| **EU RMP** | |
|---|---|
| Drug Substance | Roflumilast |
| Version Number | 24 |
| Succession Number | 1 |
| Data lock point | 05 June 2025 |
| Date of final sign off | See e-signature page |

# EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for DAXAS*™* (roflumilast)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV or deputy QPPV, as delegated by the QPPV.

## Administrative Information

### Rationale for submitting an updated RMP*:*

- The safety concerns listed in this RMP including weight decrease, diarrhoea, psychiatric disorders (depression, suicidal ideation and behaviour), malignant tumours, infections, major cardiovascular events and long-term treatment have been reclassified and removed from the RMP.

### Summary of significant changes in this RMP

### Part II SIII

Footnotes to tables added for clarity, no changes in table content.

### PART II SIV

Safety data pool has been updated to include 21 COPD studies, with corresponding revisions to the narrative text to reflect and clarify study inclusion. This update in safety data presentation is to align the study data with roflumilast PBRER (EMEA/H/C/PSUSA/00002658/202401).

### Part II SV

Updated post authorization exposure data

### Part II SVII

- Removed the following safety concerns previously classified as important identified risks:
  - Weight decrease
  - Diarrhoea
  - Psychiatric disorders (depression, suicidal ideation and behaviour)
- Removed the following safety concerns previously classified as important potential risks:
  - Malignant tumours
  - Infections
  - Major cardiovascular events
- Removed the following safety concerns previously classified as missing information:
  - Long term treatment

## Part II SVIII

- Updated summary of safety concerns in line with Part II SVII

## Part III

- Follow up questionnaires removed.

Updated in line with revised safety concerns as detailed in Part II S VII

## Part V

- Updated in line with revised safety concerns as detailed in Part II S VII

## Part VI

- Updated in line with revised safety concerns as detailed in Part II SVII

## Part VII

- Annex 4 updated in line with changes above.

## Details of currently approved RMP:

| | |
|---|---|
| **Other RMP versions under evaluation** | **Version Number**: Not applicable<br>**Submitted**: Not applicable<br>**Procedure number**: Not applicable |
| **Details of currently approved RMP** | **Version Number**: 23 S2<br>**Approved with procedure**: EMEA/H/C/PSR/S/0041<br>**Date of approval:** 15 November 2023 |

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| **Abbreviation/ Special term** | **Definition/Explanation** |
|---|---|
| ADR | Adverse Drug Reaction |
| aRMM | Additional risk minimisation measure |
| AE | Adverse Event |
| cAMP | cyclic Adenosine Monophosphate |
| CrCl | Creatinine Clearance |
| COPD | Chronic Obstructive Pulmonary Disease |
| EEA | European Economic Area |
| EMA | European Medicine Agency |
| EPAR | European Public Assessment Report |
| EU RMP | European Union Risk Management Plan |
| GI | Gastrointestinal |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| HIV | Human Immunodeficiency Virus |
| HR | Hazards Ratio |
| LABA | Long-Acting Beta-Agonist |
| LPS | Lipopolysaccharide |
| MACE | Major Cardiovascular Events |
| NYHA | New York Heart Association |
| QoL | Quality of Life |
| PV | Pharmacovigilance |
| PASS | Post-Authorisation Safety Study |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PBRER | Periodic Benefit Risk Evaluation Report |
| PDE | Phosphodiesterase |
| t PDE | Total Phosphodiesterase |
| RMM | Risk Minimisation Measure |
| RMP | Risk Management Plan |
| ROW | Rest of the World |
| SAE | Serious Adverse Event |
| SMQ | Standardised MedDRA Query |
| SOC | System Organ Class |
| SmPC | Summary of Product Characteristics |

| **Abbreviation/ Special term** | **Definition/Explanation** |
|---|---|
| TNF | Tumour Necrosis Factor |
| UK | United Kingdom |

# 1 PART I: PRODUCT OVERVIEW

## Table 1-1 Product Overview

| | |
|---|---|
| Active substance(s)<br>(INN or common name) | Roflumilast |
| Pharmacotherapeutic group(s) (ATC Code) | R03DX07 |
| Marketing Authorisation Holder | AstraZeneca AB |
| Medicinal products to which this RMP refers | 1 |
| Invented name(s) in the European Economic Area (EEA) | DAXAS |
| Marketing authorisation procedure | Centralised |
| Brief description of the product | Chemical class:<br>Selective phosphodiesterase 4 (PDE4) inhibitor |
| | Summary of mode of action:<br>Roflumilast is a non-steroid, anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with Chronic Obstructive Pulmonary Disease (COPD). The mechanism of action is the inhibition of PDE4, a major cyclic adenosine monophosphate (cAMP)-metabolizing enzyme found in structural and inflammatory cells important to the pathogenesis of COPD. Roflumilast targets the PDE4A, 4B and 4D splicing variants with similar potency in the nanomolar range. The affinity to the PDE4C splicing variants is 5 to 10-fold lower. |
| | Important information about its composition:<br>Not applicable |
| Hyperlink to the Product Information | DAXAS, Summary of Product Characteristics |
| Indication(s) in the EEA | Current:<br>Roflumilast is indicated for maintenance treatment of severe COPD ($FEV_1$ postbronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. |
| | Proposed*:* Not Applicable |

**Table 1-1 Product Overview**

| | |
|---|---|
| Dosage in the EEA | **Current**<br>One tablet of roflumilast 500 micrograms (µg) once daily.<br>**Starting dose:**<br>The recommended starting dose is one tablet of 250 µg roflumilast to be taken once daily, for 28 days. This starting dose is subtherapeutic and therefore, should be used only as a starting dose.<br>**Maintenance dose:** After 28 days of treatment with the 250 µg starting dose, patients must be up-titrated to one tablet of 500 µg roflumilast, to be taken once daily. |
| | Proposed:<br>Not applicable |
| Pharmaceutical form(s) and strengths | Current:<br>500 µg film-coated tablet<br>250 µg tablet |
| | Proposed:<br>Not Applicable |
| Is/will the product be subject to additional monitoring in the EU? | No |

# 2 PART II: SAFETY SPECIFICATION

## 2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

### 2.1.1 Chronic obstructive pulmonary disease

A high-level overview is provided below, further details on the epidemiology of COPD in Europe is provided by the European Respiratory Society's White book (www.erswhitebook.org/chapters/chronic-obstructive-pulmonary-disease/) and globally is provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (www.goldcopd.org) and the references therein.

#### Incidence

Precise estimates of incidence of spirometry-defined COPD are lacking for most countries in Europe. Furthermore, the reported incidences of COPD varied greatly between countries, and it is difficult to compare estimates because they are reported in different units, over different lengths of time and using different methods for diagnosis and classification (**Rycroft et al**

**2012**). A reasonable approximation of overall incidence of COPD is approximately 1% of the adult population per year.

**Prevalence:**

As with incidence, the overall prevalence of COPD in Europe is hard to determine precisely and is further complicated due to varying methodologies used and under-reporting/under-diagnosis of the disease (**Rycroft et al 2012**). The World Health Organization estimate from large-scale studies is between 5% and 10%. A recent study of the geographical distribution of COPD prevalence in Europe identified 62 studies conducted in 19 European countries, all studies being based on validated spirometric criteria for COPD diagnosis. Mean prevalence across the 62 studies was estimated at 12.4% (95% CI 10.8-14.0) (**Blanco et al 2017**). Prevalence estimates by European regions are summarised in Table 2-1 below.

**Table 2-1 Descriptive statistics of COPD prevalence in European regions**

| EU Region* | Number of studies | Mean prevalence (%) (95% CI) | Min value across studies | Max value across studies |
|---|---|---|---|---|
| **Northern Europe** | 21 | 11.5 (8.8-14.1) | 2.1 | 25.4 |
| **Western Europe** | 11 | 14.2 (8.8-19.6) | 3.9 | 26.4 |
| **Central Europe** | 14 | 14.1 (10.4-17.9) | 5.0 | 26.1 |
| **Southern Europe** | 16 | 10.8 (7.8-13.8) | 4.9 | 23.4 |
| **Total** | 62 | 12.4 (10.8-14.0) | 2.1 | 26.4 |

*Northern Europe: Iceland, Denmark, Norway, Sweden, Finland, Estonia, Latvia, and Lithuania; Western Europe: Belgium, Luxembourg, France, Ireland, the Netherlands, and UK; Central Europe: Germany, Austria, Poland, Slovakia, Czech Republic, Hungary, Slovenia, and Switzerland; Southern Europe: Spain, Portugal, Italy, Greece, Malta, Cyprus, and Turkey.

**Demographics of the population in the COPD indication and risk factors for the disease:**

Data from a cross-sectional multi-country European study of patients with an established history of COPD (aged ≧30 years at diagnosis, with a smoking history ≧10 pack-years) in Germany, France, Spain, Belgium, Netherlands, United Kingdom (UK), and Italy reported that 72% of patients were male, with mean age of 65 years, mean duration of disease was of 9.4 years, and mean smoking history was 40.4 pack-years (**Jones et al 2011**).

The recent review of 62 European studies of COPD prevalence in Europe reports mean age of the study populations at 55.9 (95%CI 54.4-57.5). Age distribution across European regions is summarized in Table 2-2.

**Table 2-2 Descriptive statistics of age in the COPD sample populations reported by Blanco et al, 2017**

| EU Region* | Number of studies | Mean (years) (95% CI) | Min value across studies | Max value across studies |
|---|---|---|---|---|
| **Northern Europe** | 21 | 54.8 (51.3-58.3) | 42.0 | 73.0 |
| **Western Europe** | 11 | 60.3 (56.3-64.0) | 50.9 | 69.5 |
| **Central Europe** | 14 | 55.0 (52.0-58.1) | 40.1 | 59.5 |
| **Southern Europe** | 16 | 55.2 (53.5-56.9) | 47.5 | 62.8 |
| **Total** | 62 | 55.9 (54.4-57.5) | 40.8 | 73.0 |

*Norther Europe: Iceland, Denmark, Norway, Sweden, Finland, Estonia, Latvia, and Lithuania; Western Europe: Belgium, Luxembourg, France, Ireland, the Netherlands, and UK; Central Europe: Germany, Austria, Poland, Slovakia, Czech Republic, Hungary, Slovenia, and Switzerland; Southern Europe: Spain, Portugal, Italy, Greece, Malta, Cyprus, and Turkey.

Risk factors for COPD identified in the GOLD 2025 are as follows: tobacco smoking, genes (hereditary deficiency of alpha- 1 antitrypsin; single genes such as the matrix metalloproteinase 12), age (older individuals), gender (historically males were at increased risk but prevalence is now almost equal), lung and growth development (factors affecting lung growth), exposure to particles (occupational exposures; urban air pollution), socioeconomic status (poverty and lower socioeconomic status), asthma/bronchial hyperactivity (both affecting lung function), chronic bronchitis (through mucus hypersecretion and lung function decline), and infections (through reduced lung function and increased respiratory symptoms).

**The main existing treatment options:**

The current goals of pharmacological management of COPD are to relieve symptoms, improve exercise tolerance, health status and quality of life (QoL), prevent and treat complications and exacerbations, and reduce dyspnoea, nocturnal symptoms, and use of rescue medication (GOLD 2025). Various pharmacological approaches are used to reach these goals, primarily short- and long-acting inhaled bronchodilators (β2-adrenoceptor agonists, anticholinergic/antimuscarinic agents, xanthines), but also corticosteroids (inhaled and systemic), expectorants and long-term oxygen therapy. The positive benefit-risk ratio of the PDE4 inhibitor roflumilast, as part of a combination regimen with long-acting bronchodilators, is well established in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

**Natural history of the indicated condition in the untreated population, including mortality and morbidity:**

The pathogenesis of COPD remains unclear but chronic inflammation (bronchitis) throughout airways, parenchyma and pulmonary vasculature is believed to have a central role (**Rabe et al 2007**). Indeed, chronic bronchitis and emphysema are the two most common conditions that

contribute to COPD. A comprehensive review of current knowledge on COPD indicates that although COPD is a heterogenous disease, accelerated decline in lung function over time, most often as a result of exposure to tobacco smoke, is the hallmark feature of the natural history of COPD (**Rabe and Watz 2017**). This lung function decline is strongly predictive of COPD-related morbidity and mortality. COPD is a progressive disease and no pharmacological intervention to date has been shown to reduce this accelerated decline in lung function or extend mortality. The development and progression of COPD can vary dramatically between individuals. As lung function decreases, patients initially suffer from wheezing, mucous hypersecretion, chronic and progressive cough, and/or dyspnoea, and with further decline, significant physical disability. Dyspnoea upon exertion leads to reduced activity, loss of muscle tone, and further inactivity. Exacerbations, defined as periods characterized by acute worsening of respiratory symptoms, often requiring medical attention, are another characteristic feature of COPD that is also associated with increased morbidity, accelerated mortality and poor health related QoL (**Viniol and Vogelmeier 2018**). In addition to lung function, other extrapulmonary factors including comorbid diseases contribute to morbidity and mortality related to COPD. COPD takes a tremendous toll on patients, severely limiting activities of daily living, impacting QoL and frequently increasing the risk of death. Patients experience a progressive deterioration up to end-stage COPD, with very severe airflow limitation, chronic respiratory failure, multiple comorbidities associated with advanced age, and severe systemic complications. Aside from COPD-related respiratory death including pneumonia, cardiovascular death and lung cancer are among the most common causes of death for patients with COPD.

**Important co-morbidities:**

- Chronic inflammation
- Cardiovascular Disease, including but not limited to ischaemic heart disease, heart failure, arrhythmias, peripheral vascular disease, and hypertension
- Pulmonary hypertension
- Lung cancer
- Osteoporosis
- Skeletal muscle weakness
- Depression and anxiety

## 2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage

### 2.2.1 Toxicity

Key issues identified from acute or repeat-dose toxicity studies:

No key findings identified.

Reproductive/developmental toxicity:

Tocolytic activity resulting in delivery retardation in pregnant mice: Treatment of pregnant mice at term led to a significantly prolonged duration of gestation, decrease in live-birth index, and increased postnatal mortality. These findings are seen as an exaggerated pharmacological effect of roflumilast and suggest uterine muscle relaxation in pregnant animals, prolonging the parturition process. It is unknown whether roflumilast will cause relaxation of the uterine muscle at term also in humans, but it should be considered as a potential effect.

Secretion of roflumilast and/or its metabolites into milk: After intravenous and oral administration, [$^{14}$C]-roflumilast and/or its metabolites were secreted into milk of lactating rats. It is unknown whether roflumilast is secreted into the milk of breast-feeding women, but it should be considered as a possible effect.

Genotoxicity

No key findings identified.

Carcinogenicity

No key findings identified.

### 2.2.2 Safety pharmacology

Cardiovascular system, including potential effect on the QT interval:

Roflumilast and its N-oxide did not influence the human ether-a-go-go related gene channel current at concentrations up to 100-times the free plasma maximum drug concentration in humans dosed 500 µg/day. No change was observed in the action potential in isolated papillary muscle of guinea pig hearts. The electrocardiogram in cats, dogs, and minipigs remained unchanged after high doses of roflumilast and its N-oxide.

In telemetry instrumented conscious Cynomolgus monkeys, the blood pressure decrease induced by oral bambuterol (5 mg/kg) was slightly accentuated by simultaneous oral administration of roflumilast 0.25 mg/kg), suggesting that there might be a slight synergistic/additive effect on blood pressure when roflumilast is added to oral long-acting beta-agonist (LABA). Concurrent LABA use was not precluded in the roflumilast clinical

development program and no adverse impact on blood pressure was observed in humans from concurrent administration with roflumilast.

Nervous system:

No key findings identified.

Respiratory System:

No key findings identified.

Gastrointestinal system:

Gastrointestinal (GI) changes have been found in repeat dose toxicity studies in rats and monkeys, but not in mice, hamsters and dogs, only at doses in excess of therapeutic doses. The GI changes in animals are considered to be due to high dose toxicity and stress, and not due to local intolerance. High safety ratios exist for any local GI toxicity. No safety risk is expected for human usage.

### 2.2.3 Other toxicity-related information or data

Inhibition of TNF-α release:

Roflumilast and roflumilast N-oxide have been shown to moderately inhibit TNF-α release under experimental conditions (LPS-stimulation of blood in vitro) but rather inconsistently in blood of healthy volunteers or patients (basal levels or after ex-vivo LPS stimulation). The in-vitro inhibition of lipopolysaccharide (LPS)-induced TNF-α release in whole blood from healthy volunteers by roflumilast and roflumilast N-oxide amounts to 60% at maximum. The mean ex-vivo LPS-induced TNF-α release decreased in the roflumilast treatment group by 21% as compared to a decrease of 5% in the placebo group in one study. However, such effect of roflumilast was variable and/or not significant in the other studies.

Data obtained in repeat-dose toxicity and carcinogenicity studies are consistent with the absence of classical immunosuppressive effects of roflumilast. Roflumilast or roflumilast N-oxide treatment did not result in any direct compound-related effects on lympho-hematopoietic organs in mice, rats, hamsters, dogs, or monkeys after repeated doses for up to 52 weeks. There was no evidence of increased incidence of spontaneous cage-related wounds or localised infections in these studies. Additionally, there was no evidence of compound-related neoplasias in carcinogenicity studies that could be linked to immunosuppression. These conclusions are supported by lack of immunosuppressive effects of roflumilast in a rat kidney transplant model of acute rejection.

Neutralisation of TNF-α by specific anti-TNF agents, such as Infliximab (Remicade®) or Etanercept (Enbrel®), is in the range of 90-100% throughout the dosing interval, whereas inhibition by roflumilast of TNF-α release after in-vitro LPS-stimulation is <30% at maximum and in-vivo TNF-α levels were not significantly changed by roflumilast treatment. Since roflumilast only weakly inhibits the release of TNF-α in humans compared to targeted TNF blockers, this is thought to negate any risk of triggering infections or malignancies, as supported by the low incidence of lower respiratory tract infections and pneumonia as well as of malignant tumours in the roflumilast safety database.

Retention in fat:

Studies using [ADCP-$^{14}$C]-roflumilast show a consistent pattern with respect to distribution of radioactivity into fat tissue in mice, hamsters and rats. During an early distribution phase, [$^{14}$C]-concentrations in fat increased above plasma levels up to 2.6-fold after oral administration and up to 4-fold after intravenous administration to rats, less so in the other two species. After this distribution phase, [$^{14}$C]-concentrations in fat fell faster than those in plasma showing concentration ratios below 1 after 4 to 24 hours post dosing. Thus, no signs of retention of roflumilast (and metabolites) in fat tissue were obtained in single-dose studies. This finding was confirmed by a repeat-dose study in rats, in which all [$^{14}$C]-concentrations in fat were below plasma concentrations during the elimination phase.

An early distribution phase with concentrations of radioactivity in fat above plasma levels is in line with a good penetration of the lipophilic parent compound (roflumilast) into fat and other organs and tissue. However, this distribution phase is followed by a marked elimination phase out of fat most probably due to the pronounced break-down of parent compound to roflumilast N-oxide and other metabolites. These metabolites are less lipophilic by nature than the parent compound with a much lower potential for penetration into fat.

Due to its physicochemical properties, roflumilast is readily distributed to organs and tissues. Considering data in animals and the fact that body weight did not have any impact on clearance of roflumilast or roflumilast N-oxide in humans, there is no evidence for any specific accumulation or retention of roflumilast or its metabolites in organs and fatty tissue (deep compartment).

## 2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Exposure data are presented for 24 multinational clinical trials in which 11,418 subjects were exposed to roflumilast.

Studies included are: M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128, FK1101, FK1103, IN-108, FHP030, FK1 102, JP-706, JP-

708, RO-2455-301-RD (ACROSS), RO-2455-404-RD (REACT), RO-2455-405-RD (TREAT), RO-2455-302-RD (OPTIMIZE), ROF-MD-07 (RESPOND), and RO-2455-402-RD (ROBERT/BIOPSY). Thirty-eight patients with missing treatment start date and/or end date are not included in calculation of person time.

In Table 2-3, Table 2-4, Table 2-5, and Table 2-6 below, information is provided on duration of exposure, age, gender, dose and racial group respectively for the 24 studies referred above.

**Table 2-3 Duration of exposure to Roflumilast - COPD**

| Duration of exposure | Patients | Person Time (Days) |
|---|---|---|
| <1 month | 1067 | 17431 |
| 1 to < 3 month | 2214 | 160571 |
| 3 to < 6 months | 3509 | 556436 |
| > 6 months | 4590 | 1501863 |
| Missing | 38 | - |
| **Total** | **11418** | **2236301** |

Studies included are: M2-124, M2-125, FK1 101, FK1 103, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-127, M2-128, IN-108, FHP030, FK1 102, JP-706, JP-708, RO-2455-301-RD (ACROSS), RO-2455-404-RD (REACT), RO-2455-405-RD (TREAT), RO-2455-302-RD (OPTIMIZE), ROF-MD-07 (RESPOND), and RO-2455-402-RD (ROBERT/BIOPSY). All studies are completed prior/during the reporting period. 38 patients with missing treatment start date and/or end date are not included in calculation of person time.

Source: root/cdar/d712/iemt/ar/r014/tlf/prod/program/dsur2019_ex201.sas dsur2019_ex201a.lst 31MAY2019:15:40

**Table 2-4 Age group and gender - COPD**

| | Gender | | Person Time (Days) | |
|---|---|---|---|---|
| **Age group** | **Male** | **Female** | **Male** | **Female** |
| Adults (e.g. 18-64 years) | 3931 | 1787 | 817112 | 357867 |
| Elderly people | | | | |
| 65-74 years | 3284 | 928 | 624814 | 170875 |
| 75-84 years | 1178 | 254 | 216675 | 39805 |
| 85+ years | 49 | 7 | 8581 | 572 |
| **Total** | **8442** | **2976** | **1667182** | **569119** |

Studies included are: M2-124, M2-125, FK1 101, FK1 103, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-127, M2-128, IN-108, FHP030, FK1 102, JP-706, JP-708, RO-2455-301-RD (ACROSS), RO-2455-404-RD (REACT), RO-2455-405-RD (TREAT), RO-2455-302-RD (OPTIMIZE), ROF-MD-07 (RESPOND), and RO-2455-402-RD (ROBERT/BIOPSY). All studies are completed prior/during the reporting period. 38 patients with missing treatment start date and/or end date are not included in calculation of person time.

Source: root/cdar/d712/iemt/ar/r014/tlf/prod/program/dsur2019_ex202.sas dsur2019_ex202a.lst 31MAY2019:15:44

### Table 2-5 Dose - COPD

| Dose of Exposure | Patients | Person Time (Days) |
|---|---|---|
| Roflumilast 250 µg, od, p.o. | 1056 | 157716 |
| Roflumilast 250 µg OD/ 500 ug OD | 441 | 34690 |
| Roflumilast 500µg, od, p.o. | 8642 | 1887250 |
| Roflumilast 500 µg, od, p.o. and Salmeterol 50 µg, bid, ih | 466 | 66058 |
| Roflumilast 500 µg, od, p.o. and Tiotropium 18 µg, od, ih | 374 | 56189 |
| Roflumilast 500 µgEOD/ 500 µg OD | 439 | 34398 |
| **Total** | **11418** | **2236301** |

OD: once daily, EOD: every other day, PO: per oral

Studies included are: M2-124, M2-125, FK1 101, FK1 103, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-127, M2-128, IN-108, FHP030, FK1 102, JP-706, JP-708, RO-2455-301-RD (ACROSS), RO-2455-404-RD (REACT), RO-2455-405-RD (TREAT), RO-2455-302-RD (OPTIMIZE), ROF-MD-07 (RESPOND), and RO-2455-402-RD (ROBERT/BIOPSY). All studies are completed prior/during the reporting period. 38 patients with missing treatment start date and/or end date are not included in calculation of person time.

Source: root/cdar/d712/iemt/ar/r014/tlf/prod/program/dsur2019_ex203.sas dsur2019_ex203a.lst 31MAY2019:15:47

### Table 2-6 Racial group - COPD

| Race | Patients | Person Time (Days) |
|---|---|---|
| Asian | 1502 | 242003 |
| Black / African American | 119 | 26765 |
| White | 9507 | 1916080 |
| Other | 280 | 49776 |
| Unknown | 10 | 1677 |
| **Total** | **11418** | **2236301** |

Studies included are: M2-124, M2-125, FK1 101, FK1 103, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-127, M2-128, IN-108, FHP030, FK1 102, JP-706, JP-708, RO-2455-301-RD (ACROSS), RO-2455-404-RD (REACT), RO-2455-405-RD (TREAT), RO-2455-302-RD (OPTIMIZE), ROF-MD-07 (RESPOND), and RO-2455-402-RD (ROBERT/BIOPSY). All studies are completed prior/during the reporting period. 38 patients with missing treatment start date and/or end date are not included in calculation of person time.

Source: root/cdar/d712/iemt/ar/r014/tlf/prod/program/dsur2019_ex204.sas dsur2019_ex204a.lst 31MAY2019:15:48

## 2.4 MODULE SIV: Populations not studied in clinical trials

### 2.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

This subsection summarizes exclusion criteria that were applied in at least two clinical studies included in the COPD safety pool.

The COPD safety pool comprises data from 21 clinical trials, encompassing a total of 10,932 patients exposed to roflumilast (500 µg: 9,435 patients; 250 µg: 1,497 patients). Of the initial 24 studies considered, three were excluded from the safety pool: FHP030 and RO-2455-405-RD (TREAT), due to insufficient study duration to support meaningful safety evaluation, and FK1102, which was an extension study of FK1101 and lacked a control arm, thereby limiting its interpretability for pooled safety analysis.

**Liver insufficiency**

Reason for exclusion: Patients with active liver disease/hepatic impairment were excluded to ensure safety of trial subjects, because roflumilast is metabolised by liver, and roflumilast clearance is reduced when liver function is impaired.

Is it considered to be included as missing information: No.

Rationale: Use of roflumilast in patients with moderate or severe hepatic impairment (Child-Pugh B or C) is contraindicated (Summary of Product Characteristics SmPC section 4.2 and 4.3), hence use in these patients is not anticipated. In addition, there is no evidence of a different safety profile in patients with mild hepatic impairment Child Pugh A.

**Pregnant or breastfeeding women**

Reason for exclusion: Pregnant and breast-feeding women were excluded to ensure the general safety of the foetus, and child. Uncertainty regarding the implication for human pregnancy and lactation necessitated the exclusion of this population in the pivotal clinical trials in the development programme.

Is it considered to be included as missing information: No.

Rationale: Roflumilast is not recommended in women of childbearing potential not using contraception and should not be used during breast-feeding (SmPC section 4.6). Animal studies have shown reproductive toxicity and roflumilast has been demonstrated to cross the placenta in pregnant rats. In clinical studies, 20 patients became pregnant during roflumilast treatment and there were no untoward effects in mother, unborn child or neonate. In the post-marketing experience, there were isolated case reports of exposure during pregnancy and review of these cases did not reveal any new safety information. As use in pregnant and lactating women is not recommended and the clinical impact observed to date in this utilisation is limited, it is not relevant to include these populations as missing information.

**Clinically significant cardiopulmonary abnormalities not related to COPD and that required further evaluation**

Reasons for exclusion: Ensure patient safety by minimising the likelihood of harm to the vulnerable subjects with clinically significant cardiopulmonary abnormalities.

Is it considered to be included as missing information: No.

Rationale: Patients with congestive heart failure (New York Heart Association [NYHA] grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended (SmPC section 4.4). In the COPD safety pool, 5685 patients (52%) in the roflumilast 500 μg group had a history of cardiac impairment. After adjusting the risk of cardiac events: age, gender, race, smoking status, COPD severity, region, and history of cardiac disorders, the Cox proportional hazards regression analysis for the COPD safety pool did not indicate an increased risk of cardiac AEs of interest in patients treated with roflumilast 500 μg versus placebo.

**Patients with acute serious infections or immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy)**

Reasons for exclusion: Ensure patient safety by minimising the likelihood of harm to the vulnerable subjects with acute serious infections or immunological diseases.

Is it considered to be included as missing information: No.

Rationale: Roflumilast is not recommended in patients with severe immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy), severe acute infectious diseases, cancers (except basal cell carcinoma), or patients being treated with immunosuppressive medicinal products (i.e. methotrexate, azathioprine, infliximab, etanercept, or oral corticosteroids to be taken long-term; except short-term systemic corticosteroids), thus use in these populations is not anticipated.

**Chronic gastrointestinal disorders associated with a history of recurrent gastrointestinal bleedings within the last 12 months preceding baseline**

Reasons for exclusion: In initial COPD studies, any intestinal bleeding potentially associated with roflumilast was investigated by faecal occult blood test and patients with positive faecal occult blood test (guaiac) test at baseline or at screening or 2 weeks prior to baseline were excluded. This exclusion criterion was not implemented due to a specific concern for roflumilast safety but to enable evaluation of any treatment emergent intestinal bleeding during the trial.

Is it considered to be included as missing information: No.

Rationale: In the COPD safety pool 1579 roflumilast 500 µg patients, 163 roflumilast 250 µg patients and 1363 placebo patients had a history of chronic GI disorders or bleeding. 26.7% of these roflumilast patients and 12.2% of the placebo patients developed AEs consistent with "GI disorders". This ratio is similar to the one in the entire COPD safety pool regardless of GI history: 22% for roflumilast 500 µg and 9.5% for placebo. Consequently, no increased risk was detected for patients with a history of GI events in comparison with the general COPD safety population.

**Use of immuno-suppressive medications within 4 weeks prior to baseline**

Reasons for exclusion: Patients were excluded due to potential impact on the efficacy and safety evaluation of the treatment.

Is it considered to be included as missing information: No.

Rationale: Use in patients who are concomitantly receiving immuno-suppressive medications is not anticipated as treatment with roflumilast is not recommended (SmPC section 4.4) in patients being treated with immunosuppressive medicinal products (except short-term systemic corticosteroids).

**Diagnosis, treatment, or remission of any cancer (other than basal cell carcinoma)**

Reasons for exclusion: Ensure patient safety by minimising the likelihood of harm to the vulnerable subjects with cancer.

Is it considered to be included as missing information: No.

Rationale: Use in patients with cancer is not anticipated as roflumilast is not recommended (SmPC section 4.4) in patients with a diagnosis of cancer (other than basal cell carcinoma) due to lack of relevant experience. This population is therefore not relevant for consideration as missing information.

### 2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare AEs, AEs due to prolonged exposure, adverse reactions due to cumulative effects, or adverse reactions which have a long latency.

## 2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

### Table 2-7 Exposure of special populations included or not in clinical trial development programmes

| Type of special population | Exposure |
|---|---|
| Pregnant women | Twenty female subjects became pregnant during treatment with roflumilast in indications other than COPD |
| Breast-feeding women | Not included in the clinical development program |
| Patient with relevant comorbidities: | |
| Patients with hepatic impairment | 277 subjects with history of hepatic impairment in the COPD safety pool |
| • Patients with renal impairment (defined as endogenous creatinine clearance [ClCr] of 10 ≤ ClCr ≤30 ml/min/1.73 m2 body surface area in Study FHP020 | 12 subjects with renal impairment in study FHP020and 164 subjects with history of renal impairment in the COPD safety pool |
| • Patients with cardiovascular impairment | 5685 subjects with history of cardiac impairment (Hypertension, atherosclerotic heart disease, chronic ischaemic heart disease, acute myocardial infarction, angina pectoris, atrial fibrillation and flutter, pulmonary heart disease, and heart failure) in the COPD safety pool |
| • Patients with acute serious infections (e.g. tuberculosis, HIV infection, active hepatitis) | Not included in the clinical development program. |
| • Patients with a medical history of serious chronic infections | 598 roflumilast subjects in the COPD safety pool. had a medical history of pulmonary tuberculosis or an abnormal tuberculin test. Furthermore, viral hepatitis, herpes viral infection and zoster were documented as medical history in 23, 12, and 51 roflumilast patients, respectively. |
| • Patients with chronic gastrointestinal disorders associated with a history of recurrent gastrointestinal bleedings within the last 12 months | Not included in the clinical development program |
| • Patients with a disease severity different from inclusion criteria in clinical trials | Not included in clinical development programme |
| Patients with relevant different ethnic origin | Refer Table 2-6 (Racial group – COPD) |
| Subpopulations carrying relevant genetic polymorphisms | Not applicable |

# 2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

## 2.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented here is based on roflumilast's monthly actual ex-factory sales volume from each local affiliate. These data represent all roflumilast formulation delivered to various distribution channels (e.g., wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the tablets distributed. The estimated post-marketing patient exposure data is an approximation based on the assumption that each patient took 1 tablet of roflumilast a day. Therefore, a patient-year worth of exposure is calculated by multiplying the number of tablets per day by 365 days (365 tablets per patient year).

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to roflumilast. More detailed patient-level data (e.g. gender, ethnicity, age category, off-label use, specific population, etc) are not available.

## 2.5.2 Exposure

The cumulative regional sales figures are presented in Table 2-8

**Table 2-8 Roflumilast cumulative sales, number of tablets, by region**

| Formulation | Europe | Rest of the world | Total |
|---|---|---|---|
| Tablet | 121007919 | 22,42,73,882 | 345281801 |

The cumulative global post-marketing patient exposure for roflumilast (1 tablet per day), since launch to 31 May 2025, has been estimated to be approximately 1575391patient-years.

# 2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

**Potential for misuse for illegal purposes**

From roflumilast studies, as well as from the current knowledge on PDE4 inhibitors, it is considered that roflumilast does not have a potential for misuse for illegal purposes.

# 2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

## 2.7.1 Identification of safety concerns in the initial RMP submission

### 2.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

#### 2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

### 2.7.2 New safety concerns and reclassification with a submission of an updated RMP

AstraZeneca has revised the list of safety concerns for roflumilast following completion of Post-Authorisation Safety Study (PASS) D7120R00003 and review of cumulative post-marketing surveillance.

A summary of the rationale for the reclassification of safety concerns, previously classified as important identified and important potential risks is presented below:

#### 2.7.2.1 Reclassification of important identified risks

**Weight decrease**

Weight decrease previously classified as an important identified risk is removed from the list of safety concerns.

Weight decrease is a known, well-characterised adverse reaction of roflumilast described in SmPC sections 4.4 and 4.8, with routine risk minimisation in place (regular body-weight monitoring and discontinuation in case of clinically concerning, unexplained weight loss).

Over > 15 years of marketing and approximately 1.5 million patient-years of exposure, post-marketing reports of weight decrease has remained low and stable, with the majority of cases being non-serious and no new significant information emerging in the last decade. The completed PASS (D7120R00003; assessing ‘abnormal and unexplained weight loss’ as secondary outcome did not identify new significant information. The adjusted hazard ratios (HRs) for abnormal and unexplained weight loss were 2.49 (95% CI: 1.65, 3.76) in Germany, 1.57 (95% CI: 0.88, 2.83) in Sweden, and 1.76 (95% CI: 1.67, 1.86) in the US. These findings are consistent with the safety concerns identified in the roflumilast clinical programme. In Norway (1.64 [95% CI 0.80-3.37]), the precision of the adjusted HR estimates was low for abnormal and unexplained weight loss due to the small number of events.

No additional pharmacovigilance (PV) activities or additional risk minimisation are warranted. In line with GVP Module V (Rev. 2), as the risk is fully characterised and adequately managed by routine measures without impact on the benefit–risk balance, Weight decrease’ is removed from the list of safety concerns and will continue to be monitored through routine PV activities.

## Diarrhoea

Diarrhoea previously classified as an important identified risk is removed from the list of safety concerns.

Diarrhoea is a known, well-characterised adverse reaction of roflumilast, described in SmPC 4.4 and 4.8, typically occurring early and resolving on continued treatment, with reassessment advised if persistent; routine measures are in place. Across >15 years and ~1.5 million patient-years of exposure, post-marketing reports have remained stable and mostly non-serious, with no new significant information.

The completed PASS (D7120R00003), assessing hospitalisation due to non-infectious diarrhoea as a secondary outcome, identified no new or clinically important findings; current-use HRs were modestly elevated in Norway (2.03; 95% CI 1.12-3.67), Sweden (1.55; 95% CI 1.08–2.24), and the US (1.24; 95% CI 1.08–1.42), but not in Germany (1.07; 95% CI 0.7-1.59), while recent-use estimates were imprecise with wide 95% CIs that often include 1, and past-use showed no increase.

Given the modest magnitude, inconsistency across countries/time windows, wide confidence intervals, and country-specific coding/admission thresholds, these findings do not alter the overall benefit–risk balance and do not warrant measures beyond routine PV activities.

No additional PV activities or additional risk minimisation are warranted. In line with GVP Module V (Rev. 2), as the risk is fully characterised and adequately managed by routine measures without impact on the benefit–risk balance, ‘Diarrhoea’ is removed from the list of safety concerns and will continue to be monitored through routine PV activities.

## Psychiatric disorders (depression, suicidal ideation and behaviour)

Psychiatric disorders (depression, suicidal ideation and behaviour) previously classified as an important identified risk is removed from the list of safety concerns.Psychiatric disorders are known, well characterised adverse reactions of roflumilast described in SmPC sections 4.4 and 4.8, with routine risk minimisation in place (use is not recommended in patients with a history of depression associated with suicidal ideation or behaviour; patients/caregivers should promptly report mood or behaviour changes or suicidal ideation; discontinue roflumilast if new or worsening psychiatric symptoms, suicidal ideation, or a suicide attempt occurs.

Over >15 years of marketing and approximately 1.5 million patient-years of exposure, post-marketing reporting has remained low with a decreasing trend over the last decade; the majority of events have been non-serious, and many were confounded by pre-existing psychiatric conditions, comorbidities, or concomitant medications. Given the very limited

number of validated fatal cases, and effective routine risk minimisation already described in the SmPC, the benefit–risk balance is unchanged.

The completed PASS (D7120R00003; secondary outcomes included death by suicide or hospitalisation for suicide attempt and new diagnoses of depression) did not identify new significant information. Increased risks of new diagnosis of depression were observed for current versus never roflumilast use in all countries, with adjusted HRs of 1.58 (95% CI: 1.29, 1.93) in Germany, 1.69 (95% CI: 0.64, 4.46) in Sweden, and 1.36 (95% CI: 1.25, 1.48) in the US and was consistent with clinical programme observations. In Norway (1.53 [95% CI: 0.43, 5.40]), the precision of the adjusted HR estimates was low for abnormal and unexplained weight loss due to the small number of events. Hospitalisation for suicide attempt showed no significant or consistent risk increase across countries for current use.

No additional PV activities or additional risk minimisation are warranted. In line with GVP Module V (Rev. 2), as the risk is fully characterised and adequately managed by routine measures without impact on the benefit–risk balance, 'Psychiatric disorders (depression, suicidal ideation and behaviour)' is removed from the list of safety concerns and will continue to be monitored through routine PV activities.

#### 2.7.2.2 Reclassification of important potential risks

**Malignant tumours**

Malignant tumours previously classified as an important potential risk is removed from the list of safety concerns.

Over > 15 years and approximately 1.5 million patient-years of post-marketing exposure, reports of malignancies has been low and stable, and predominantly in elderly COPD patients (≥65 years; ~67%). They were frequently confounded by prior/history of cancer and baseline risk factors (e.g., smoking).

The completed PASS (D7120R00003) used Sweden and Norway cancer registry linkage (more complete, clinically validated ascertainment) while Germany and the United States was based on claims data ( higher risk of incomplete case capture), With hazard ratios close to 1 (1.11 [95% CI: 1.05, 1.17] in Germany, 1.03[95% CI: 0.94, 1.14] in Sweden, 1.04 [95% CI: 0.98, 1.11] in the US, and 1.06 [95% CI 0.91, 1.23] in Norway) and the most reliable cancer ascertainment from Sweden's registry, the evidence indicates no consistent or clinically meaningful increase in cancer risk with roflumilast. .

Malignancy is not identified as an adverse reaction in the SmPC, and the available evidence is insufficient to support a causal association; therefore, this potential risk does not impact the benefit–risk balance and does not warrant additional PV or additional risk minimisation

beyond routine measures. This risk will be monitored via routine PV activities. Hence, it is removed from the list of safety concerns in the RMP.

**Infections**

Infections previously classified as an important potential risk is removed from the list of safety concerns.

Over >15 years and approximately 1.5 million patient-years of exposure, post-marketing reports of infection has been low and stable and predominantly include events of respiratory tract infections (65%). Cases were frequently confounded by COPD comorbidities, concomitant medications (notably inhaled corticosteroids), or limited information, and no causal pattern was identified.

The completed PASS (D7120R00003)—assessing new diagnoses of tuberculosis and severe viral hepatitis (HBV/HCV)—found no increased risk and identified no new significant information versus the clinical programme. The SmPC already provides appropriate precautions (e.g., avoid treatment in immunocompromised patients or those with acute severe infections) and lists respiratory infections (excluding pneumonia) as rare, indicating that routine risk minimisation is sufficient.

Currently, there are no additional PV activities in place for this risk. From the data available to date, there is insufficient evidence to establish causal association between infections and roflumilast, hence considered not to impact the benefit-risk profile of roflumilast. This risk will be monitored via routine PV activities. Hence, it is removed from the list of safety concerns in the RMP.

**Major Cardiovascular Events**

Major Cardiovascular Events (MACE) previously classified as an important potential risk is removed from the list of safety concerns.

Over >15 years and approximately 1.5 million patient-years of exposure, post-marketing reporting of MACE has been low with a declining trend and events were frequently confounded by pre-existing cardiovascular disease and multiple baseline risk factors (advanced age, smoking, hypertension, hypercholesterolaemia, diabetes, renal failure, obesity).

The completed PASS (D7120R00003) evaluated hospitalisations for MACE and did not indicate an increased risk with roflumilast; no new significant information emerged from post-marketing surveillance.

There is insufficient evidence to establish a causal association, and this potential risk does not materially impact the benefit–risk balance or warrant additional PV or additional risk minimisation beyond routine measures; hence it is removed from the list of safety concerns in the RMP It will continue to be monitored through routine PV activities.

#### 2.7.2.3 Reclassification of missing information

**Long term treatment**

The completed PASS (D7120R00003) evaluated the long-term safety of roflumilast in routine practice with a primary focus on 5-year all-cause mortality and multiple safety outcomes, enrolling a cumulative total of 135,856 patients across four countries (Germany: 50,567; Sweden: 19,025; US: 56,792; Norway: 9,472) with median follow-up of 1,844–2,020 days (~5 years).

Across this extensive cohort and follow-up, the safety profile during prolonged use was consistent with the clinical development programme, with no additional risks identified beyond those already characterised.

In accordance with EMA GVP Module V (Rev. 2), the knowledge gap on long-term safety is therefore considered resolved; no further additional PV activities are required and roflumilast will continue to be monitored via routine PV activities.

### 2.7.3 Details of important identified risks, important potential risks and missing information

#### 2.7.3.1 Presentation of important identified risks and important potential risks

There are no important identified risks and important potential risks for roflumilast.

#### 2.7.3.2 Presentation of missing information

There are no missing information for roflumilast.

## 2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

### 2.8.1 Summary of the safety concerns

There are no safety concerns for roflumilast.

# 3 PART III: PHARMACOVIGILANCE PLAN

## 3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

**Specific adverse reaction follow-up questionnaires for safety concern(s):**

None

**Other forms of routine pharmacovigilance activities for safety concerns:**

None.

## 3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional PV activities.

## 3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIE

There are no ongoing or planned additional PV activities.

# 4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

# 5 PART V: RISK MINIMISATION MEASURES

## 5.1 ROUTINE RISK MINIMISATION MEASURES

Not applicable

## 5.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable

## 5.3 SUMMARY OF RISK MINIMISATION MEASURES

Not applicable

# 6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR DAXAS (ROFLUMILAST)

This is a summary of the 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 SmPC for EU RMP 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.

## 6.1 THE MEDICINE AND WHAT IT IS USED FOR

DAXAS is authorised for maintenance treatment of severe COPD ($FEV_1$ 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.

## 6.2 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 PV activities.

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

### 6.2.1 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).

There are no important risks or missing information for roflumilast.

### 6.2.2 Summary of important risks

The safety information in the Product Information is aligned to the reference medicinal product.

### 6.2.3 Post-authorisation development plan

#### 6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of DAXAS.

#### 6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for DAXAS.

# 7 PART VII: ANNEXES

## 7.1 ANNEX 4: Specific adverse drug reaction follow-up forms

Not applicable

## 7.2 ANNEX 6: Details of proposed additional risk minimisation activities

Not applicable

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