SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Summary of Product Characteristic (SmPC) 1.Name of the medicinal product

Onriva Plus Bexicap

2. Qualitative and quantitative composition

Each capsule contains Glycopyrrolate USP equivalent to Glycopyrronium 50 µg and Indacaterol Maleate INN equivalent to Indacaterol 110 µg.

Excipient with known effect:

Lactose

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dry Powder Inhaler

4. Clinical particulars

4.1. Therapeutic indications

Onriva Plus Bexicap is indicated as a maintenance bronchodilator treatment to relieve symptomsin adult patients with chronic obstructive pulmonary disease (COPD).

4.2. Posology and method of administration

Posology

The recommended dose is the inhalation of the content of one capsule once daily using the Onriva Plus Bexicap inhaler.

Onriva Plus Bexicap is recommended to be administered at the same time of the day each day. Ifa dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day.

Special populations

Elderly population

Onriva Plus Bexicap can be used at the recommended dose in elderly patients (75 years of age and older).

Renal impairment

Onriva Plus Bexicap can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk (see sections 4.4 and 5.2).

Hepatic impairment

Onriva Plus Bexicap can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Onriva Plus Bexicap in patients with severe hepatic impairment, therefore caution should be observed in these patients (see section 5.2).

Paediatric population

There is no relevant use of Onriva Plus Bexicap in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Onriva Plus Bexicap in children have not been established. No data are available.

Method of administration

For inhalation use only. The capsules must not be swallowed.

The capsules must be administered only using the Onriva Plus Bexicap inhaler (see section 6.6). The inhaler provided with each new prescription should be used.

Patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicinal product rather than inhaling it.

For instructions on use of the medicinal product before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Onriva Plus Bexicap should not be administered concomitantly with medicinal products containing other long-acting beta-adrenergic agonists or long-acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Onriva Plus Bexicap belong (see section 4.5).

Asthma

Onriva Plus Bexicap should not be used for the treatment of asthma due to the absence of data inthis indication.

Long-acting beta2-adrenergic agonists may increase the risk of asthmarelated serious adverseevents, including asthma-related deaths, when used for the treatment of asthma.

Not for acute use

Onriva Plus Bexicap is not indicated for the treatment of acute episodes of bronchospasm.

Hypersensitivity

Immediate hypersensitivity reactions have been reported after administration of indacaterol or glycopyrronium, which are the active substances of Onriva Plus

Bexicap . If signs suggesting allergic reactions occur, in particular, angioedema (difficulties in breathing or swallowing, swelling of the tongue, lips and face) urticaria or skin rash, treatment should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

Administration of Onriva Plus Bexicap may result in paradoxical bronchospasm which can be life-threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted.

Anticholinergic effects related to glycopyrronium

Narrow-angle glaucoma

No data are available in patients with narrow-angle glaucoma, therefore Onriva Plus Bexicap should be used with caution in these patients.

Patients should be informed about the signs and symptoms of acute narrowangle glaucoma and should be informed to stop using Onriva Plus Bexicap should any of these signs or symptoms develop.

Urinary retention

No data are available in patients with urinary retention, therefore Onriva Plus Bexicap should beused with caution in these patients.

Patients with severe renal impairment

A moderate mean increase in total system exposure (AUClast) to glycopyrronium of up to 1.4- fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end-stage renal disease. In patients with severe renal impairment (estimated glomerular filtration rate below 30 ml/min/1.73 m^2), including those with end-stage renal disease requiring dialysis, Onriva Plus Bexicap should be used only if the expected benefit outweighs the potential risk (see section 5.2). These patients should be monitored closely for potential adverse reactions.

Cardiovascular effects

Onriva Plus Bexicap should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension).

Beta2-adrenergic agonists may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur with this medicinal product, treatment may need to be discontinued. In addition, betaadrenergic agonists have been reported to produce electrocardiographic (ECG) changes, such as flattening of the T wave, prolongation of QT interval and ST segment depression, although the clinical significance of these observations is unknown. Therefore, long-acting beta2-adrenergic agonists (LABA) or LABA-

containing combination products such as Onriva Plus Bexicap should be used with caution in patients with known or suspected prolongation of the QT interval or treated with medicinal products affecting the QT interval.

Patients with unstable ischaemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation), a history of long QT syndrome or whose QTc (Fridericia method) was prolonged (>450 ms) were excluded from the clinical trials, and therefore there is no experience in these patient groups. Onriva Plus Bexicap should be used with caution in these patient groups.

Hypokalaemia

Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has thepotential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias (see section 4.5)

Clinically relevant effects of hypokalaemia have not been observed in clinical studies of OnrivaPlus Bexicap at the recommended therapeutic dose (see section 5.1).

Hyperglycaemia

Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onriva Plus Bexicap plasma glucose should be monitored more closely in diabetic patients.

During long-term clinical studies, more patients on Onriva Plus Bexicap experienced clinically notable changes in blood glucose (4.9%) at the recommended dose than on placebo (2.7%). Onriva Plus Bexicap has not been investigated in patients for whom diabetes mellitus is not well controlled, therefore caution and appropriate monitoring are advised in such patients.

General disorders

Onriva Plus Bexicap should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists.

Excipients

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

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant administration of orally inhaled indacaterol and glycopyrronium, under steady-stateconditions of both active substances, did not affect the pharmacokinetics of either active substance.

No specific interaction studies were conducted with Onriva Plus Bexicap. Information on the potential for interactions is based on the potential for each of its two active substances.

Concomitant use not recommended

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta2adrenergic agonists. Therefore Onriva Plus Bexicap should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective betaadrenergic blockers should be preferred, although they should be administered with caution.

Anticholinergics

The co-administration of Onriva Plus Bexicap with other anticholinergiccontaining medicinal products has not been studied and is therefore not recommended (see section 4.4).

Sympathomimetics

Concomitant administration of other sympathomimetics (alone or as part of combination therapy) may potentiate the adverse events of indacaterol (see section 4.4).

Caution required with concomitant use

Hypokalaemic treatment

Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non- potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution (see section 4.4).

To be taken into account with concomitant use

Metabolic and transporter-based interactions

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and Pglycoprotein (P-gp), raises the systemic exposure of indacaterol up to twofold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose.

Cimetidine or other inhibitors of organic cation transport

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport which is thought to contribute to the renal excretion of

glycopyrronium, increased total exposure (AUC) to glycopyrronium by 22% and decreased renal clearance by 23%. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of the organic cation transport.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Onriva Plus Bexicap in pregnant women available. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3).

Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Onriva Plus Bexicap should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Breast-feeding

It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. Available pharmacokinetic/toxicological data have shown excretion of indacaterol, glycopyrronium and their metabolites in the milk of lactating rats. The use of Onriva Plus Bexicap by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant (see section 5.3).

Fertility

Reproduction studies and other data in animals do not indicate a concern regarding fertility ineither males or females.

4.7. Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive and use machines. However, the occurrence of dizziness may influence the ability to drive and use machines (see section 4.8).

4.8. Undesirable effects

The presentation of the safety profile is based on the experience with Onriva Plus Bexicap and the individual active substances.

Summary of the safety profile

The safety experience with Onriva Plus Bexicap was comprised of exposure of up to 15 months at the recommended therapeutic dose.

Onriva Plus Bexicap showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination.

The safety profile is characterised by typical anticholinergic and betaadrenergic symptoms related to the individual components of the combination. Other most

common adverse reactions related to the medicinal product (at least 3% of patients for Onriva Plus Bexicap and also greaterthan placebo) were cough, nasopharyngitis and headache.

Tabulated summary of adverse reactions

Adverse reactions detected during clinical trials and from post-marketing sources are listed by MedDRA system organ class (Table 1). Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the correspondingfrequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000,

<1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse reactions	Frequency category
Infections and infestations	
Upper respiratory tract infection	Very common
Nasopharyngitis	Common
Urinary tract infection	Common
Sinusitis	Common
Rhinitis	Common
Immune system disorders	
Hypersensitivity	Common
Angioedema2	Uncommon
Metabolism and nutrition disorders	
Hyperglycaemia and diabetes mellitus	Common
Psychiatric disorders	
Insomnia	Uncommon
Nervous system disorders	
Dizziness	Common
Headache	Common
Paraesthesia	Rare
Eye disorders	
Glaucoma1	Uncommon
Cardiac disorders	
Ischaemic heart disease	Uncommon
Atrial fibrillation	Uncommon
Tachycardia	Uncommon
Palpitations	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Oropharyngeal pain including throat irritation	Common
Paradoxical bronchospasm	Uncommon

Dysphonia2	Uncommon
Epistaxis	Uncommon
Gastrointestinal disorders	
Dyspepsia	Common
Dental caries	Common
Gastroenteritis	Uncommon
Dry mouth	Uncommon
Skin and subcutaneous tissue disorders	
Pruritus/rash	Uncommon
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain	Uncommon

Muscle spasm	Uncommon
Myalgia	Uncommon
Pain in extremity	Uncommon
Renal and urinary disorders	
Bladder obstruction and urinary retention	Common
General disorders and administration site conditions	
Pyrexia1	Common
Chest pain	Common
Oedema peripheral	Uncommon
Fatigue	Uncommon

[1] Adverse reaction observed with Onriva Plus Bexicap , but not with the individual components.

[2] Reports received from post-marketing experience; frequencies calculated, however, on thebasis of clinical trial data.

Description of selected adverse reactions

Cough was common, but usually of mild intensity.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the PPB website

https://pv.pharmacyboardkenya.org

4.9. Overdose

There is no information on clinically relevant overdosing with Onriva Plus Bexicap .

An overdose could lead to exaggerated effects typical of beta2-adrenergic stimulants, i.e. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia and

hyperglycaemia or could induce anticholinergic effects such as increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised. Use of cardioselective beta blockers may be considered for treating beta2-adrenergic effects, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blockers may provoke bronchospasm.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics, ATC code: R03AL04

Mechanism of action

Onriva Plus Bexicap

When indacaterol and glycopyrronium are administered together in Onriva Plus Bexicap , they provide additive efficacy due to their different mode of action targeting different receptors and pathways to achieve smooth muscle relaxation. Due to the differential density of beta2- adrenoceptors and M3receptors in central versus peripheral airways, beta2-agonists should be more effective in relaxing peripheral airways, whilst an anticholinergic compound may be more effective in central airways. Thus for bronchodilation in both peripheral and central airways of the human lung a combination of a beta2-adrenergic agonist and a muscarinic antagonist may be beneficial.

Indacaterol

Indacaterol is a long-acting beta2-adrenergic agonist for once-daily administration. The pharmacological effects of beta2-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol has multi-fold greater agonist activity at beta2-receptors compared to beta1 and beta3receptors.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a partialagonist at the human beta2-adrenergic receptor with nanomolar potency.

Although beta2-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-adrenergic receptors are the predominant receptors in the human heart, there are also beta2-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. Their presence in the heart raises the possibility that even highly selective beta2-adrenergic agonists may have cardiac effects.

Glycopyrronium

Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anticholinergic) for once-daily maintenance bronchodilator treatment of COPD. Parasympathetic nerves are the major bronchoconstrictive neural pathway in airways, and cholinergic tone is the key reversible component of airflow obstruction in COPD. Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.

Glycopyrronium bromide is a high affinity muscarinic receptor antagonist. A greater than 4-fold selectivity for the human M3 receptors over the human M2 receptor has been demonstrated usingradioligand binding studies.

Pharmacodynamic effects

The combination of indacaterol and glycopyrronium in Onriva Plus Bexicap showed a rapid onset of action within 5 minutes after dosing. The effect remains constant over the whole 24-h dosing interval.

The mean bronchodilator effect derived from serial FEV1 measurements over 24 h was 320 ml after 26 weeks of treatment. The effect was significantly greater for Onriva Plus Bexicap , when compared to indacaterol, glycopyrronium or tiotropium alone (difference 110 ml, for each comparison). There was no evidence for tachyphylaxis to the effect of Onriva Plus Bexicap over time when compared to placebo or its monotherapy components.

Effects on heart rate

Heart rate effects in healthy volunteers were investigated after a single dose of 4 times the recommended therapeutic dose of Onriva Plus Bexicap administered in four dose steps each separated by one hour and compared to the effects of placebo, indacaterol, glycopyrronium and salmeterol.

The largest time-matched heart rate increase compared to placebo was +5.69 bpm (90% CI [2.71,8.66]), the largest decrease was -2.51 bpm (90% CI [-5.48, 0.47]). Overall the effect on heart rateover time did not show a consistent pharmacodynamic effect of Onriva Plus Bexicap .

Heart rate in COPD patients at supratherapeutic dose levels was investigated. There were no relevant effects of Onriva Plus Bexicap on mean heart rate over 24 h and heart rate assessed after 30 minutes, 4 h and 24h A thorough QT (TQT) study in healthy volunteers with high doses of inhaled indacaterol (up to twice the maximum recommended therapeutic dose) did not demonstrate a clinically relevant effect on the QT interval. Similarly, for glycopyrronium no QT prolongation was observed in a TQT study after an inhaled dose of 8 times the recommended therapeutic dose.

The effects of Onriva Plus Bexicap on QTc interval were investigated in healthy volunteers afterinhalation of Onriva Plus Bexicap up to 4 times the recommended therapeutic dose in four dose steps each separated by one hour. The largest time-matched difference versus placebo was 4.62 ms (90% CI 0.40, 8.85 ms), the largest time-matched decrease was -2.71 ms (90% CI -6.97, 1.54

ms), indicating that Onriva Plus Bexicap had no relevant impact on the QT interval, as was expected by the properties of its components.

In COPD patients, supratherapeutic doses between 116 micrograms/86 micrograms and 464 micrograms/86 micrograms of Onriva Plus Bexicap showed a higher proportion of patients with QTcF increases vs. baseline between 30 ms and 60 ms (ranging from 16.0% to 21.6% vs. 1.9% for placebo), but there were no QTcF increases >60 ms from baseline. The highest dose level of 464 micrograms/86 micrograms Onriva Plus Bexicap also showed a higher proportion ofabsolute QTcF values >450 ms (12.2% vs. 5.7% for placebo).

Serum potassium and blood glucose

In healthy volunteers, after the administration of 4 times the recommended therapeutic dose of Onriva Plus Bexicap , the effect on serum potassium was very small (maximal difference –0.14 mmol/l when compared to placebo). The maximal effect on blood glucose was 0.67 mmol/l.

Clinical efficacy and safety

The Onriva Plus Bexicap clinical Phase III development programme included six studies in which over 8,000 patients were enrolled: 1) a 26-week placeboand active-controlled (indacaterol once daily, glycopyrronium once daily, open-label tiotropium once daily) study; 2) a 26-week active-controlled (fluticasone/salmeterol twice daily) study; 3) a 64-week active- controlled (glycopyrronium once daily, open-label tiotropium once daily) study; 4) a 52week placebo-controlled study; 5) a 3-week placebo- and active-controlled (tiotropium once daily) exercise tolerance study; and 6) a 52-week activecontrolled (fluticasone/salmeterol twice daily) study.

In four of these studies patients were enrolled who had a clinical diagnosis of moderate to severe COPD. In the 64-week study patients were enrolled who had severe to very severe COPD with a history of ≥1 moderate or severe COPD exacerbation in the previous year. In the 52-week active-controlled study, patients were enrolled who had moderate to very severe COPD with a historyof ≥1 moderate or severe COPD exacerbation in the previous year.

Effects on lung function

Onriva Plus Bexicap showed clinically meaningful improvements in lung function (as measured by the forced expiratory volume in one second, FEV1) in a number of clinical studies. In Phase III studies, bronchodilator effects were seen within 5 minutes after the first dose and were maintained over the 24-hour dosing interval from the first dose. There was no attenuation of the bronchodilator effect over time

Trough and peak FEV1:

Onriva Plus Bexicap increased post-dose trough FEV1 by 200 ml compared to placebo at the 26- week primary endpoint ($p<0.001$) and showed statistically significant increases compared to eachmonotherapy component treatment arm

(indacaterol and glycopyrronium) as well as the tiotropium treatment arm, as shown in the below table.

Post-dose trough FEV1 (least squares mean) at day 1 and week 26 (primary endpoint)

Treatment difference	Day 1	Week 26
Onriva Plus Bexicap – placebo	190 ml (p<0.001)	200 ml (p<0.001)
Onriva Plus Bexicap – indacaterol	80 ml (p<0.001)	70 ml (p<0.001)
Onriva Plus Bexicap – glycopyrronium	80 ml (p<0.001)	90 ml (p<0.001)
Onriva Plus Bexicap – tiotropium	80 ml (p<0.001)	80 ml (p<0.001)

The mean pre-dose FEV1 (average of the values taken at -45 and -15 minutes prior to the morning dose of study medication) was statistically significant in favour of Onriva Plus Bexicap at week 26 compared to fluticasone/salmeterol (least squares [LS] mean treatment difference 100ml, p<0.001), at week 52 compared to placebo (LS mean treatment difference 189 ml, p<0.001) and at all visits up to week 64 compared to glycopyrronium (LS mean treatment difference 70-80ml, p<0.001) and tiotropium (LS mean treatment difference 60-80 ml, p<0.001). In the 52-week active-controlled study, the mean predose FEV1 was statistically significant in favour of Onriva Plus Bexicap at all visits up to week 52 compared to fluticasone/salmeterol (LS mean treatment difference 62-86 ml, p<0.001). At week 26, Onriva Plus Bexicap produced statistically significant improvement in peak FEV1 compared to placebo in the first 4 hours post dose (LS mean treatment difference 330 ml) (p<0.001).

FEV1 AUC:

Onriva Plus Bexicap increased post-dose FEV1 AUC0-12 (primary endpoint) by 140 ml at 26 weeks (p<0.001) compared to fluticasone/salmeterol.

Symptomatic outcomesBreathlessness:

Onriva Plus Bexicap statistically significantly reduced breathlessness as evaluated by the Transitional Dyspnoea Index (TDI); it demonstrated a statistically significant improvement in the TDI focal score at week 26 compared to placebo (LS mean treatment difference 1.09, p<0.001), tiotropium (LS mean treatment difference 0.51, p=0.007) and fluticasone/salmeterol (LS mean treatment difference 0.76, p=0.003). Improvements versus indacaterol and glycopyrronium were 0.26 and 0.21, respectively.

A statistically significantly higher percentage of patients receiving Onriva Plus Bexicap responded with a 1 point or greater improvement in the TDI focal score at week 26 compared to placebo (68.1% and 57.5% respectively, p=0.004). A higher proportion of patients demonstrated clinically meaningful response at week 26 on Onriva Plus Bexicap as compared to tiotropium (68.1% Onriva Plus

Bexicap versus 59.2% tiotropium, p=0.016) and fluticasone/salmeterol (65.1% Onriva Plus Bexicap versus 55.5% fluticasone/salmeterol, p=0.088).

Health-related quality of life:

Onriva Plus Bexicap has also shown a statistically significant effect on health-related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ) as indicated by a reduction in SGRQ total score at 26 weeks compared to placebo (LS mean treatment difference - 3.01, p=0.002) and tiotropium (LS mean treatment difference -2.13, p=0.009) and reductions versus indacaterol and glycopyrronium were -1.09 and -1.18, respectively. At 64 weeks, the reduction compared to tiotropium was statistically significant (LS mean treatment difference - 2.69, p<0.001). At 52 weeks, the reduction compared to fluticasone/salmeterol was statistically significant (LS mean treatment difference -1.3, p=0.003).

A higher percentage of patients receiving Onriva Plus Bexicap responded with a clinically meaningful improvement in SGRQ score (defined as a decrease of at least 4 units from baseline) at week 26 compared to placebo (63.7% and 56.6% respectively, p=0.088) and tiotropium(63.7% Onriva Plus Bexicap vs. 56.4% tiotropium, p=0.047), at week 64 compared to glycopyrronium and tiotropium (57.3% Onriva Plus Bexicap versus 51.8% glycopyrronium, p=0.055; versus 50.8% tiotropium, p=0.051, respectively), and at week 52 compared to fluticasone/salmeterol (49.2% Onriva Plus Bexicap vs. 43.7% fluticasone/salmeterol, odds ratio:1.30, p<0.001).

Daily activities

Onriva Plus Bexicap demonstrated a statistically superior improvement versus tiotropium in the percentage of “days able to perform usual daily activities” over 26 weeks (LS mean treatment difference 8.45%, p<0.001). At week 64, Onriva Plus Bexicap showed numerical improvement over glycopyrronium (LS mean treatment difference 1.95%; p=0.175) and statistical improvement over tiotropium (LS mean treatment difference 4.96%; p=0.001).

COPD exacerbations

In a 64-week study comparing Onriva Plus Bexicap (n=729), glycopyrronium (n=739) and tiotropium (n=737), Onriva Plus Bexicap reduced the annualised rate of moderate or severe COPD exacerbations by 12% compared to glycopyrronium (p=0.038) and by 10% compared to tiotropium (p=0.096). The number of moderate or severe COPD exacerbations/patient-years was

0.94 for Onriva Plus Bexicap (812 events), 1.07 for glycopyrronium (900 events) and 1.06 for tiotropium (898 events). Onriva Plus Bexicap also statistically significantly reduced the annualised rate of all COPD exacerbations (mild, moderate or severe) by 15% as compared to glycopyrronium (p=0.001) and 14% as compared to tiotropium (p=0.002). The number of all COPD exacerbations/patient-years was 3.34 for Onriva Plus Bexicap (2,893 events), 3.92 for glycopyrronium (3,294 events) and 3.89 for tiotropium (3,301 events).

In the 52-week study comparing Onriva Plus Bexicap (n=1,675) and fluticasone/salmeterol (n=1,679), Onriva Plus Bexicap met the primary study objective of non-inferiority in rate of all COPD exacerbations (mild, moderate or severe) compared to fluticasone/salmeterol. The number of all COPD exacerbations/patient-years was 3.59 for Onriva Plus Bexicap (4,531 events) and

4.03 for fluticasone/salmeterol (4,969 events). Onriva Plus Bexicap further showed superiority in reducing the annualised rate of all exacerbations by 11% versus fluticasone/salmeterol (p=0.003).

Compared to fluticasone/salmeterol, Onriva Plus Bexicap reduced the annualised rate of both moderate or severe exacerbations by 17% (p<0.001), and of severe exacerbations (requiring hospitalisation) by 13% (not statistically significant, p=0.231). The number of moderate or severe COPD exacerbations/patient-years was 0.98 for Onriva Plus Bexicap (1,265 events) and

1.19 for fluticasone/salmeterol (1,452 events). Onriva Plus Bexicap prolonged time to first moderate or severe exacerbation with a 22% reduction in risk of an exacerbation (p<0.001) and prolonged time to first severe exacerbation with a 19% reduction in risk of an exacerbation (p=0.046).

The incidence of pneumonia was 3.2% in the Onriva Plus Bexicap arm compared to 4.8% in the fluticasone/salmeterol arm (p=0.017). Time to first pneumonia was prolonged with Onriva Plus Bexicap compared to fluticasone/salmeterol (p=0.013).

In another study comparing Onriva Plus Bexicap (n=258) and fluticasone/salmeterol (n=264), for 26 weeks, the number of moderate or severe COPD exacerbations/patient-years was 0.15 versus 0.18 (18 events versus 22 events), respectively (p=0.512), and the number of all COPD exacerbations/patients-years (mild, moderate or severe) was 0.72 versus

0.94 (86 events versus 113 events), respectively (p=0.098).

Use of rescue medication

Over 26 weeks, Onriva Plus Bexicap statistically significantly reduced the use of rescue medication (salbutamol) by 0.96 puffs per day (p<0.001) compared to placebo, 0.54 puffs perday (p<0.001) compared to tiotropium and 0.39 puffs per day (p=0.019) compared to fluticasone/salmeterol. Over 64 weeks, this reduction was 0.76 puffs per day (p<0.001) compared to tiotropium. Over 52 weeks, Onriva Plus Bexicap reduced the use of rescue medication by 0.25 puffs per day compared to fluticasone/salmeterol (p<0.001).

Exercise tolerance

Onriva Plus Bexicap , dosed in the morning, reduced dynamic hyperinflation and improved the length of time exercise could be maintained from the first dose onwards. On the first day of treatment, inspiratory capacity under

exercise was significantly improved (LS mean treatment difference 250 ml, p<0.001) compared to placebo. After three weeks of treatment, the improvement in inspiratory capacity with Onriva Plus Bexicap was greater (LS mean treatment difference 320 ml, p<0.001) and exercise endurance time increased (LS mean treatment difference 59.5 seconds, p=0.006) compared to placebo.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Onriva Plus Bexicap in all subsets of the paediatric population in chronic obstructive pulmonarydisease (COPD) (see section 4.2 for information on paediatric use).

5.2. Pharmacokinetic properties

Absorption

Onriva Plus Bexicap

Following inhalation of Onriva Plus Bexicap , the median time to reach peak plasma concentrations of indacaterol and glycopyrronium was approximately 15 minutes and 5 minutes, respectively.

Based on the *in vitro* performance data, the dose of indacaterol delivered to the lung is expected to be similar for Onriva Plus Bexicap and indacaterol monotherapy product. Steady-stateexposure to indacaterol after Onriva Plus Bexicap inhalation was either similar or slightly lower than systemic exposure after indacaterol monotherapy product inhalation.

Following inhalation of Onriva Plus Bexicap , the absolute bioavailability of indacaterol has been estimated to range from 61 to 85% of the delivered dose, and that of glycopyrronium was about 47% of the delivered dose.

Steady-state exposure to glycopyrronium after Onriva Plus Bexicap inhalation was similar to systemic exposure after glycopyrronium monotherapy product inhalation.

Indacaterol

Steady state concentrations of indacaterol were achieved within 12 to 15 days following once- daily administration. The mean accumulation ratio of indacaterol, i.e. AUC over the 24-h dosing interval on day 14 or day 15 compared to day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 60 micrograms and 480 micrograms (delivered dose).

Glycopyrronium

In patients with COPD, pharmacokinetic steady-state of glycopyrronium was reached within one week of the start of treatment. The steady-state mean peak and trough plasma concentrations of glycopyrronium at the recommended once-daily dosing regimen were 166 picograms/ml and 8 picograms/ml,

respectively. Steady-state exposure to glycopyrronium (AUC over the 24-hour dosing interval) was about 1.4- to 1.7-fold higher than after the first dose.

Distribution

Indacaterol

After intravenous infusion the volume of distribution of indacaterol during the terminal elimination phase was 2557 litres indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was about 95%.

Glycopyrronium

After intravenous dosing, the steady-state volume of distribution of glycopyrronium was 83 litresand the volume of distribution in the terminal phase was 376 litres. The apparent volume of distribution in the terminal phase following inhalation was almost 20-fold larger, which reflects the much slower elimination after inhalation. The *in vitro* human plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 nanograms/ml.

Biotransformation

Indacaterol

After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) study, unchanged indacaterol was the main component in serum, accounting for about one third of total drug-related AUC over 24 hours. A hydroxylated derivative was the most prominent metabolite in serum. Phenolic O-glucuronides of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro the UGT1A1 isoform is a major contributor to the metabolic clearance of indacaterol. However, as shown in a clinical study in populations with different UGT1A1 genotypes, systemic exposure to indacaterol is not significantly affected by the UGT1A1-genotype.

Oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

Glycopyrronium

In vitro metabolism studies showed consistent metabolic pathways for glycopyrronium bromide between animals and humans. Hydroxylation resulting in a variety of mono- and bis- hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9) were seen. *In vivo*, M9 is formed from the swallowed dose fraction of inhaled glycopyrronium bromide. Glucuronide and/or sulfate conjugates of

glycopyrronium were found in urine of humans after repeated inhalation, accounting for about 3% of the delivered dose.

Multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium.Inhibition or induction of the metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the active substance.

In vitro inhibition studies demonstrated that glycopyrronium bromide has no relevant capacity to inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR, and the uptake transporters OCT1 or OCT2. *In vitro* enzyme induction studies did not indicate a clinically relevant induction by glycopyrronium bromide for any of the cytochrome P450 isoenzymes tested or for UGT1A1 and the transporters MDR1 and MRP2.

Elimination

Indacaterol

In clinical studies, the amount of indacaterol excreted unchanged via urine was generally lower than 2.5% of the delivered dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.2 litres/hour. When compared with the serum clearance of indacaterol of 23.3 litres/hour, itis evident that renal clearance plays a minor role (about 2 to 5% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study, indacaterol given orally was excreted into human faeces primarily as unchanged parent substance (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective halflife, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 52 hours which is consistent with the observed time-tosteady state of approximately 12-15 days

Glycopyrronium

After intravenous administration of [^{3}H]-labelled glycopyrronium bromide, the mean urinary excretion of radioactivity in 48 hours amounted to 85% of the dose. A further 5% of the dosewas found in the bile.

Renal elimination of parent drug accounts for about 60 to 70% of total clearance of systemically available glycopyrronium whereas non-renal clearance accounts for about 30 to 40%. Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

Mean renal clearance of glycopyrronium following inhalation was in the range of 17.4 and 24.4 litres/h. Active tubular secretion contributes to the renal

elimination of glycopyrronium. Up to 23% of the delivered dose was found in urine as parent drug.

Glycopyrronium plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 to 57 hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration. The elimination pattern suggests sustained lungabsorption and/or transfer of glycopyrronium into the systemic circulation at and beyond 24 h after inhalation.

Linearity/non-linearity

Indacaterol

Systemic exposure to indacaterol increased with increasing (delivered) dose (120 micrograms to480 micrograms) in a dose proportional manner.

Glycopyrronium

In COPD patients both systemic exposure and total urinary excretion of glycopyrronium at pharmacokinetic steady state increased about doseproportionally over the (delivered) dose rangeof 44 to 176 micrograms.

Special populations

Onriva Plus Bexicap

A population pharmacokinetic analysis of data in COPD patients after inhalation of Onriva Plus Bexicap indicated no significant effect of age, gender and (lean body) weight on the systemic exposure to indacaterol and glycopyrronium. Lean body weight (which is a function of weight and height) was identified as a covariate. A negative correlation between systemic exposure and lean body weight (or body weight) was observed; however, no dose adjustment is recommended due to the magnitude of the change or the predictive precision of lean body weight.

Smoking status and baseline FEV1 had no apparent effect on systemic exposure to indacateroland glycopyrronium after inhalation of Onriva Plus Bexicap .

IndacaterolA population pharmacokinetic analysis showed that there is no clinically relevant effect of age (adults up to 88 years), sex, weight (32-168 kg) or race on the pharmacokinetics of indacaterol. It did not suggest any difference between ethnic subgroups in this population.

Glycopyrronium

A population pharmacokinetic analysis of data in COPD patients identified body weight and age as factors contributing to inter-patient variability in systemic exposure. Glycopyrronium at the recommended dose can be safely used in all age and body weight groups.

Gender, smoking status and baseline FEV1 had no apparent effect on systemic exposure.

Patients with hepatic impairmentOnriva Plus Bexicap :

Based on the clinical pharmacokinetic characteristics of its monotherapy components, Onriva Plus Bexicap can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment.

Indacaterol:

Patients with mild and moderate hepatic impairment showed no relevant changes in Cmax or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

Glycopyrronium:

Clinical studies have not been conducted in patients with hepatic impairment. Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion. Impairment of the hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase of systemic exposure.

Patients with renal impairmentOnriva Plus Bexicap :

Based on the clinical pharmacokinetic characteristics of its monotherapy components, Onriva Plus Bexicap can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis, Onriva Plus Bexicap should be used only if the expected benefit outweighs thepotential risk.

Indacaterol:

Due to the very low contribution of the urinary pathway to total body elimination of indacaterolmaleate, a study in renal impaired subjects was not performed.

Glycopyrronium:

Renal impairment has an impact on the systemic exposure to glycopyrronium bromide. A moderate mean increase in total systemic exposure (AUClast) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severerenal impairment and end-stage renal disease. In COPD patients with mild and moderate renal impairment (estimated glomerular filtration rate, eGFR ≥30 ml/min/1.73 m^2) glycopyrroniumbromide can be used at the recommended dose

Ethnicity

Onriva Plus Bexicap :

There were no major differences in total systemic exposure (AUC) for both compounds between Japanese and Caucasian subjects. Insufficient pharmacokinetic data is available for other ethnicities or races.

Indacaterol:

No difference between ethnic subgroups was identified. Limited treatment experience is available for the black population.

Glycopyrronium:

There were no major differences in total systemic exposure (AUC) between Japanese and Caucasian subjects. Insufficient pharmacokinetic data is available for other ethnicities or races.

5.3. Preclinical safety data

Onriva Plus Bexicap

Pre-clinical studies included *in vitro* and *in vivo* safety pharmacology assessments, repeated-doseinhalation toxicity studies in rats and dogs and an inhalation embryo-foetal development study inrats.

Increased heart rates were apparent in dogs at all doses of Onriva Plus Bexicap and each monotherapy component. The effects on heart rate for Onriva Plus Bexicap increased in magnitude and duration when compared with the changes observed for each component alone consistent with an additive response. Shortening of electrocardiograph intervals and decreased systolic and diastolic blood pressure were also apparent. Indacaterol administered to dogs alone or in Onriva Plus Bexicap was associated with a similar incidence and severity of myocardial lesions. Systemic exposures (AUC) at the no-observed-adverse-effect level (NOAEL) for myocardial lesions were 64- and 59-fold higher than in humans, for each component respectively.

No effects on the embryo or foetus were seen at any dose level of Onriva Plus Bexicap during an embryo-foetal development study in rats. Systemic exposures (AUC) at the no-observed- adverse-effect level (NOAEL) were 79and 126-fold higher than in humans, for indacaterol and glycopyrronium respectively.

Indacaterol

Effects on the cardiovascular system attributable to the beta2-agonistic properties of indacaterol included tachycardia, arrhythmias and myocardial lesions in dogs. Mild irritancy of the nasal cavity and larynx were seen in rodents. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F1 offspring was observed in the peri- and post- developmental rat study at an exposure 14fold higher than in humans treated with indacaterol.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential. Carcinogenicity was assessed in a two-year rat study and a six-month transgenic mouse study. Increased incidences ofbenign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in rats were consistent with similar findings reported for other beta2-adrenergic agonists. No evidence of

carcinogenicity was seen in mice. Systemic exposures (AUC) in rats and mice at the no-observed-adverse-effect levels in these studies were at least 7- and 49-fold higher, respectively, than in humans treated with indacaterol once a day at the maximum recommended therapeutic dose.

Glycopyrronium

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Effects attributable to the muscarinic receptor antagonist properties of glycopyrronium bromide included mild to moderate increases in heart rate in dogs, lens opacities in rats and, reversible changes associated with reduced glandular secretions in rats and dogs. Mild irritancy or adaptive changes in the respiratory tract were seen in rats. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Glycopyrronium was not teratogenic in rats or rabbits following inhalation administration. Fertility and pre- and post-natal development were not affected in rats. Glycopyrronium bromide and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. Glycopyrronium bromide (including its metabolites) was excreted into the milk of lactatingrats and reached up to 10-fold higher concentrations in the milk than in the blood of the dam.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium bromide. Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity at systemic exposures (AUC) of approximately 53fold higher in mice and 75-fold higher in rats than the maximum recommended dose once daily for humans.

6. Pharmaceutical particulars

6.1. List of excipients

Capsule content

Lactose Monohydrate(Respitose SV010)

Lactose Monohydrate (Inhalac 500)

Magnesium Stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

18 months when stored below 30°C.

6.4. Special precautions for storage

Store in a dry place at a temperature not exceeding 30°C.Protect from light.

Keep out of reach of children.

6.5. Nature and contents of container

Onriva Plus Bexicap Dry Powder Inhaler is supplied in an Alu-Alu form pack of 10's capsule contains size # 3 hard capsule shell.

3 x 10’s

6.6 Special precautions for use and handling <and disposal>

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Beximco Pharmaceuticals Limited

8. MARKETING AUTHORISATION NUMBER(S)

H2022/CTD10144/21595

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2023 June 22

10. DATE OF REVISION OF THE TEXT

2023 June 22