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Summary of the risk management plan (RMP) for Incruse (umeclidinium bromide)

This is a summary of the risk management plan (RMP) for Incruse, which details the measures to be taken in order to ensure that Incruse is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Incruse, which can be found on Incruse's EPAR page.

Overview of disease epidemiology

Chronic obstructive pulmonary disease (COPD) is a long-term disease in which the airways and air sacs inside the lungs become damaged or blocked, leading to difficulty breathing. Symptoms of COPD usually develop over a number of years and can include breathlessness (especially after physical activity), persistent cough sometimes with mucus, wheezing, and frequent chest infections. The main cause of COPD is smoking. The disease is aggravated by bacterial and viral chest infections which cause exacerbations (flare-ups). Both exacerbations and chest infections can require admission to hospital and in some cases can lead to death.

It is estimated that there are around 210 million people with COPD worldwide. Males are more often affected than females and Europeans are more often affected than Asians and particularly more than Africans. Generally, with increasing age, more people suffer from COPD. Less than 6% of people between the ages of 25-44 years suffer from mild and moderate COPD, while, more than 40% of people in the age group of 75 years and older suffer from mild and moderate COPD.

Summary of treatment benefits

Incruse contains umeclidinium bromide, which is a 'long-acting muscarinic receptor antagonist' (LAMA). It works by opening up the airways and make it easier for air to get in and out of the lungs (bronchodilator). When used regularly, it can help to control breathing difficulties and minimise the effects of the disease on everyday life.

It is used to treat the symptoms of chronic obstructive pulmonary disease (COPD) in adults.

Incruse should not be used to relieve a sudden attack of breathlessness or wheezing. If patients get this sort of attack they must use a quick-acting reliever inhaler (such as salbutamol).

Incruse was studied in 4 main studies, involving over 4,000 patients. Three studies compared Incruse with placebo (a dummy treatment), while one study compared Incruse with tiotropium (another medicine for COPD). The main measure of effectiveness was based on changes in the patients' forced expiratory volumes (FEV_1, the maximum volume of air a person can breathe out in one second). Results showed that Incruse improved lung function by an average FEV_1 by 133 ml more than placebo after 12 weeks of treatment and by 125 ml after 24 weeks of treatment. Incruse given at double that dose only showed small improvements compared with the lower dose, which were not considered

relevant. In the study comparing Incruse with tiotropium, FEV_1 improvements over 24 weeks were similar for both medicines.

The studies also showed an improvement in symptoms such as breathlessness and wheezing.

Taken together, the results from all the studies support the use of Incruse as a once-daily bronchodilator treatment to relieve symptoms in adult patients with COPD.

Unknowns relating to treatment benefits

Most of the patients included in the studies were white (89%), male (65%) and had an average age of 63 years, across all treatments. There is no evidence to suggest that results would be different in non-white subjects.

Summary of safety concerns

Important identified risks

None identified.

Important potential risk

Risk	What is known
Problems affecting the heart and the blood vessels in the brain. (Cardio- and Cerebrovascular disorders)	Umeclidinium bromide is a LAMA. It is known that other LAMAs have been associated with effects on the heart such as irregular heart beat (including atrial fibrillation and tachycardia). There is also a potential risk of cebrovascular events (stroke, transient ischaemic attack, central nervous system haemorrhages). Incruse should be used with caution in patients with severe heart problems.
Temporary narrowing of the airways (paradoxical bronchospasm) which occurs suddenly leading to difficulties in breathing or wheezing (Paradoxical bronchospasm)	Inhaled medicines which make breathing easier have sometimes caused the opposite effect, and may cause tightness of the chest, coughing, wheezing or breathlessness immediately after taking the medicine, which may be life threatening. If any of these symptoms occur, the use of Incruse should be stopped and medical help should be sought immediately.
Narrow angle glaucoma (a type of condition with high eye pressure)	Long-acting muscarinic antagonists like Incruse have been reported to cause a rare type of glaucoma called narrow angle glaucoma. Some people with pre-existing eye conditions may be more prone to this effect. As it is important that COPD be adequately treated, some patients with pre-existing narrow angle glaucoma may receive Incruse following medical advice, if considered necessary.

Risk	What is known
Sudden inability to pass urine (Urinary retention)	Long-acting muscarinic antagonists like Incruse have been reported to cause a sudden inability to pass urine (urinary retention). Some elderly male patients who have other medical conditions, such as an enlarged prostate may be more prone to urinary retention. It is important for COPD to be well treated, so some patients with these conditions may receive Incruse following medical advice.
Lower respiratory tract infection (including pneumonia)	Pneumonia is inflammation of the tissue in one or both of the lungs and it is usually caused by an infection. Pneumonia can be more common and serious in people who smoke or have lung conditions, such as COPD. In studies with Incruse, a higher number of lung infections, including pneumonia, were seen in those patients taking twice the recommended dose compared to patients taking a placebo.

Missing information

Risk	What is known
Safety in patients who are pregnant or breast-feeding	For Incruse, there are no studies on exposure during pregnancy. During pregnancy, Incruse should be used with caution. In patients with COPD who become pregnant, it is important that COPD is controlled, so some patients may receive Incruse following medical advice. It is not known whether Incruse passes into human breast milk and it should therefore be used with caution in breastfeeding women.
Safety in patients who have used the medicine long-term	LAMAs have been used successfully in the long term treatment of COPD (beyond one year). Incruse has been studied for periods of up to one year. Despite this limited information, there is no indication that Incruse is less safe when used long-term.
Use in patients with severe liver problems	Incruse has not been studied in patients with severe liver problems. Therefore, the safety of Incruse in these patients is unknown. It is important for COPD to be well treated, so some patients with severe hepatic impairment may

Risk	What is known
	receive Incruse following medical advice.
Interaction with other medicines	Incruse has been tested to see if it interacts with other medicines. Some additional laboratory tests have been requested. As some medicines may affect how Incruse works, patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Incruse can be found on Incruse's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study 201038:A Post-Authorisation Safety Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular Events in COPD patients using Inhaled UMEC/VI or Inhaled UMEC versus Tiotropium Handihaler.	To quantify the incidence of selected cardiovascular and cerebrovascular events of interest after the start of exposure to umeclidinium bromide (UMEC)/ vilanterol (VI) combination or UMEC alone in the licensed indication, in the post marketing setting, specifically in the COPD patients managed in primary care in multiple European countries and compare with the incidence of cardiovascular events of	Cardio- and Cerebrovascular Disorders Lower repiratory tract infections (including pneumonia) Safety in long-term use	Planned	Final report: Q3 2024

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	interest after the start of exposure to tiotropium (Handihaler) over 24 months follow-up.			
WWE117397 (formerly WEUSKOP6679): Post-authorisation Safety Electronic Medical Records Database Cohort Study of New Users of Inhaled UMEC/VI or new users of inhaled UMEC in the Primary Care Setting: UK EMR Distributed Network Study.	Primary: Drug utilisation review of new users of UMEC/VI and new users of UMEC compared to the COPD patients initiating long-acting bronchodilators. Secondary: Quantify the disease burden of COPD and estimate the incidence of cardiovascular and cerebrovascular events of interest among new users of UMEC/VI, new users of UMEC and a comparator (selected from new long-acting bronchodilator users) among those with no ongoing management for the events of interest at observation start.	Cardio- and Cerebrovascular Disorders Lower repiratory tract infections (including pneumonia)	Planned	Final report: Q2 2020
Regulatory review of the submission has highlighted additional in vitro drug interaction investigations which should be completed.	Additional investigations to provide information to address: binding of UMEC to microsomes and recalculation of I/Ki in the gut based on free drug concentrations providing data for UMEC as a substrate for BCRP and BSEP provide further clarification for the lack of effect of UMEC in CYP	A series of post authorisation in vitro studies will determine the potential for drug-drug interactions.	Planned	Final report: Q1 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	2D6 poor metabolisers provide data for UMEC as a substrate of OATP1B1 and 1B3			

Studies which are a condition of the marketing authorisation

Study 201038 is a condition of the market authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 04-2014.