PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. SUMMARY OF THE RISK MANAGEMENT PLAN FOR DAXAS (ROFLUMILAST)

This is a summary of the risk management plan (RMP) for DAXAS. The RMP details important risks of DAXAS, how these risks can be minimised, and how more information will be obtained about DAXAS's risks and uncertainties (missing information).

DAXAS's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how DAXAS should be used.

This summary of the RMP for DAXAS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of DAXAS's RMP.

I.1 THE MEDICINE AND WHAT IT IS USED FOR

DAXAS is authorised for maintenance treatment of severe COPD (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. It contains roflumilast as the active substance and it is given by oral route of administration. Roflumilast is available as 500 µg film-coated tablets and as 250 µg tablets in EU.

Further information about the evaluation of DAXAS's benefits can be found in DAXAS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/daxas.

I.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of DAXAS, together with measures to minimise such risks and the proposed studies for learning more about DAXAS's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PBRER assessments so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of DAXAS is not yet available, it is listed under 'missing information' below.

I.2.1 List of important risks and missing information

Important risks of DAXAS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of roflumilast. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. long-term use of the medicine).

Table I-1 List of important risks and missing information

Important identified risks	Weight decrease
	Diarrhoea
	Psychiatric disorders (depression, suicidal ideation and behaviour)
Important potential risks	Malignant tumours
	Infections
	Major cardiovascular events
Missing Information	Long-term treatment

I.2.2 Summary of important risks

Table I-2 Important identified risk: Weight decrease

Evidence for linking the risk to the medicine	Weight decrease in patients taking roflumilast is related to PDE4 inhibition, which is based on the interplay between the PDE4 and the regulation of glucagonlike peptide-1 (GLP-1), an incretin hormone with glucose and weight-lowering properties. In clinical studies (pivotal studies M2-124 and M2-125) weight decrease was more frequent in patients in the roflumilast groups.
Risk factors and risk groups	Weight loss associated with roflumilast was greater in patients with gastrointestinal adverse events or headache, or both.
Risk minimisation measures	SmPC sections 4.4 and 4.8 PL sections 2 and 4 SmPC section 4.4 recommends patients to check their body weight regularly and to discontinue roflumilast in case of unexplained and clinically concerning weight loss. PL section 2 advises to monitor body weight regularly and consult the physician in case of unintentional weight loss.
Additional pharmacovigilance activities	Post-Authorisation Safety Study D7120R00003

Table I-3 Important identified risk: Diarrhoea

Evidence for linking the risk to the medicine	Diarrhoea may be caused by PDE4 (mainly PDE4D) inhibition in the gut, considering the activation by roflumilast of the cystic fibrosis transmembrane conductance regulator (CFTR) in human colonic T84 cells and the role of CFTR in intestinal fluid transport. In clinical studies diarrhoea was more frequent in patients in the roflumilast groups and there is a plausible mechanism of action for how roflumilast may lead to diarrhoea. In the COPD safety pool, 10.1% of patients receiving roflumilast 500 µg experienced diarrhoea. In clinical studies (pivotal studies M2-124 and M2-125 and the two 6-month studies M2-127 and M2-128) diarrhoea was more frequent in patients in the roflumilast groups compared to placebo / comparator + placebo.
Risk factors and risk groups	In general, risk factors of diarrhoea in adults are gastroenteritis, hypersensitivity reactions and tumours located in the gastrointestinal tract, elderly patients (e.g. burden of acute or chronic multisystem illnesses, under-nutrition) as well as systemic conditions (e.g. hyperthyroidism) and medications (e.g. broad-spectrum antibiotics). Diarrhoea is one of the AEs reported due to consequence of increased exposure in special populations such as black, non-smoking females, or in patients concomitantly treated with CYP1A2/2C19/3A4 inhibitors.
Risk minimisation measures	SmPC section 4.4 and 4.8. PL sections 2 and 4. SmPC section 4.4 recommends the physicians to discontinue roflumilast in case of persistent intolerability (diarrhoea) PL section 2 recommends the patients to inform the physicians if diarrhoea do not resolve within the first weeks of treatment.

Table I-3 Important identified risk: Diarrhoea

Additional pharmacovigilance activities	Post-Authorisation Safety Study D7120R00003

Table I-4 Important identified risk: Psychiatric disorders (depression, suicidal ideation and behaviour)

Evidence for linking the risk to the medicine	Psychiatric disorders (depression, suicidal ideation and behaviour) were more common in the roflumilast group compared to the placebo in the COPD clinical programme. In the clinical development programme, 3 cases of "completed suicide" were reported in the roflumilast groups compared to none reported on placebo. In addition, 2 suicide attempts were reported in the roflumilast 500 µg group compared to none on placebo.
Risk factors and risk groups	The global prevalence of clinically relevant depression and anxiety is 40% in patients with COPD compared with 10% in the general population. Cigarette smoking has long been recognized as the primary cause of COPD in developed countries, and individuals with psychiatric comorbidities are twice as likely to be cigarette smokers relative to those without psychiatric comorbidities, suggesting that psychiatric morbidity could precede the development of COPD. In the COPD safety pool, a slightly higher number of patients in the placebo group had a previous medical history of depression compared to the roflumilast 500 µg group (8.1% vs 7.4%). Risk factors include: mental disorders (particularly clinical depression) or history of mental disorders, family history of suicide, previous suicide attempt(s), history of alcohol and substance abuse, epilepsy, personality traits, loss (relational, social, work, or financial), physical illness and certain medications. There have been post marketing reports of depression, suicidal ideation, depression suicidal and panic attack in patients receiving roflumilast for COPD.
Risk minimisation measures	SmPC sections 4.4 and 4.8 PL sections 2 and 4 SmPC section 4.4 advises the physicians to assess the risks and benefits of roflumilast therapy in patients with previous or existing psychiatric symptoms or if the patients are taking concomitant medications which could cause psychiatric events. Also, patients and caregivers are instructed to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation and to discontinue roflumilast in case of new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt. PL section 2 recommends the patients to inform the physicians if they have any symptoms sleeplessness, anxiety, nervousness, or depressive mood before initiation of roflumilast. Patients / care givers should inform the physicians in case of any changes in behaviour or mood and of any suicidal thoughts.
Additional pharmacovigilance activities	AE follow-up questionnaire. Post-Authorisation Safety Study D7120R00003

Table I-5 Important potential risk: Malignant tumours

Evidence for linking the risk to the medicine	Findings from long term observational studies in Europe and the USA have reported the incidence of lung cancer in patients with COPD between 2.9 and 16.7 per 1,000 person-years, with an overall risk of lung cancer at least four times higher than the general population. There have been post marketing reports of malignant tumours in patients receiving roflumilast for COPD.
Risk factors and risk groups	It is well known that COPD is a significant risk factor for lung cancer. Approximately 1% of COPD patients develop lung cancer every year, which may be associated with genetic susceptibility to cigarette smoke. Although a correlation of chronic inflammation and smoking has been well established, increasing evidence supports the association between COPD and lung cancer independent of smoking status. Chronic inflammation caused by toxic gases can induce COPD and lung cancer. Known risk factors include family history of cancer, advanced age, exposure to chemicals causing cancer, smoking, tobacco, and alcohol.
Risk minimisation measures	SmPC section 4.4. PL section 2 SmPC section 4.4 recommends not to initiate or existing treatment with roflumilast should be stopped in patients with cancers (except basal cell carcinoma) PL section 2 recommends not to take roflumilast in patients with cancer (except basal-cell carcinoma)
Additional pharmacovigilance activities	Post-Authorisation Safety Study D7120R00003

Table I-6 Important potential risk: Infections

Evidence for linking the risk to the medicine	The most common co-morbid conditions at the time of COPD diagnosis were related to respiratory infections including pneumonia. Compared to the non-COPD cohort, COPD patients are at increased risk for pneumonia (relative risk [RR] = 16.0) and for respiratory infections (RR = 2.2). Considering that TNF-α is involved in host defence, there are concerns of potential side effects such as the increased risk of infections associated with TNF-α blocker therapies. There have been post marketing reports of severe infections like pneumonia, herpes zoster and respiratory infections in patients receiving roflumilast for COPD.
Risk factors and risk groups	Elderly patients as well as typical concomitant medications in the target population (e.g. chronic corticosteroid intake potentially leading to immune suppression).

Risk minimisation measures	SmPC section 4.4 and 4.8 (frequency rare: Respiratory tract infections (excluding Pneumonia)) PL section 2. SmPC section 4.4 recommends not to initiate or existing treatment with roflumilast should be stopped in patients with severe acute infectious diseases. PL section 2 recommends not to take roflumilast in patients with severe acute infectious diseases such as tuberculosis, or acute hepatitis
Additional pharmacovigilance activities	Post-Authorisation Safety Study D7120R00003

Table I-7 Important potential risk: Major cardiovascular events

Evidence for linking the risk to the medicine	Results of a large cohort study showed that cardiovascular diseases are remarkably prevalent in COPD patients. Patients with COPD had high prevalence of coronary artery disease (33.6%), congestive heart failure (24.4%), and atrial fibrillation (14.3%), which were statistically significantly higher than those among the matched non-COPD cohort (27.1%, 13.5%, and 10.4%, respectively; $p < 0.001$). There have been post marketing reports of major cardiovascular events such as myocardial infarction, atrial fibrillation cardiac failure, and cardiac failure congestive.
Risk factors and risk groups	Anticipated patient groups at risk of major cardiovascular events include the more elderly and those with a history of cardiac disease, hypertension, dyslipidaemia, hyperglycaemia or diabetes mellitus. No specific groups and risks were identified with regard to roflumilast. In particular, CVD and COPD share similar risk factors such as ageing, history of cigarette smoking, and both diseases frequently coexist.
Risk minimisation measures	SmPC sections 4.4 and 4.8. PL section 2. SmPC section 4.4 does not recommend roflumilast in patients with congestive heart failure (NYHA grades 3 and 4) PL section 2 recommends not to take roflumilast in patients with severe impairment of the heart function
Additional pharmacovigilance activities	AE follow-up questionnaire Post-Authorisation Safety Study D7120R00003

Table I-8 Missing information: Long-term treatment

Risk minimisation measures	SmPC section 4.2 Roflumilast has been studied in clinical trials for up to one year.
Additional pharmacovigilance activities	Post-Authorisation Safety Study D7120R00003

I.2.3 Post-authorisation development plan

I.2.3.1 Studies which are conditions of the marketing authorisation

The following study is condition of the marketing authorisation.

Study short name: Long-term post-marketing observational study of roflumilast D7120R00003 (RO-2455-403-RD); Category 1.

Purpose of the study: To investigate 5-year mortality and morbidity of roflumilast in the COPD patient population. The secondary objective of the study was to evaluate potential risks identified during the clinical trials of roflumilast as secondary outcomes. Specifically, this study aimed to compare the incidences of death by suicide or hospitalisation for suicide attempt, hospitalisation for any cause, major cardiovascular events, respiratory disease related hospitalisation, new diagnosis of depression, new diagnosis of malignant neoplasm, abnormal and unexplained weight loss, hospitalisation due to serious diarrhoea of non-infectious origin, and new diagnosis of tuberculosis or hepatitis B or C or other severe viral hepatitis infection (except hepatitis A).

I.2.3.2 Other studies in post-authorisation development plan

There are no studies required for DAXAS.