Assessment report for

Libertek

International Nonproprietary Name: roflumilast

Procedure No. EMEA/H/C/002399

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

CHMP:	Committee for Medicinal Products for Human Use.
COPD:	Chronic Obstructive Pulmonary Disease.
eCTD:	electronic Common Technical Document.
EEA:	European Economic Area.
FEV1:	Forced Expiratory Volume in one second.
GMP:	Good Manufacturing Practice.
MA:	Marketing Authorisation.
MAA:	Marketing Authorisation Application.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Nycomed GmbH submitted on 30 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Libertek, through the centralised procedure under Article 3 (2) (a) or of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20-23 September 2010.

The applicant applied for the following indication treatment of chronic obstructive pulmonary disease (COPD).

The legal basis for this application refers to Article 10(c) of Directive 2001/83/EC, as amended – relating to informed consent from a marketing authorisation holder for an authorised medicinal product

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH, Nycomed GmbH, allowing the cross reference to relevant quality, non-clinical and clinical data.

Information on Paediatric requirements

Not applicable

Scientific Advice:

Not applicable.

Licensing status

The initial product Daxas, has been given a Marketing Authorisation in: European Union, Iceland, Liechtenstein, Norway.

Pending: Australia, Brazil, Canada, Korea, Malaysia, New Zealand, Philippines, Russia, South Africa, Switzerland, Turkey, USA, Venezuela.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Gonzalo Calvo Rojas** Co-Rapporteur: **David Lyons**

- The application was received by the EMA on 30 September 2010.
- The procedure started on 17 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 November 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 November 2010.
- During the meeting on 13-16 December 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Libertek on 16 December 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 December 2010.

2. Scientific discussion

2.1. Introduction

Roflumilast is a selective phosphodiesterase type 4 (PDE4) inhibitor. PDE4 is an important regulator of cyclic AMP in most cell types involved in inflammatory processes. Inhibition of PDE4 reduces the breakdown of cAMP, which in turn down-regulates the inflammatory process.

This Marketing Authorisation Application has been submitted as an informed consent application to the marketing authorisation for Daxas in accordance with Article 10c of Directive 2001/83/EC as amended. Therefore, consent from the marketing authorisation holder of the Daxas application, which had been submitted as a full application under Art 8(3) of Directive 2001/83/EC as amended, has been given allowing access to Module 2 to Module 5 of the initial dossier of this authorised product and any subsequent postmarketing procedures submitted, assessed and approved. The application for Libertek consists only of Module 1 information

As a consequence, quality, safety and efficacy of the Libertek medicinal product are identical to the up-to-date quality, safety and efficacy profile of Daxas. Information on the scientific discussions can be found in the Daxas CHMP assessment report and in the European Public Assessment Report (EPAR).

Libertek 500 micro-grams film-coated tablets is indicated for the 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 bron-chodilator treatment.

The medicinal product is a film-coated tablet containing 500 microgram roflumilast. The recommended dose is one 500 microgram tablet once daily.

2.2. Quality aspects

Since the application is an informed consent of the Daxas marketing authorisation, the quality data in support of the Libertek application are identical to the up-to-date quality data of the Daxas dossier which have been assessed and approved (including all post-marketing procedures).

2.3. Non-clinical aspects

Since this application is an informed consent of the Daxas marketing authorisation, the non-clinical data in support of the Libertek application are identical to the up-to-date non-clinical data of the Daxas dossier, which have been assessed and approved (including all post-marketing procedures).

2.3.1. Ecotoxicity/environmental risk assessment

An environmental risk assessment has been provided in 1.6.1 Non-GMO. The Applicant refers to the Guideline on the environmental risk assessment of medicinal products for human use (June 2006, EMEA/CHMP/SWP/4447/00) to demonstrate that on the basis of the data provided it is not considered that roflumilast has a risk to the environment.

Roflumilast is highly metabolized, with no parent compound detected in urine. Low dosages result in a PEC (0.0025 µg/L) below the action limit of 0.01 µg/L, and acute short-term studies from each of the 3 trophic levels (fish, Daphnia, algae) show, that the algae is the most sensitive species. The derived PNEC is 0.024 µg/L and the PEC/PNEC ratio is below 1 (0.104). Furthermore, the log P (o/w) was also found to be below the action limit. A comparison of calculated plasma levels in fish with those measured at NOAELs in rats showed sufficient safety margins towards adverse reproductive effects. Thus, it is concluded that the use of roflumilast is unlikely to represent a risk to the environment following its prescribed usage in patients, and no further actions have to be taken.

2.4. Clinical aspects

Since this application is an informed consent of the Daxas marketing authorisation, the clinical data in support of the Libertek application are identical to the up-to-date clinical data of the Daxas dossier, which have been assessed and approved (including all post-marketing procedures).

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risk		
Weight decrease	Routine PV Close follow-up of reported cases and special section in PSUR. Long-term comparative observational post-marketing study	Section 4.4 of the SmPC: In 1-year studies (M2-124, M2-125), a decrease of body weight occurred more frequently in patients treated with Libertek compared to placebo-treated patients. After discontinuation of Libertek, 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 Libertek should be stopped and body weight should be further followed-up. SmPC Section 4.8: Weight decreased is included as common adverse reaction.

		Educational material for prescribers and patients will be distributed.
Psychiatric disorders (insomnia, anxiety, nervousness, depression)	Routine PV	Section 4.4 of the SmPC states that Libertek treatment is associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression and that the risks and benefits of starting or continuing treatment with Libertek should be carefully assessed if patients reported previous or existing psychiatric symptoms or if concomitant treatment with other medications likely to cause psychiatric events is intended. In section 4.8 of the SmPC insomnia is considered as common adverse reaction of roflumilast treatment. Anxiety is labelled as uncommon adverse reaction and nervousness and depression as rare adverse reactions.. Educational material for prescribers and patients will be distributed.
Important potential risk		
Malignant tumours	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Libertek should not be initiated and existing treatment with Libertek should be stopped in patients with cancers (except basal cell carcinoma). Educational material for prescribers and patients will be distributed.
Infections	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Libertek should not be initiated and existing treatment with Libertek should be stopped in patients with severe acute infectious diseases. Experience in patients with latent infections such as tuberculosis, viral hepatits, herpes viral infection or herpes zoster is limited. Educational material for prescribers and patients will be distributed.
Mesenteric vasculitis / ischemic colitis	Routine PV	As no specific risk for mesenteric vasculitis / ischemic colitis has been detected, no risk minimisation activities are deemed necessary.
Cardiac safety	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that patients with congestive heart failure (NYHA grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended. Educational material for prescribers will be distributed.
Risk of triggering suicide	Routine PV Long-term comparative observational post-marketing study Close follow-up of reported cases and special section in PSUR	In section 4.4 of the SmPC a warning is included concerning rare instances of suicidal ideation and behaviour, including completed suicide observed in clinical trials. The risks and benefits of starting or continuing treatment with Libertek should be carefully assessed if

		patients report previous or existing psychiatric symptoms or if concomitant treatment with medicinal products likely to cause psychiatric events is intended. Patients should be instructed to notify their prescriber of any changes in behaviour or mood and of any suicidal ideation. Moreover, Libertek is not recommended in patients with a history of depression associated with suicidal ideation or behaviour. In section 4.8 of the SmPC a statement is included to point out that in clinical studies, rare instances of suicidal thinking and behaviour (including completed suicide) were reported. Patients should be instructed to notify their prescriber of any suicidal ideation. Educational material for prescribers and patients will be distributed.
Serious diarrhoea	Routine PV Long-term comparative observational post-marketing study	Diarrhoea is considered a common adverse reaction of roflumilast treatment (section 4.8 of the SmPC). No reference to serious diarrhoea in the SmPC is deemed necessary. However, as information on serious diarrhoea is limited, further monitoring of events is considered appropriate.
Gynaecomastia	Routine PV	Gynaecomastia is considered a rare adverse reaction of roflumilast treatment (section 4.8 of the SmPC). No further risk minimisation activities are considered necessary.
Persistent intolerability in high-exposure populations	Routine PV	Use of Libertek in populations such as black, non-smoking females, might lead to an increase of exposure and persistent intolerability. In this case, Libertek treatment should be reassessed (see section 4.4 of the SmPC). Educational material for prescribers will be distributed.
Off-label use: Asthma adult Asthma paediatric COPD other than indicated Alpha 1 anti-trypsin deficiency	Routine PV	The proposed indication is defined in section 4.1 of the SmPC as: Libertek is indicated for maintenance treatment of severe COPD (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. Section 4.2 of the SmPC: There is no relevant use of Libertek in the paediatric population (under 18 years). Educational material for prescribers will be distributed.
Important missing/limited information		
Use during pregnancy and lactation	Routine PV Close follow-up of reported cases and special section in PSUR	Section 4.6 of the SmPC: 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). Libertek 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. Libertek should not be used during breast-feeding. Pregnancies will be closely monitored according to established company procedures. Considering the very low likelihood of a pregnancy in the indicated patients, no further risk minimisation activities were considered necessary.
HIV infection or active hepatitis	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Libertek should not be initiated and existing treatment with Libertek should be stopped in patients with severe acute infectious diseases or severe immunological diseases (e.g. HIV infection). Experience in patients with latent infections such as viral hepatitis is limited. Educational material for prescribers and patients will be distributed.
Intake of immunosuppressive medication (excl. short-term systemic corticosteroids)	Routine PV	SmPC section 4.4: Due to lack of relevant experience, treatment with Libertek should not be initiated and existing treatment with Libertek should be stopped in patients being treated with immunosuppressive medicinal products (except short-term systemic corticosteroids). Educational material for prescribers and patients will be distributed.
Severe immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy)	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Libertek should not be initiated and existing treatment with Libertek should be stopped in patients with severe immunological diseases. Educational material for prescribers and patients will be distributed.
Mild, moderate or severe hepatic impairment classified as Child Pugh A, B or C	Routine PV	Sections 4.2, 4.3 of the SmPC state that patients with moderate or severe hepatic impairment classified as Child Pugh B or C, respectively should not take Libertek, i.e. that these patients are contraindicated. Section 4.2 of the SmPC mentions that clinical data are considered insufficient to recommend a dose adjustment for mild hepatic impairment (Child-Pugh A). Caution is thus considered necessary in these patients. Educational material for prescribers will be distributed.

History of malignant tumours	Routine PV	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Libertek should not be initiated and existing treatment with Libertek should be stopped in patients with cancers (except basal cell carcinoma). Educational material for prescribers and patients will be distributed.
Severe heart failure (NYHA grades 3 and 4)	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that patients with congestive heart failure (NYHA grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended. Educational material for prescribers will be distributed.
Severe acute infections or acute relevant lung diseases and lower respiratory tract infections (esp. tuberculosis)	Routine PV Long-term comparative observational post-marketing study	Section 4.4 of the SmPC states that due to lack of relevant experience, treatment with Libertek should not be initiated and existing treatment with Libertek should be stopped in patients with severe acute infectious diseases. Educational material for prescribers and patients will be distributed.
Combination of roflumilast with theophylline for maintenance therapy	Routine PV	Section 4.4 of the SmPC: There are no clinical data to support the concomitant treatment with theophylline for maintenance therapy. Therefore, the concomitant treatment with theophylline is not recommended. Educational material for prescribers and patients will be distributed.
Long-term treatment	Routine PV Long-term comparative observational post-marketing study	Section 4.2 of the SmPC: Libertek has been studied in clinical trials for up to one year. No further risk minimisation activities are considered necessary.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The Member States must ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented in their national territory:

- Prior to launch of the product in the Member State, the national competent authority shall agree the content and format of the educational material with the Marketing Authorisation Holder
- The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to prescribe Libertek are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet for Libertek
- Educational material for the physician.

- Copies of the patient card to be given to patients before they receive Libertek

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

- The specific indication approved. The fact that Libertek 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 trypsine deficiency.
- The need to inform patients about the risks of Libertek 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 Libertek 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. Libertek 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. Libertek 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: Libertek 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 erythematous, multifocal leukoencephalopathy) or treated with immunosuppressive therapy (other than short-term systemic corticosteroids) and that Libertek should not be initiated or should be stopped in these patients.
- The potential cardiac risk: Libertek 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. Libertek 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 Libertek 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

2.6. Recommendation

Since this application is an informed consent of the Daxas marketing authorisation, the CHMP considered that the risk-benefit balance of Libertek was favourable and therefore recommended the granting of the marketing authorisation for the following indication:

Libertek is indicated for the 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.