20 February 2014
EMA/CHMP/175185/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Ulunar Breezhaler

International non-proprietary names: indacaterol / glycopyrronium bromide

Procedure No. EMEA/H/C/003875/0000

Note

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

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Product information

Name of the medicinal product:	Ulunar Breezhaler
Applicant:	Novartis Europharm Ltd Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom
Active substances:	indacaterol maleate / glycopyrronium bromide
International Nonproprietary Names/Common Names:	indacaterol / glycopyrronium bromide
Pharmaco-therapeutic group (ATC Code):	R03AL04: Adrenergics in combination with anticholinergic
Therapeutic indication:	Ulunar Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Pharmaceutical form:	Inhalation powder, hard capsule
Strengths:	85 mcg / 43 mcg
Route of administration:	Inhalation use
Packaging:	blister (PA/Alu/PVC-Alu)
Package sizes:	6 x 1 capsule + 1 inhaler 12 x 1 capsule + 1 inhaler 30 x 1 capsule + 1 inhaler 90 (3 packs of 30 x 1) capsules + 3 inhalers (multipack) 96 (4 packs of 24 x 1) capsules + 4 inhalers (multipack) 150 (25 packs of 6 x 1) capsules + 25 inhalers (multipack)

Table of contents

List of abbreviations

COPD	Chronic Obstructive Pulmonary Disease
EU	European Union
DPI	Dry powder inhaler
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GOLD	Global Initiative For Chronic Obstructive Lung Disease
ICS	Inhaled Corticosteroids
LABA	Long Acting Beta-2 Agonist
LAMA	Long Acting Muscarinic Antagonist
MA	Marketing Authorisation
MAA	Marketing authorisation application
MAH	Marketing Authorisation holder
NVA237	Glycopyrronium bromide
PIL	Patient Information Leaflet
PI	Product Information
q.d.	Once a Day
QAB149	Indacaterol maleate
QVA149	Indacaterol maleate/glycopyrronium bromide
SDDPI	Single Dose Dry Powder Inhaler

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 4 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ulunar Breezhaler, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 October 2013.

The applicant applied for the following indication:

"Ulunar Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)."

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – 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, Novartis Europharm Ltd. allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Ultibro Breezhaler authorised on 19 September 2013 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/5/2008 on the granting of a product-specific waiver and on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Scientific Advice

Not applicable.

Licensing status

The cross-referred product Ultibro Breezhaler as well as the multiple Xoterna Breezhaler were given a Community Marketing Authorisation on 19 September 2013.

1.2. Manufacturers

Manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Jens Heisterberg Co-Rapporteur: David Lyons

- The application was received by the EMA on 4 December 2013.
- The procedure started on 22 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 31 January 2014.
- During the meeting on 20 February 2014, 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 Ulunar Breezhaler.

2. Scientific discussion

2.1. Introduction

Chronic obstructive pulmonary disease (COPD) is an illness characterised by air flow limitation that is not fully reversible. It is usually progressive and is associated with pathological changes in the lung - a combination, varying between individual patients, of obstructive bronchiolitis and parenchymal destruction (emphysema). The most widely accepted classification of the severity of COPD is according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD classification is based on the degree of impairment of lung function. Four categories are recognised: mild, moderate, severe, very severe (Stages I-IV).

The prevalence of COPD in the population is difficult to estimate, but it is a major public health problem and currently the fourth leading cause of chronic morbidity and mortality. Mortality due to COPD is again difficult to estimate, but it appears to be increasing. It is estimated that by 2020, COPD will be the third leading cause of global mortality (GOLD 2009).

The aims of pharmacological treatment in COPD, as described in the GOLD guideline are to prevent and control symptoms, to reduce the frequency and severity of exacerbations, to improve health status, and to improve exercise tolerance. GOLD guidelines recognize that bronchodilators (by reducing airflow limitation) are central to the management of symptoms in COPD and recommend regular use of long-acting bronchodilators for patients with moderate to severe COPD. Within the class of long-acting bronchodilators, long-acting β2 agonists (LABAs) and long-acting antimuscarinic (LAMAs) are available. There are several marketed LABAs such as formoterol, salmeterol, and indacaterol and for the group of LAMAs tiotropium, glycopyrronium bromide and aclidinium bromide are currently available. LABAs and LAMAs as single-agent are recommended first-line treatments in moderate to severe COPD. Combination

treatment with LABA and LAMA is recommended as option by the 2013 version of the GOLD COPD guidelines when symptoms are not improved with single agent in patients classified as group B (low risk, more symptoms). Similarly, the combination of a LABA and a LAMA in addition to an inhaled corticosteroid is recommended as alternative to a single-agent LABA or LAMA plus an inhaled corticosteroid in patients classified as group C (high risk, less symptoms). The GOLD 2013 states that "Both long-acting anticholinergic and long-acting beta 2 agonists reduce the risk of exacerbations, and although good long-term studies are lacking, the principle of combination treatment seems sound" (GOLD 2013).

Ulunar Breezhaler (also referred to as QVA149) is a fixed-dose combination of indacaterol maleate (QAB149) and glycopyrronium bromide (NVA237) (ATC code: R03AL04; Pharmacotherapeutic Group: Adrenergics in combination with anticholinergic) intended as a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with COPD.

QAB149 (indacaterol maleate) is a long-acting beta2-adrenergic agonist (LABA). When inhaled, indacaterol acts locally in the lung as a bronchodilator.

NVA237 (glycopyrronium bromide) is a long acting muscarinic receptor antagonist (LAMA). Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.

Ulunar Breezhaler is to be administered once daily (o.d.) as a capsule via a low resistance single dose dry powder inhaler (SDDPI) also referred to as Concept1 or Breezhaler.

Ulunar Breezhaler is a duplicate application to the marketing authorisation (MA) of Ultibro Breezhaler (EU/1/13/862/001-006) approved in the EU on 19 September 2013. Another duplicate of Ultibro Breezhaler, Xoterna Breezhaler (EU/1/13/863/001-006), was approved at the same time as Ultibro Breezhaler.

The application is submitted in accordance with Regulation (EC) No 726/2004 and is regarded to have automatic access for substances already authorised via Centralised Procedure. Eligibility based on automatic access was confirmed by the CHMP on 24 October 2013.

The legal basis of this application is Article 10c of Directive 2001/83/EC Informed consent application and accordingly a complete Module 1 is submitted. A letter of consent dated on 8 November 2013 from the MAH of Ultibro Breezhaler, which was submitted as a full application under Art 8(3) of Directive 2001/83/EC as amended, has been allowing access to Module 2 to Module 5 of the initial dossier of this authorised product and any subsequent post-marketing procedures submitted, assessed and approved. The Applicant (Novartis Europharm Ltd.) is the marketing authorisation holder of the cross-referred medicinal product Ultibro Breezhaler.

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

The PI is identical to that of Ultibro Breezhaler PI except for the administrative information related to Ulunar Breezhaler-specific information.

2.2. Quality aspects

The present submission is an informed consent application. No additional quality data have been submitted in connection with this application. The manufactures of Ulunar Breezhaler are the

same as for the currently approved Ultibro Breezhaler. Satisfactory GMP certificates have been provided.

2.3. Non-clinical aspects

No non-clinical data have been submitted in the Ulunar Breezhaler dossier, since this application is an informed consent of the Ultibro Breezhaler application: the non-clinical data in support of the Ulunar Breezhaler application are identical to the up-to-date non-clinical data of the Ultibro Breezhaler dossier, which have been assessed and approved.

2.4. Environmental risk assessment

An environmental Risk Assessment has been provided, which is identical to the one that was submitted for Ultibro Breezhaler.

Ulunar Breezhaler is submitted as an informed consent application intended to be administered at the same dose levels as Ultibro Breezhaler and for the same indication as already approved in the EU. Based on the assumption that the product is to be substituted for the identical product Ultibro Breezhaler or the already approved copy Xoterna Breezhaler the total amount of drug substance released into the environment has not changed.

2.5. Clinical aspects

No new clinical data has been provided within this application. The clinical data in support of the Ulunar Breezhaler application is identical to the up-to-date clinical data of the Ultibro Breezhaler dossier which have already been assessed and approved by the CHMP.

2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.7. Risk Management Plan

A RMP version 1.4 was provided with this submission. This RMP version 1.4 is identical to the RMP approved for Ultibro Breezhaler, no further assessment was needed and therefore no PRAC Advice was sought.

Below is a short overview of the content of the Risk Management Plan which is identical to Ultibro Breezhaler:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Important identified risks	QTc prolongation Ischemic heart disease Myocardial infarction Cardiac arrhythmias (Brady- and Tachyarrhythmias) Cardiac failure Cerebrovascular events Hyperglycemia Hypokalemia Narrow-angle glaucoma Bladder obstruction/urinary retention Use in patients with severe renal impairment and end-stage renal disease (ESRD) Paradoxical bronchospasm Interactions with - -Inhibitors of CYP3A4
Important potential risks	Atrial fibrillation Intubation, hospitalization and death due to asthma related events in asthma population (off-label use) Medication error Interactions with: - Inhibitors of P-glycoprotein - Subpopulation with uridine-diphosphate glucuronyl transferase (UGT1A1) deficiency - Drugs known to prolong QTc interval - Sympathomimetic agents - Drugs associated with hypokalemia - Beta-adrenergic blockers
Missing information	Use in unstable, clinically significant cardiovascular conditions Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome Use in patients with type I or uncontrolled type II diabetes Use in patients with severe liver impairment Use in patients with moderate to severe renal impairment Long-term exposure to study medication beyond 18 months Use in COPD not related to smoking or smoking exposure less than 10 pack years Use in pregnancy and lactation Use in patients with ethnic origin other than Caucasian and Asian

Summary table of Risk Minimization Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important Identified risks		

QTc prolongation	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4) Pharmacodynamic properties (section 5.1)	None
Ischemic heart disease	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4) Undesirable effects (SmPC Section 4.8)	None
Myocardial infarction	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4)	None
Cardiac arrhythmias (Brady- and Tachyarrhythmias)	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4)	None
Cardiac failure	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4)	None
Cerebrovascular events	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4)	None
Hyperglycemia	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Hypokalemia	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5). Overdose (SmPC Section 4.9)	None
Narrow-angle glaucoma	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Bladder obstruction/urinary retention	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None

Use in patients with severe renal impairment and end-stage renal disease (ESRD)	Label including Patient Information is sufficient: Posology and method of administration (SmPC Section 4.2) Special warnings and precautions for use (SmPC Section 4.4) Pharmacokinetic properties (SmPC Section 5.2)	None
Paradoxical bronchospasm	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Interaction with Inhibitors of CYP3A4	Label including Patient Information is sufficient. Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5) Pharmacokinetic Properties (SmPC Section 5.2):	None
Important Potential risks		
Atrial fibrillation	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Undesirable Effects (SmPC Section 4.8)	None
Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)	Special warnings and precautions for use (SmPC Section 4.4)	None
Medication error	Label including Patient Information is sufficient. Posology and method of administration (SmPC Section 4.2) INSTRUCTIONS FOR USE OF ULTIBRO BREEZHALER INHALER (part of the Package Leaflet) Patient leaflet (part 3) Package material (outer box)	None
Interaction with inhibitors of P-glycoprotein	Label including Patient Information is sufficient. Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5) Pharmacokinetic Properties (SmPC Section 5.2):	None
Interaction with Subpopulation with uridine-diphosphate glucuronyl transferase (UGT1A1) deficiency	Label including Patient Information is sufficient. Pharmacokinetic Properties (SmPC Section 5.2):	None

Interaction with Drugs known to prolong QTc interval	This important interaction will be monitored and the SmPC will be updated if further information is detected.	None
Interaction with Sympathomimetic agents	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4): Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5)	None
Interaction with Drugs associated with hypokalemia	Label including Patient Information is sufficient: Special warnings and precautions for use (SmPC Section 4.4) Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5).	None
Interaction with Beta-adrenergic blockers	Label including Patient Information is sufficient. Interaction with other medicinal products and other forms of interaction (SmPC Section 4.5).	None
Missing Information		
Use in unstable, clinically significant cardiovascular conditions	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4)	None
Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4)	None
Use in patients with type I or uncontrolled type II diabetes	Label including Patient Information is sufficient. Special warnings and precautions for use (SmPC Section 4.4)	None
Use in patients with severe liver impairment	Label including Patient Information is sufficient. Posology and method of administration (SmPC Section 4.2) Pharmacokinetic properties (SmPC Section 5.2)	None
Use in patients with moderate to severe renal impairment	Label including Patient Information is sufficient. Posology and method of administration (SmPC Section 4.2) Special warnings and precautions for use (SmPC Section 4.4) Pharmacokinetic properties (SmPC Section 5.2)	None
Long-term exposure to study medication beyond 18 months	Label including Patient Information is sufficient. Undesirable effects (SmPC Section 4.8)	None

Use in COPD not related to smoking or smoking exposure less than 10 pack years	This missing information will be monitored and the SmPC will be updated if further information is detected.	None
Use in pregnancy and lactation	Label including Patient Information is sufficient. Fertility, pregnancy and lactation (SmPC Section 4.6) Preclinical safety data (SmPC Section 5.3)	None
Use in patients with ethnic origin other than Caucasian and Asian	Label including Patient Information is sufficient. Pharmacokinetic Properties (5.2)	None

Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
PASS of indacaterol/glycopyrronium in Europe (Category 1)	To assess the incidence rates and relative risks of various adverse events among new users of indacaterol/glycopyrronium with COPD compared to new users of comparator drugs with COPD.	Ischemic heart disease Glaucoma Bladder obstruction/urinary retention Atrial fibrillation Myocardial infarction Cardiac arrhythmias (Brady- and Tachyarrhythmias) Cardiac failure Cerebrovascular events Bronchospasm Diabetes	Planned	Yearly interim reports in parallel with PSURs. Final report at 5 years after drug launch in the first country.
Drug utilization study of indacaterol/glycopyrronium (Category 3): Multinational, multi-database drug utilization study of indacaterol/glycopyrronium bromide in Europe	To assess the characteristics of patients being newly prescribed indacaterol/glycopyrronium with a specific focus on the prevalence of off-label use, and of conditions associated with special warnings and precautions for indacaterol/glycopyrronium use.	Off-label use Use in unstable, clinically significant cardiovascular conditions Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome Use in patients with diabetes Use in patients with liver	Planned	Yearly interim reports in parallel with PSURs. Final report within one year after completion of the study.

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		impairment Use in patients with moderate and severe renal impairment Long-term exposure to study medication beyond 18 months Use in COPD not related to smoking or smoking exposure less than 10 pack years (if available) Use in pregnancy and lactation		

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The CHMP confirmed that no changes are needed for this Risk Management Plan of Ulunar Breezhaler.

2.8. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The Applicant provided the report on the results from the user consultation done for Ultibro Breezhaler. The CHMP considered it acceptable to refer to the user consultation done for Ultibro Breezhaler as the package leaflet is identical and no separate user testing for this informed consent application is considered necessary.

3. Benefit-Risk Balance

3.1. Final overall conclusion and risk benefit assessment

The application has been submitted in accordance with Article 10c of Directive 2001/83/EC as amended (Informed consent Application) under automatic access to the centralised procedure.

Ulunar Breezhaler is identical to Ultibro Breezhaler previously approved by the CHMP. The quality, non-clinical, efficacy and safety data for Ulunar Breezhaler is therefore considered satisfactorily and the benefit-risk profile for Ulunar Breezhaler is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ulunar Breezhaler as a maintenance bronchodilator to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Multinational multi-database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe.	- Protocol submission: 3 months following EU Commission Decision - Final report: Q4 2018.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.