PART VI.2 ELEMENTS FOR A PUBLIC SUMMARY

Part VI.2.1 Overview of disease epidemiology

The incidence, prevalence and mortality of COPD vary across countries and different age groups within countries, and are influenced by the distribution of risk factors for COPD and differences in how COPD is diagnosed [R10-2308, R08-4924, R10-2316, P12-01205].

In Europe, the estimated incidence rates range between 2.0 and 9.2 per 1000 person-years [R11-4219, R10-2329] and prevalences between 2.8 and 26.1% [R11-4215, R10-2328]. Worldwide COPD ranked 4th in 2004 as a leading cause of death, attributable for 5.1% of all deaths worldwide [R09-4326]. Approximately 200 000 to 300 000 people die in Europe from COPD each year [R10-2310].

Smoking, outdoor air pollution, occupational exposures, a history of asthma and possible genetic factors are the main risk factors for COPD [R13-0339, R13-0333, R13-0348].

People who have COPD also frequently have other common illnesses such as hypertension, diabetes mellitus, or heart failure. 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

Two classes of inhaled bronchodilators are currently utilised: β2-agonists and muscarinic antagonists. The first β2-agonists and muscarinic antagonists to be developed have a limited duration of action that necessitates 4 times daily dosing to maintain bronchodilator activity over a 24-hour period. Subsequently, β2-agonists and muscarinic antagonists have been developed with a longer duration of action, allowing for a twice daily or once daily posology (LABAs, LAMAs).

Treatment guidelines present a rationale for combining bronchodilators with different mechanisms, noting that this strategy may result in an increase in the degree of bronchodilation for equivalent or lesser side effects. When β2-agonists and muscarinic antagonists with matching posologies are combined, the opportunity exists for offering a simpler and more convenient administration regimen with the development of fixed combinations within the same inhaler device. Fixed-dose combinations of a short-acting β2 agonist and a short-acting muscarinic antagonist have been developed and have been shown to be safe, efficacious, and convenient for the patient [P10-11858]. Recently, the first once daily LAMA/LABA fixed combinations have been approved in the EU and US.

The development programme for tiotropium+olodaterol is intended to support its use as a once daily maintenance bronchodilator treatment in patients with COPD.

The combination therapy of tiotropium (LAMA) and olodaterol (LABA) is proposed for the treatment of patients with COPD. It has been tested in a Phase III clinical trial programme that included trials of up to 52 weeks duration and involved more than 7000 patients across all stages of COPD severity from moderate to very severe. Tiotropium+olodaterol, delivered once daily at the 5 µg/5 µg dose (2 actuations of 2.5 µg / 2.5 µg) demonstrated a fast onset of action and showed significant improvements in lung function (FEV1 AUC0-3h response on Day 169 and trough FEV1 response on Day 170) and health related quality of life (SGRQ total score on Day 169).

Part VI.2.3 Unknowns relating to treatment benefits

In the main and supporting studies, tiotropium+olodaterol was investigated in patients older than 40 years. Tiotropium+olodaterol was not investigated in patients with hepatic impairment. Patients with hepatic impairment were investigated in the Olo mono programme and dose adjustment was not considered necessary. Patients with hepatic impairment were not investigated in the Tio mono programme. Tiotropium+olodaterol has not been investigated in patients with renal impairment; however patients with mild to moderate renal impairment were not excluded from the clinical trials. Patients with renal impairment were investigated in the respective mono therapy programmes and no dose adjustment was deemed necessary for these patients. Patients with a high prevalence of cardiovascular comorbidity have been studied extensively with tiotropium+olodaterol, except for patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia, and decompensated heart failure. Tiotropium+olodaterol was not investigated in pregnant or breast-feeding women; in the clinical development programme no cases of pregnancy/breast-feeding have been reported so far. Tiotropium+olodaterol has been clinically tested for up to 52 weeks. Long-term experience with tiotropium+olodaterol above 1 year of treatment is currently limited.

Part VI.2.4 Summary of safety concerns

There are no important identified risks defined for tiotropium+olodaterol.

PVI.Table 5 Important potential risks

Risk	**What is known (incl. reason why it is considered a potential risk)**
Blood and lymphatic system disorders	Elderly persons with COPD may concurrently have certain diseases, or take certain medicines, which can cause blood and lymphatic system disorders, e.g. abnormal counts of blood cells or enlarged lymph nodes. There is no evidence that patients using tiotropium+olodaterol are at higher risk than other patients.
High blood sugar levels (blood glucose increased)	Patients with COPD often have type 2 diabetes mellitus as concomitant disease. There is no evidence that patients using tiotropium+olodaterol are at higher risk of increased blood glucose than other patients.
Psychiatric disorders	Depression, anxiety, panic attacks, and other psychiatric disorders occur frequently in patients with COPD. There is no evidence that patients using tiotropium+olodaterol are at higher risk of psychiatric disorders than other patients.
Loss of consciousness (syncope)	Syncope (loss of consciousness or fainting) occurs frequently in elderly persons, including those with COPD. There is no evidence that patients using tiotropium+olodaterol are at higher risk of syncope than other patients.
Cardiac disorders (heart disease, irregular heartbeat, heart failure) (myocardial ischaemia, cardiac arrhythmia, cardiac failure)	Some cardiac disorders, such as irregular heartbeat and heart disease, are considered potential risks for tiotropium+olodaterol because they are common to the class of medicines to which its component Olo belongs. These and other cardiac disorders (e.g. heart attack, heart failure, and chest pain) are common in elderly people, including those with COPD. However, there is no evidence that patients using tiotropium+olodaterol are at higher risk of cardiac disorders than other patients.
Cardiac mortality	This is a potential risk for any patient with COPD. Boehringer Ingelheim carefully evaluates all reports of cardiac mortality for patients on tiotropium+olodaterol as part of the pharmacovigilance programme.
Vascular disorders (aneurysm)	Bulges in a blood vessel (aneurysms) occur frequently in patients that are of advanced age and have diseases such as COPD. The risk to develop both conditions simultaneously increases with age. There is no evidence to suggest that patients using Tiotropium+olodaterol are at higher risk of aneurysm than other patients.
Renal failure	Elderly persons, including those with COPD, are at risk for renal failure. There is no evidence that patients using tiotropium+olodaterol are at higher risk of renal failure than other patients.

PVI.Table 5 (cont'd) Important potential risks

Risk	**What is known (incl. reason why it is considered a potential risk)**
Overdose	Overdose of any drug is an issue of concern. Overdose with tiotropium+olodaterol, i.e. multiple sequential inhalation at a time, is unlikely, because the device requires loading before each actuation. Cases of overdose of tiotropium+olodaterol occur very rarely and are not expected to have serious clinical consequences.
Low blood potassium (hypokalaemia)	Decrease of potassium levels in the blood is a well-known effect of the class of medicines to which Olo belongs. The extent of potassium decrease is marginal and not of clinical importance at regular therapeutic inhaled doses of tiotropium+olodaterol.
Off-label use in asthma	There is the potential risk for off-label use of tiotropium+olodaterol in asthma if a correct differential diagnosis is not performed, i.e. if not all appropriate tests and examinations are done to distinguish a disease or condition (e.g. COPD) from others presenting with similar signs and symptoms (e.g. asthma). Tiotropium+olodaterol is not be used in asthma, since long-term efficacy and safety of Olo has not been established in patients with asthma.

PVI.Table 6 Missing information

Risk	What is known
Long-term data beyond 1 year of use (adverse cardiovascular outcome)	There is extensive market experience and clinical trial experience at least up to 48 months with the Tio component of tiotropium+olodaterol. The longest exposure to the Olo component to date is 48 weeks in studies. The combination of Tio and Olo has been clinically tested only up to 52 weeks. Therefore, there is no experience with adverse drug reactions occurring after 1 year.
Pregnant and breast-feeding women	There are no adequate and well-controlled studies in pregnant women. In the indication COPD, which is mostly a disease of the elderly, exposure during pregnancy is 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.
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 tiotropium+olodaterol clinical trials. Therefore, no data are available on this patient population.
Patients with hepatic impairment	Tiotropium+olodaterol has not been investigated in patients with hepatic impairment in clinical studies. Patients with hepatic impairment were investigated in the Olo mono programme and dose adjustment was not considered necessary. Patients with hepatic impairment were not investigated in the Tio mono programme. Therefore, information on these patients is limited.
Patients with severe renal impairment	Tiotropium+olodaterol has not been investigated in patients with renal impairment; however patients with mild to moderate renal impairment were not excluded from the clinical trials. Patients with renal impairment were investigated in the respective mono therapy programmes and no dose adjustment was deemed necessary for these patients. Therefore, information on these patients is limited.

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 tiotropium+olodaterol can be found on the product's EPAR page.

This medicine has no additional risk minimisation measures.

Part VI.2.6 Planned post-authorisation development plan

The development plan for the combination tiotropium+olodaterol currently does not include any post-authorisation studies.

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

Not applicable as this is the first RMP for tiotropium+olodaterol.

PART VI.3 ABBREVIATIONS

COPD	Chronic obstructive pulmonary disease
DLP	Data lock point
EPAR	European public assessment report
MAH	Marketing authorisation holder
Olo	Olodaterol
PL	Package leaflet
RMP	Risk management plan
SmPC	Summary of product characteristics
SGRQ	St. Georges' Respiratory Questionnaire
Tio	Tiotropium bromide

PART VI.4 REFERENCES

Part VI.4.1 Published references

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Part VI.4.2 Unpublished references

Not applicable