PRODUCT MONOGRAPH

PrDAXAS®

roflumilast film-coated tablets, 500 mcg

Phosphodiesterase 4 (PDE4) Inhibitor

AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario
L4Y 1M4
www.astrazeneca.ca

Date of Revision: January 19, 2017

Submission Control No: 200054

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 4
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 7
DRUG INTERACTIONS 10
DOSAGE AND ADMINISTRATION 11
OVERDOSAGE 12
ACTION AND CLINICAL PHARMACOLOGY 12
STORAGE AND STABILITY 15
DOSAGE FORMS, COMPOSITION AND PACKAGING 15
PART II: SCIENTIFIC INFORMATION 16
PHARMACEUTICAL INFORMATION 16
CLINICAL TRIALS 16
DETAILED PHARMACOLOGY 22
TOXICOLOGY 24
REFERENCES 29
PART III: CONSUMER INFORMATION 30

PrDAXAS®

roflumilast film-coated tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	500 mcg Film-coated Tablet	Hypromellose, lactose monohydrate, Macrogol 4000, magnesium stearate, maize starch, povidone, titanium dioxide and yellow iron oxide

INDICATIONS AND CLINICAL USE

DAXAS (roflumilast) administered once daily (500 mcg tablet per day) is indicated, as add-on therapy to bronchodilator treatment, for the maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis (i.e. patients with a history of chronic cough and sputum) in adult patients with a history of frequent exacerbations.

DAXAS should not be used as a rescue medication.

Geriatrics (≥ 65 years of age):

In clinical studies with DAXAS, there were no overall differences in safety and effectiveness of DAXAS in the elderly compared to younger patients with COPD. Therefore, no dose adjustment is necessary (See ACTION AND PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (< 18 years of age):

Safety and effectiveness of DAXAS in children and adolescents below 18 years of age have not been established. DAXAS is not recommended in this population.

CONTRAINDICATIONS

DAXAS (roflumilast) is contraindicated in:

- Patients who are hypersensitive to roflumilast or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

- Patients who have moderate or severe hepatic impairment (Child-Pugh B or C).

WARNINGS AND PRECAUTIONS

General

Roflumilast, a phosphodiesterase 4 (PDE4) inhibitor, is not indicated for the relief of acute bronchospasms.

DAXAS (roflumilast) should not be used more frequently than once daily.

DAXAS should not be used on its own but as add-on therapy to bronchodilator treatment.

Hypersensitivity reactions may occur after administration of DAXAS. DAXAS is not recommended in patients who are hypersensitive to roflumilast or to any ingredient in the formulation (see CONTRAINDICATIONS).

DAXAS tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take DAXAS.

Carcinogenesis and Mutagenesis

Roflumilast has been demonstrated to produce carcinoma of the olfactory epithelium in hamsters. Carcinogenesis was related to a rodent-specific toxic metabolite. The relevance of this finding to humans is unknown (see TOXICOLOGY, Carcinogenicity).

Due to lack of relevant experience, treatment with DAXAS should not be initiated or existing treatment with DAXAS should be stopped in patients with cancer (except basal cell carcinoma).

Cardiovascular

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

Supra-ventricular arrhythmia including atrial fibrillation had been reported as a common adverse event (>1%) in the clinical trials (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions). If the patient develops supra-ventricular arrhythmia, the risk and benefit of continuing with DAXAS should be evaluated cautiously.

Infections

Due to lack of relevant experience, treatment with DAXAS should not be initiated or existing treatment with DAXAS should be stopped in patients with severe acute infectious diseases. Experience in patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection and herpes zoster is limited and DAXAS should be used with caution in these patients.

Neuropsychiatric

An increased number of neuropsychiatric events such as anxiety, depression, insomnia/sleep disorders, dizziness, headache and tremor have been reported in patients treated with DAXAS in comparison with those treated with placebo (see ADVERSE REACTIONS). Rare instances of suicide behaviours/ideation, and completed suicide, have been reported in patients treated with DAXAS with or without prior history of depression, and causal relation to roflumilast treatment could not be ruled out.

Physicians should discuss neuropsychiatric adverse events with their patients and/or caregivers. Patients and/or caregivers should be instructed to notify their physician if these events do occur. Physicians should carefully evaluate the risks and benefits of continuing treatment with DAXAS if such events occur.

DAXAS is not recommended in patients who have a history of depression associated with suicidal behaviours or ideation.

Gastrointestinal

In the COPD safety pool, diarrhea was reported by 11.6% of patients in the DAXAS (500 mcg QD) group and 3.2% of patients in the placebo group. Ten (0.2%) patients in the DAXAS group reported diarrhea as a serious AE in comparison with one (0.02%) patient in the placebo group. About 2.5% of patients in the DAXAS group and 0.1% in the placebo group withdrew prematurely from the studies due to diarrhea.

Additionally, “Weight decreased” was reported by 6.8% of patients treated with DAXAS and by 1.8% of patients treated with placebo. More patients withdrew prematurely from the studies due to weight decrease in the DAXAS group (0.5%) than in the placebo group (<0.1%). In the pivotal studies, DAXAS treated patients lost an average of 2 kg of weight while the weight in the placebo group remained stable (see ADVERSE REACTIONS). After discontinuation of DAXAS, the majority of patients had regained body weight after 3 months.

Physicians should discuss gastrointestinal adverse events related to the use of DAXAS (e.g. diarrhea and weight decrease) with their patients and/or caregivers. Patients and/or caregivers should be instructed to monitor their weight regularly. Physicians should carefully evaluate the risks and benefits of continuing treatment with DAXAS if weight decrease does occur. Treatment with DAXAS should not be initiated or existing treatment with DAXAS should be stopped in patients with an unexplained and pronounced weight decrease.

Hepatic/Biliary

The clinical data with roflumilast 250 mcg in patients with mild to moderate hepatic impairment (classified as Child-Pugh A and B) showed an increased AUC and C_{max} in hepatic impairment patients when compared with healthy subjects (see ACTION AND CLINICAL PHARMACOLOGY). Pharmacokinetic studies have not been performed with roflumilast 500 mcg in hepatically impaired patients.

Clinicians should consider the risk-benefit of administering DAXAS to patients who have mild liver impairment (Child-Pugh A). DAXAS is not recommended for use in patients with moderate or severe liver impairment (see CONTRAINDICATIONS).

Immune System

Due to lack of relevant experience, treatment with DAXAS should not be initiated or existing treatment with DAXAS should be stopped in patients with severe immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy) or patients being treated with immunosuppressive medicinal products (e.g. methotrexate, azathioprine, infliximab, etanercept, or long-term oral corticosteroids; this does not include short-term systemic corticosteroids such as those used for the treatment of COPD exacerbations).

Special Populations

Pregnant Women: Studies in animals have shown reproductive toxicity at doses above the human recommended dose (see TOXICOLOGY, Reproductive Toxicity).

There are no adequate and well controlled studies in pregnant women. The potential risk for humans is unknown. DAXAS should not be used during pregnancy and in women of childbearing potential not using adequate contraception.

Nursing Women: Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or metabolites into human milk is probable. DAXAS should not be used during breast-feeding.

Pediatrics (< 18 years of age): Safety and effectiveness of DAXAS in children and adolescents below 18 years of age have not been established. DAXAS is not recommended in this population.

Geriatrics (≥ 65 years of age): In clinical studies with DAXAS, there were no overall differences in safety and effectiveness of DAXAS in the elderly compared to younger patients with COPD. Therefore, no dose adjustment is necessary (See ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

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, DAXAS 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 African

American, non-smoking females or in patients concomitantly treated with the CYP1A2 inhibitor fluvoxamine or the dual CYP3A4/1A2 inhibitor enoxacin and the triple CYP1A2/2C19/3A4 inhibitor cimetidine (see DRUG INTERACTIONS, Drug-Drug Interactions).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions (as determined by investigators) were experienced by approximately 17.4% of patients treated with roflumilast 500 mcg compared to 5.4% of patients treated with placebo. The most common adverse events related to roflumilast 500 mcg were: diarrhea (11.6%), weight decreased (6.8%), nausea (5.2%), headache (4.6%) and abdominal pain (4.2%) (Table 1). The events diarrhea, nausea and headache usually began within the first 4 weeks of treatment and usually resolved within 4 weeks while still on continued treatment. Approximately 70% of the events of "Weight decreased" occurred within the first 6 months of therapy (see WARNINGS AND PRECAUTIONS). Overall, approximately 80% of the adverse events with roflumilast were mild or moderate, and resolved on continued treatment.

Rarely, other adverse events observed during clinical studies of DAXAS (roflumilast) included completed suicide and/or suicidal ideation or behaviour, hypersensitivity and aspartate aminotransferase (AST) increased (see WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Based on phase II/III clinical studies in COPD patients (COPD safety pool), exposure to DAXAS (500 mcg QD) in 5766 COPD patients included 3453 patients exposed for up to 6 months, 1081 exposed for up to one year, and 1232 exposed for at least one year. This population was 25 to 93 years old (median age 64), 72% were male, and 89% were Caucasian.

Table 1 lists the adverse events reported in 1% or more of DAXAS-treated patients in placebo-controlled Phase II/III studies who were administered 500 mcg roflumilast per day for up to 12 months.

The overall incidence of serious adverse events (SAEs) and adverse events (AEs) in general were similar between DAXAS and the placebo groups. For the COPD safety pool, the respective SAE rates were 13.5% for the DAXAS group and 14.2% for the placebo group. The number of deaths was similar between DAXAS (n=84) and placebo (n=86).

In general, patients who were elder (>65 years) and female had more AEs related to study drug and more early withdrawal because of AEs.

Table 1 Treatment-Emergent Adverse Events reported by ≥ 1% of DAXAS-treated COPD patients in Phase II/III placebo-controlled studies

Preferred Term (MedDRA)[a]	% Incidence			
	DAXAS N=5766		Placebo N=5491	
	N	%	N	%
Cardiac disorders				
Supra-ventricular arrhythmia	71	(1.2)	40	(0.7)
Gastrointestinal disorders				
Abdominal Pain	240	(4.2)	107	(1.9)
Diarrhea	668	(11.6)	176	(3.2)
Gastritis	65	(1.1)	21	(0.4)
Nausea	297	(5.2)	79	(1.4)
Vomiting	76	(1.3)	32	(0.6)
General disorders				
Fatigue	66	(1.1)	31	(0.6)
Metabolism and nutrition disorders				
Decreased appetite	165	(2.9)	29	(0.5)
Weight decreased	394	(6.8)	101	(1.8)
Musculoskeletal and connective tissue disorders				
Back pain	189	(3.3)	122	(2.2)
Muscle spasms	112	(1.9)	52	(0.9)
Nervous system disorders				
Dizziness	177	(3.1)	89	(1.6)
Headache	266	(4.6)	110	(2.0)
Tremor	98	(1.7)	15	(0.3)
Psychiatric disorders				
Anxiety	80	(1.4)	43	(0.8)
Depression	73	(1.3)	46	(0.8)
Insomnia	168	(2.9)	60	(1.1)

[a]MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, DAXAS = roflumilast 500 mcg once daily.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Additional treatment-emergent adverse events occurring in these clinical trials involving DAXAS with an incidence of less than 1% and at a greater incidence with DAXAS than with placebo include the following:

Blood and lymphatic disorders: Anemia.

Endocrine disorders: Gynecomastia.

Gastrointestinal disorders: Constipation, dyspepsia, gastro-esophageal reflux disease, hematochezia.

General disorders and administration site conditions: Arthralgia, asthenia, malaise, myalgia, pain in extremity.

Hepatobiliary disorders: Gamma-GT increased, transaminases (AST) increased.

Immune system disorders: Hypersensitivity.

Investigations: Blood LDH increased.

Musculoskeletal and connective tissue disorders: Arthritis, muscle weakness.

Nervous system disorders: Dysgeusia, paraesthesia, vertigo.

Psychiatric disorders: Nervousness.

Respiratory, thoracic and mediastinal disorders: Epistaxis, respiratory tract infections (excluding pneumonia).

Skin and subcutaneous tissue disorders: Rash, urticaria.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during the post-approval use of DAXAS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency. A causal relation to roflumilast treatment could not be ruled out.

Immune System Disorders: Angioedema.

Psychiatric Disorders: Suicidal ideation and behavior including completed suicide.

DRUG INTERACTIONS

Overview

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP 3A4 and CYP 1A2. Both roflumilast and roflumilast N-oxide have intrinsic PDE4 inhibitory activity. Therefore, following administration of DAXAS (roflumilast), the total PDE4 inhibition (tPDE4i) is considered to be the combined effect of both roflumilast and roflumilast N-oxide (see ACTION AND CLINICAL PHARMACOLOGY).

Drug-Drug Interactions

No clinically relevant interactions with the following drugs were observed: salbutamol, formoterol, budesonide, montelukast, digoxin, warfarin, sildenafil, midazolam.

Co-administration with an antacid did not alter the absorption or pharmacokinetics of roflumilast or its N-oxide.

Co-administration with theophylline resulted in an increase of 8% of the tPDE4i.

In an interaction study with an oral contraceptive containing gestodene and ethinyl oestradiol, the tPDE4i was increased by 17%. The concurrent use should be with caution.

Drugs That Inhibit Cytochrome P450 (CYP) Enzymes:

Clinical drug-drug interaction studies have shown that the CYP 3A4 inhibitors, erythromycin and ketoconazole increased the tPDE4i (i.e. total exposure to roflumilast and roflumilast N-oxide) by 9%, whereas the CYP 1A2/3A4 inhibitor enoxacin, the CYP1A2/2C19/3A4 inhibitor cimetidine and the CYP1A2 inhibitor fluvoxamine increased the tPDE4i by 25%, 47% and 59%, respectively. The co-administration of DAXAS (500 mcg) with these inhibitors might lead to an increase of exposure and persistent intolerability resulting in increased adverse reactions (Table 2). In this case, DAXAS treatment should be reassessed.

Drugs That Induce Cytochrome P450 (CYP) Enzymes:

Administration of the cytochrome P450 enzyme inducer rifampicin reduced the tPDE4i by 58%. This suggests that strong cytochrome P450 inducers may reduce the therapeutic effect of roflumilast. The use of strong cytochrome P450 inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DAXAS is not recommended (Table 2).

Table 2 Established or Potential Drug-Drug Interactions

Proper Name	Ref.	Effect	Clinical Comment
Erythromycin	P/CT	↑ tPDE4i by 9%	Use with caution
Ketoconazole	P/CT	↑ tPDE4i by 9%	Use with caution
Fluvoxamine	P/CT	↑ tPDE4i by 59%	Use with caution
Enoxacin	P/CT	↑ tPDE4i by 25%	Use with caution
Cimetidine	P/CT	↑ tPDE4i by 47%	Use with caution
Rifampicin	P/CT	↓ tPDE4i by 58%	Concurrent use is not recommended. Rifampicin and other strong cytochrome P450 inducers (e.g. phenobarbital, carbamazepine, phenytoin) may reduce the therapeutic effect of DAXAS.

Legend: CT = Clinical Trial; tPDE4i = Total PDE4 inhibition; P = Potential

Drug-Food Interactions

Food intake does not affect the tPDE4i, 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 (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).

Drug-Lifestyle Interactions

In smokers, tPDE4i was slightly decreased. However, the clinical effectiveness was comparable irrespective of the current smoking status.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dosage for patients with COPD is 500 mcg tablet per day, with or without food.

In PK studies, increased exposure to roflumilast and roflumilast N-oxide was seen in elderly patients >65 year of age, females and patients with mild hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

No dosage adjustment is required in elderly patients, patients with renal impairment, or patients with mild hepatic impairment. DAXAS (roflumilast) is not recommended for use in patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS).

Missed Dose

Patients should be advised that if they forget to take a tablet at the usual time, they should take the tablet as soon as they remember or continue on the next day with the next tablet at the usual time. Patients should not take a double dose to make up for a forgotten dose.

OVERDOSAGE

No case of overdose has been reported in clinical studies with DAXAS (roflumilast). During the phase I studies of DAXAS the following symptoms were observed at an increased rate after single oral doses of 2500 mcg and one single dose of 5000 mcg (ten times the recommended dose): headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Roflumilast is a selective PDE4 inhibitor. It is a non-steroid, anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with COPD. The mechanism of anti-inflammatory action of roflumilast 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 splice variant with similar potency in the nanomolar range. The affinity to the PDE4C splice variant 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.

Pharmacodynamics

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. Based on this mechanism, roflumilast in animals suppressed the release of inflammatory mediators, i.e. cytokines and reactive oxygen species from cells and lung tissue *in vitro* and *in vivo*. In addition, roflumilast inhibited the infiltration of leukocytes, in particular neutrophils, into the lungs of animals. Roflumilast also reduced the smoke-induced destruction of lung parenchyma and prevented lung fibrotic and vascular remodeling in animal models *in vivo*. It stimulated bronchial ciliary activity *in vitro* and inhibited the formation of MUC5AC, a goblet cell-derived gel-forming mucin, in human

airway epithelial cells and in animal experiments. These effects also apply to roflumilast N-oxide and respective *in vitro* and *in vivo* data concur with its PDE4 inhibitory potency.

Roflumilast attenuated the influx of neutrophils and eosinophils into the airways of endotoxin (lipopolysaccharide) challenged healthy volunteers (see DETAILED PHARMACOLOGY).

Cardiac Electrophysiology: In a placebo-controlled, parallel arm study, healthy subjects (N=40/treatment arm) with a mean heart rate of about 60 bpm at baseline were randomised to receive 5 weeks of treatment with placebo or roflumilast. Roflumilast once daily was administered according to the following upward titration regimen: 500 mcg for 14 days, 750 mcg for 7 days, and 1000 mcg for 14 days. Roflumilast was found to increase heart rate. At the therapeutic 500 mcg dose, heart rate was increased from 1 to 24 h post-dosing, with a maximum increase of 5.7 (90% CI 2.7, 8.8) bpm at 1 h post-dosing. At the supratherapeutic 1000 mcg dose, heart rate was significantly increased from 1 to 12 h post-dosing, with a maximum increase of 6.2 (90% CI 3.3, 9.2) bpm at 2 h post-dosing. In the same study, roflumilast up to 1000 mcg once daily for 14 days did not affect the QT/QTc interval or other electrophysiological variables.

Pharmacokinetics

Roflumilast is extensively metabolized in humans, with the formation of a major pharmacodynamically active metabolite, roflumilast N-oxide. Since its plasma AUC on average is about 10-fold greater than the plasma AUC of roflumilast, the N-oxide metabolite is considered the main contributor to the tPDE4i *in vivo* in humans (see Table 3). Therefore, pharmacokinetic considerations are based on tPDE4i (i.e. total exposure to roflumilast and roflumilast N-oxide).

The pharmacokinetics of roflumilast and its N-oxide metabolite are dose-proportional over a range of doses from 250 mcg to 1000 mcg.

Table 3 Summary of Roflumilast's and Roflumilast N-oxide's Pharmacokinetic Parameters after a single dose of 500 mcg of roflumilast (morning or evening) in healthy young male and female subjects under fasting conditions

Study	AUC_{inf} [mcg X h/L]	C_{max} [mcg/L]
Roflumilast		
Median	40.5	7.04
Range (min, max)	(26.6, 61.0)	(3.06, 9.56)
Roflumilast N-oxide		
Median*	415	9.49
Range (min, max)	(154, 780)	(6.61, 13.1)

*Median of geometric means of 15 single-dose phase I studies

Absorption: The absolute bioavailability of roflumilast following a 500 mcg 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 while plateau-like 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 tPDE4i, 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 500 mcg roflumilast is about 2.9 L/kg. Studies in rats with radiolabeled roflumilast indicate low penetration across the blood-brain barrier. Roflumilast has been demonstrated to cross the placenta in pregnant rats. In addition, it is secreted into milk of breeding dams.

Metabolism: Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the major metabolite observed in the plasma of humans. *In vitro* studies and clinical drug-drug interaction studies suggest that the metabolism of roflumilast to its N-oxide metabolite is mediated by CYP 1A2 and 3A4. Based on further in vitro results in human liver microsomes, therapeutic plasma concentrations of roflumilast and roflumilast N-oxide do not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A9/11. Therefore, there is a low probability of relevant interactions with substances metabolized by these P450 enzymes. In addition, *in vitro* studies demonstrated no induction of the CYP 1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP 2B6 by roflumilast.

In human drug-drug interaction studies, the moderate CYP 3A4 inhibitor erythromycin increased the AUC of roflumilast by 70% and that of roflumilast N-oxide by 4%. The tPDE4i was increased by 9%. The strong CYP 3A4 inhibitor ketoconazole increased the AUC of roflumilast by 99% and that of roflumilast N-oxide by 3%. The tPDE4i was increased by 9%. The strong CYP 1A2 inhibitor fluvoxamine increased the AUC of roflumilast by 156 % and that of roflumilast N-oxide by 52%. The tPDE4i was increased by 59%. The dual CYP 1A2/ 3A4 inhibitor enoxacin increased the AUC of roflumilast by 57% and that of roflumilast N-oxide by 19%. The tPDE4i was increased by 25%. The triple CYP 1A2/ 3A4/ 2C19 inhibitor cimetidine increased the AUC of roflumilast by 84% and that of roflumilast N-oxide by 27%. The tPDE4i was increased by 47%. The CYP 3A4 inducer rifampicin decreased the AUC of roflumilast by 80% and that of roflumilast N-oxide by 56%. The tPDE4i was decreased by 58%.

Excretion: The plasma clearance after short term intravenous infusion of roflumilast is on average about 9.6 L/h. At steady state 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 radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

Special Populations and Conditions

Geriatrics: In the elderly, tPDE4i was increased by about 20%. There were no overall differences in safety and effectiveness of roflumilast in the elderly compared to younger patients with COPD. Dosage modifications are not required.

Gender: In women, tPDE4i was increased when compared with men. No dose adjustment is necessary based on gender.

Race: In African Americans and Hispanics, simulations suggest that tPDE4i is higher than in Caucasians. No dose adjustment is necessary based on race.

Hepatic Insufficiency: The pharmacokinetics of DAXAS (roflumilast) 250 mcg once daily were tested in patients with mild-to-moderate hepatic impairment classified as Child-Pugh A and B. In these patients, the tPDE4i was increased by about 20% in patients with Child-Pugh A and about 90% in patients with Child-Pugh B. Roflumilast is contraindicated in patients with moderate or severe hepatic impairment classified as Child-Pugh B or C (see CONTRAINDICATIONS).

Renal Insufficiency: In patients with severe renal impairment (creatinine clearance 10-30 mL/min), tPDE4i was decreased by 9%. This difference is not considered to be clinically relevant. Dosage modifications are not required.

STORAGE AND STABILITY

Store DAXAS (roflumilast) 500 mcg film-coated tablets at 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

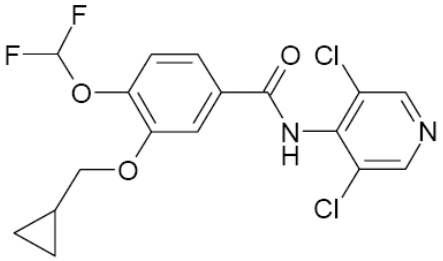
DAXAS (roflumilast) is supplied as a yellow, D-shaped film-coated tablet, embossed with "D" on one side that contains 500 mcg of roflumilast. Each film-coated tablet of DAXAS for oral administration contains the following inactive ingredients: lactose monohydrate, maize starch, povidone and magnesium stearate. In addition, the film-coat contains: hypromellose, Macrogol 4000, titanium dioxide and yellow iron oxide.

DAXAS tablets are available in PVC/PVDC aluminum blister packs containing 7, 10, 30 or 90 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	roflumilast
Chemical name:	N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide
Molecular formula:	$C_{17}H_{14}Cl_2F_2N_2O_3$
Molecular mass:	403.22
Structural formula:	
Physicochemical properties:	roflumilast is poorly soluble in water.
pH:	of a saturated solution at 21-22 °C is 6.35
pKa:	8.74
Melting point:	approximately 159.7 °C
Partition coefficient:	The partition coefficient of roflumilast between 1-octanol and aqueous phosphate buffer at pH 7.4 is logP = 3.99.

CLINICAL TRIALS

The efficacy and safety of DAXAS (roflumilast) was evaluated in two confirmatory replicate one-year trials (M2-124, M2-125) and four supplementary/supportive trials [i.e. two one-year trials (M2-111 and M2-112) and two six-month trials (M2-127 and M2-128)]. A total number of 7453 patients were randomized and treated, of whom 3701 were treated with DAXAS (roflumilast). All trials were randomized, double-blind, placebo-controlled, parallel-group studies. In all studies, DAXAS was administered once daily (500 mcg tablet), but the inclusion and exclusion criteria and concomitant medications were not identical (see Table 4).

Table 4 Summary of Patient Demographics for Pivotal Clinical Trials (M2-124 and M2-125) and Supportive Trials (M2-127, M2-128, M2-111 and M2-112) in Patients with COPD.

Study #	Trial Design and Duration	Route of Administration and Dosage	Study Subjects (N=number of subjects randomised and treated)	Median Age (Range)	Gender (%)	Main Inclusion / Exclusion criteria	Concomitant medication permitted	Primary Efficacy Endpoint
M2-124	Fifty-two weeks, randomized, double-blind, parallel group, placebo controlled.	Oral, once daily DAXAS; 500 mcg	765	63 (40-89)	M:71; F:29	Age ≥ 40; Post-FEV_1 ≤ 50% predicted.; chronic bronchitis[b]; history of exacerbation[a]	Salbutamol as needed, LABA SAMA (for those patients not taking LABA)	Pre-FEV_1; exacerbation rate (moderate or severe)
		Placebo	758	63 (40-92)	M:71; F:29			
M2-125	Fifty-two weeks, randomized, double-blind, parallel group, placebo controlled	Oral, once daily DAXAS; 500 mcg	772	64 (40-90)	M:79; F:21	Age ≥ 40; Post-FEV_1 ≤ 50% predicted; chronic bronchitis[b]; history of exacerbation[a]	Salbutamol as needed, LABA SAMA (for those patients not taking LABA)	Pre-FEV_1; exacerbation rate (moderate or severe)
		Placebo	796	65 (40-90)	M:81; F:19			
M2-127	Twenty-four weeks, randomized, double-blind, parallel group, placebo controlled	Oral, once daily DAXAS; 500mcg (concomitant therapy: salmeterol 50 mcg twice daily, inhalation)	466	65 (42-87)	M:68; F:32	Age ≥ 40; Post-FEV_1 40-70% predicted; Reversibility in FEV_1 ≤12% or ≤200 mL	Salbutamol as needed, all patients on concomitant salmeterol	Pre-FEV_1
		Placebo (concomitant therapy: salmeterol 50 mcg twice daily, inhalation)	467	65 (40-89)	M:64; F:36			

Study #	Trial Design and Duration	Route of Administration and Dosage	Study Subjects (N=number of subjects randomised and treated)	Median Age (Range)	Gender (%)	Main Inclusion / Exclusion criteria	Concomitant medication permitted	Primary Efficacy Endpoint
M2-128	Twenty-four weeks, randomized, double-blind, parallel group, placebo controlled	Oral, once daily DAXAS; 500 mcg (concomitant therapy: tiotropium 18 mcg once daily, inhalation)	371	65 (40-91)	M:71; F:29	Age ≥ 40; Post-FEV_1 40-70% predicted; Reversibility in FEV_1 ≤12% or ≤200 mL; chronic bronchitis[b]; pre-treatment with tiotropium	Salbutamol as needed, all patients on concomitant tiotropium,	Pre-FEV_1
		Placebo (concomitant therapy: tiotropium 18 mcg once daily, inhalation)	372	65 (41-87)	M:72; F:28			
M2-111	Fifty-two weeks, randomized, double-blind, parallel group, placebo controlled	Oral, once daily DAXAS; 500 mcg	567	65 (40-87)	M:68; F: 32	Age ≥ 40; Post-FEV_1 ≤ 50% predicted	Salbutamol as needed, ICS up to 2000 µg BDP or equivalent SAMA	Pre-FEV_1; exacerbation rate (moderate or severe)
		Placebo	606	64 (41-86)	M:66; F:34			
M2-112	Fifty-two weeks, randomized, double-blind, parallel group, placebo controlled	Oral, once daily DAXAS; 500 mcg	760	66 (40-88)	M:75; F:25	Age ≥ 40; Post-FEV_1 ≤ 50% predicted; Reversibility in FEV_1 ≤15% and/or ≤200 mL	Salbutamol as needed, ICS up to 2000 µg BDP or equivalent SAMA	Post-FEV_1; exacerbation rate (moderate or severe)
		Placebo	753	65 (40-89)	M:76; F:24			

[a]At least one exacerbation defined by systemic glucocorticosteroid intake and/or hospitalization within 1 year prior study start.

[b]Chronic productive cough for 3 months in each of the 2 years prior to study enrollment.

Post-FEV_1 = post-bronchodilator FEV_1. Pre-FEV_1 = pre-bronchodilator FEV_1. LABA = long acting $beta_2$-agonist. ICS = inhaled corticosteroid. SAMA = short-acting muscarinic antagonist.

Pivotal Trials

Studies M2-124 and M2-125 included patients with a history of COPD associated with chronic bronchitis for at least 12 months prior to baseline, with symptoms at baseline as determined by cough and sputum score, non-reversible airway obstruction, an $FEV_1 \leq 50\%$ of predicted and at least one documented COPD exacerbation in the previous year.

In these one-year trials, long-acting $beta_2$-agonists (LABA) were allowed and used in approximately 50% of the study population. The use of inhaled corticosteroids was terminated at randomization. Lung function (pre-bronchodilator forced expiratory volume in one second, FEV_1) and the rate of moderate exacerbations (requiring intervention with systemic glucocorticosteroids) or severe exacerbations (resulting in hospitalization and/or leading to death) were co-primary endpoints. Secondary endpoints in both studies included further evaluation of exacerbations and lung function parameters, and dyspnea.

In studies M2-124 and M2-125, DAXAS 500 mcg once daily significantly improved lung function compared to placebo by 39 mL (p=0.0003) and 58 mL (p<0.0001), respectively (pre-bronchodilator FEV_1, primary endpoint) (Table 5). In the pooled analysis, DAXAS significantly improved pre-bronchodilator FEV_1 by 48 mL (p<0.0001), and post-bronchodilator FEV_1 by 55 mL (p<0.0001). Pre-bronchodilator forced vital capacity (FVC) was significantly greater with DAXAS than placebo in both studies by 89 mL (p<0.0001) in the M2-124 study and 108 mL (p<0.0001) in the M2-125 study. Similar significant improvements were seen in post-bronchodilator FVC and pre-bronchodilator mid-expiratory flow. DAXAS 500 mcg increased mean pre-bronchodilator FEV1 by 46 mL (p<0.0001), as compared to placebo, in patients with concomitant LABA treatment.

Table 5 Primary endpoint: pre-bronchodilator FEV_1 [L] – Studies M2-124 and M2-125 and pooled studies M2-124 and M2-125 (ITT, rep. measures)

Study or pool	Roflumilast 500 mcg		Placebo		Roflumilast 500 mcg vs. Placebo	
	n	Change from baseline [L]	n	Change from baseline [L]	Absolute Differences (95% CI)	P-value[a]
M2-124	745	0.046	745	0.008	0.039 (0.018, 0.060)	0.0003
M2-125	730	0.033	766	-0.025	0.058 (0.041, 0.075)	<0.0001
124+125 pooled	1475	0.040	1511	-0.009	0.048 (0.035, 0.062)	<0.0001

[a]2-sided.

CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, n = number of patients included in the analysis, rep. = repeated, vs = versus.

The endpoint of moderate or severe exacerbations (primary endpoint) was reduced by 15% in the M2-124 study (p=0.0278), 19% in the M2-125 study (p=0.0035) and by 17% (p=0.0003) for the pooled analysis (Table 6). DAXAS 500 mcg incrementally decreased exacerbations by 21% (p<0.0011), as compared to placebo, in patients with concomitant LABA treatment. The number of patients experiencing a moderate exacerbation in the DAXAS group was 624 versus 723 in the placebo group (Risk Ratio: 0.88; p=0.0011). The number of patients experiencing a severe exacerbation in the DAXAS group was 157 versus 198 in the placebo group (Risk Ratio: 0.84; p=0.0715).

Disease specific quality of life measured by St. George's Respiratory Questionnaire (SGRQ) was not captured in the two pivotal studies. The transitional dyspnea index (TDI) improved slightly with DAXAS 500 mcg by on average 0.25 (p<0.0009) as compared to placebo.

Table 6 Primary endpoint: Rate of moderate or severe exacerbation - Studies M2-124 and M2-125 and pooled studies M2-124 and M2-125 (ITT, Poisson regression)

Exacerbation	**Roflumilast 500 mcg**		**Placebo**		**Roflumilast 500 mcg vs. Placebo**			
Study or pool	n	Rate	n	Rate	% Change	Rate ratio	95% CI	P-value[a]
M2-124	765	1.077	758	1.266	-14.9	0.851	0.737, 0.982	0.0278
M2-125	772	1.210	796	1.485	-18.5	0.815	0.710, 0.935	0.0035
124+125 pooled	1537	1.142	1554	1.374	-16.9	0.831	0.752, 0.918	0.0003

[a]2-sided.
CI = confidence interval, ITT = intention-to-treat, n = number of patients included in the analysis, vs. = versus.

Supportive Trials

Two 1-year supportive studies (M2-111 and M2-112) evaluated a broad population of patients with severe COPD. In contrast to the two confirmative studies, a history of chronic bronchitis and of COPD exacerbations was not required for patients' inclusion. Inhaled corticosteroids were used in 809 (61%) of the roflumilast treated patients, whereas the use of LABAs was prohibited (Table 4).

In both the individual studies and the pooled analysis, DAXAS 500 mcg once daily statistically 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) for the pooled analysis. The reduction in rate of moderate to severe exacerbations (as defined in the protocols) between the roflumilast and placebo groups did not reach statistical significance in the individual studies (relative risk reduction: 13.5% in study M2-111 (p=0.14) and 6.6% in study M2-112 (p=0.45)). In the M2-111 study DAXAS treated patients showed an improved TDI focal score by 0.4 (p=0.0020) and an improved SGRQ total score by -1.5 (p= 0.0162) as

compared to placebo. In the M2-112 study there were no statistically significant differences between treatments for both the TDI focal and SGRQ total score.

The six-month studies M2-127 and M2-128 included patients with a history of COPD for at least 12 months prior to baseline. In addition, in the M2-128 study, documentation of chronic bronchitis and high reliever medication use was required. Both studies included patients with a non-reversible airway obstruction and a FEV_1 of 40% to 70% of predicted. DAXAS or placebo treatment was added to continuous treatment with a long-acting bronchodilator: salmeterol in the M2-127 study or tiotropium in the M2-128 study (Table 4).

In these two studies, pre-bronchodilator FEV_1 was significantly improved by 49 mL (primary endpoint, $p<0.0001$) beyond the bronchodilator effect of concomitant treatment with salmeterol in the M2-127 study and by 80 mL (primary endpoint, $p<0.0001$) incremental to concomitant treatment with tiotropium in the M2-128 study. The corresponding post-bronchodilator values were 60 mL ($p<0.0001$) and 81 mL ($p<0.0001$) in the M2-127 and M2-128 studies respectively.

Both studies showed that patients treated with roflumilast 500 mcg had lower exacerbation rate than those treated with placebo, but the results were not statistically significant at 0.05 level. These six-month studies were neither designed nor powered to show a statistically significant effect on exacerbations. In the M2-128 study the TDI focal score improved in DAXAS treated patients by 0.4 ($p=0.0032$) beyond the bronchodilator effect of tiotropium. In the M2-127 study, however, no treatment effect of roflumilast 500 mcg on the TDI focal score was observed.

In the one-year and six-month studies, the improvement in lung function was sustained over the treatment period. Smoking status did not influence the improvement in lung function or reduction in exacerbations. Effects were similar independent of previous treatment with inhaled corticosteroids.

In all COPD studies, safety and tolerability of roflumilast treatment were investigated by assessing adverse events, physical examinations, vital signs, clinical laboratory parameters and electrocardiograms (ECGs).

The overall incidence of adverse events was slightly higher in the roflumilast 500 mcg QD group than in the placebo group. Treatment-related adverse events and adverse events leading to study discontinuation were more frequent with roflumilast 500 mcg QD than with placebo. Adverse events leading to deaths were infrequent with no relevant observed differences between treatment arms (see ADVERSE REACTIONS).

DETAILED PHARMACOLOGY

Animal Pharmacology

Roflumilast and its active metabolite (roflumilast N-oxide) are potent and selective PDE4 inhibitors. Inhibition of PDE4 activity leads to accumulation of intracellular cyclic AMP known to inhibit the production of multiple pro-inflammatory factors which may contribute to the pathogenesis of COPD.

In vitro studies with human neutrophils, monocytes/macrophages, lymphocytes, airway smooth muscle cells, lung fibroblasts, endothelial and alveolar epithelial cells show that roflumilast and roflumilast N-oxide inhibit different cellular functions contributing to lung inflammation, pulmonary remodeling and mucociliary malfunction.

In experimental animal models of COPD, roflumilast blocked the infiltration of neutrophils and other leukocytes into the lung and reduced the smoke-induced destruction of lung parenchyma, bleomycin-induced lung fibrosis and monocrotaline and hypoxia-induced vascular remodeling.

Studies on secondary pharmacodynamics investigated receptor interactions in isolated organ systems and the effects of roflumilast in animal models of other inflammatory diseases. In functional studies using isolated organs and appropriate receptor agonists, no competitive antagonism was exerted by roflumilast or its N-oxide on muscarinic, adrenergic, dopaminergic, histaminergic, and purinergic receptors.

Safety pharmacology studies investigated the effects of roflumilast and its N-oxide on the central and autonomic nervous system as well as on the cardiovascular, respiratory, renal, and gastrointestinal system. Roflumilast and roflumilast N-oxide induced effects on the central and autonomic nervous system of mice that are characteristic for PDE4 inhibitors, like hypoactivity and hypothermia. Following high doses which produce systemic drug exposure about 40-times higher than the human exposure at the 500 mcg dose, potentiation of seizures due to pentetrazole or electrical stimulation or their sequelae was observed.

Roflumilast and its N-oxide induced cardiac inotropic effects and vasodilation in cats and dogs and chronotropic effects in minipigs. *In vitro*, roflumilast and its N-oxide did not influence the human ether-a-go-go related gene (hERG) channel current at concentrations up to 100-times the free plasma maximum drug concentration (C_{max}) in humans dosed 500 mcg/day. No change was observed in the action potential in isolated papillary muscle of guinea pig hearts. The electrocardiogram (ECG) in cats, dogs, and minipigs remained unchanged after high doses of roflumilast and its N-oxide.

In animals, neither drug induced depressant effects on the respiratory system. Roflumilast increased gastric acid secretion in rats, retarded gastric emptying in mice, and induced emesis in dogs. Urinary volume decreased in parallel to decreases in blood pressure and urinary potassium excretion increased following high-dose roflumilast and its N-oxide to rats.

Clinical Pharmacology

Pharmacodynamics

The anti-inflammatory effect of roflumilast has been demonstrated in two pharmacodynamic studies. One double-blind, randomized, placebo-controlled, 2-parallel group comparison study investigated the effect of roflumilast on inflammatory cells and mediators in broncho-alveolar lavage fluid (BALF) over 28 days in 43 healthy subjects after segmental pulmonary lipopolysaccharide (LPS) challenge. In a second study, the effect on sputum cells and biochemical markers was examined in 41 COPD patients over 28 days in a double-blind, randomized, placebo-controlled, 2-period cross over study.

Roflumilast significantly reduced the influx of absolute numbers of neutrophils, eosinophils and total cells into the airways as demonstrated in BALF of healthy subjects after segmental pulmonary LPS challenge. These findings are consistent with the anti-inflammatory properties of roflumilast shown in non-clinical COPD models. In COPD patients, there was a decrease of TNF-alpha formation (in whole blood *ex vivo* after *in vitro* LPS stimulation) paralleled by improvement of pulmonary function as assessed by FEV_1.

Male Fertility

A fertility study in rats showed that roflumilast decreased fertility rate in male rats at the high dose (see TOXICOLOGY, Chronic Toxicity). A human spermatogenesis study investigated reproductive safety of 500 mcg roflumilast in healthy male volunteers. No adverse treatment effects were found on parameters of the male reproductive system including reproductive hormones.

TOXICOLOGY

Acute Toxicity

The single-dose toxicity of roflumilast and roflumilast N-oxide has been investigated in mice, rats, and dogs. The results (Table 7 and Table 8) show a range of non-lethal doses of at least 100 mg/kg in rodents (15,000-times the 500 mcg dose in a 75-kg human) after oral drug administration and of at least 20 mg/kg after intravenous administration.

Target organs at necropsy were the forestomach (hyperplasia), glandular stomach (ulcer, hemorrhage), small intestine (thickening, submucosal cell infiltration, serositis), testes (atrophy), and olfactory epithelium (inflammation).

Table 7 Acute toxicity of roflumilast in various species

Species	**Mouse**	**Mouse**	**Rat**	**Rat**	**Dog**
Route of administration	**p.o**	**i.v.**	**p.o.**	**i.v.**	**p.o.**
MTD[a] (mg/kg)	600	20	100-400	n.a[b]	18
LD_{50} (mg/kg)	1100-1600	>20	400-700	12-16	>18

[a] maximum tolerated (non-lethal) dose
[b] not ascertained because of high death rate in controls due to emulsion medium

Table 8 Acute toxicity of roflumilast N-oxide in various species

Species	**Mouse**	**Mouse**	**Rat**	**Rat**	**Dog**
Route of administration	**p.o**	**i.v.**	**p.o.**	**i.v.**	**p.o.**
MTD (mg/kg)	200	40	<200	40	18
ALR[a] (mg/kg)	500-2000	40-100	<200	40-100	>18

[a] approximate lethal range according to 'acute toxic class method'

In dogs, the highest dose of 18 mg/kg roflumilast or its N-oxide induced vomiting and tremor but caused no mortality.

Chronic Toxicity

The chronic toxicity of roflumilast (and in some instances of roflumilast N-oxide) was investigated in five animal species (longest duration in parentheses): mouse (6 months), rat (6 months), hamster (3 months), dog (12 months), and monkey (42 weeks). The experimental details of these studies are provided in Table 9.

Table 9 Chronic toxicity studies with oral administration of roflumilast or roflumilast N-oxide

Species, strain	No/sex/group (+ recovery)	Duration (+ recovery)	Doses[a] (mg/kg/day)	Primary target organs according to histopathology[b]
Mouse, B6C3F1	10	3 months	0, 6, 12, 18 Rof	Olfactory epithelium, x-zone of adrenals
Mouse, B6C3F1	20 (+ 8)	6 (+1) months	0, 4, 12, 36 Rof	Olfactory epithelium, adrenals
Mouse, B6C3F1	20 (+ 8)	6 (+1) months	0, 4, 10, 25 R-NO	Olfactory epithelium, exorbital lacrimal gland, adrenals
Rat, Wistar	10 (+ 8)	1 (+1) month	0, 0.5, 2, 8 Rof	Testes, epididymides, stomach, intestine, peritoneum
Rat, Wistar	10 (+ 8)	1 (+1) month	0, 0.4, 1.2, 3.6 R-NO	Testes, epididymides, intestine, pancreas
Rat, Wistar	8 (+ 8)	1+3 (+2) months	0, 0.02, 0.2, 2 Rof	Olfactory epithelium, testes, epididymides
Rat, Wistar, juvenile	10 (+ 8)	3 (+1) months	0, 0.2, 0.5, 0.8 Rof	---
Rat, Wistar	20 (+ 8)	6 (+1) months	0, 0.5, 1.5, 2.5 Rof	Olfactory epithelium, epididymides
Rat, Wistar	20 (+ 8)	6 (+1) months	0, 0.8 Rof	---
Hamster, Syrian Golden	10	3 months	0, 4, 8, 16 Rof	Olfactory epithelium, Harderian gland
Dog, Beagle	3 (+ 2)	1 (+ 1) month	0, 2, 6, 18 Rof	Heart (right auricle and atrium)
Dog, Beagle	3 (+ 2)	1 (+ 1) month	0, 0.6, 1.2, 2.4 R-NO	Heart (right auricle and atrium)
Dog, Beagle	5 (+ 2)	6 (+ 1) months	0, 0.2, 1, 4 Rof	Heart (right auricle and atrium)
Dog, Beagle	5 (+ 2)	12 (+ 1) months	0, 0.2, 0.6, 2.0 Rof	Heart (right auricle)
Dog, Beagle	5 (+ 2)	12 (+ 1) months	0, 0.1, 0.4, 0.8, 1.2 R-NO	---
Monkey, Cynomolgus	3	1 month	0, 0.1, 0.25, 0.5 Rof	Stomach
	4 (+ 2)	9 (+ 2) months	0, 0.1, 0.25, 0.5 Rof	---

Rof = roflumilast
R-NO = roflumilast N-oxide
[a] Roflumilast and roflumilast N-oxide were administered orally
[b] Organs with atrophic changes being likely due to inanition are not listed

Dose-related changes in rodent olfactory mucosa consisted of disorganization and degeneration/necrosis accompanied by basal cell hyperplasia and inflammatory changes of Bowman's gland and submucosa. The rat was the most sensitive species (NOAEL 0.8 mg/kg/day), while mice and hamsters were less sensitive (NOAELs 4 mg/kg/day). No equivalent changes in the olfactory mucosa of dogs and monkeys were seen despite high systemic exposures to roflumilast and roflumilast N-oxide. Nasal mucosa lesions in the olfactory region are attributed to a rodent-specific metabolite. Humans do not have the corresponding olfactory-specific enzyme.

GI effects in rats (erosion, ulceration, and/or inflammation) were seen primarily in the 4-week studies with roflumilast and roflumilast N-oxide at the highest doses. GI effects seen in monkeys (inflammation in the pyloric region) were minimal and transient as they occurred after 4 weeks but were absent after 42 weeks of dosing. The safety margins (plasma AUC of free drug fraction) for any potential GI effects are 3.7- and 7.4-fold for rats, and 15- and 9.3-fold for monkeys, for roflumilast and the metabolite roflumilast N-oxide, respectively. For mice, hamsters, and dogs, the safety margins at the highest dose tested are 628-, 22-, and 47-fold for roflumilast and 249-, 56-, and 3.8-fold for roflumilast N-oxide, respectively.

Epididymal spermiogenic granuloma as well as tubular dilation and degeneration in the testes were observed in rats treated with roflumilast or roflumilast N-oxide at doses >0.8 mg/kg/day or >1.2 mg/kg/day, respectively. No drug-related changes in the testis or epididymis were noted in other species.

Cardiac lesions such as focal hemorrhages, hemosiderin deposits and lympho-histiocytic cell infiltration in the right atria/auricles were found in repeat-dose toxicity studies with roflumilast and roflumilast N-oxide in dogs. The cardiac lesions in dogs are considered a species-specific phenomenon, since no such cardiac lesions occurred in other species, including mice, rats, hamsters, and monkeys.

Decreased food consumption, reduced body weight gain, and adrenal hypertrophy (in mice accompanied by a premature involution of the juxtamedullary x-zone) occurred in mice, rats, and hamsters at high-doses of roflumilast (exposure ratios exceeding 9- to 650-fold the human plasma levels of unbound roflumilast or roflumilast N-oxide).

Carcinogenicity

In a 2-year carcinogenicity study in mice, roflumilast was administered by gavage at doses up to 18 mg/kg/day in males, and 12 mg/kg/day in females. No compound-related tumors occurred. In the two 2-year carcinogenicity studies in hamsters, roflumilast was administered by gavage at doses up to 16 mg/kg/day. Nasal neoplasms (undifferentiated carcinomas of the olfactory epithelium and adenocarcinoma of Bowman’s gland) were observed at high doses of roflumilast. No other treatment-related neoplastic findings were observed. Overall, the tumor-free level in the animals was 4 mg/kg/day. The significance of this finding to humans is unknown.

Genotoxicity

Roflumilast did not reveal a genotoxic potential in a standard battery of genotoxicity assays *in vitro* and *in vivo* (Ames test, E coli bacterial gene mutation test, gene mutation test in V79 Chinese Hamster cells, unscheduled DNA-synthesis test, cytogenetic study with human lymphocytes micronucleus test) assessing different genetic endpoints.

Reproductive Toxicity

Roflumilast was not teratogenic in rats and rabbits following oral administration up to the highest doses of 1.8 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. Administered at the same doses, roflumilast has been shown to induce mild retardation of embryo-fetal development (incomplete ossification) in the rat, but not in the rabbit. Exposure of pregnant rats to unbound roflumilast and roflumilast N-oxide was 1.7 and 10.8 times higher, respectively, than exposure of women at the 500 mcg roflumilast dose. In one of three rat studies on fertility and embryo-fetal-development, post-implantive losses were observed at oral doses of 0.6 mg/kg/day and 1.8 mg/kg/day. Post-implantive losses were not seen in rabbits up to doses of 0.8 mg/kg/day. Rat and rabbit fetuses were exposed to roflumilast and the permeability of the placental barrier for drug-related material increased with the progression of pregnancy. Prolongation of gestation was seen in mice due to a potential tocolytic effect.

There was no effect on female fertility up to the highest roflumilast dose of 1.5 mg/kg/day in rats. Slight reduction in male fertility was seen in conjunction with epididymal toxicity in rats dosed with 1.8 mg/kg/day (about 2.2 and 8.8 times human exposure to unbound roflumilast and roflumilast N-oxide, respectively). This finding is not considered relevant to humans (see TOXICOLOGY, Chronic Toxicity).

REFERENCES

Bundschuh DS, Eltze M, Barsig J, Wollin L, Hatzelmann A et al. In Vivo Efficacy in Airway Disease Models of Roflumilast, a Novel Orally Active PDE4 Inhibitor. The Journal of Pharmacology and Experimental Therapeutics 2001; 297: 280-290.

Calverley PMA, Sanchez-Toril F, McIvor A, Teichmann P, Bredenbroeker D et al. Effect of 1-Year Treatment with Roflumilast in Severe Chronic Obstructive Pulmonary Disease. American Journal of Critical Care Medicine 2007; 176: 154-161.

Calverley PMA, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomized clinical trials. Lancet 2009;374:685-94.

Fabbri LM, Calverley PMA, Izquierdo-Alonso JL, Bundschuh DS, Brose M et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long acting bronchodilators: two randomised clinical trials. Lancet 2009;374:695-703.

Grootendorst DC, Gauw SA, Verhoosel RM, Sterk PJ, Hospers JJ et al. Reduction in sputum neutrophil and eosinphil numbers by the PDE4 inhibitor roflumilast in patients with COPD. Thorax 2007; 62: 1081-1087.

Hatzelmann A, Schudt C. Anti-Inflammatory and Immunomodulatory Potential of the Novel PDE4 Inhibitor Roflumilast in Vitro. The Journal of Pharmacology and Experimental Therapeutics 2001; 297: 267-279.

Hohlfeld JM, Schoenfeld K, Lavae-Mokhtari M, Schaumann F, Jueller Meike et al. Roflumilast attenuates pulmonary inflammation upon segmental endotoxin challenge in healthy subjects. A randomized placebo-controlled trial. Pulmonary Pharmacology & Therapeutics 2008; 21: 616-623.

Martorana P, Beume R, Lucattelli M, Wollin L, Lungarella G. Roflumilast Fully Prevents Emphysema in Mice Chronically Exposed to Cigarette Smoke. American Journal of Critical Care Medicine 2005; 172: 848-853.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrDAXAS®

roflumilast film-coated tablets

This leaflet is part III of a three-part "Product Monograph" published when DAXAS® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DAXAS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DAXAS is an anti-inflammatory medicine taken orally to treat chronic obstructive pulmonary disease (COPD) in adults with a history of chronic coughing with phlegm and frequent flare-ups. DAXAS is only used in addition to a bronchodilator medication. COPD is a progressive condition that causes tightening (narrowing) of breathing tubes (airways), and swelling and irritation (inflammation) of the walls of the small airways deep inside the lungs. Ongoing obstruction and inflammation in airways leads to symptoms such as coughing, wheezing, chest tightness or difficulty in breathing that get worse over time. Patients with COPD also have flare-ups (exacerbations) where symptoms suddenly get worse. Additional medications, emergency visits or hospitalization may be required to treat flare-up episodes.

What it does:
DAXAS contains the active substance roflumilast, which is an anti-inflammatory medicine called a phosphodiesterase 4 inhibitor. DAXAS reduces the activity of phosphodiesterase 4, which results in less inflammation in the lungs. This helps to stop the narrowing of airways which occurs in COPD.

When it should not be used:
Do not take DAXAS if:
- you are allergic (hypersensitive) to roflumilast or any of the other ingredients of DAXAS (see below What the nonmedicinal ingredients are).
- you have moderate or severe liver disease.

What the medicinal ingredient is:
Roflumilast

What the nonmedicinal ingredients are:
Hypromellose, yellow iron oxide, lactose monohydrate, macrogol, maize starch, magnesium stearate, povidone and titanium dioxide

What dosage forms it comes in:
Film-coated tablets 500 mcg
The tablets are yellow and D-shaped. They are marked with a 'D' on one side.

WARNINGS AND PRECAUTIONS

BEFORE you use DAXAS talk to your doctor or pharmacist if:
- you are pregnant or planning to become pregnant. Female patients who can get pregnant should use effective methods of birth control while receiving DAXAS.
- you are breast-feeding.
- you have liver disease.
- you have a history of depression linked to suicidal thoughts or behaviour.
- you are taking other medicines at the same time.
- you are under 18 years of age.
- you have a fast and/or irregular heart beat or pulse.

Take DAXAS only once a day, but be sure to take it every day.

You should immediately inform your doctor if you start to have any suicidal thoughts.

You should check your body weight on a regular basis. Talk to your doctor if you observe an unintentional loss of body weight (not related to a diet or exercise program).

DAXAS is not recommended for use in patients under 18 years of age.

DAXAS is not intended for the treatment of a sudden attack of breathlessness. In order to relieve a sudden attack of breathlessness it is very important that your doctor provides you with another medication to be available to you at all times that can cope with such an attack. DAXAS will not help you in this situation.

You must take DAXAS as add-on therapy to a daily bronchodilator treatment. Always follow your doctor's orders.

DAXAS is not recommended for patients having severe immunological diseases (such as HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy, and others), severe acute infectious diseases (such as tuberculosis, or acute hepatitis), cancer (except basal-cell carcinoma, a slow-growing type of skin cancer), or severe impairment of heart function. You should talk to your doctor, if you are diagnosed with any of these diseases.

Severe allergic reactions can occur when you use DAXAS. In the rare case of severe allergic reaction, stop taking DAXAS and contact your doctor immediately, or go immediately to the emergency department in the nearest hospital. Take your medication and this leaflet with you to provide full information for your proper treatment.

INTERACTIONS WITH THIS MEDICATION

DAXAS may be taken simultaneously with other medicines used in the treatment of COPD such as inhaled bronchodilators, inhaled combination bronchodilator/corticosteroids and short-term oral corticosteroids. DAXAS works in addition to your bronchodilator medications. It works in a different way to provide additional improvement to your breathing ability and increased protection against exacerbations. Do not stop taking any of your breathing medicines or reduce their dose unless advised by your doctor.

Please let your doctor know before you start to take DAXAS if you already take medicine containing erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine or take medicine used for treatment of immunological diseases, such as methotrexate, azathioprine, infliximab, etanercept, or oral corticosteroids to be taken long-term.

The effect of DAXAS may be reduced if taken together with rifampicin (an antibiotic medicine) or with phenobarbital, carbamazepine or phenytoin (medicines usually prescribed for the treatment of epilepsy). Ask your doctor for advice before you start to take DAXAS.

To look after you properly, it is important for your doctor to know about all medications you are taking, including those for your COPD. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including prescription medicines, medicines obtained without a prescription and natural health products.

PROPER USE OF THIS MEDICATION

Usual dose:
Always take DAXAS exactly as your doctor has told you. You should check with your doctor or pharmacist if you have any questions about how to take DAXAS.

- The usual dose is one 500 microgram tablet taken orally once daily. Do not take more tablets than your doctor has recommended.
- Swallow the tablet with some water.
- You may take this medicine with or without food.
- Take the tablet at the same time every day.

You cannot see or feel the inflammation that is occurring deep inside your lungs that DAXAS works to reduce. This is why it is important to continue taking DAXAS for as long as prescribed by your doctor, even if you have no symptoms or feel no immediate benefit from taking DAXAS. This will help to maintain control of your lung function and help protect you from exacerbations.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you forget to take a tablet at the usual time, take the tablet as soon as you remember. If on one day you have forgotten to take a tablet of DAXAS, just carry on the next day with the next tablet as usual. Continue taking your medicine at the usual times. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like most prescription medicines, DAXAS can cause some side effects including nausea, dizziness, tremor and abdominal pain. Patients who experienced these side effects found they mainly occurred within the first weeks of therapy and resolved on continued treatment. Tell your doctor or pharmacist if any of these side effects become bothersome to you or persist (do not go away after the first few weeks of treatment).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical assistance
		Only if severe	In all cases	
Very common	Diarrhea	X		
Common	Anxiety		X	
	Depressive mood		X	
	Headache	X		
	Irregular heart beat		X	
	Sleeplessness	X		
	Weight decrease	X		
Uncommon	Allergic reactions, symptoms include: difficulty swallowing or breathing, rash, hives, swelling of the face, lips, or throat.			X
Rare	Nervousness	X		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical assistance
		Only if severe	In all cases	
	Suicidal thinking and behaviour		X	

This is not a complete list of side effects. For any unexpected effects while taking DAXAS, contact your doctor or pharmacist.

HOW TO STORE IT

Store DAXAS between 15-30°C.

Keep out of the reach and sight of children.

Do not use DAXAS after the expiry date which is stated on the carton and blister (EXP). The expiry date refers to the last day of that month.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

The Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: www.astrazeneca.ca,
or by contacting the sponsor, AstraZeneca Canada Inc. at:
Questions or concerns: 1-800-668-6000.

This leaflet was prepared by:
AstraZeneca Canada Inc. Mississauga, Ontario L4Y 1M4

DAXAS® is a registered trademark of Takeda GmbH, used under license by AstraZeneca Canada Inc.

The AstraZeneca logo is a registered trademark of AstraZeneca AB, used under license by AstraZeneca Canada Inc.

Last revised: January 19, 2017