

ANNEX I
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: This product contains 199 mg lactose monohydrate per film-coated tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow, D-shaped film-coated tablet, 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) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet of 500 micrograms roflumilast once daily.

Daxas may need to be taken for several weeks to achieve its effect (see section 5.1). Daxas has been studied in clinical trials for up to one year.

Special populations

Elderly (65 years and older)

No dose adjustment is necessary.

Renal impairment

No dose adjustment is necessary.

Hepatic impairment

The clinical data with Daxas 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 should not take Daxas (see section 4.3).

Paediatric population

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

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 roflumilast or to any of the excipients (see 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 and should be given a patient card before starting Daxas.

Rescue medicinal products

Roflumilast is an anti-inflammatory substance indicated for maintenance treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. It 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 Daxas compared to placebo-treated patients. After discontinuation of Daxas, 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 Daxas should be stopped and body weight should be further followed-up.

Special clinical conditions

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), 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

Daxas is associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression. Rare instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials (see section 4.8). Therefore, the risks and benefits of starting or continuing treatment with Daxas 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. Patients should be instructed to notify their prescriber of any changes in behavior or mood and of any suicidal ideation. Moreover, Daxas is not recommended in patients with a history of depression associated with suicidal ideation or behavior.

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 black, non-smoking females (see section 5.2) or in patients concomitantly treated with the CYP1A2 inhibitor fluvoxamine or the dual CYP3A4/1A2 inhibitors enoxacin and cimetidine (see section 4.5).

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

Daxas tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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. Clinical interaction studies with CYP 3A4 inhibitors erythromycin and ketoconazole showed increases of 9% of the total PDE4 inhibitory activity (i.e. total exposure to roflumilast and roflumilast N-oxide). Interaction studies with CYP1A2 inhibitor fluvoxamine, and the dual CYP3A4/1A2 inhibitors enoxacin and cimetidine resulted in increases of the total PDE4 inhibitory activity of 59%, 25% and 47%, respectively. A combination of Daxas with these active substances might lead to an increase of exposure and persistent intolerability. In this case, Daxas 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 inducers (e.g. phenobarbital, carbamazepine, phenytoin) may reduce the therapeutic efficacy of roflumilast.

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 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

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). Daxas is not recommended during pregnancy and in women of childbearing potential not using contraception.

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 suckling child cannot be excluded. Daxas 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

In clinical COPD studies, approximately 16% of patients experienced adverse reactions with roflumilast (compared to 5% in placebo). The most commonly reported adverse reactions were diarrhoea (5.9%), weight decreased (3.4%), nausea (2.9%), abdominal pain (1.9%) and headache (1.7%). The majority of these adverse reactions were mild or moderate. These adverse reactions mainly occurred within the first weeks of therapy and mostly resolved on continued treatment.

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

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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

Frequency	Common	Uncommon	Rare
System Organ Class			
Immune system disorders		Hypersensitivity	
Endocrine disorders			Gynaecomastia
Metabolism and nutrition disorders	Weight decreased Decreased appetite		
Psychiatric disorders	Insomnia	Anxiety	Depression Nervousness
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	Haematochezia Constipation

Frequency	Common	Uncommon	Rare
System Organ Class			
		reflux disease Dyspepsia	
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	

In clinical studies, rare instances of suicidal thinking and behavior (including completed suicide) were reported. Patients should be instructed to notify their prescriber of any suicidal ideation (see also section 4.4).

4.9 Overdose

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.

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 agent 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, tumor 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

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 randomized and treated of whom 2,374 were treated with Daxas. 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 [FEV₁ (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, Daxas 500 micrograms once daily significantly improved lung function compared to placebo, on average by 48 ml (pre-bronchodilator FEV₁, primary endpoint, $p < 0.0001$), and by 55 ml (post-bronchodilator FEV₁, $p < 0.0001$). 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 Daxas 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 randomized 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. Daxas 500 micrograms once daily significantly improved lung function compared to placebo, on average by 51 ml (pre-bronchodilator FEV₁, $p < 0.0001$), and by 53 ml (post-bronchodilator FEV₁, $p < 0.0001$). 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 FEV₁ 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.

No study has been conducted to compare Daxas to the combination of LABA plus inhaled corticosteroids or on top of the combination of LABA plus inhaled corticosteroids.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Daxas 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 radiolabeled 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 radiolabeled 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 elderly, 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, Daxas treatment should be reassessed (see 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 Daxas 250 micrograms once-daily was tested in 8 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 Daxas 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 Daxas (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

Core

Lactose monohydrate

Maize starch

Povidone (K90)

Magnesium stearate

Coating

Hypromellose 2910

Macrogol 4000

Titanium dioxide (E171)

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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 10, 30, or 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Nycomed GmbH

Byk-Gulden-Straße 2

D-78467 Konstanz

Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Nycomed GmbH
Production Site Oranienburg
Lehnitzstrasse 70-98
D-16515 Oranienburg
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to prescribe Daxas are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet for Daxas
- Educational material for the physician.
- Copies of the patient card to be given to patients before they receive Daxas

The educational material for the prescriber should include information on the following key elements:

- The specific indication approved. The fact that Daxas is not indicated for the treatment of COPD patients other than those covered by the approved indication, nor for use in patients with asthma or alpha 1 anti trypsin deficiency.
- The need to inform patients about the risks of Daxas and the precautions for safe use
- The risk of weight decrease in underweight patients and the need to monitor the body weight at each visit and to stop the treatment in the event of an unexplained and clinically concerning weight decrease. Patients should be advised to weigh themselves at regular intervals and record the weight in the patient card.
- The risk of psychiatric disorders such as insomnia, anxiety, depression in patients receiving Daxas and the potential risk of suicide. Hence, the need to carefully assess the benefit risk balance of this treatment in patients with existing psychiatric symptoms or with history of depression and to inform patients to report any changes in behaviour, mood and any suicidal ideation. Daxas is not recommended in patients with a history of depression associated with suicidal ideation or behaviour.

- The potential risk of malignant tumours and the lack of experience in patients with past history of cancer. Daxas should not be initiated or should be stopped in patients with cancers (except basal cell carcinoma).
- That increased exposure might occur in certain populations and increase the risk of persistent intolerability:
 - Special populations who have increased PDE4 inhibition such as black non smoking females
 - Patients concomitantly treated with CYP1A2 inhibitors (such as fluvoxamine) or dual CYP3A4/1A2 inhibitors (such as enoxacin and cimetidine)
- The potential risk of infections: Daxas should not be initiated, or treatment should be stopped, in patients with severe acute infectious diseases. The limited experience in patients with latent infections such as tuberculosis, viral hepatitis or herpes infections.
- The lack of experience in patients with HIV infection or active hepatitis, with severe immunological diseases (e.g. multiple sclerosis, lupus erythematosus, multifocal leukoencephalopathy) or treated with immunosuppressive therapy (other than short-term systemic corticosteroids) and that Daxas should not be initiated or should be stopped in these patients.
- The potential cardiac risk: Daxas has not been studied in patients in congestive heart failure (NYHA grade 3 and 4); hence, it is not recommended in this population.
- The limited or missing information in patients with liver impairment. Daxas is contraindicated in patients with moderate or severe liver impairment (Child Pugh B or C). Clinical data are considered insufficient to recommend dose adjustment and caution should be observed in patients with mild liver impairment (child Pugh A).
- The lack of clinical data to support the combination with theophylline and that such combination is not recommended.

Patient Card

The patient card should contain the following key elements:

That they should tell their doctor if they have a history of any of the following conditions

- cancer
- insomnia, anxiety, depression, suicidal ideation or behaviour
- multiple sclerosis or SLE
- infection with tuberculosis, herpes, hepatitis, HIV

That patients should tell their doctor if they develop symptoms indicative of:

- insomnia, anxiety, depression, suicidal ideation or behaviour
- severe infection

That patients should tell their doctor if they are taking any other medicines.

That Daxas may cause weight loss and patients should weigh themselves regularly and record their weight on the patient card.

The patient card should include an area where patients can record their weight and the date they weighed themselves and they should be asked to bring the patient card with them at each visit.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 1.0 dated 28 April 2009 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 6.0 dated 21 April 2010 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Daxas 500 micrograms film-coated tablets
roflumilast

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 micrograms roflumilast.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nycomed GmbH
Byk-Gulden-Straße 2
D-78467 Konstanz
Germany

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Daxas 500

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Daxas 500 micrograms tablets
roflumilast

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Nycomed

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Daxas 500 micrograms film-coated tablets Roflumilast

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Daxas is and what it is used for
2. Before you take Daxas
3. How to take Daxas
4. Possible side effects
5. How to store Daxas
6. Further information

1 WHAT DAXAS IS AND WHAT IT IS USED FOR

Daxas contains the active substance roflumilast, which is an anti-inflammatory medicine called phosphodiesterase 4 inhibitor. Roflumilast reduces the activity of phosphodiesterase 4, a protein occurring naturally in body cells. When the activity of this protein is reduced, there is less inflammation in the lungs. This helps to stop narrowing of airways occurring in chronic obstructive pulmonary disease (COPD). Thus Daxas eases breathing problems.

Daxas is used to treat severe COPD in adults. COPD is a chronic disease of the lungs that results in tightening of the airways (obstruction) and swelling and irritation of the walls of the small air passages (inflammation) leading to symptoms such as coughing, wheezing, chest tightness or difficulty in breathing. Daxas is to be used in addition to bronchodilators.

2 BEFORE YOU TAKE DAXAS

Do not take Daxas

- if you are allergic (hypersensitive) to roflumilast or any of the other ingredients of Daxas (listed in section 6 'What Daxas contains')
- if you have moderate or severe liver disease.

Take special care with Daxas

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

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

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 the heart function, due to

lack of relevant experience with Daxas under these conditions. You should talk to your doctor, if you are diagnosed with any of these diseases.

Experience is also limited in patients with a previous diagnosis of tuberculosis, viral hepatitis, herpes viral infection or herpes zoster.

You may experience diarrhoea, nausea, abdominal pain or headache during the first weeks of treatment with Daxas. Talk to your doctor if these side effects do not resolve within the first weeks of treatment.

You may also experience sleeplessness, anxiety, nervousness, or depressive mood. Before starting treatment with Daxas, inform your doctor if you are suffering from any symptoms of this kind and of any additional medicinal products you may take since some of those could increase the probability of these side effects. You should also immediately inform your doctor of any suicidal thoughts you may have.

Children

Daxas should not be used by children and adolescents under 18 years of age.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Daxas may be taken with other medicines used in the treatment of COPD such as inhaled or oral corticosteroids or bronchodilators. Do not stop taking these 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:

- a medicine containing theophylline (a medicine to treat respiratory diseases), or
- a medicine used for treatment of immunological diseases, such as methotrexate, azathioprine, infliximab, etanercept, or oral corticosteroids to be taken long-term.
- a medicine containing fluvoxamine, enoxacin or cimetidine.

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.

Taking Daxas with food and drink

You may take this medicine with or without food.

Pregnancy and breast-feeding

Do not take Daxas if you are or plan to become pregnant, think you may be pregnant, or are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

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

Important information about some of the ingredients of Daxas

Daxas tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3 HOW TO TAKE DAXAS

Always take Daxas exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one 500 micrograms tablet 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 may need to take Daxas for several weeks to achieve its beneficial effect.

If you take more Daxas than you should

Tell your doctor or pharmacist straight away. If possible take your medicine and this leaflet with you.

If you forget to take Daxas

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 stop taking Daxas

It is important to continue taking Daxas for as long as prescribed by your doctor, even when you have no symptoms, in order to maintain control of your lung function.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Daxas can cause side effects, although not everybody gets them.

Side effects may occur with certain frequencies, which are defined as follows:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Common side effects

Weight decrease, decreased appetite; sleeplessness; headache; diarrhoea, nausea, stomach ache.

Uncommon side effects

Hypersensitivity (a generalised allergic reaction that may affect the skin, mouth and tongue, possibly leading to difficulties in breathing and/or a drop in blood pressure and accelerated heartbeat); feeling anxious; trembling, sensation of spinning head (vertigo), dizziness; sensation of rapid or irregular heartbeat (palpitations); gastritis, vomiting, reflux of stomach acid to the gullet (acid regurgitations), indigestion; rash; muscle pain or cramps; back pain; feeling of weakness or tiredness; feeling unwell.

Rare side effects

Male breast enlargement; feeling nervous or depressed; decreased sense of taste; respiratory tract infections (excluding pneumonia); bloody stools, constipation; elevation of liver or muscle enzymes (seen in blood tests); wheals (urticaria).

In the rare case of a severe allergic reaction, stop taking Daxas and contact your doctor immediately, or go immediately to the emergency department in the nearest hospital. Take your medicine and this leaflet with you to provide full information of your proper treatment. Typical symptoms of a severe allergic reaction are: swelling of the face, lips, mouth, tongue and/or throat, which may cause difficulty in swallowing or breathing, hives (nettle rash), severe dizziness with very fast heartbeat and heavy sweating.

In clinical studies, some instances of suicidal thinking and behavior (including suicide) were reported. Please notify your doctor immediately of any suicidal thoughts you may have.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DAXAS

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 after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Daxas contains

- The active substance is roflumilast. Each film-coated tablet (tablet) contains 500 micrograms roflumilast.
- The other ingredients are:
 - Core: lactose monohydrate, maize starch, povidone (K90), magnesium stearate,
 - Coating: hypromellose 2910, Macrogol 4000, titanium dioxide (E171), and iron oxide yellow (E172).

What Daxas looks like and contents of the pack

Daxas 500 micrograms film-coated tablets are yellow, D-shaped film-coated tablets, embossed with 'D' on one side.

Each PVC/PVDC aluminium blister pack contains 10, 30, or 90 film-coated tablets.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>