Plan (RMP) when this module was last updated	2.2

PART VI.1 ELEMENTS FOR SUMMARY TABLES IN THE EPAR

PVI.Table 1 Summary table of safety concerns

Important identified risks	None
Important potential risks	Cardiac arrhythmia Myocardial ischaemia Hypokalaemia Off-label use in asthma
Important missing information	Long-term data beyond 1 year of use (adverse cardiovascular outcome) Patients with a recent history of: • myocardial infarction • unstable or life-threatening cardiac arrhythmia • paroxysmal tachycardia • decompensated heart failure Patients with hepatic impairment Patients with severe renal impairment Safety in pregnant or breast-feeding women

PVI.Table 2 Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports[1]
1222.54 Cohort study of cardiovascular events in patients with chronic obstructive pulmonary disease initiating olodaterol or other long-acting beta2-agonists (non-interventional cohort study, 3)	Primary: Obtain further information on the risk of • selected cardiac arrhythmias • acute myocardial infarction (AMI) and other serious ischaemic heart disease events, including unstable angina in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs. Secondary: Obtain further information on the risk of overall mortality in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs.	• Cardiac arrhythmia • Myocardial ischaemia • Long-term data beyond 1 year of use (adverse cardiovascular outcome)	Protocol agreed	Interim reports: Q3 2017, 2018, 2019 Final report: Q3 2020
1222.53 Drug Utilisation Study for Olodaterol (non-interventional drug utilisation study, 3)	Primary: Determine the frequency of off-label use in asthma patients of olodaterol and indacaterol among new users of these medications. Obtain information on the baseline characteristics of new users of olodaterol and new users of indacaterol. Secondary: Obtain information on the characteristics of the prescribing physicians.	Off-label use in asthma	Protocol agreed	Interim report: Q3 2017 Final report: Q3 2018

[1] Timelines are considered preliminary, because they are strongly depending on the market uptake of olodaterol.

The development plan for olodaterol does not include any ongoing or planned post-authorisation efficacy studies.

PVI.Table 3 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risk		
Cardiac arrhythmia	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Section 4.4).	None
Myocardial ischaemia	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Section 4.4).	None
Hypokalaemia	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.4 and 4.5).	None
Off-label use in asthma	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.4 and 4.1).	None
Important missing information		
Long-term data beyond 1 year of use (adverse cardiovascular outcome)	Routine risk minimisation by routine pharmacovigilance	None
Patients with a recent history of: • myocardial infarction • unstable or life-threatening cardiac arrhythmia • paroxysmal tachycardia • decompensated heart failure	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Section 4.4).	None
Patients with hepatic impairment	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Section 4.2).	None
Patients with severe renal impairment	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Section 4.2).	None
Safety in pregnant or breast-feeding women	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.6).	None

PART VI.2 ELEMENTS FOR A PUBLIC SUMMARY

Part VI.2.1 Overview of disease epidemiology

Smoking, outdoor air pollution, occupational exposures and a history of asthma are main risk factors for chronic obstructive pulmonary disease (COPD) [R13-0339, R13-0333]. There is also evidence for the influence of genetic factors [R13-0348]. The prevalence, incidence, morbidity and mortality of COPD vary across countries and different groups within countries and are influenced by risk factors for COPD and differences in diagnostic criteria [R10-2308, R08-4924, R10-2316, P12-01205].

In European countries, reported incidence rates (per 100 person-years) range from 0.3 in the Netherlands (observation period: 2000-2007, persons aged 55 and older) [R11-4213], to 1.5 in Norway (observation period: 1985-1997, persons aged 45-74) [R10-2312] and 1.6 in Sweden (observation period: 1996-2003, persons aged 53-84) [R10-2317]. The reported prevalences of COPD range from 2.8% in Italy (study period: 2009, persons aged 15 years and older) [P10-13578] to 26.1% in Austria (study period: not specified, persons aged 40 and older) [R10-2328]. However, the diagnostic approaches and criteria for diagnosing COPD and age distributions of the study populations differed between the studies.

In 2004, COPD ranked fourth as a leading cause of death with 5.1% of all deaths and is projected to become the third leading cause of death in the world by 2030 with 8.6% [R09-4326]. Approximately 200 000 to 300 000 patients die in Europe from COPD each year [R10-2310]. Mortality rates from COPD depend on the severity of COPD.

Use of concomitant non-COPD medications goes alongside with the prevalence of common COPD comorbidities, such as hypertension, diabetes mellitus or heart failure, and risk factors for COPD. COPD has been also linked to psychiatric illness. Patients with COPD are at significantly higher risk of having depressive symptoms [R10-2327] that are strongly associated with worse respiratory-specific and overall physical health-related quality of life.

Part VI.2.2 Summary of treatment benefits

Bronchodilator medications are central to symptom management in COPD [P13-02399]. They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. Long-acting inhaled bronchodilators are convenient and more effective at producing maintained symptom relief than short-acting bronchodilators.

Striverdi® Respimat® is a long-acting inhaled bronchodilator (long-acting beta$_2$-adrenergic agonist [LABA]). It has been tested in a Phase 3 clinical trial programme that included trials of 48-week and 6-week duration, and involved more than 3500 patients across all stages of COPD severity.

Striverdi® Respimat®, delivered once daily at the 5 mcg dose, demonstrated a fast onset of action and showed significant improvements in lung function, as measured by forced

expiratory volume in 1 second (FEV_1), in patients with moderate to very severe COPD compared to placebo. These improvements in lung function were maintained throughout the 48-week treatment period. Striverdi® Respimat® further showed improvements on heath-related quality of life, and on exercise tolerance, in patients with moderate to very severe COPD compared to placebo. In an effort to more accurately represent the real-life setting, patients involved in the study were allowed to continue on their usual care with the exception of long-acting beta agonists. Usual care included long- and short-acting anticholinergics, short-acting beta agonists, inhaled corticosteroids and xanthines.

In the 48-week studies, olodaterol 5 mcg once daily (876 patients) showed statistically significant improvements compared to placebo (885 patients) for FEV_1 AUC_{0-3} response and trough FEV_1 response, which were maintained over the 48 week treatment period and were comparable to formoterol 12 mcg twice daily (460 patients).

The bronchodilatory profile of olodaterol 5 mcg was confirmed in 4 supportive 6-week studies, in which the mean FEV_1 improvements over 24 hrs were comparable to formoterol 12 mcg twice daily (and tiotropium HandiHaler® 18 mcg once daily).

Part VI.2.3 Unknowns relating to treatment benefits

All phase 3 trials had similar inclusion criteria (with 1 exception for trials 1222.37 and 1222.38, as noted below). Eligible patients were outpatients of either sex, 40 years of age or older, with a diagnosis of COPD, and a smoking history of more than 10 pack-years. Patients were required to have relatively stable, moderate to very severe airway obstruction. In trials 1222.37 and 1222.38, an upper age limit of 75 years was adopted due to the requirement to perform several cycle ergometry tests to assess symptom-limited exercise endurance. The results of the pivotal phase 3 trials were analysed within a variety of patient subgroups including baseline disease severity, gender, age, race, co-medication, and smoking status at baseline, and overall, olodaterol 5 mcg was shown to be an efficacious bronchodilator across patient populations and subgroups.

Patients with a history of asthma, myocardial infarction within 1 year before the screening visit, unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure within the previous year, a diagnosis of thyrotoxicosis or paroxysmal tachycardia (more than 100 beats/minute), or a significant disease other than COPD that might compromise patient safety or compliance were excluded. There is no evidence that efficacy is different in these patients.

Part VI.2.4 Summary of safety concerns

Currently, there are no important identified risks for olodaterol.

PVI.Table 4 Important potential risks

Risk	What is known (incl. reason why it is considered a potential risk)
Cardiac arrhythmia	The general occurrence of cardiac arrhythmia was low in the olodaterol long-term studies. Frequency of adverse events (AEs) was similar among the treatment groups with placebo, olodaterol 5 mcg olodaterol 10 mcg, and formoterol 12 mcg. There was no increase of events with the olodaterol dose of 10 mcg compared to 5 mcg, which makes an identified effect of the therapeutic olodaterol dose of 5 mcg on cardiac arrhythmia events unlikely. Overall, about 5% of all patients treated with olodaterol experienced cardiac arrhythmia of any kind (serious or non-serious). Less than 1% were rated as serious. Cardiac arrhythmia is considered a potential risk because it is an acknowledged pharmacodynamic effect of all beta-adrenergic agonists (class effect).
Myocardial ischaemia	The general occurrence of myocardial ischaemia was low in the olodaterol long-term studies. Frequency of AEs was similar among the treatment groups with placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol 12 mcg. There was no increase of events with the olodaterol dose of 10 mcg compared to 5 mcg, which makes an identified effect of the therapeutic olodaterol dose of 5 mcg on myocardial ischaemia events unlikely. Overall, about 1.5% of all patients treated with olodaterol experienced myocardial ischaemia. Less than 1% were rated as serious. Myocardial ischaemia is considered a potential risk because it is an acknowledged pharmacodynamic effect of all beta-adrenergic agonists (class effect).
Hypokalaemia	The total number of reported hypokalaemia events was low and similar in all treatment groups (3 for placebo, 4 for olodaterol 5 mcg, 4 for olodaterol 10 mcg). All events were reported as non-serious. Hypokalaemia is considered a potential risk because decrease of potassium is a well known direct cellular pharmacodynamic effect of all beta-adrenergic agonists in high systemically available doses (class effect).

PVI.Table 4 (cont'd) Important potential risks

Risk	What is known (incl. reason why it is considered a potential risk)
Off-label use in asthma	There is a potential risk for off-label use of Striverdi® Respimat® in asthma if a differential diagnosis is not performed by the treating physician. The Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) has reviewed the safety of formoterol and salmeterol, which are products of the same therapeutic class (LABA) as olodaterol, in the management of asthma. The PhVWG has concluded that LABAs in asthma should only be used with an inhaled corticosteroid and doses should be monitored carefully. The PhVWG recommends that the summary of product characteristics (SmPC) and package leaflet for all LABAs with asthma use shall reflect this information, which is consistent with international asthma treatment guidelines. This recommendation is completely followed for the product information of Striverdi® Respimat®. In the olodaterol Phase 2 programme, olodaterol studies in asthma have been conducted. The occurrence of adverse events was low. There has been no safety concern from any asthma study. However, long-term efficacy and safety in asthma patients of olodaterol has not been established since the olodaterol asthma database is very limited and does not provide sufficient basis for conclusions to be drawn on the efficacy and safety in asthma.

PVI.Table 5 Important missing information

Risk	What is known
Long-term data beyond 1 year of use (adverse cardiovascular outcome)	At this point in time, the maximum exposure to olodaterol treatment is approximately 1 year, so there is no experience with adverse drug reactions occurring after1 year.
Patients with a recent history of: • myocardial infarction • unstable or life-threatening cardiac arrhythmia • paroxysmal tachycardia • decompensated heart failure	These patients were excluded from the olodaterol clinical trials. Therefore, there is no data on these patient populations available.
Patients with hepatic impairment	Olodaterol has been investigated in patients with hepatic impairment; however due to the low patient numbers (n=16), information on patients with hepatic impairment is limited in the current clinical trial database.
Patients with severe renal impairment	Olodaterol has been extensively investigated in patients with mild to moderate renal impairment (n=1345); however due to the low numbers of patients with severe renal impairment (n=22) information on these patients is limited in the current clinical trial database.
Safety in pregnant or breast-feeding women	Olodaterol has not been investigated in pregnant or lactating women. There are no adequate and well controlled studies in pregnant women. In clinical studies conducted so far with olodaterol, exposure during pregnancy or lactation did not occur. In the authorised indication COPD, which is clearly a disease of the elderly, exposure during pregnancy is highly unlikely, however, considering the possibility of off-label use in asthma, it cannot be completely excluded that the product might be used incorrectly by this population.

Part VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PL for Striverdi® Respimat® can be found in the Striverdi® Respimat® European Public Assessment Report (EPAR) page.

This medicine has no additional risk minimisation measures.

Part VI.2.6 Planned post-authorisation development plan

PVI.Table 6 List of studies in post-authorisation development plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports[1]
1222.54 Cohort study of cardiovascular events in patients with chronic obstructive pulmonary disease initiating olodaterol or other long-acting beta2-agonists (non-interventional cohort study, 3)	Primary: Obtain further information on the risk of • selected cardiac arrhythmias • acute myocardial infarction (AMI) and other serious ischaemic heart disease events, including unstable angina in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs. Secondary: Obtain further information on the risk of overall mortality in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs.	• Cardiac arrhythmia • Myocardial ischaemia • Long-term data beyond 1 year of use (adverse cardiovascular outcome)	Protocol agreed	Interim reports: Q3 2017, 2018, 2019 Final report: Q3 2020
1222.53 Drug Utilisation Study for Olodaterol (non-interventional drug utilisation study, 3)	Primary: Determine the frequency of off-label use in asthma patients of olodaterol and indacaterol among new users of these medications. Obtain information on the baseline characteristics of new users of olodaterol and new users of indacaterol. Secondary: Obtain information on the characteristics of the prescribing physicians.	Off-label use in asthma	Protocol agreed	Interim report: Q3 2017 Final report: Q3 2018

[1] Timelines are considered preliminary, because they are strongly depending on the market uptake of olodaterol.

Studies which are a condition of the marketing authorisation:
None of the above studies is a condition of the marketing authorisation.

Part VI.2.7 Summary of changes to the RMP over time

PVI.Table 7 Major changes to the RMP over time

Version	Date	Safety concerns	Comment
2.2	18 Aug 2016	-	Revised protocol (1222.53) attached in Appendix 6.
2.1	22 Oct 2014	-	Revised protocols (1222.53 and 1222.54) attached in Appendix 6.
2.0	31 Jan 2014	-	Inclusion of final protocols for PASS (1222.54) and DUS (1222.53) in Appendix 6, and update of corresponding sections in Parts III, VI, and Appendix 5.

PART VI.3 ABBREVIATIONS

AE	Adverse Event
AUC	Area under the Curve
CHMP	Committee for Medicinal Products for Human Use in the EU
COPD	Chronic Obstructive Pulmonary Disease
EPAR	European Public Assessment Report
FEV1	Forced expiratory volume in 1 second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
LABA	Long-Acting Beta$_2$-Adrenergic Agonist
PASS	Post Authorisation Safety Study
PhVWG	Pharmacovigilance Working Party of the CHMP
PL	Package Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART VI.4 REFERENCES

Part VI.4.1 Published references

P10-13578 Cazzola M, Segreti A, Bettoncelli G, Paolini I, Cricelli C, Saltini C. Changes in drug prescription for asthma (A) and COPD (C) by GPs in Italy. 20th Ann Cong of the European Respiratory Society (ERS), Barcelona, 18 - 22 Sep 2010 Eur Respir J 2010;36(Suppl 54):139S Abstr P855.

P12-01205 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (revised 2011). Website: goldcopd.org/uploads/users/files/GOLD_Report_2011_Jan21.pdf (access date: 2 February 2012) (2011)

P13-02399 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2013). Website: goldcopd.org/uploads/users/files/GOLD_Report_2013Feb13.pdf (access date: 20 Feb 2013) ; Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2013)

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R09-4326 World Health Organization (WHO). World health statistics 2008. Geneva: WHO (2008)

R10-2308 Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, Connell C, Jemal A, Lee TA, Miravitlles M, Aldington S, Beasley R. Epidemiology and costs of chronic obstructive pulmonary disease. Eur Respir J. 2006 Jan;27(1):188-207. Review. PubMed PMID: 16387952.

R10-2310 European Lung foundation: Website: de.european-lung-foundation.org/uploads/Document/WEB_CHEMIN_385_1148398246.pdf, accessed 1 March 2010].

R10-2312 Johannessen A, Omenaas E, Bakke P, Gulsvik A. Incidence of GOLD-defined chronic obstructive pulmonary disease in a general adult population. Int J Tuberc Lung Dis. 2005 Aug;9(8):926-32. PubMed PMID: 16104642.

R10-2316 Lindberg A, Jonsson AC, Rönmark E, Lundgren R, Larsson LG, Lundbäck B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest. 2005 May;127(5):1544-52. PubMed PMID: 15888826.

R10-2317 Lindberg A, Eriksson B, Larsson LG, Rönmark E, Sandström T, Lundbäck B. Seven-year cumulative incidence of COPD in an age-stratified general population sample. Chest. 2006 Apr;129(4):879-85. PubMed PMID: 16608933.

R10-2327 Omachi TA, Katz PP, Yelin EH, Gregorich SE, Iribarren C, Blanc PD, Eisner MD. Depression and health-related quality of life in chronic obstructive pulmonary disease. Am J Med. 2009 Aug;122(8):778.e9-15. PubMed PMID: 19635280] ; PubMed Central PMCID: PMC2724315.

R10-2328 Schirnhofer L, Lamprecht B, Vollmer WM, Allison MJ, Studnicka M, Jensen RL, Buist AS. COPD prevalence in Salzburg, Austria: results from the Burden of Obstructive Lung Disease (BOLD) Study. Chest. 2007 Jan;131(1):29-36. PubMed PMID: 17218553.

R11-4213 Afonso AS, Verhamme KM, Sturkenboom MC, Brusselle GG. COPD in the general population: Prevalence, incidence and survival. Respir Med. 2011 Aug 16. [Epub ahead of print] PubMed PMID: 21852081.

R13-0333 Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR, Environmental and Occupational Health Assembly Committee on Nonsmoking COPD. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 182, 693 - 718 (2010)

R13-0339 Lokke A, Lange P, Scharling H, Fabricius P, Vestbo J. Developing COPD: a 25 year follow up study of the general population. Thorax 61, 935 - 939 (2006)

R13-0348 Serres FJ de. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys. Chest 122 (5), 1818 - 1829 (2002)

Part VI.4.2 Unpublished references

Not applicable.