SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Daxas 500 micrograms film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms of roflumilast.

Excipient with known effect:
Each film-coated tablet contains 198.64 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow, D-shaped film-coated tablet of 9 mm, embossed with “D” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Daxas is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (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.

4.2 Posology and method of administration

Posology

Starting dose
The recommended starting dose is one tablet of 250 micrograms roflumilast to be taken once daily, for 28 days.

This starting dose is intended to reduce adverse reactions and patient discontinuation when initiating therapy, but it is a sub-therapeutic dose. Therefore, the 250 micrograms dose should be used only as a starting dose (see sections 5.1 and 5.2).

Maintenance dose
After 28 days of treatment with the 250 micrograms starting dose, patients must be up-titrated to one tablet of 500 micrograms roflumilast, to be taken once daily.

Roflumilast 500 micrograms may need to be taken for several weeks to achieve its full effect (see sections 5.1 and 5.2). Roflumilast 500 micrograms has been studied in clinical trials for up to one year, and is intended for maintenance treatment.

Special populations

Elderly
No dose adjustment is necessary.

Renal impairment
No dose adjustment is necessary.

Hepatic impairment
The clinical data with roflumilast in patients with mild hepatic impairment classified as Child-Pugh A are insufficient to recommend a dose adjustment (see section 5.2) and therefore Daxas should be used with caution in these patients.

Patients with moderate or severe hepatic impairment classified as Child-Pugh B or C must not take Daxas (see section 4.3).

Paediatric population
There is no relevant use of Daxas in the paediatric population (under 18 years) for the indication of COPD.

Method of administration
For oral use.
The tablet should be swallowed with water and taken at the same time every day. The tablet can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Moderate or severe hepatic impairment (Child-Pugh B or C).

4.4 Special warnings and precautions for use

All patients should be informed about the risks of Daxas and the precautions for safe use before starting treatment.

Rescue medicinal products
Daxas is not indicated as rescue medicinal product for the relief of acute bronchospasms.

Weight decrease
In 1-year studies (M2-124, M2-125), a decrease of body weight occurred more frequently in patients treated with roflumilast compared to placebo-treated patients. After discontinuation of roflumilast, the majority of patients had regained body weight after 3 months.
Body weight of underweight patients should be checked at each visit. Patients should be advised to check their body weight on a regular basis. In the event of an unexplained and

clinically concerning weight decrease, the intake of roflumilast should be stopped and body weight should be further followed-up.

Special clinical conditions

Due to lack of relevant experience, treatment with roflumilast should not be initiated or existing treatment with roflumilast should be stopped 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). Experience in patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection and herpes zoster is limited.

Patients with congestive heart failure (NYHA grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended.

Psychiatric disorders

Roflumilast is associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression. Rare instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression, usually within the first weeks of treatment (see section 4.8). The risks and benefits of starting or continuing treatment with roflumilast should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended.

Roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behaviour. Patients and caregivers should be instructed to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation. If patients suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with roflumilast.

Persistent intolerability

While adverse reactions like diarrhoea, nausea, abdominal pain and headache mainly occur within the first weeks of therapy and mostly resolve on continued treatment, roflumilast treatment should be reassessed in case of persistent intolerability. This might be the case in special populations that may have higher exposure, such as in black, non-smoking females (see section 5.2) or in patients concomitantly treated with CYP1A2/ 2C19/3A4 inhibitors (such as fluvoxamine and cimetidine) or the CYP1A2/3A4 inhibitor enoxacin (see section 4.5).

Body weight <60 kg

Treatment with roflumilast may lead to a higher risk of sleep disorders (mainly insomnia) in patients with a baseline body weight of <60 kg, due to a higher total PDE4 inhibitory activity found in these patients (see section 4.8).

Theophylline

There are no clinical data to support the concomitant treatment with theophylline for maintenance therapy. Therefore, the concomitant treatment with theophylline is not recommended.

Lactose content
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. Both roflumilast and roflumilast N-oxide have intrinsic phosphodiesterase-4 (PDE4) inhibitory activity. Therefore, following administration of roflumilast, the total PDE4 inhibition is considered to be the combined effect of both roflumilast and roflumilast N-oxide.
Interaction studies with CYP1A2/3A4 inhibitor enoxacin and the CYP1A2/2C19/3A4 inhibitors cimetidine and fluvoxamine, resulted in increases of the total PDE4 inhibitory activity of 25%, 47% and 59%, respectively. The tested dose of fluvoxamine was 50 mg. A combination of roflumilast with these active substances might lead to an increase of exposure and persistent intolerability. In this case, roflumilast treatment should be reassessed (see section 4.4).

Administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in total PDE4 inhibitory activity by about 60%. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin) may reduce the therapeutic efficacy of roflumilast. Thus, roflumilast treatment is not recommended in patients receiving strong cytochrome P450 enzyme inducers.

Clinical interaction studies with CYP3A4 inhibitors erythromycin and ketoconazole showed increases of 9% of the total PDE4 inhibitory activity. Co-administration with theophylline resulted in an increase of 8% of the total PDE4 inhibitory activity (see section 4.4). In an interaction study with an oral contraceptive containing gestodene and ethinyl oestradiol, the total PDE4 inhibitory activity was increased by 17%. No dose adjustment is necessary in patients receiving these active substances.

No interactions were observed with inhaled salbutamol, formoterol, budesonide and oral montelukast, digoxin, warfarin, sildenafil and midazolam.

Co-administration with an antacid (combination of aluminium hydroxide and magnesium hydroxide) did not alter the absorption or pharmacokinetics of roflumilast or its N-oxide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing age should be advised to use an effective method of contraception during treatment. Roflumilast is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are limited amount of data from the use of roflumilast in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). Roflumilast is not recommended during pregnancy.

Roflumilast has been demonstrated to cross the placenta in pregnant rats.

Breastfeeding
Available pharmacokinetic data in animals have shown excretion of roflumilast or its metabolites in milk. A risk to the breastfed infant cannot be excluded. Roflumilast should not be used during breast-feeding.

Fertility
In a human spermatogenesis study, roflumilast 500 micrograms had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period.

4.7 Effects on ability to drive and use machines

Daxas has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions are diarrhoea (5.9%), weight decreased (3.4%), nausea (2.9%), abdominal pain (1.9%) and headache (1.7%). These adverse reactions mainly occurred within the first weeks of therapy and mostly resolved on continued treatment.

Tabulated list of adverse reactions
Within the following table, adverse reactions are ranked under the MedDRA frequency classification:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with roflumilast in clinical COPD studies and post-marketing experience

Frequency **System Organ Class**	**Common**	**Uncommon**	**Rare**
Immune system		Hypersensitivity	Angioedema

disorders			
Endocrine disorders			Gynaecomastia
Metabolism and nutrition disorders	Weight decreased Decreased appetite		
Psychiatric disorders	Insomnia	Anxiety	Suicidal ideation and behaviour* Depression Nervousness Panic attack
Nervous system disorders	Headache	Tremor Vertigo Dizziness	Dysgeusia
Cardiac disorders		Palpitations	
Respiratory, thoracic and mediastinal disorders			Respiratory tract infections (excluding Pneumonia)
Gastrointestinal disorders	Diarrhoea Nausea Abdominal pain	Gastritis Vomiting Gastro-esophageal reflux disease Dyspepsia	Haematochezia Constipation
Hepatobiliary disorders			Gamma-GT increased Aspartate aminotransferase (AST) increased
Skin and subcutaneous tissue disorders		Rash	Urticaria
Musculoskeletal and connective tissue disorders		Muscle spasms and weakness Myalgia Back pain	Blood creatine phosphokinase (CPK) increased
General disorders and administration site conditions		Malaise Asthenia Fatigue	

Description of selected adverse reactions

* In clinical studies and post-marketing experience, rare instances of suicidal ideation and behaviour, including suicide, were reported. Patients and caregivers should be instructed to notify the prescriber of any suicidal ideation (see also section 4.4).

Other special populations

Elderly

A higher incidence of sleep disorders (mainly insomnia) in patients ≥75 years or older was observed in Study RO-2455-404-RD for patients treated with roflumilast when compared to those treated with placebo (3.9% vs 2.3%). The incidence observed was also higher in patients less than 75 years old, treated with roflumilast when compared to those treated with placebo (3.1% vs 2.0%).

Body weight <60kg
A higher incidence of sleep disorders (mainly insomnia) in patients with a baseline body weight <60 kg was observed in Study RO-2455-404-RD for patients treated with roflumilast when compared to those treated with placebo (6.0% vs 1.7%). The incidence was 2.5% vs 2.2% in patients with a baseline body weight ≥60 kg, treated with roflumilast when compared to those treated with placebo.

Concomitant treatment with long acting muscarinic antagonists (LAMA)
A higher incidence of weight decrease, decreased appetite, headache and depression was observed during Study RO-2455-404-RD in patients receiving concomitant roflumilast and long-acting muscarinic antagonists (LAMA) plus concomitant inhaled corticosteroids (ICS) and long acting B2 agonists (LABA) compared to those treated only with concomitant roflumilast, ICS and LABA.
Difference of incidence between roflumilast and placebo was quantitatively greater with concomitant LAMA for weight decreased (7.2% vs 4.2%), decreased appetite (3.7% vs 2.0%), headache (2.4% vs 1.1%) and depression (1.4% vs -0.3%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
In Phase I studies, the following symptoms were observed at an increased rate after single oral doses of 2,500 micrograms and one single dose of 5,000 micrograms (ten times the recommended dose): headache, gastrointestinal disorders, dizziness, palpitations, light-headedness, clamminess and arterial hypotension.

Management
In case of overdose, it is recommended that the appropriate supportive medical care is provided. Since roflumilast is highly protein bound, haemodialysis is not likely to be an efficient method of its removal. It is not known whether roflumilast is dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX07

Mechanism of action

Roflumilast is a PDE4 inhibitor, a non-steroid, anti-inflammatory active substance designed to target both the systemic and pulmonary inflammation associated with 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. This mechanism of action and the selectivity also apply to roflumilast N-oxide, which is the major active metabolite of roflumilast.

Pharmacodynamic effects

Inhibition of PDE4 leads to elevated intracellular cAMP levels and mitigates COPD-related malfunctions of leukocytes, airway and pulmonary vascular smooth muscle cells, endothelial and airway epithelial cells and fibroblasts in experimental models. Upon *in vitro* stimulation of human neutrophils, monocytes, macrophages or lymphocytes, roflumilast and roflumilast N-oxide suppress the release of inflammatory mediators e.g. leukotriene B4, reactive oxygen species, tumour necrosis factor α, interferon γ and granzyme B.

In patients with COPD, roflumilast reduced sputum neutrophils. Furthermore, roflumilast attenuated influx of neutrophils and eosinophils into the airways of endotoxin challenged healthy volunteers.

Clinical efficacy and safety

In two confirmative replicate one-year studies (M2-124 and M2-125) and two supplementary six-month studies (M2-127 and M2-128), a total number of 4,768 patients were randomised and treated of whom 2,374 were treated with roflumilast. The design of the studies was parallel-group, double-blind and placebo-controlled.

The one-year studies included patients with a history of severe to very severe COPD [FEV_1 (forced expiratory volume in one second) $\leq$50% of predicted] associated with chronic bronchitis, with at least one documented exacerbation in the previous year and with symptoms at baseline as determined by cough and sputum score. Long-acting beta-agonists (LABAs) were allowed in the studies and were used in approximately 50% of the study population. Short-acting anticholinergics (SAMAs) were allowed for those patients not taking LABAs. Rescue medicinal products (salbutamol or albuterol) were allowed on an as-needed basis. The use of inhaled corticosteroids and theophylline was prohibited during the studies. Patients with no history of exacerbations were excluded.

In a pooled analysis of the one-year studies M2-124 and M2-125, roflumilast 500 micrograms once daily significantly improved lung function compared to placebo, on average by 48 ml (pre-bronchodilator FEV_1, primary endpoint, $p<0.0001$), and by 55 ml (post-bronchodilator FEV_1, $p<0.0001$). The improvement in lung function was apparent at the first visit after 4 weeks and was maintained up to one year (end of treatment period). The rate (per patient per year) of moderate exacerbations (requiring intervention with systemic glucocorticosteroids) or severe exacerbations (resulting in hospitalisation and/or leading to death) after 1 year was 1.142 with roflumilast and 1.374 with placebo corresponding to a

relative risk reduction of 16.9% (95% CI: 8.2% to 24.8%) (primary endpoint, p=0.0003). Effects were similar, independent of previous treatment with inhaled corticosteroids or underlying treatment with LABAs. In the subgroup of patients with history of frequent exacerbations (at least 2 exacerbations during the last year), the rate of exacerbations was 1.526 with roflumilast and 1.941 with placebo corresponding to a relative risk reduction of 21.3% (95% CI: 7.5% to 33.1%). Roflumilast did not significantly reduce the rate of exacerbations compared with placebo in the subgroup of patients with moderate COPD. The reduction of moderate or severe exacerbations with roflumilast and LABA compared to placebo and LABA was on average 21% (p=0.0011). The respective reduction in exacerbations seen in patients without concomitant LABAs was on average 15% (p=0.0387). The numbers of patients who died due to any reason were equal for those treated with placebo or roflumilast (42 deaths each group; 2.7% each group; pooled analysis).

A total of 2,690 patients were included and randomised in two supportive 1-year studies (M2-111 and M2-112). In contrast to the two confirmative studies, a history of chronic bronchitis and of COPD exacerbations was not requested for patients' inclusion. Inhaled corticosteroids were used in 809 (61%) of the roflumilast treated patients, whereas the use of LABAs and theophylline was prohibited.
Roflumilast 500 micrograms once daily significantly improved lung function compared to placebo, on average by 51 ml (pre-bronchodilator FEV_1, p<0.0001), and by 53 ml (post-bronchodilator FEV_1, p<0.0001). The rate of exacerbations (as defined in the protocols) were not significantly reduced by roflumilast in the individual studies (relative risk reduction: 13.5% in Study M2-111 and 6.6% in Study M2-112; p= not significant). Adverse events rates were independent of concomitant treatment with inhaled corticosteroids.

Two six-month supportive studies (M2-127 and M2-128) included patients with a history of COPD for at least 12 months prior to baseline. Both studies included moderate to severe patients with a non-reversible airway obstruction and a FEV_1 of 40% to 70% of predicted. Roflumilast or placebo treatment was added to continuous treatment with a long-acting bronchodilator, in particular salmeterol in Study M2-127 or tiotropium in Study M2-128. In the two six-month studies, pre-bronchodilator FEV1 was significantly improved by 49 ml (primary endpoint, p<0.0001) beyond the bronchodilator effect of concomitant treatment with salmeterol in Study M2-127 and by 80 ml (primary endpoint, p<0.0001) incremental to concomitant treatment with tiotropium in Study M2-128.

Study RO-2455-404-RD was a one-year study in COPD patients with a baseline (pre-bronchodilator) FEV_1 <50% of predicted normal and a history of frequent exacerbations. The study assessed the effect of roflumilast on COPD exacerbation rate in patients treated with fixed combinations of LABA and inhaled corticosteroids, compared to placebo. A total of 1935 patients were randomised to double-blind medication and approximately 70% were also using a long-acting muscarinic antagonist (LAMA) through the course of the trial. The primary endpoint was reduction in rate of moderate or severe COPD exacerbations per patient per year. The rate of severe COPD exacerbations and changes in FEV_1 were evaluated as key secondary endpoints.

Table 2. Summary of COPD exacerbation endpoints in Study RO-2455-404-RD

Exacerbation Category	Analysis model	Roflumilast (N=969) Rate (n)	Placebo (N=966) Rate (n)	Ratio Roflumilast/Placebo			2-Sided p-value
				Rate Ratio	Change (%)	95% CI	
Moderate or severe	Poisson regression	0.805 (380)	0.927 (432)	0.868	-13.2	0.753, 1.002	0.0529
Moderate	Poisson regression	0.574 (287)	0.627 (333)	0.914	-8.6	0.775, 1.078	0.2875
Severe	Negative binomial regression	0.239 (151)	0.315 (192)	0.757	-24.3	0.601, 0.952	0.0175

There was a trend towards a reduction in moderate or severe exacerbations in subjects treated with roflumilast compared with placebo over 52 weeks, which did not achieve statistical significance (Table 2). A pre-specified sensitivity analysis using the negative binomial regression model treatment showed a statistically significant difference of -14.2% (rate ratio: 0.86; 95% CI: 0.74 to 0.99).

The per-protocol Poisson regression analysis and the non-significant sensitivity to drop-out Poisson regression intention-to-treat analysis rate ratios were 0.81 (95% CI: 0.69 to 0.94) and 0.89 (95% CI: 0.77 to 1.02), respectively.

Reductions were achieved in the subgroup of patients concomitantly treated with LAMA (rate ratio: 0.88; 95% CI: 0.75 to 1.04) and in the subgroup not treated with LAMA (rate ratio: 0.83; 95% CI: 0.62 to 1.12).

The rate of severe exacerbations was reduced in the overall patient group (rate ratio: 0.76; 95% CI: 0.60 to 0.95) with a rate of 0.24 per patient/year compared to a rate of 0.32 per patient/year in patients treated with placebo. A similar reduction was achieved in the subgroup of patients concomitantly treated with LAMA (rate ratio: 0.77; 95% CI: 0.60 to 0.99) and in the subgroup not treated with LAMA (rate ratio: 0.71; 95% CI: 0.42 to 1.20).

Roflumilast improved lung function after 4 weeks (sustained over 52 weeks). Post bronchodilator FEV_1 increased for the roflumilast group by 52 mL (95% CI: 40, 65 mL) and decreased for the placebo group by 4 mL (95% CI: -16, 9 mL). Post-bronchodilator FEV_1 showed a clinically significant improvement in favour of roflumilast by 56 mL over placebo (95% CI: 38, 73 mL).

Seventeen (1.8%) patients in the roflumilast group and 18 (1.9%) patients in the placebo group died during the double-blind treatment period due to any reason and 7 (0.7%) patients in each group due to a COPD exacerbation. The proportion of patients who experienced at least 1 adverse event during the double-blind treatment period were 648 (66.9%) patients and 572 (59.2%) patients in the roflumilast and placebo groups, respectively. The observed adverse reactions for roflumilast in Study RO-2455-404-RD were in line with those already included in section 4.8.

More patients in the roflumilast group (27.6%) than placebo (19.8%) withdrew study medication due to any reason (risk ratio: 1.40; 95% CI: 1.19 to 1.65). The major reasons for trial discontinuation were withdrawal of consent and reported adverse events.

Starting dose titration trial

The tolerability of roflumilast was evaluated in a 12-week randomised, double-blind, parallel group trial (RO-2455-302-RD) in patients with severe COPD associated with chronic bronchitis. At screening, patients were required to have had at least one exacerbation in the previous year and on standard of care COPD maintenance treatment for at least 12 weeks. A total of 1323 patients were randomised to receive roflumilast 500 micrograms once a day for 12 weeks (n=443), roflumilast 500 micrograms every other day for 4 weeks followed by roflumilast 500 micrograms once a day for 8 weeks (n=439), or roflumilast 250 micrograms once a day for 4 weeks followed by roflumilast 500 micrograms once a day for 8 weeks (n=441).

Over the entire study period of 12 weeks, the percentage of patients discontinuing treatment due to any reason was statistically significantly lower in patients initially receiving roflumilast 250 micrograms once a day for 4 weeks followed by roflumilast 500 micrograms once a day for 8 weeks (18.4%) compared to those receiving roflumilast 500 micrograms once a day for 12 weeks (24.6%; Odds Ratio 0.66, 95% CI [0.47, 0.93], p=0.017). The discontinuation rate for those receiving 500 micrograms every other day for 4 weeks followed by 500 micrograms once a day for 8 weeks was not statistically significantly different to those receiving 500 micrograms once a day for 12 weeks. The percentage of patients experiencing a Treatment Emergent Adverse Event (TEAE) of interest, defined as diarrhoea, nausea, headache, decreased appetite, insomnia, and abdominal pain (secondary endpoint), was nominally statistically significantly lower in patients initially receiving roflumilast 250 micrograms once a day for 4 weeks followed by roflumilast 500 micrograms once a day for 8 weeks (45.4%) compared to those receiving roflumilast 500 micrograms once a day for 12 weeks (54.2%, Odds Ratio 0.63, 95% CI [0.47, 0.83], p=0.001). The rate of experiencing a TEAE of interest for those receiving 500 micrograms every other day for 4 weeks followed by 500 micrograms once a day for 8 weeks was not statistically significantly different to those receiving 500 micrograms once a day for 12 weeks.

Patients receiving a 500 micrograms dose once a day had a median PDE4 inhibitory activity of 1.2 (0.35, 2.03) and those receiving a 250 micrograms dose once a day had a median PDE4 inhibitory activity of 0.6 (0.20, 1.24). Long-term administration at the 250 micrograms dose level may not induce sufficient PDE4 inhibition to exert clinical efficacy. 250 micrograms once a day is a sub-therapeutic dose, and should be used only as a starting dose for the first 28 days (see sections 4.2 and 5.2).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with roflumilast in all subsets of the paediatric population in chronic obstructive pulmonary disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Roflumilast is extensively metabolised in humans, with the formation of a major pharmacodynamically active metabolite, roflumilast N-oxide. Since both roflumilast and roflumilast N-oxide contribute to PDE4 inhibitory activity *in vivo*, pharmacokinetic considerations are based on total PDE4 inhibitory activity (i.e. total exposure to roflumilast and roflumilast N-oxide).

Absorption

The absolute bioavailability of roflumilast following a 500 micrograms oral dose is approximately 80%. Maximum plasma concentrations of roflumilast typically occur approximately one hour after dosing (ranging from 0.5 to 2 hours) in the fasted state. Maximum concentrations of the N-oxide metabolite are reached after about eight hours (ranging from 4 to 13 hours). Food intake does not affect the total PDE4 inhibitory activity, but delays time to maximum concentration (t_{max}) of roflumilast by one hour and reduces C_{max} by approximately 40%. However, C_{max} and t_{max} of roflumilast N-oxide are unaffected.

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for single dose of 500 micrograms roflumilast is about 2.9 l/kg.

Due to the physico-chemical properties, roflumilast is readily distributed to organs and tissues including fatty tissue of mice, hamster and rat. An early distribution phase with marked penetration into tissues is followed by a marked elimination phase out of fatty tissue most probably due to pronounced break-down of parent compound to roflumilast N-oxide. These studies in rats with radiolabelled roflumilast also indicate low penetration across the blood-brain barrier. There is no evidence for a specific accumulation or retention of roflumilast or its metabolites in organs and fatty tissue.

Biotransformation

Roflumilast is extensively metabolised via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the major metabolite observed in the plasma of humans. The plasma AUC of the N-oxide metabolite on average is about 10-fold greater than the plasma AUC of roflumilast. Thus, the N-oxide metabolite is considered to be the main contributor to the total PDE4 inhibitory activity *in vivo*.

In vitro studies and clinical interaction studies suggest that the metabolism of roflumilast to its N-oxide metabolite is mediated by CYP1A2 and 3A4. Based on further *in vitro* results in human hepatic microsomes, therapeutic plasma concentrations of roflumilast and roflumilast N-oxide do not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A9/11. Therefore, there is a low probability of relevant interactions with substances metabolised by these P450 enzymes. In addition, *in vitro* studies demonstrated no induction of the CYP1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP2B6 by roflumilast.

Elimination

The plasma clearance after short-term intravenous infusion of roflumilast is about 9.6 l/h. Following an oral dose, the median plasma effective half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state plasma concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once-daily dosing. Following intravenous or oral administration of radiolabelled roflumilast, about 20% of the radioactivity was recovered in the faeces and 70% in urine as inactive metabolites.

Linearity/non-linearity

The pharmacokinetics of roflumilast and its N-oxide metabolite are dose-proportional over a range of doses from 250 micrograms to 1,000 micrograms.

Special populations

In older people, females and in non-Caucasians, total PDE4 inhibitory activity was increased. Total PDE4 inhibitory activity was slightly decreased in smokers. None of these changes were considered to be clinically meaningful. No dose adjustment is recommended in these patients. A combination of factors, such as in black, non-smoking females, might lead to an increase of exposure and persistent intolerability. In this case, roflumilast treatment should be reassessed (see section 4.4).

In Study RO-2455-404-RD when compared with the overall population, the total PDE4 inhibitory activity determined from *ex vivo* unbound fractions was found to be 15% higher in patients ≥75 years of age, and 11% higher in patients with baseline body weight <60 kg (refer to section 4.4).

Renal impairment
Total PDE4 inhibitory activity decreased by 9% in patients with severe renal impairment (creatinine clearance 10-30 ml/min). No dose adjustment is necessary.

Hepatic impairment
The pharmacokinetics of roflumilast 250 micrograms once-daily was tested in 16 patients with mild to moderate hepatic impairment classified as Child-Pugh A and B. In these patients, the total PDE4 inhibitory activity was increased by about 20% in patients with Child-Pugh A and about 90% in patients with Child-Pugh B. Simulations suggest dose proportionality between roflumilast 250 and 500 micrograms in patients with mild and moderate hepatic impairment. Caution is necessary in Child-Pugh A patients (see section 4.2). Patients with moderate or severe hepatic impairment classified as Child Pugh B or C should not take roflumilast (see section 4.3).

5.3 Preclinical safety data

There is no evidence for an immunotoxic, skin sensitising or phototoxic potential.

A slight reduction in male fertility was seen in conjunction with epididymal toxicity in rats. No epididymal toxicity or changes in semen parameters were present in any other rodent or non-rodent species including monkeys in spite of higher exposures.

In one of two rat embryofetal development studies, a higher incidence of incomplete skull bone ossification was seen at a dose producing maternal toxicity. In one of three rat studies on fertility and embryofetal development, post-implantation losses were observed. Post-implantation losses were not seen in rabbits. Prolongation of gestation was seen in mice.

The relevance of these findings to humans is unknown.

Most relevant findings in safety pharmacology and toxicology studies occurred at higher doses and exposure than that intended for clinical use. These findings consisted mainly of gastrointestinal findings (i.e. vomiting, increased gastric secretion, gastric erosions, intestine inflammation) and cardiac findings (i.e. focal haemorrhages, haemosiderin deposits and lympho-histiocytic cell infiltration in the right atria in dogs, and decreased blood pressure and increased heart rate in rats, guinea pigs and dogs).

Rodent-specific toxicity in the nasal mucosa was observed in repeat-dose toxicity and carcinogenicity studies. This effect seems to be due to an ADCP (4-Amino-3,5-dichloro-pyridine) N-oxide intermediate specifically formed in rodent olfactory mucosa, with special binding affinity in these species (i.e. mouse, rat and hamster).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC aluminium blisters in packs of 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
1 Francis Crick Avenue,
Cambridge,
CB2 0AA,
UK

8. MARKETING AUTHORISATION NUMBER(S)

PLGB 17901/0318

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 July 2010
Date of latest renewal: 20 May 2020

10. DATE OF REVISION OF THE TEXT

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

25/03/2024