Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for olodaterol (as hydrochloride)

Proprietary Product Name: Striverdi Respimat

Sponsor: Boehringer Ingelheim Pty Ltd

March 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	12 November 2013
Active ingredient:	olodaterol
Product name:	Striverdi Respimat
Sponsor's name and address:	Boehringer Ingelheim Pty Ltd PO Box 1969 Macquarie Centre North Ryde NSW 2113
Dose form:	Solution for Inhalation
Strength:	2.5 microgram (as hydrochloride)
Container:	Cartridge
Pack size:	One cartridge (60 metered actuations) with Respimat inhaler
Approved therapeutic use:	Striverdi Respimat is a long acting beta 2 agonist indicated for once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).
Route of administration:	Oral inhalation
Dosage:	**Adults** The recommended dose for adults is 5 microgram olodaterol given as two puffs from the Striverdi Respimat inhaler once daily, at the same time of the day. **Elderly** Elderly patients can use Striverdi Respimat at the recommended dose. **Children** COPD does not normally occur in children. The safety and effectiveness of Striverdi Respimat in the paediatric population have not been established. **Patients with hepatic impairment** Patients with mild and moderate hepatic impairment can use Striverdi Respimat at the recommended dose. There are no data available for use of Striverdi Respimat in patients with severe hepatic impairment.

	Patients with renal impairment Renally impaired patients can use Striverdi Respimat at the recommended dose.
ARTG number:	199568

Product background

Olodaterol is a selective long acting beta 2 adrenergic agonist (LABA). Activation of beta 2 receptors in the airways results in stimulation of intracellular adenyl cyclase, which mediates the synthesis of cyclic-3', 5' adenosine monophosphate (cAMP). Elevated levels of cAMP in turn induce bronchodilatation via relaxation of airway smooth muscle cells.

This AusPAR describes the application by the sponsor to register Striverdi Respimat as a New Chemical Entity for the proposed indication:

> *'for long term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema'*[1].

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, and the prevalence and burden of COPD are projected to increase due to continued exposure to COPD risk factors and the changing age structure of the world's population, with more people living longer and therefore expressing the long term effects of exposure to COPD risk factors.

Two classes of inhaled bronchodilators are currently available: beta 2 agonists and anticholinergics. The initial beta 2 agonists (for example salbutamol) and anticholinergics (for example ipratropium) have short duration of action, necessitating multiple daily dosing regimens in order to maintain bronchodilator activity. More recent beta 2 agonists (for example formoterol, salmeterol), called long acting beta 2 agonists (LABAs), have longer duration of action, allowing for a twice daily dosing regimen. Within the anticholinergic class, a more recent anticholinergic agent, tiotropium (Spiriva; developed by the sponsor), may retain bronchodilator effect for 24 h, thus allowing for a once daily dosing regimen and had been established as part of standard treatment regimen in COPD.

Indacaterol (developed by Novartis) has been recently approved in the European Union (EU) and the United States (US) as a once daily LABA for the maintenance treatment of airflow obstruction in COPD. Striverdi Respimat[2] is intended to be an alternative once daily maintenance bronchodilator treatment in patients with COPD. The proposed dose for adults is 5 µg/day olodaterol given as two puffs from an inhaler. The Striverdi Respimat Inhaler is a propellant free, metered dose inhaler (MDI) and is the same device as in Spiriva Respimat (tiotropium 2.5 µg per actuation; AUST R 132578) registered to the same sponsor in Australia.

The Striverdi Respimat Inhaler is for use only with the Striverdi Respimat Cartridge. There is no intention to use this submission to supply the Striverdi Respimat Inhaler separately as a medical device without the drug containing cartridge.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) Registration on 20 November 2013.

[1] Proposed Australian Product Information, Infortispir Respimat.
[2] The trade name "Infortispir Respimat" was initially proposed and later altered to "Striverdi Respimat".

At the time the TGA considered this application, similar applications had been submitted to the European Union (EU) (via decentralised procedure; application submitted separately in all member states including Netherlands, Germany, Sweden and United Kingdom (UK)), on 16 May 2012, the United States of America (USA) on 13 May 2012, Canada on 27 June 2012 and Switzerland on 12 June 2012, and that the applications were still under evaluation at the time of the submission to the TGA.

Product Information

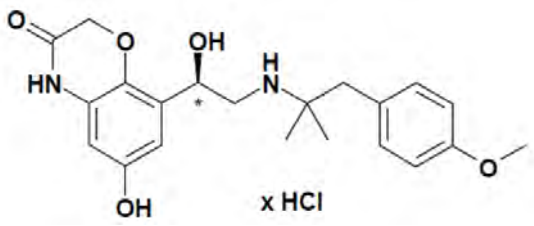
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Olodaterol is 6-hydroxy-8-[(1R)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]amino]ethyl]- 2H-1,4-benzoxazin-3H(4H)-one. The drug substance is the monohydrochloride salt.

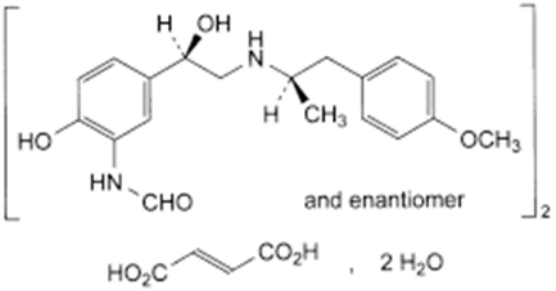
Figure 1. olodaterol hydrochloride



C21H26N2O5 HCl, MW 386.45g/mol (free base), Company Code: BI 1744 CL.

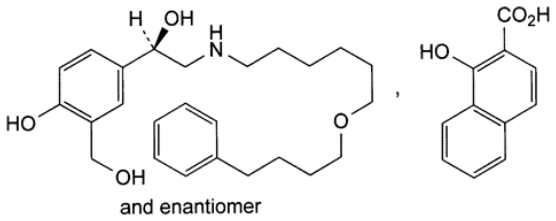
Olodaterol has one chiral centre: the R enantiomer is used. It is manufactured by chemical synthesis. The drug substance is structurally related to eformoterol, salmeterol, fenoterol and indacaterol.

Figure 2. eformoterol fumarate



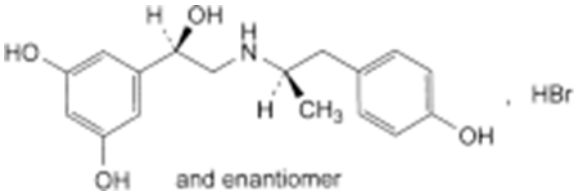
Oxis 6 and 12 micrograms; Foradile12 micrograms dry powder inhalers

Figure 3. salmeterol xinafoate



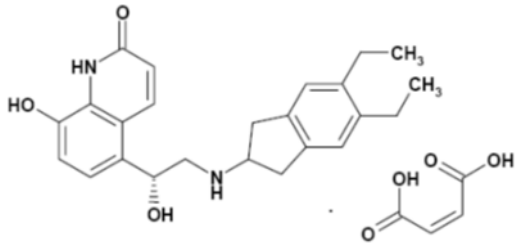
Serevent 50 micrograms dry powder inhaler

Figure 4. fenoterol



Berotec Boehringer (cancelled)

Figure 5. indacaterol maleate



Onbrez 150 and 300 micrograms dry powder inhaler

Olodaterol hydrochloride salt is used to make Striverdi Respimat. The olodaterol (base) content is labelled in keeping with current policy. The salt is readily soluble in water at the concentration used.

Drug product

Boehringer Ingelheim proposes registration of a pack which consists of a cartridge, containing 60 actuations of an aqueous solution of olodaterol hydrochloride and a Respimat inhaler. The solution in the cartridge is metered and nebulised by the inhaler to give a fine aerosol cloud for inhalation by the patient. Each actuation delivers 2.5 µg of olodaterol from the mouthpiece. One dose of 5 micrograms of olodaterol consists of two actuations. The cartridges cannot be used with other nebuliser devices.

The Respimat inhaler is a nebulising device: only Spiriva Respimat is currently registered in Australia (tiotropium 2.5 µg per actuation). The device is described later in this summary.

The inhalation solution is formulated with olodaterol hydrochloride (labelled in terms of the olodaterol base content), benzalkonium chloride (antimicrobial agent); disodium edetate; citric acid and purified water.

The use of benzalkonium chloride and disodium edetate as preservatives is perhaps controversial. The use of benzalkonium chloride in nebulising solutions has been queried for a long time, especially by Beasley.[3]

Single dose nebulising solutions are preservative free.

Note, however, that the same benzalkonium chloride concentration is used in the registered Spiriva Respimat and proposed Striverdi Respimat products.

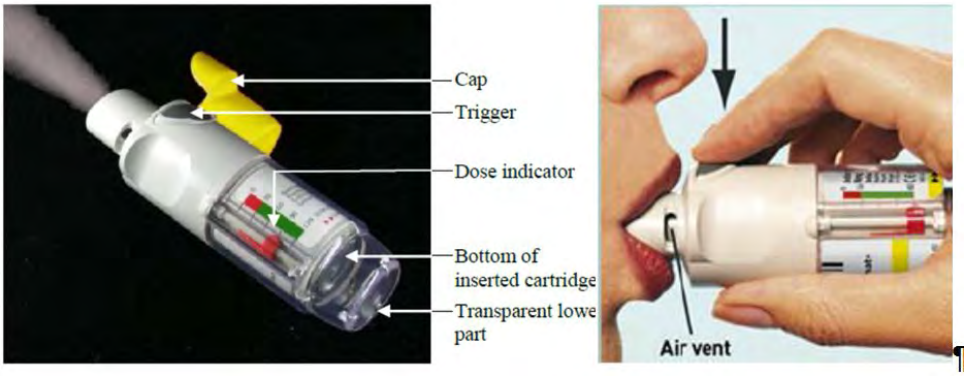
The solution for inhalation is a filled into cartridges. Each cartridge is filled with at least 4.0 mL of solution. The solution is in a plastic container which is crimped into an aluminium cylinder to form the cartridge. Then when the cartridge is inserted into the Respimat device, a capillary tube is forced into the solution. An in use shelf life (3 months) begins when the cartridge is put into the device.

The Respimat inhaler is a hand held, metered dose, "soft mist" inhaler. It works by forcing, on manual actuation, a metered volume of drug solution at high pressure through a nozzle containing two tiny holes. This generates two liquid jets that hit each other and atomise to form a soft mist of fine slowly moving droplets during the approximately 1.5 second spray time.

In use the Respimat inhaler meters and nebulises 29.8 µL of solution (metered volume per dose of 2 actuations). During the nebulisation process, some of the spray generated is deposited around the nozzle and on the inner surface of the mouthpiece, so the delivered volume is about 22.1 µL.

The device requires priming before first doses are delivered. The device has a dose count indicator; the device includes a locking mechanism which prevents use when the labelled number of actuations has been reached. (The Respimat can only be used with a single cartridge.)

Figure 6. Respimat inhaler with inserted cartridge and generated aerosol



The patient uses the nebuliser somewhat like a pressurised metered dose inhaler, firing an actuation while inhaling through the mouthpiece. Thus there is the potential for some similar dosing problems in use, giving poor delivery (actuation while exhaling, actuation but nasal inhalation, shallow inspiration, variable breath holding, etcetera).

In use the inhaler delivers aerosol droplets across the respirable range. Specifications control the "fine particle dose" in the delivered aerosol.

[3] R Beasley *et al* Benzalkonium Chloride and bronchoconstriction Lancet 1986; ii 1227, C.Burgess, S. Holt, Call for worldwide withdrawal of benzalkonium chloride from nebulizer solutions J *Allergy Clin Immunology* 2001 Pt 1, Vol 107(2); Beasley CRW, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide [Atrovent] nebuliser solution. BMJ 1987; 294:1197-8; R Beasley, C.Burgess, S Holt, Call for worldwide withdrawal of benzalkonium chloride from nebulizer solutions J *Allergy Clin Immunology* 2001 Pt 1, Vol 107(2).

Biopharmaceutics

The product is for local use in the lung (and non steroidal) and therefore no bioavailability or bioequivalence data are reviewed by the TGA.

Advisory committee considerations

The submission was considered at the 151st (2013/3) meeting of the Pharmaceutical Subcommittee (PSC). The PSC considered that the sponsor should:

- Include a bioburden test prior to the filtration step in the drug product manufacturing process given that the product is delivered into compromised lungs.
- Disclose the preservative quantitatively on the label given known clinical reactions to inhaled benzalkonium chloride.

[Recommendation No. 2323]

The TGA notes that the product is for oral inhalation, is not sterile and recommends that bioburden testing should be left as a Good Manufacturing Practice (GMP) issue.

The product labelling will be reviewed following the Advisory Committee for Prescription Medicines (ACPM) meeting.

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

The submission to register olodaterol hydrochloride included toxicity studies. The overall quality of the submitted dossier was high, with all pivotal toxicity studies conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (inhalation).

Pharmacology

Primary pharmacology

In vitro, olodaterol had agonistic activity at the human beta 2 adrenoceptor (EC_{50} 0.12 nM, 88% maximal activity). *In vivo*, olodaterol had bronchodilating activity on acetylcholine-induced bronchoconstriction in guinea pigs and dogs with fully effective doses (FEDs) of 2.74 µg/kg inhalation (IH) and 0.55 µg/kg intratracheal (IT), respectively (at least 5 times the clinical dose on a µg/kg basis). The onset of action was rapid (within 10 min) and significant bronchodilation was still evident at 12 and 24 hours post dose (at the FED) in both systems. The onset of action was faster than salmeterol but similar to formoterol. The duration of action was longer than salbutamol and formoterol. The submitted data support the use of olodaterol as a rapid onset, long acting bronchodilator.

The S enantiomer of olodaterol had lower potency at the human beta 2 receptor than the proposed clinical R enantiomer. Olodaterol glucuronide, the major human metabolite in plasma (but unlikely to be formed in lung tissue), had poor activity at the beta 2 adrenoceptor and poor bronchodilating activity in guinea pigs. The desmethyl metabolite,

SOM 1522, and its sulphate derivative (both minor human metabolites) had some activity at the beta 2 receptor. Given the poor metabolism of olodaterol in lung tissue and the lower potency of the olodaterol metabolites at human beta 2 receptors, bronchodilation following inhalational administration can be attributed solely to olodaterol.

Secondary pharmacodynamics

Olodaterol was tested for activity at 76 receptors, ion channels and transporters. Olodaterol had agonistic activity at the human beta 1 and beta 3 receptors with agonistic activity detected on beta 1 adrenoceptors in isolated guinea pig atrial tissue. Some antagonistic activity was seen on alpha 1 adrenoceptors and 5 HT receptors in isolated rabbit thoracic aorta. Given the low systemic exposures of olodaterol in patients, these activities are unlikely to be clinically relevant. The main human metabolite, olodaterol glucuronide, had no significant activity at the human beta 1 adrenoceptor. Therefore, no off target activities are predicted during clinical use.

Safety pharmacology

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular, respiratory, renal and gastrointestinal systems. All pivotal *in vivo* CNS, cardiovascular and respiratory studies were GLP compliant with the renal and gastrointestinal studies adequately conducted. Another beta 2 agonist, formoterol, was used as a comparator in some studies. In general, similar effects on the cardiovascular, respiratory, renal and gastrointestinal systems were seen with formoterol, suggesting a lack of novel activities with olodaterol.

Neurobehaviour and body temperature were unaffected in male rats receiving an inhalational dose of 483 µg/kg (exposure ratio based on C_{max} (ERCmax) approximately 4000). While some perturbation of motor activity and motor coordination was seen in mice receiving an SC dose of 10 µg/kg (no observable effect level (NOEL) 3 µg/kg subcutaneous (SC)), the peak plasma levels are likely to be far in excess of that seen clinically and therefore these findings are not of particular concern.

In vitro, no effect on hERG K+ tail current was seen at less than or equal to 30 µM olodaterol while a concentration dependent shortening of action potential duration was seen in guinea pig papillary muscles at greater than or equal to 1 µM. However, no effect on electrocardiogram (ECG) parameters was seen in dogs receiving inhalational doses up to 9.14 µg/kg (ERCmax 20 to 30). Corrected QT interval (QTc) shortening was seen with oral doses resulting in higher plasma levels but given the safety margins, no effect on QT interval in patients is predicted from the available data.

Tachycardia, lasting up to 5 h post dose, with a compensatory decrease in blood pressure was consistently seen in rats (greater than or equal to 0.9 mg IH) and dogs (greater than or equal to 2.74 µg/kg IH). A trend to tolerance was evident with repeat dosing. The maximum concentration (Cmax) at the NOEL in dogs was approximately equivalent to the clinical Cmax. The Cmax at the NOEL in rats is unknown. Given the lack of an adequate safety margin, tachycardia may be seen in patients. Relevant precautionary statements are included in the draft Product Information document.

A transient antidiuretic effect was seen in rats that received an inhalational dose of greater than or equal to 0.27 mg olodaterol and a decrease in gastric emptying, gastrointestinal transit and acid output was seen at greater than or equal to 0.91 mg IH. Similar effects were seen with formoterol.

Overall, the safety pharmacology profile of olodaterol was similar to that seen with other beta 2 agonists.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies with olodaterol/tiotropium, olodaterol/ciclesonide and olodaterol/tiotropium/ciclesonide combinations were performed in anticipation of future fixed dose combination products. Synergistic bronchoprotection was seen with the combinations of olodaterol/tiotropium bromide (0.27/0.1 µg/kg IH or IT to guinea pigs and dogs), olodaterol/ciclesonide (0.27 µg/kg/0.1 mg/kg IH to dogs) and olodaterol/tiotropium bromide/ciclesonide (0.27/0.06/100 µg/kg IH to dogs). With fixed intratracheal doses of tiotropium bromide (0.1 µg/kg) and/or ciclesonide (0.1 mg/kg), the Median Effective Dose, (produces desired effect in 50% of population, (ED_{50})) of olodaterol for a bronchoprotective effect in guinea pigs was reduced from 0.2 µg/kg (olodaterol alone) to 0.03 and 0.02 µg/kg when combined with tiotropium or ciclesonide, respectively, and 0.003 µg/kg when provided in triple combination. These nonclinical data support the use of olodaterol/tiotropium, olodaterol/ciclesonide and olodaterol/tiotropium/ciclesonide combinations as bronchodilators.

Pharmacokinetics

Absorption was rapid following oral and inhalational dosing to mice, rats, dogs and humans (0.17 to 1 hour). Olodaterol was considered to be a moderately permeable compound, but oral bioavailability was low in mice, rats and humans (1 to 4%) and slightly higher in dogs (12%). The low oral bioavailability can be attributed, in part, to efflux by P glycoprotein (P-gp). Inhalational bioavailability was moderate in mice (54%) but lower in rats, dogs and humans (10 to 30%). Taken together, it can be assumed the systemic exposure in human subjects following inhalational administration is predominantly due to absorption in the respiratory tract. Exposure was generally dose proportional in mice, rats, dogs and humans following inhalational dosing. There were no significant sex differences in exposure in these species. The plasma elimination half-life was moderate following intravenous (IV) administration to mice and rats (5.8 to 13 hours) and slightly longer in dogs and humans (19 to 22 hours) with clearance rates similar in animal species and slightly lower in humans. There was no evidence of accumulation following repeat inhalational or oral dosing to rats and dogs, or repeat IV dosing to dogs. Exposure was lower after 13 weeks of inhalational dosing to mice and 2 weeks IV dosing to rats, which may be associated with an induction of metabolism at the high systemic exposures.

Protein binding was independent of concentration and was similar in mice, rats, rabbits, dogs and humans (55 to 78%). There was no significant difference in plasma protein binding in healthy human subjects and subjects with mild to moderate liver impairment or severe renal impairment. The distribution of olodaterol into blood cells from rats, dogs and humans was high (2.5 to 5.7 times the level in plasma). Metabolites of olodaterol had a different blood cell/plasma partitioning profile. The volume of distribution was greater than total body water in mice, rats, dogs and humans. Following IV dosing of radioactively labelled (^{14}C) olodaterol to rats, tissue distribution of radioactivity was wide with most tissues having higher radioactivity levels than blood. The highest radioactivity levels were seen in the kidney, pituitary, choroid plexus, Harderian gland, pancreas and adrenal gland. Radioactivity levels in the brain were low, in part due to efflux by P glycoprotein. Only marginally higher (up to 2.5 times) brain to blood ratios of drug related material were observed in rodents lacking P glycoprotein or with P glycoprotein inhibition compared with animals having a functional P glycoprotein, suggesting P glycoprotein efflux is not a major determinant of the low brain levels. A distinct affinity and retention of radioactivity was evident in the melanin containing parts of the eye but such retention was not seen in pigmented skin. Following intratracheal dosing, the distribution profile was similar to that seen with IV dosing, with the exception of high levels in the lungs. There was no evidence of retention of radioactivity in the lungs. With repeated intratracheal dosing, only slight

accumulation (up to 3 fold) was seen in the lungs, but an equivalent accumulation was also seen in blood.

At least 6 metabolites of olodaterol were detected in mice, rats, rabbits, dogs and humans. Metabolites were formed by glucuronidation (2 entities) and demethylation (to SOM 1522) followed by glucuronidation (2 entities) or sulfation. No oxidative metabolism or glucuronidation was seen in human lung microsomes, suggesting all metabolites of olodaterol are formed following systemic exposure. Following IV and IT dosing to rats, IV dosing to dogs and IH dosing to human subjects, olodaterol was the main circulating species, while olodaterol glucuronide (one entity; CD 992) was the main circulating species in mice following IT and IV dosing and rabbits following IV dosing. The metabolic profile was similar following IV and intratracheal dosing to rats and mice. Following both IV and IH dosing to human subjects, olodaterol glucuronide exposures were significant (at least 28% of olodaterol levels). The exposure level to olodaterol glucuronide (CD 992) in animals was considered adequate during the toxicity assessment (see Repeat dose toxicity). *In vitro* studies with human enzymes indicated a major role of CYP2C8 and 2C9 and to a lesser extent CYP3A4 in the formation of SOM 1522, and UGT2B7, with minor contributions from UGT1A1, 1A7 and 1A9, in the formation of olodaterol glucuronide. With SOM 1522 as a substrate, similar sulfation rates were seen with SULT1A1 and 1A3.

With the exception of sulphated SOM 1522, all human metabolites were found in animal species. SOM 1522 sulphate is only a minor metabolite in humans and, combined with the extremely low systemic exposures to total drug related material, the absence of this metabolite in animals is not expected to affect the validity of the toxicity profile. Chiral inversion of olodaterol (R isomer) to the S isomer is not expected to occur *in vivo*.

Excretion of drug related material was predominantly in the faeces of mice, rats and dogs following intratracheal and IV dosing, and both the urine and faeces of rabbits and humans following IV dosing. Drug related material in the faeces of mice, rats, rabbits and humans consisted of predominantly olodaterol and SOM 1522 while unchanged drug was the main drug related entity in the faeces of dogs. Drug related material in the urine from mice, rabbits and humans was both olodaterol and metabolites while drug related material in the urine from rats and dogs consisted of primarily unchanged drug. Biliary excretion was demonstrated in rats, rabbits and dogs, with a low level and slow rate of enterohepatic recycling demonstrated in rats. Drug related material in bile from rats and dogs was predominantly olodaterol, olodaterol glucuronide and SOM 1522 glucuronide and in bile from rabbits, predominantly olodaterol glucuronide. A high level of unchanged drug was seen in the faeces of all species following oral dosing, which is likely due to poor absorption.

Overall, the pharmacokinetic profile of olodaterol was qualitatively similar in the tested animal species and humans, thus supporting the use of the chosen species in the toxicity studies.

Pharmacokinetic drug interactions

In human liver microsomes, there was no significant inhibition of cytochrome P450 isozymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2E1 or 3A4 with olodaterol (less than or equal to 100 μM) or olodaterol glucuronide (less than or equal to 1 nM) or CYP2A6 or 4A11 with olodaterol (less than or equal to 100 μM)). Olodaterol was an inhibitor of CYP2D6 and olodaterol glucuronide was a mechanism based inhibitor of this isozyme (Ki 99 μM). However, given the low systemic exposures to olodaterol and olodaterol glucuronide, this is not likely to be clinically relevant. There was no significant induction of CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4 in human liver microsomes with olodaterol (less than or equal to 1 nM) or olodaterol glucuronide (less than or equal to 180 pM). Overall, olodaterol is not expected to alter the systemic exposure of co administered drugs via interactions with CYP

enzymes. As multiple enzymes are involved in the metabolism of olodaterol, co administered drugs are not expected to alter the systemic exposure of olodaterol via interactions with CYP enzymes.

Olodaterol is a substrate of P glycoprotein, OAT1, OAT3 and OCT1, but not BCRP, OATP2, OATP8, OATP-B, OCT2 or OCT3. There was, however, no clinically relevant inhibition of these transporters. Inhibitors of P glycoprotein, OAT1, OAT3 or OCT1 may alter the systemic exposure or disposition of olodaterol, but given the large safety margins (see Toxicity), this is not expected to raise any safety concerns.

Interactions involving tiotropium or ciclesonide

Previously submitted studies indicated that only limited metabolism of tiotropium occurs in human subjects with 74% renal excretion of unchanged drug after an IV dose. The metabolism that does occur involves primarily non enzymatic ester cleavage and metabolism by CYP2D6 and, to a lesser extent, CYP3A4. Tiotropium does not inhibit CYP1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes at clinically relevant concentrations (based on systemic exposure following inhalational administration[4]). Based on the available data, pharmacokinetic drug interactions between olodaterol and tiotropium involving CYP450s are not anticipated.

Ciclesonide is primarily hydrolysed by esterases (likely to be multiple enzymes) with the hydrolysis product further metabolised by CYP3A4 to form hydroxylated metabolites. CYP3A4 inhibitors have been shown to increase the exposure to the hydrolysis product (but not ciclesonide itself[5]). As stated above, olodaterol is not expected to have pharmacokinetic drug interactions with co administered drugs via interactions with CYP450 enzymes, and as ciclesonide is hydrolysed by multiple esterases, it is not expected that olodaterol would affect the metabolism of ciclesonide.

Both *in vitro* and *in vivo* studies were conducted to assess potential pharmacokinetic drug interactions involving olodaterol and tiotropium, while only *in vitro* interactions were assessed with ciclesonide. Consistent with the above, *in vitro* studies with human liver microsomes suggested a lack of effects of olodaterol on the metabolism of either tiotropium or ciclesonide and these compounds had no effect on the metabolism of olodaterol. However, in both rats and dogs, the systemic exposure (area under the plasma concentration time curve (AUC)) to tiotropium was marginally and consistently lower (by 14 to 34%) when co administered with olodaterol via the inhalational route. The reason for this effect is unknown. Tiotropium had no effect on the systemic exposure (AUC or Cmax) to olodaterol in rats and dogs.

Toxicology

Acute toxicity

Single dose toxicity studies with olodaterol were conducted in mice and rats following inhalation (the clinical route), oral and IV administration. All studies were conducted under GLP conditions and were in accordance with the EU guideline for single dose toxicity (3BS1a)[6] with an appropriate observation period. No deaths were observed at the maximum feasible inhalational dose, while maximum non-lethal doses were 1000 mg/kg PO and 20 mg/kg IV in mice and 316 mg/kg PO and 40 mg/kg IV in rats. Premature decedents at higher IV doses in mice and higher oral and IV doses in rats had gross pathological evidence of cardiovascular failure. Clinical signs in surviving animals were

[4] Spiriva Product Information document.
[5] Alvesco Product Information document.
[6] Single Dose Toxicity, Directive 75/318/EEC, 1987

similar in all studies; reduced motor activity, ventral recumbency, ataxia and increased breathing rate. Based on the extremely high relative exposures (AUC and Cmax) which would be expected at the maximum non-lethal doses, olodaterol was considered to have a low order of acute toxicity.

Repeat dose toxicity

Repeat dose toxicity studies were conducted in mice (13 weeks), rats (up to 26 weeks) and dogs (up to 52 weeks) using the proposed clinical route (inhalation). Based on the MMAD (mass median aerodynamic diameter), particle sizes were deemed to be respirable in the chosen species. All pivotal studies were GLP compliant and considered adequately conducted with appropriate group sizes and suitable monitoring and analyses performed. The pivotal rat and dog studies used the proposed clinical formulation. High systemic and local exposures to olodaterol were achieved (see Table 1 below). Plasma levels of olodaterol glucuronide, the main human metabolite, were not monitored in the studies but the formation of this metabolite in all of the tested species and the high systemic exposure to the parent compound in the toxicity studies, suggest the toxicity of olodaterol glucuronide was adequately assessed. The toxicity of olodaterol following oral and IV administration was also assessed in rats and dogs.

Relative exposure

Exposure ratios were calculated to assess the clinical relevance of both systemic and local effects (Table 1). Exposure ratios for systemic effects were calculated based on animal: human plasma Area Under the Curve during 24 hours ($AUC_{0\text{-}24h}$), while exposure ratios for local effects were calculated based on animal:human lung deposited dose adjusted for lung weight. Lung deposited doses were calculated based on 10%, 25% and 40% deposition in rodents, dogs and humans, respectively[7] and using animal weights of 0.03, 0.25 and 10 kg for mice, rats and dogs, respectively, and lung weights of 0.2, 1.5, 110 and 1000 g for mice, rats, dogs and humans, respectively.

[7] Wolff, R.K. and M.A. Dorato. (1993) Toxicologic testing of inhaled pharmaceutical aerosols. Crit. Rev. *Toxicol*. 23: 343-369.

Table 1. Systemic and local relative exposures achieved in the inhalational toxicity studies

Species	Study & duration	Dose (µg/kg/day IH)	Lung deposited dose (µg/g)	AUC_{0-24h} (nM·h)[a]	Exposure ratio	
					Local	Systemic
Mouse (CD-1)	U07-1341 [13 weeks]	63	0.95^	13.8	473	102
		211	3.17^	42.4	1583	314
		900	13.5^	138	6750	1022
		3258	48.9^	556	24435	4119
	U12-1065-01 [carcinogenicity]	26.1	0.39^	5.72	196	42
		76.9	1.15^	14.9	577	110
		255	3.83^	52	1913	385
Rat (Wistar Han)	U08-1691-01 [26 weeks]	49	0.82	8.45	408	63
		200	3.33	37.7	1667	279
		3400	56.7	773	28333	5726
	U11-2661-01 [carcinogenicity]	23.5/28 (♂/♀)	0.43	2.65	215	20
		69.5/82.4 (♂/♀)	1.27	8.62	633	64
		249/290 (♂/♀)	4.50	28.8	2250	213
Dog (Beagle)	U08-1740-01 [52 weeks]	15	0.34	2.86	170	21
		60	1.36	8.94	682	66
		330	7.50	48.1	3750	356
Human (COPD patients)	steady state	[5 µg/day]	0.002	0.135	–	–

[a]Data are the average of male/female data from last day sampled ^ Lung deposited dose assumed to be 10%

Major toxicities

Only findings in the longer term inhalational studies are discussed below. Lower doses were used in the shorter term inhalational studies and findings in these studies were generally similar to the pivotal studies. These studies are only cited with reference to onset of toxicity. Toxicity studies using the oral and IV routes were also conducted in both rats and dogs. The findings in these studies were generally similar to those seen in the inhalational studies. Any exceptional findings are discussed where relevant below.

The systemic toxicity profile of olodaterol was mostly consistent across the species and consistent with that seen with other beta 2 agonists and included cardiovascular effects, effects on body weight, skeletal muscle, adipose tissue and altered glycogen storage in the liver consistent with an anabolic effect, and effects on the female reproductive organs (rodents only). Local reactions in the respiratory tract of rodents were generally similar to those seen previously with inhaled products and appear largely to be due to irritant properties.

Body weight and skeletal muscle

Increased body weight gain and food consumption was seen in mice at greater than or equal to 63 µg/kg/day IH, rats at greater than or equal to 49 µg/kg/day IH and dogs (body weight gain only) at greater than or equal to 15 µg/kg/day IH. Increased muscle mass was seen in both mice and rats (at respective doses of greater than or equal to 26.1 and 23.5 µg/kg/day IH in the carcinogenicity studies) with a dose dependent increase in incidence and shortening of time of onset. This was associated with histopathological signs of skeletal muscle hypertrophy in some mice and muscle fibre necrosis in some rats, the latter of which was considered adverse. Consistent with an anabolic effect was a coincident

reduction in the size of adipose tissue in rats. These effects on skeletal muscle and adipose tissue are known pharmacological effects of beta agonists and were reversible after cessation of treatment.[8]

Cardiovascular effects

As discussed in the Safety Pharmacology section, olodaterol had positive chronotropic and inotropic effects in dogs, with a trend to tolerance with repeat dosing. There was some evidence of myocardial damage with elevated serum cardiac troponin I levels (in the first week of dosing only) and fibrotic foci in the myocardium at inhalational doses greater than or equal to 60 µg/kg/day (NOEL 15 µg/kg/day IH; Exposure ratio based on AUC (ER_{AUC}) 21). The fibrotic lesions were not reversible after a 6 week treatment free period. In the 2 year mouse study, an increased incidence of heart lesions (myocardial fibrosis, vacuolation, epicardial fibrosis and atrial thrombus) was seen in treated mice (particularly males) at greater than or equal to 26.1 µg/kg/day (ER_{AUC} 42), suggesting olodaterol treatment exacerbated the progressive cardiomyopathy seen in older mice. Reversible heart enlargement (but without histopathological findings) was seen in rats treated with greater than or equal to 49 µg/kg/day IH for 26 weeks (ER_{AUC} 63). Heart dilatation was not seen in rats treated for longer at higher doses, suggesting adaptation with prolonged dosing. All of these cardiovascular findings have been reported previously with other beta agonists and given the high safety margins for adverse cardiovascular effects, no greater risk of myocardial damage appears to exist with olodaterol.

Alteration in glycogen storage in liver

A slight reduction in liver weights was seen in treated mice and rats (at greater than or equal to 63 µg/kg/day IH in mice and greater than or equal to 49 µg/kg/day IH in rats) and altered glycogen storage was seen in the liver of treated dogs (greater than or equal to 60 µg/kg/day IH; NOEL 15 µg/kg/day IH, ER_{AUC} 21). These findings are considered to be associated with the pharmacology of olodaterol (glucagon receptor down regulation and stimulation of lipolysis), are not considered adverse, were fully reversible and are unlikely to be seen clinically.

Female reproductive tract

The female reproductive tract was a target organ in rodents. Ovarian cysts, smooth muscle hyperplasia and tubulostromal hyperplasia were seen in rats treated for 2 years with greater than or equal to 28 µg/kg/day IH olodaterol. Ovarian findings in mice included increased corpora lutea and sex cord/stromal hyperplasia at 255 µg/kg/day IH. Uterine tumours (leiomyoma and leiomyosarcoma) and cystic glands were seen in long term studies in mice (greater than or equal to 26.1 µg/kg/day IH). A NOEL was not established for an effect on the female reproductive system. Exposures at the lowest observable effect level (LOEL) were 42 and 20 times the clinical AUC in mice and rats, respectively. The findings in the uterus and ovaries of rodents are considered to be due to the pharmacological action of olodaterol but are not expected to be of clinical concern (see Carcinogenicity). There were no drug related effects on the female reproductive system in dogs at less than or equal to 330 µg/kg/day IH (ER_{AUC} 356) for 52 weeks.

Local reactions in the nasal cavity, larynx and trachea

Local irritation reactions in the larynx of rodents and nasal cavity and trachea of rats were a feature in the toxicity studies. A dose related increase in incidence and severity of transitional cell hyperplasia, leading to squamous metaplasia at higher doses, was seen in mice treated with greater than or equal to 63 µg/kg/day IH olodaterol for 13 weeks. After 104 weeks, the incidence of squamous metaplasia was significantly higher in mice treated

[8] Yang, Y.T. and M.A. McElligott. (1989) Multiple actions of beta-adrenergic agonists on skeletal muscle and adipose tissue. *Biochem.* J. 261: 1–10.

with 255 µg/kg/day IH olodaterol compared with those that received the vehicle (NOEL 76.9 µg/kg/day IH; relative local exposure (LER) 577). Squamous metaplasia was also observed in the larynx, nasal cavity and trachea of olodaterol treated rats (at greater than or equal to 200 µg/kg/day IH for laryngeal findings and at 3400 µg/kg/day IH for nasal cavity and tracheal findings). The NOEL for laryngeal findings was 49 µg/kg/day; LER 408). After 104 weeks of treatment, squamous metaplasia was also seen in the trachea of rats that received the vehicle (containing the excipients proposed for the clinical formulation, benzalkonium chloride, disodium edetate and citric acid) although a higher incidence was seen in rats that received olodaterol, suggesting some relationship of the finding with drug treatment.

A higher incidence of atrophy of the epithelium of the trachea and nasal cavity and degeneration/regeneration of the U shaped cartilage of the larynx was seen in rats treated for 26 weeks at 3400 µg/kg/day IH. The local exposure at the NOEL (200 µg/kg/day IH) was approximately 1660. Degeneration of the U shaped cartilage and squamous metaplasia of the larynx of treated rats was not reversible after a 4 week treatment free period. No dose related alterations were seen in the larynx or nasal cavity of treated dogs (NOEL 330 µg/kg/day; LER 3750).

Both the nasal cavity and laryngeal findings are commonly seen in inhalational studies in rodents and are thought to be associated with irritation reactions. Deposition of test article occurs in the respiratory tract of rats, leading to an inflammatory response. As the intended administration of olodaterol is through a mouth nebuliser, the nasal cavity effects are not considered clinically relevant. Squamous metaplasia of the larynx of rodents in inhalational studies is considered an adaptive response of the respiratory mucosa to chronic irritation rather than a toxicological response.[9] Given the absence of laryngeal findings in dogs and the high local exposures at the NOEL for drug related effects, squamous metaplasia of the larynx in rodents is not considered clinically relevant.

Other toxicities

Reddening of the skin and muzzle mucosa and swelling of the ears was seen in dogs treated with oral doses of greater than or equal to 50 µg/kg/day. These findings were not considered to be a pseudo allergic reaction but might be associated with peripheral vasodilation. Systemic exposure (plasma AUC) at the NOEL (16 µg/kg/day PO) was 2.94 nM.h, this is 22 times the clinical value and suggests this finding is not likely to be clinically relevant.

In the pivotal rat study, notable ocular findings included irreversible exophthalmos and prominent Harderian glands with corneal epithelial atrophy evident in microscopic analyses. These findings were seen in all dose groups at greater than or equal to 49 µg/kg/day IH olodaterol. The sponsor claims that these findings were due to exposure to the eyes during the inhalation process. Given that there were no drug related ophthalmological findings in any other rat study, including the 2 year carcinogenicity study at similar or higher exposures and no ophthalmological findings in treated mice or dogs, this explanation seems plausible. Therefore, given the nature of administration during clinical use, these findings are not considered to be of clinical concern.

Combination studies with tiotropium bromide

Two repeat dose toxicity studies were submitted that assessed the toxicity of the combination of olodaterol and tiotropium when administered by the inhalational route to dogs. The studies were of 13 weeks duration with a 6 week treatment free period included to assess the reversibility of toxicity findings. Different dose ratios were assessed (1:1, 1:2.5 and 2:1 olodaterol/tiotropium.) With combinations of 1:2.5 and 2:1

[9] Osimitz, T.G., W. Droege and J.M. Finch. (2007) Toxicologic significance of histologic change in the larynx of the rat following inhalation exposure: A critical review. *Toxicol. Appl. Pharmacol*. 225: 229-237.

olodaterol/tiotropium, the toxicity findings appeared to be largely additive and included dry mouth mucosa, dry nose and pupillary rigidity (attributable to tiotropium), positive inotropic effects with irreversible myocardial fibrosis/fibroplasia detected during post mortem analyses (attributable to olodaterol), altered glycogen storage in the liver (attributable to olodaterol) and dilatation of the intraglandular excretory ducts and neutrophils in the salivary gland ducts (attributable to tiotropium). Although a higher incidence of dilated pupils appeared to occur in the olodaterol/tiotropium combination groups, there appeared to be no significant exaggerated toxicities and no unexpected toxicities in the combination groups. The findings in the tiotropium groups were consistent with those reported previously for this compound.

With 1:1 olodaterol/tiotropium combinations, the toxicity findings were generally similar to those reported above except that tachycardia was more significant and myocardial damage appeared to be greater with the combination compared with monotherapies.

The local no observed adverse effect level (NOAEL) for the combinations was considered to be the highest tested doses: 310/290 µg/kg/day (1:1), 130/300 µg/kg/day (1:2.5) and 300/140 µg/kg/day (2:1) IH olodaterol/tiotropium. The systemic NOAEL (based on cardiovascular findings, was considered to be 16/14 µg/kg/day (1:1) and 16/36 µg/kg/day (1:2.5) IH olodaterol/tiotropium. A systemic NOAEL was not determined for the 2:1 group with myocardial damage evident in the only dose group assessed (300/140 µg/kg/day IH olodaterol/tiotropium).

Genotoxicity

The potential genotoxicity of olodaterol was assessed in the standard battery of tests. Concentrations in the *in vitro* tests were adequate, while the highest dose in the rat micronucleus test (40 mg/kg IV) was appropriate based on toxicity. Negative results were returned in the *in vitro* assays (a bacterial mutagenicity assay and an *in vitro* forward mutation assay in mouse lymphoma cells). An increase in micronucleated polychromatic erythrocytes (higher than concurrent and historical controls) was seen in rats treated with single IV doses of olodaterol greater than or equal to 10 mg/kg (ER_{AUC} approximately 65,000 based on data in Study U09-1845-01). The maximal increase was approximately 40% of the positive control response, and the no effect dose was 1 mg/kg IV (estimated ER_{AUC} greater than 6000). The increase occurred coincidentally with an increase in total polychromatic erythrocytes (PCEs). A mechanistic study indicated the induction of erythropoiesis at 40 mg/kg IV (the only dose tested). Increased erythropoiesis is known to increase the number of PCEs in bone marrow.[10] Therefore, such a mechanism is a plausible explanation for the positive genotoxicity result in the bone marrow of rats. Bone marrow samples were collected for the assessment of micronuclei after 4 weeks treatment in a repeat dose toxicity study in rats (Study U05-2133).

There was no evidence of an induction of micronuclei at inhalational doses less than or equal to 1360 µg/kg/day olodaterol ($AUC_{0\text{-}24h}$ 149 nM.h; ER_{AUC} approximately 1100). While it cannot be definitively stated that the increase in PCEs is associated with erythropoiesis, given (i) the exposures at the NOEL would far exceed those anticipated clinically, (ii) only negative results were seen in the *in vitro* genotoxicity assays and (iii) there was no evidence of an increase in a particular tumour type originating from a genotoxic mechanism in either the mouse or rat carcinogenicity studies at high systemic exposures (see below), the positive finding in one *in vivo* genotoxicity study is not considered to be of concern for the intended clinical use of olodaterol.

[10] Yajima, N., Y. Kurata, E. Imai, T. Sawai and Y. Takeshita. (1993) Genotoxicity of genetic recombinant human erythropoietin in a novel test system. *Mutagen*. 8: 231–236; Yajima, N., Y. Kurata, T. Sawai and Y. Takeshita. (1993b) Comparative studies in induction of micrpnuclei by three genetically recombinant and urinary human erythropoietins. *Mutagen*. 8: 237–241.

Carcinogenicity

The carcinogenic potential of olodaterol was investigated in 2 year carcinogenicity studies in mice and rats. Group sizes were appropriate and the proposed clinical route (inhalation) was used. Sufficiently high systemic exposures were achieved to assess the carcinogenic potential of olodaterol. An increased incidence of neoplastic and preneoplastic lesions in the female reproductive tract was seen in both species following olodaterol treatment. Uterine leiomyoma and leiomyosarcoma were seen in mice at greater than or equal to 26.1 µg/kg/day IH (ER_{AUC} 42). Sex cord stromal hyperplasia and luteal hyperplasia were seen in the ovary of mice at 255 µg/kg/day IH (ER_{AUC} 385). An increased incidence of mesovarian leiomyoma was seen in rats treated with 290 µg/kg/day IH olodaterol (ER_{AUC} 213) with preneoplastic lesions and cysts seen in the ovaries at greater than or equal to 28 µg/kg/day IH (ER_{AUC} 20).

Mesovarian leiomyomas in rats and uterine leiomyomas in mice are commonly reported for beta 2 adrenoceptor agonists and have been attributed to prolonged and intense activation of beta 2 adrenoceptors in the smooth muscle of the affected tissue, thereby leading to proliferative effects.[11] These tumours as a result of beta 2 adrenoceptor activation are generally not considered to indicate a risk for human use. Therefore, the profile in carcinogenicity studies with olodaterol is similar to that seen with other beta 2 adrenoceptor agonists and therefore olodaterol does not appear to pose a greater risk for carcinogenicity than currently registered beta 2 agonists.

Reproductive toxicity

A standard set of reproductive toxicity studies was submitted and covered effects on fertility and early embryonic development in rats, embryofoetal development in rats and rabbits and pre/postnatal development in rats. All pivotal studies were GLP compliant, used adequate animal numbers and dosing was performed in the appropriate periods. The clinical route (inhalation) was used in all studies and adequate systemic exposures were achieved in the embryofetal development studies with exposures in the remaining studies estimated to be sufficiently high (Table 2). There was considerable inter individual variability in plasma levels in rabbits (up to 10 fold). This is not expected to significantly affect the safety assessment, given the high exposure ratios.

Table 2. Relative systemic exposure in reproductive toxicity studies

Species	Study	Dose (µg/kg/day IH)	AUC_{0-24h} (nM·h)	Exposure ratio[#]
Rat (SD)	Fertility[a] [U08-2297-01]	55/64 (♂/♀)	4.8/6.0	36/44
		188/204 (♂/♀)	17.1/16.9	127/125
		2980/3241 (♂/♀)	309/372	2289/2756
	Embryofetal development [U05-2534]	64	29.1	216
		222	101	748
		1054	480	3556
	Pre/Postnatal development[a] [U08-1971-01]	59	5.3	39
		297	25.9	192
		3665	402	2978
Rabbit (NZW)	Embryofetal development [U06-1019]	274	39.7	294
		914	182	1348
		2741	959	7104
Human (COPD patients)	steady state	[5 µg]	0.135	–

[#] = animal:human plasma AUC_{0-24h}; [a] AUC values estimated from data in Study U05-2133 (4 week study)

[11] Jack, D., D. Poynter and N.W. Spurling. (1983) Beta-adrenoceptor stimulants and mesovarian leiomyomas in the rat. *Toxicol*. 27: 315–320; Sells, D.M. and J.P. Gibson. (1987) Carcinogenicity studies with medroxalol hydrochloride in rats and mice. *Toxicol. Pathol*. 15: 457–467.

Reduced epididymal and testicular weights were seen in male rats treated with greater than or equal to 55 µg/kg/day IH (ER_{AUC} 36) but there was no effect on sperm count, concentration or motility and no effect on functional fertility when both males and females were treated. The NOEL for fertility was considered to be 2980 µg/kg/day IH in males and 3241 µg/kg/day IH in females (estimated ER_{AUC} greater than 2000). Therefore, no effects on fertility are predicted during clinical use.

Olodaterol and or its metabolites crossed the placenta in rats. No adverse effects on embryofetal development were seen in rats treated with less than or equal to 1054 µg/kg/day IH olodaterol (ER_{AUC} 3556). Although there was a very slight delay in development in foetuses from rats treated with greater than or equal to 222 µg/kg/day IH, which was associated by an increased incidence of incomplete ossification, this was not considered an adverse effect. A higher incidence of major abnormalities (short or bent bones, cleft palate, cardiovascular abnormalities, patchy ossification) was seen in foetuses of rabbits treated with 2741 µg/kg/day IH. The NOAEL was considered to be 914 µg/kg/day IH olodaterol, achieving systemic exposures far in excess of those anticipated clinically (greater than 1300 times), suggesting these foetal findings are not expected to be clinically relevant.

Excretion of olodaterol and or its metabolites into milk was shown to be high in lactating rats with exposures in milk up to 6 times those of maternal plasma levels. In the pre and postnatal study in rats, dosing was temporarily ceased close to parturition because of the known tocolytic effect of beta 2 agonists. Otherwise, no adverse effects on pre and postnatal development were seen at doses less than or equal to 3665 µg/kg/day IH (ER_{AUC} almost 3000).

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.[12] Given the increased incidence of foetal major abnormalities seen in the rabbit embryofetal development toxicity study, this is considered appropriate.

Local tolerance

Local reactions in the respiratory tract following inhalational dosing are discussed in the Repeat dose toxicity section. Olodaterol was a slight irritant following IV dosing to rabbits (at 0.01 mg/mL), but no notable effects were seen following paravenous, IM or intraarterial injection. Olodaterol was not a dermal irritant but was found to be a mild to moderate ocular irritant to rabbits. Less than 1% haemolysis was observed in a human blood compatibility study. These nonclinical local tolerance findings do not signal any clinical concerns.

Paediatric use

Olodaterol is not intended to be used for the treatment of paediatric patients as COPD does not normally occur in children. Nonetheless, the sponsor submitted two juvenile dog studies conducted with inhalational olodaterol, a dose ranging study and a 13 week study. Animals were 14 to 19 days old at the commencement of treatment. In general, the findings were similar to those seen in adult dogs and included positive chronotropic and inotropic effects with a trend to reduced effects with repeat dosing and increased periportal glycogen storage in the liver. These effects were reversible. A distinctly different plasma concentration time profile of olodaterol was noted in animals aged approximately

[12] Pregnancy Category B3. Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

3.5 months compared with 15 to 19 days old, suggesting a possible age related effect on the disposition of olodaterol.

Excipients

Striverdi Respimat contains benzalkonium chloride (BZK) as a preservative. BZK is not a novel excipient for the inhalational route. The anticipated daily dose of BZK at the maximum recommended human dose (MRHD) of Striverdi Respimat is lower than that achieved at the MRHDs of other registered inhalational products and the concentration is similar to other products. All inhalational toxicity studies used formulations of olodaterol containing BZK at the proposed clinical concentration. Therefore, there are no toxicological concerns with the proposed use of BZK in Striverdi Respimat.

Details of recommended revisions to nonclinical statements in the proposed PI are beyond the scope of this AusPAR.

Nonclinical summary and conclusions

- The pharmacology studies support the use of olodaterol as a rapid onset, long acting bronchodilator.
- Inhibitors of P glycoprotein may increase the systemic exposure to olodaterol but this is not likely to raise any safety concerns.
- The toxicity profile of olodaterol was similar to that seen with other inhalational beta 2 agonists. The nonclinical studies suggest that the only notable effect which may be seen during clinical use is tachycardia which may become less evident with repeat dosing.
- The positive finding in one genotoxicity study is not considered to be clinically relevant.
- The uterine and mesovarian tumours seen in rodents are considered class and species specific effects and not considered to be of clinical concern.
- The reproductive toxicity studies revealed no safety concerns at clinically relevant exposures.
- There are no objections on nonclinical grounds to the registration of olodaterol.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The submission contained the following clinical information:

- 15 clinical pharmacology studies, including 14 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 7 dose finding Phase II studies (3 conducted in COPD patients, and 4 in asthma patients).
- 4 pivotal efficacy/safety (Phase III) studies consisting of 2 sets of replicate, randomised, double blind, parallel group studies, each with a 48 week treatment duration. One set of replicate Studies (Studies 1222.11 and 1222.12) was placebo

controlled, while the other set (Studies 1222.13 and 1222.14) was both placebo and active controlled (active control: formoterol).

- 6 other efficacy/safety studies (Phase III) including 2 sets of replicate, randomised, double blind, placebo and active controlled, cross over studies, each with a 6 week treatment duration, evaluating the lung function profile of olodaterol over 24 hours. In the first set of replicate studies (Studies 1222.24 and 1222.25), formoterol was the active control, and in the second set of replicate studies (Studies 1222.39 and 1222.40), tiotropium was the active control. In addition, there was 1 set of replicate, randomised, double blind, placebo controlled, cross over studies with a 6 week treatment duration to evaluate the effect of olodaterol on symptom limited exercise tolerance (Studies 1222.37 and 1222.38).
- Other reports including 9 combined pooled analyses reports. These consisted of the combined analyses of the respective sets of replicate Phase III studies (Studies 1222.11/1222.12 (report 1222-9992), Studies 1222.13/1222.14 (report 1222-9993), Studies 1222.24/1222.25 (report 1222-9991) and Studies 1222.39/1222.40 (1222-9994)), a Summary of Clinical Efficacy Supplement (report 1222-9995), a Summary of Clinical Safety Supplement (report 1222-9996), a meta-analysis of ADRB2 haplotypes across Studies 1222.11, 1222.12, 1222.13 and 1222.14 (report 1222-0050), a combined analysis of two Phase II Studies (1222.5 and 1222.6) evaluating the covariate effects on olodaterol pharmacokinetic (PK) parameters in patients with COPD (Study 1222.5) and those with persistent asthma (Study 1222.6) (report 1222-9956), and an "embellished narrative summary table", which is an additional tabulation of subjects in Studies 1222.11, 1222.12, 1222.13, 1222.14, 1222.39 and 1222.40 with serious adverse event (SAE) or non-SAE leading to discontinuation.
- No population pharmacokinetic analyses were provided.

In this evaluation, the four (2 sets of replicate studies) 48 week Phase III studies (Studies 1222.11/1222.12 and 1222.13/ 1222.14) will be evaluated as pivotal efficacy/safety studies, with the other six (3 sets of replicate studies) Phase III studies (Studies 1222.24/1222.25, 1222.39/1222.40, and 1222.37/1222.38) evaluated as supporting efficacy/safety studies. The 3 Phase II studies in COPD patients will be evaluated with regards to the rationale for the selected dosing regimen in the Phase III studies. As this submission is for the indication for use of olodaterol in COPD patients, and as per instructions in the TGA's "notes to evaluator", the 4 Phase II studies conducted in asthma patients will be evaluated only for safety and will be described and evaluated in the safety section in this report. With regards to the combined/pooled analyses reports submitted, the sponsor's Summary of Clinical Safety Supplement and the "embellished narrative summary table" involved only safety data and will be described and evaluated in the safety section in this report. The sponsor's Summary of Clinical Efficacy Supplement and the Summary of Clinical Safety Supplement consisted of a listing of tables on efficacy and safety data, respectively, from the Phase III efficacy/safety studies, which were referenced in the sponsor's Summary of Clinical Efficacy and the Summary of Clinical Safety, respectively, but not found in the individual or combined study reports (for example combined dataset from all 4 pivotal Phase III studies). As such, they will not be presented separately but data drawn from these 2 reports will be incorporated and discussed in the evaluation of efficacy and safety.

In addition, there are additional reports submitted, consisting of 4 Phase II studies, all with treatment duration of 4 weeks (one study was a dose response and PK study in Japanese COPD patients, while the other 3 studies involved the evaluation of a fixed dose combination of tiotropium and olodaterol in COPD patients). As these studies are not relevant to the evaluation of this submission, the sponsor is not proposing a fixed dose combination formulation in this submission, and these studies are not referenced either in the Summary of Clinical Efficacy and Summary of Clinical Safety or in the TGA's "notes to

evaluator", these studies will be evaluated with regards to whether the results has raised concerns relevant to this submission.

Paediatric data

The submission did not include paediatric data. As COPD is not a disease affecting paediatric patients the use of olodaterol in the treatment of COPD is not considered relevant in the paediatric population.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.[13]

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 below provides a summary of the studies providing PK data.

Table 3. Submitted pharmacokinetic studies

PK topic	Subtopic		Study ID	*
PK in healthy adults	General PK	- Single dose	U06-1418	*
			U08-1081	*
			U08-1060	*
			U08-2268	
			U08-3758	*
		- Multi-dose	U07-2062	*
			U08-3758	*
	Food effect		No studies	
PK in special populations	Target population COPD		U09-1422	
	Hepatic impairment		U10-2864	*
	Renal impairment		U10-2081	*
	Neonates/infants/children/adolescents		No studies	
	Elderly		No studies	
Genetic/gender -related PK	Males vs. Females		No specific studies	

[13] European Medicines Agency, "ICH Topic E 6 (R1) Guideline for Good Clinical Practice Step 5: Note for guidance on good clinical practice (CPMP/ICH/135/95)", July 2002, Web, accessed 6 February 2014 <www.edctp.org/fileadmin/documents/EMEA_ICH-GCP_Guidelines_July_2002.pdf>

PK topic	Subtopic	Study ID	*
PK interactions	Tiotropium	U09-1422	*
	Ketoconazole	U10-3390	*
	Fluconazole	U10-3391	*
Population PK analyses	Healthy subjects	No studies	
	Target population	No studies	

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacokinetics

In general the PK studies presented by the sponsor were well designed and for the most part subject numbers were based on a priori power calculations, with the numbers of subjects investigated meeting the requirement for the pre-determined power. Dose proportionality of kinetics was demonstrated across a range of doses which exceeded that recommended for therapeutic use.

Metabolism of the medication was thoroughly investigated and although there is an active metabolite it is present in concentrations unlikely to contribute to pharmacological activity. The effects of renal and hepatic impairment on single dose PK were investigated in two studies. These were adequately powered and suggested that hepatic impairment does not significantly alter the PK of olodaterol. On the other hand, severe renal impairment increases systemic exposure to olodaterol.

There was no specific study examining extremes of age on the PK of olodaterol. The effect of age on PK was inferred from a multivariate analysis. A study in Japanese subjects suggested that systemic exposure after both single and repeated doses (by inhalation) was increased compared to Caucasians. This conclusion relied on a post hoc comparison across different studies so was not derived from a simultaneous assessment. Similarly the PK in Black subjects was available from post hoc comparisons in limited PK sampling in the clinical trial program. Numbers of subjects may have been inadequate to draw meaningful conclusions about PK in such populations. There was no population PK analysis performed based on sparse sampling although there appears to be data available to perform such an analysis with standard methods. Such an analysis would allow for further exploration of issues known to influence clearance (such as age, weight, ethnicity) and would further add to the conclusions drawn from multivariate analysis.

Based on the known metabolic profile of olodaterol and the enzymes responsible, some drug-drug interaction studies were performed. These were adequately powered and suggested that olodaterol PK was not affected by fluconazole (CYP2C9 inhibitor) but systemic exposure was increased by ketoconazole (P-gp inhibitor). The lack of specificity of ketoconazole (for P-gp) leaves open the possibility of CYP enzymes being involved in this observation. A study with a selective P-gp inhibitor (for example, quinidine) would have been more informative. Thus questions remain about the PK interaction potential of olodaterol with other commonly prescribed agents. Furthermore neither study had a physiological end point included, such as Forced Expiratory Volume in One Second (FEV1), which might have been more relevant to assess interaction potential given the proposed therapeutic indication.

An interaction study with tiotropium was also performed with the view that both drugs may be used concomitantly for COPD treatment. While there no interaction on the PK of either drug no physiologically relevant end point was included. Tiotropium was the only medication regularly used in the treatment of COPD for which an interaction with olodaterol was studied. There were no studies which examined the potential interaction with other bronchodilators and inhaled steroids. Similarly, no studies were presented which examined the potential interaction of olodaterol with antibiotics which are often co administered in COPD patients.

Pharmacodynamics

Studies providing pharmacodynamics data

Table 4 below shows the studies relating to each pharmacodynamic topic.

Table 4. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on cyclic AMP	U06-1418 U07-2062 U08-1060	
		U08-1081	
Secondary Pharmacology	Effect on heart rate	U08-1543 U09-3125	 §
	Effect on blood pressure	U08-1543 U06-1418	
	Effect on potassium concentrations	U06-1418 U07-2062 U07-1743 U07-2062 U08-1060 U08-1081 U09-3125 U10-3192 U10-3193 U10-3194 U10-3195	 § § § § § §
	Effect on QTc interval	U08-1543	*
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	U08-1543	
	Effect of age	No Studies	

PD Topic	Subtopic	Study ID	*
PD Interactions		No Studies	
Population PD and PK-PD analyses	Healthy subjects	No Studies	
	Target population	No Studies	

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacodynamics

A thorough QTc study was performed using moxifloxacin as a positive control to investigate the effects of olodaterol on the corrected interval. The effect was less than 10 ms on the QT interval even at doses which exceeded that to be used in clinical practice (5 to 10 µg). Olodaterol had effects on plasma cAMP concentrations and on plasma potassium. The former increased and the latter decreased dose dependently. The consequences of increased cAMP are not known. The decrease in potassium was relatively small and probably not clinically significant. The lack of drug interaction studies evaluating PD based outcomes is surprising given the indication for the medication and the potential for it to be used with other agents in management of COPD.

Dosage selection for the pivotal studies

The sponsor had provided the rationale for the dose selection of olodaterol for the Phase III studies (5 µg and 10 µg once daily). The dose selection for the Phase III clinical development program for olodaterol was based on the safety and tolerability results and the dose response relationship results in 2 Phase II studies, Study 1222.3 (single dose study in COPD patients) and Study 1222.5 (4 week once daily dosing study in COPD patients). These 2 studies showed no safety or tolerability concerns after single dose administration of up to 40 µg (Study 1222.3) and after 4 week once daily dosing of up to 20 µg (Study 1222.5). In addition, in Study 1222.5, the effects of olodaterol on systemic pharmacodynamic (PD) parameters (serum potassium and creatine phosphokinase) were used to identify the threshold for the onset of systemic PD activity, and hence support an appropriate dose selection for the Phase III studies. Results showed that after the first dose, serum potassium levels for olodaterol 2 µg, 5 µg and 10 µg were similar to placebo, while there were small but statistically significant reductions in serum potassium levels for olodaterol 20 µg compared to placebo. After 4 weeks of treatment, there were no statistically significant differences in serum potassium levels at any dose compared to placebo. Evaluations of serum creatine phosphokinase showed a similar pattern, suggesting that the threshold for systemic PD activity for olodaterol was about 20 µg in patients with COPD.

Evaluation of the efficacy dose response relationship of olodaterol in Studies 1222.3 and 1222.5 (doses of 2 µg, 5 µg, 10 µg and 20 µg olodaterol were investigated in both studies) showed no clear evidence of an incremental increase in efficacy for olodaterol 20 µg compared to olodaterol 10 µg based on FEV1 (forced expiratory volume in one second) responses. The efficacy associated with administration of olodaterol 2 µg was consistently lower than that with olodaterol 10 µg or 20 µg, while the relative efficacy of olodaterol 5 µg was more variable than the response with 2 µg and with 10 µg, such that the position of olodaterol 5 µg on the dose response curve could only be characterised as intermediate between suboptimal (2 µg) and plateauing in efficacy (10 or 20 µg). These efficacy results will be described later in this section.

The sponsor had judged that the above results supported the selection of olodaterol 10 µg for further evaluation in the Phase III studies, while olodaterol 5 µg was also included because it was judged that the variability in efficacy observed in the Phase II studies warranted further investigation in larger Phase III studies. Prior to initiation of the Phase III program, the decision to evaluate olodaterol 5 µg and olodaterol 10 µg in the Phase III studies had been accepted by the FDA at the end of Phase II meeting and by the Netherlands Medicines Evaluations Board[14] at the Scientific Advice Meeting.

The efficacy results of Studies 1222.3 and 1222.5 will be described briefly in this section. Studies 1222.3 and 1222.5 were Phase II studies in COPD patients. Study 1222.3 was a single dose, randomised, double blind, placebo controlled, 5 way cross over study evaluating the efficacy and safety of single doses of orally inhaled olodaterol (2 µg, 5 µg, 10 µg, and 20 µg) in COPD patients, followed by an optional period of open label olodaterol 40 µg (to assess pharmacokinetics (PK) of 40 µg olodaterol[15]). The primary endpoint was FEV1 at 24 hours post dose (that is, trough FEV1). Results from Study 1222.3 showed that all single doses of olodaterol (2 µg, 5 µg, 10 µg, and 20 µg) had statistically significantly greater FEV1 at 24 hour post dose compared to placebo.

Study 1222.5 was a 4 week, randomised, double blind, placebo controlled parallel group study evaluating the efficacy and safety after 4 weeks of once daily treatment of orally inhaled olodaterol (2 µg, 5 µg, 10 µg, and 20 µg) in COPD patients. The primary endpoint was the trough FEV1 response after 4 weeks of treatment. Results showed that after 4 weeks of treatment, there were statistically significantly greater mean trough FEV1 response and FEV1 area under the time curve from 0 to 3 hours after dosing ($AUC_{0\text{-}6h}$) response for all olodaterol doses compared to placebo. With regards to dose response relationship, doses of olodaterol 10 µg and olodaterol 20 µg showed increased efficacy (in terms of trough FEV1 response) compared with olodaterol 2 µg, suggesting that olodaterol 2 µg was on the steep portion of the dose response curve. The efficacy of olodaterol 10 µg and olodaterol 20 µg was similar, suggesting that both doses were on, or close to, the plateau of the dose response curve. Over the 4 week study duration, the relative efficacy of olodaterol 5 µg compared with olodaterol 2 µg and olodaterol 10 µg was variable, such that in some cases, similar efficacy was observed between olodaterol 2 µg and olodaterol 5 µg, in some cases, similar efficacy was observed between olodaterol 5 µg and olodaterol 10 µg, and in some cases, the efficacy of olodaterol 5 µg was between those of olodaterol 2 µg and olodaterol 10 µg.

> Comments: The evaluator considered the rationale for the dose selection in the Phase III studies is appropriate.

Efficacy

Studies providing efficacy data

Four pivotal Phase III studies were submitted to support clinical efficacy for the proposed indication. These consisted of 2 sets of replicate, randomised, double blind, parallel group studies, each with a 48 week treatment duration, where one set of replicate studies (Studies 1222.11 and 1222.12) was placebo controlled, while the other set (Studies

[14] Netherlands is the Reference Member State in EU.

[15] The open-label period of study 1222.3 was conducted to characterise the PK of two metabolites of olodaterol, SOM 1522 BS and BI 1744 BS–glucuronide, following single inhalation of 40 µg of olodaterol in COPD patients. The PK results of this open label period were presented in report 1222.9003. These PK results are not relevant to the evaluation of this submission for registration of olodaterol. They were evaluated for the purpose of this evaluation, and the results did not raise any concerns relevant to this submission, and hence will not be further described in this evaluation. Safety results of subjects on 40 µg of olodaterol was described in the main study report (1222.3), and will be described and evaluated in the Safety section of this report.

1222.13 and 1222.14) was both placebo and active controlled (active control: formoterol). All 4 studies evaluated the efficacy of olodaterol with respect to bronchodilatation (peak and trough lung function responses). In addition, the replicate Studies 1222.13 and 1222.14 included endpoints evaluating potential symptomatic benefit by reduction of dyspnoea (assessed via the Mahler Transition Dyspnoea Index (TDI) focal score), and by improvement of health related quality of life (assessed via the St. George's Respiratory Questionnaire (SGRQ) total score). The sponsor had stated that Studies 1222.11 and 1222.12 were designed to satisfy the clinical regulatory standards in the US, with primary efficacy evaluation after 12 weeks of treatment, efficacy endpoints based upon lung function assessment, and being placebo controlled. However Studies 1222.13 and 1222.14 were designed to satisfy the clinical regulatory standards in the EU, with primary efficacy evaluation after 24 weeks of treatment, efficacy endpoints based upon assessment of both lung function and symptomatic benefit, and being both placebo and active controlled with an active comparator of known therapeutic benefit.

In addition, 6 supporting Phase III efficacy studies were submitted. These included 2 sets of replicate, randomised, double blind, placebo and active controlled, cross over studies, each with a 6 week treatment duration, evaluating the lung function profile over a 24 hour dosing interval in order to characterise the bronchodilator profile of olodaterol over 24 hours. The first set of replicate studies, Studies 1222.24 and 1222.25, used formoterol as the active control, and the second set of replicate studies, Studies 1222.39 and 1222.40, used tiotropium as the active control. In addition, there is another set of replicate, randomised, double blind, placebo controlled, cross over studies (Studies 1222.37 and 1222.38) with a 6 week treatment duration to evaluate the effect of olodaterol on symptom limited exercise tolerance. An overview of the main efficacy variables in the olodaterol Phase III studies is presented in the table below.

Table 5. Main efficacy variables overview

	Trial				
Variable	1222.11 1222.12	1222.13 1222.14	1222.24 1222.25	1222.39 1222.40	1222.37 1222.38
Pulmonary function					
FEV_1	X	X	X	X	X
FVC	X	X	X	X	X
Morning PEFR	X	X			
Evening PEFR	X	X			
Functional Residual Capacity (FRC)					X
Inspiratory Capacity (IC)					X
Symptomatic benefit					
Mahler Transition Dyspnea Index (TDI)		X			
St. George's Respiratory Questionnaire (SGRQ)		X			
Daily rescue medication (salbutamol/albuterol)	X	X			
Patient's global rating (PGR)	X	X			
Exercise					
Exercise endurance time					X
Inspiratory capacity (IC) during exercise					X
Breathing discomfort during exercise					X
COPD Exacerbations					
Time to first exacerbation	X	X			

Other studies to be evaluated for efficacy included the 3 Phase II studies conducted in COPD patients, and the combined/pooled analyses reports. In this efficacy section of this evaluation report, the respective sets of replicate studies will be presented in the same sub sections, together with their combined analysis results, for ease of reference.

Evaluator's overall conclusions on efficacy

The bronchodilator efficacy of olodaterol was evaluated through effects on FEV1 as well as effects on symptom relief and health related quality of life. Overall, analyses on effects of olodaterol on FEV1 compared to placebo yielded results which were supportive of the

efficacy claim of both doses of olodaterol (5 µg four times daily (qd) and 10 µg qd) over placebo. Analyses on effects of olodaterol on symptom relief and health related quality of life compared to placebo also yielded results which were generally supportive of the efficacy claim of both doses of olodaterol over placebo.

With regards to effects on FEV1, efficacy results in the 4 pivotal Phase III studies showed that both olodaterol 5 µg qd and olodaterol 10 µg qd had statistically significantly greater mean change from pre-treatment baseline in FEV1 AUC_{0-3h} and in trough FEV1 compared to placebo, after 12 weeks of treatment (Studies 1222.11 and 1222.12) and after 24 weeks of treatment (Studies 1222.13 and 1222.14).

Secondary endpoints in Studies 1222.11 and 1222.12 characterising the 12 hour post dose FEV1 profile on Day 85 (that is, after 12 weeks of treatment) showed that the mean FEV1 increased within 5 minutes after the administration of both olodaterol dose levels, peaked around 2 to 3 hours post dose and then reduced progressively towards baseline, although at 12 hours post dose, the difference from placebo was still statistically significant in favour of both doses of olodaterol. The statistically significantly greater mean trough FEV1 response at Day 85 with both doses of olodaterol compared to placebo suggested that the bronchodilator effect of both doses of olodaterol was sustained at the end of the 24 hour dosing interval. This FEV1 time profile of olodaterol was supported by that found in Studies 1222.13 and 1222.14. The statistically significantly greater mean trough FEV1 response at Day 169 with both doses of olodaterol compared to placebo suggested that the bronchodilator effect of both doses of olodaterol was sustained at the end of the 24 hour dosing interval after 24 weeks of treatment. The 24 hour bronchodilatory profile of olodaterol was also supported by the results in the 2 sets of replicate, non-pivotal 6 week Phase III studies conducted to evaluate FEV1 profile of olodaterol over a continuous 24 hour dosing interval (Studies 1222.24/1222.25 and1222.39/1222.40). In these studies, there were statistically significantly greater mean FEV1 AUC_{0-12h} response, FEV1 AUC_{12-24h} response, and FEV1 AUC_{0-24h} response at Day 43 (that is, Week 6) for both olodaterol 5 µg qd and olodaterol 10 µg qd compared to placebo.

Evaluation of FEV1 profile over 48 weeks of treatment duration showed that there were statistically significant differences in FEV1 at all individual post dose time points up to 3 hour post dose over 48 weeks (at Day 1 and after 2, 6, 12, 24 and 48 weeks) between placebo and both olodaterol doses (in favour of olodaterol) in all 4 pivotal Phase III studies. Analyses on the effects of olodaterol on FEV1 area under the time curve from 0 to 3 hours (AUC_{0-3h}) response, trough FEV1 response, and FEV1 $peak_{0-3h}$ response over 48 weeks also showed statistically significantly greater responses for both olodaterol 5 µg qd and olodaterol 10 µg qd compared to placebo on all test days (at Day 1 and after 2, 6, 12, 24 and 48 weeks) in all 4 pivotal Phase III studies, except for olodaterol 10 µg on Day 225 (Week 32) in Study 1222.12 for the endpoint of trough FEV1 response, and olodaterol 5 µg on Day 281 (Week 40) in Study 1222.13 for the endpoint of trough FEV1 response confirming the long term efficacy of olodaterol.

Comparison between the olodaterol and the formoterol in the pooled dataset of Studies 1222.13 and 1222.14 showed that there was no statistically significant difference between olodaterol 5 µg qd and formoterol 12 µg twice daily (bid) for the primary endpoints of FEV1 AUC_{0-3h} response and trough FEV1 response at Day 169, and between olodaterol 10 µg qd and formoterol 12 µg bid for the primary endpoint of FEV1 AUC_{0-3h} response. For the primary endpoint of trough FEV1 response, there was a statistically significantly greater mean trough FEV1 response at Day 169 with olodaterol 10 µg qd compared to formoterol 12 µg bid. In addition, the post dose FEV1 time profile was similar between both olodaterol doses and formoterol, with increase in FEV1 occurring within 5 minutes post dose and then sustained over the 3 hour post dose evaluation period. These results were generally supported by those in the replicate non pivotal Phase III Studies 1222.24 and 1222.25, showing that there was no statistically significant difference between both

olodaterol doses and formoterol in the pooled dataset in the mean FEV1 $AUC_{0\text{-}24h}$ response at Day 43, although evaluating the mean FEV1 area under the time curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) response and the mean FEV1 area under the time curve from 12 to 24 hours ($AUC_{12\text{-}24h}$) response at Day 43 separately showed that while there were no statistically significant differences between either dose of olodaterol and formoterol in the mean FEV1 $AUC_{0\text{-}12h}$ response, the mean FEV1 $AUC_{12\text{-}24h}$ response for formoterol 12 µg bid was statistically significantly greater than that for olodaterol 10 µg qd (−40 mL difference, p=0.0024) and for olodaterol 5 µg qd (−50 mL difference, p=0.0001), likely due to the second evening dose of formoterol.

Comparison with tiotropium 18 µg qd in the replicate non pivotal Phase III Studies 1222.39 and 1222.40 also showed that there was no statistically significant difference between both olodaterol doses and tiotropium in the pooled dataset in the mean FEV1 $AUC_{0\text{-}24h}$ response at Day 43. Evaluating the mean FEV1 $AUC_{0\text{-}12h}$ response and the mean FEV1 $AUC_{12\text{-}24h}$ response at Day 43 separately showed that there were no statistically significant differences between either dose of olodaterol and tiotropium in the mean FEV1 $AUC_{0\text{-}12h}$ response, and between olodaterol 5 µg and tiotropium in the mean FEV1 $AUC_{12\text{-}24h}$ response. The mean FEV1 $AUC_{12\text{-}24h}$ response for olodaterol 10 µg qd was statistically significantly greater than that for tiotropium 18 µg qd.

The evaluation of the effects of olodaterol on symptom relief and health related quality of life was assessed primarily in the replicate pivotal Phase III Studies 1222.13 and 1222.14 using the Mahler TDI focal score at Day 169 (co primary endpoint; pooled dataset) and the St. George's Respiratory Questionnaire (SGRQ) total score at Day 169 (key secondary endpoint; pooled dataset). This was supplemented by analyses of rescue medication use, the 7 point Patient's Global Rating (PGR) scale (used by the subjects to rate perceived changes in their respiratory condition), and COPD exacerbations in the 4 pivotal Phase III studies, and of exercise endurance time during constant work rate cycle ergometry in the replicate non pivotal Phase III Studies 1222.37 and 1222.38.

Analysis of the mean Mahler TDI focal (that is, total) score at Day 169 in the pooled dataset of Studies 1222.13 and 1222.14 showed that there was no statistically significant difference between both olodaterol doses and placebo. The sponsor had stated that the results of the Mahler TDI focal score in the combined dataset might not be reliable as the analyses in the individual studies yielded inconsistent results between the 2 studies. However, it was noted that despite the inconsistency between studies, both individual studies had yielded results that were not statistically significant, although it is acknowledged that the studies had not been powered to show statistical significance for this endpoint at the level of analyses in the individual studies, only for analysis in the combined dataset. Nonetheless, analyses of the Mahler TDI component scores at Day 169 in the pooled dataset also showed no statistically significant difference between both olodaterol doses and placebo across all 3 components, and analyses of the Mahler TDI focal and component scores over 48 weeks in both individual studies showed that the differences between both olodaterol doses and placebo were mostly not statistically significant. However, it is noted that analyses in the formoterol group yielded similar results, showing no statistically significant difference between formoterol and placebo in the mean Mahler TDI focal and component scores at Day 169 in the pooled dataset. In addition, comparison between olodaterol and formoterol group in the pooled dataset showed that there was no statistically significant difference between both olodaterol doses and formoterol in the Mahler TDI focal score at Day 169.

Analyses of the SGRQ total and component scores at Day 169 in the pooled dataset of Studies 1222.13 and 1222.14 showed that there were statistically significantly lower SGRQ total and component scores (that is, better outcome) at Day 169 for both olodaterol doses compared to placebo. By comparison, there was no statistically significant difference in the SGRQ total or component scores at Day 169 between formoterol and placebo.

Analyses of rescue medication use and the PGR generally supported the efficacy claim for olodaterol over placebo. Analyses of the weekly mean number of daytime rescue medication, night time rescue medication, and daily (24 hour) rescue medication showed that reductions from placebo were statistically significant for both olodaterol doses at most time points in the pooled dataset of Studies 1222.11 and 1222.12, and that of 1222.13 and 1222.14 (although in the individual Study 1222.14, while the results were mostly statistically significant in favour of olodaterol 10 µg over placebo, they were mostly not statistically significant for olodaterol 5 µg). Analyses of the PGR over 48 weeks (Weeks 6, 12, 24 and 48) showed that there were statistically significantly lower scores (that is, better rating) for both olodaterol doses compared to placebo, at all (in pooled dataset of Studies 1222.11 and 1222.12) or most (in pooled dataset of Studies 1222.13 and 1222.14) time points. The results comparing formoterol and placebo were similar.

However, analyses of the endpoints of exacerbations of COPD showed that there was no statistically significant difference in the time to first COPD exacerbation, first moderate COPD exacerbation, or first COPD exacerbation leading to hospitalisation between both olodaterol doses and placebo, in all 4 individual pivotal Phase III studies, as well as their respective pooled datasets. There were also no statistically significant differences between both olodaterol doses and placebo in the mean number of COPD exacerbations, mean number of moderate COPD exacerbations, or mean number of COPD exacerbations leading to hospitalisation in all 4 individual pivotal Phase III studies and their respective pooled datasets. It is, however, noted that analyses comparing formoterol and placebo also yielded similar results, with no statistically significant difference observed between formoterol and placebo for these endpoints.

Results in the replicate non pivotal Phase III Studies 1222.37 and 1222.38 showed that after six weeks of treatment, mean endurance time during constant work rate cycle ergometry was statistically significantly longer for both olodaterol doses compared with placebo. Compared to placebo, endurance time was longer by about 12% to14% with olodaterol 5 µg qd and about 11% to 14% with olodaterol 10 µg qd, although the difference in treatment means between both olodaterol doses and placebo was less than 1 minute.

Although 2 doses of olodaterol were tested in the Phase III studies, the recommended dose in the proposed Product Information (PI) was 5 µg of olodaterol given as two puffs from the Respimat inhaler once daily. The sponsor had provided a comparison of the difference from placebo in mean FEV1 $AUC_{0\text{-}3h}$ response and trough FEV1 response for olodaterol 5 µg and for olodaterol 10 µg in the Phase III studies, which showed that the results were similar between the 2 doses. A comparison of the difference from placebo in mean FEV1 $AUC_{0\text{-}12h}$ response and FEV1 $AUC_{0\text{-}24h}$ response for olodaterol 5 µg and for olodaterol 10 µg in the Phase III studies also showed results were generally comparable between the 2 doses. The FEV1 time profiles on Day 1 were also similar between olodaterol 5 µg and olodaterol 10 µg in the 4 pivotal Phase III studies. For both doses, FEV1 increased within 5 minutes after the first administration (increases from pre-treatment baseline in mean FEV1 of 0.128 L and 0.129 L for olodaterol 5 µg and olodaterol 10 µg, respectively, in Study 1222.11, 0.135 L and 0.133 L, respectively, in Study 1222.12, 0.136 L and 0.133 L, respectively, in Study 1222.13, and 0.121 L and 0.131 L, respectively, in Study 1222.14), with further increases after 15 minutes (increases from pre-treatment baseline in mean FEV1 of 0.168 L and 0.166 L for olodaterol 5 µg and olodaterol 10 µg, respectively, in Study 1222.11, 0.169 L and 0.166 L, respectively, in Study 1222.12, 0.176 L and 0.167 L, respectively in Study 1222.13, and 0.154 L and 0.166 L, respectively, in Study 1222.14), and 30 minutes (increases from pre-treatment baseline in mean FEV1 of 0.183 L and 0.181 L for olodaterol 5 µg and olodaterol 10 µg, respectively, in Study 1222.11, 0.187 L and 0.188 L, respectively, in Study 1222.12, 0.191 L and 0.187 L, respectively in Study 1222.13, and 0.167 L and 0.186 L, respectively, in Study 1222.14).

With regards to effects on symptomatic relief and health related quality of life between olodaterol 5 µg and olodaterol 10 µg, the TDI focal scores for both doses of olodaterol were similar throughout the 48 weeks of treatment in the pooled dataset of Studies 1222.13 and 1222.14, and analysis showed there was no statistically significant difference between the 2 doses for this endpoint. There was also no statistically significant difference between the 2 doses for the SGRQ total score at Day 85, Day 169 and Day 337.

Overall, these results showed that there was no obvious clinically meaningful increase in benefit with olodaterol 10 µg once daily compared to olodaterol 5 µg once daily. The selection of olodaterol 5 µg once daily as the recommended therapeutic dose in the proposed PI is appropriate.

With regards to the proposed posology of once daily administration instead of twice daily, results in the pivotal Phase III studies showed statistically significantly greater mean trough FEV1 response at Day 85 and at Day 169 with olodaterol 5 µg qd compared to placebo, suggesting that the bronchodilator effect of both doses of olodaterol was sustained at the end of the 24 hour dosing interval after 12 and 24 weeks of treatment. Comparison of olodaterol 5 µg qd with formoterol 12 µg bid (pooled dataset of Studies 1222.13 and 1222.14) also showed that there were no statistically significant difference in trough FEV1 response between olodaterol 5 µg qd and formoterol 12 µg bid at Day 169. This was supported by results in the pooled dataset of the replicate Phase II Studies 1222.24 and 1222.25, which showed that there were no statistically significant differences in mean FEV1 $AUC_{0\text{-}24h}$ and mean trough FEV1 responses between olodaterol 5 µg qd and formoterol 12 µg bid. Results in the Phase II Study 1222.26 supported the dose regimen of olodaterol 5 µg qd instead of olodaterol 2 µg bid, showing that despite the additional evening dose of olodaterol 2 µg there was no statistically significant difference in the effect on FEV1 between olodaterol 5 µg qd and olodaterol 2 µg bid in the 12 to 24 hours post dose period (FEV1 $AUC_{12\text{-}24h}$), and that overall in the 24 hour post dose period (FEV1 $AUC_{0\text{-}24h}$), there was no statistically significant difference in the effect on FEV1 between olodaterol 10 µg qd and olodaterol 5 µg bid.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies (Studies 1222.11, 1222.12, 1222.13 and 1222.14), the following safety data were collected:

- General adverse events (AEs) were assessed by the investigator obtaining and recording all AEs at each scheduled visit
- AEs of particular interest
  - The sponsor had stated that in Studies 1222.11 and 1222.12, particular attention was to be paid to respiratory events indicative of bronchoconstriction related to administration of the study drug. Specifically, a drop in FEV1 greater than or equal to 15%, the need for rescue medication, cough, wheeze or dyspnoea within 30 minutes after inhaling randomised treatment on each test day were to be characterised. This was due to the occurrence of administration related bronchoconstriction observed with some marketed bronchodilators.

  - In the 4 pivotal studies, Holter[16] monitoring was to be performed (in a subset of subjects at selected sites; 50 subjects per treatment group) over a 24 hour period prior to the randomisation visit (Visit 2), and repeated after the completion of all study related tests at Visits 5, 7, 9, and 10. Across the 4 pivotal studies, Holter monitoring was done in 772 subjects: 225, 234, 233 and 80 subjects in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively.

- Laboratory tests performed included haematology, blood chemistry (alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, serum potassium, sodium, chloride, creatinine, blood urea nitrogen (BUN), fasting glucose, calcium, inorganic phosphorus, uric acid, creatine phosphokinase (CPK)[17]), and urinalysis. Laboratory tests were performed according to a schedule. In addition, serum potassium was to be collected at 1 and 3 hours post dose at Visits 4 (Week 6; Day 43) and 5 (Week 12; Day 85).
- Other safety endpoints included vital signs (seated pulse rate and blood pressure) and 12 lead electrocardiogram (ECG) performed according to a schedule.

Dose response and non-pivotal efficacy studies

The dose response and non-pivotal efficacy studies provided safety data, as follows:

- The 6 non pivotal Phase III studies (Studies 1222.24, 1222.25, 1222.39, 1222.40, 1222.37 and 1222.38) provided data on adverse events, vital signs, routine laboratory evaluations and 12 lead ECG.
- The 7 Phase II studies (COPD: Studies 1222.3, 1222.5, 1222.26; asthma: 1222.4, 1222.6, 1222.27 and 1222.29) provided data on adverse events, vital signs, routine laboratory evaluations and 12 lead ECG.

The Phase II studies in asthma patients have not been described in the efficacy section in this report.

Other studies evaluable for safety only

As previously described, the sponsor had submitted a "Summary of Clinical Safety Supplement" and an "embellished narrative summary table" which contained only safety data.

The Summary of Clinical Safety supplement consisted of a listing of tables on safety data from the Phase III efficacy/safety studies which were referenced in the Summary of Clinical Safety but not found in the individual or combined study reports (for example, combined dataset from all 4 pivotal Phase III studies). The "embellished narrative summary table" is an additional tabulation of subjects in Studies 1222.11, 1222.12, 1222.13, 1222.14, 1222.39 and 1222.40 with SAE or non-SAEs leading to discontinuation.[18] These 2 reports will not be discussed as separate sections, but the content evaluated and incorporated into the safety evaluation.

[16] A portable electrocardiograph worn by a patient over an extended period of time to assess the effects on heart function.
[17] In cases where CPK values were greater than 1.5 times ULN, both CPK and fractionated CPK were analysed at all subsequent visits for that subject.
[18] In the Phase III studies SAEs or non-SAEs leading to discontinuation were categorised as fatal SAEs, drug-related or trial-related SAEs, SAEs leading to discontinuation, all other SAEs, or non-SAEs leading to discontinuation. The "embellished narrative summary table" is an additional tabulation of subjects in Studies 1222.11, 1222.12, 1222.13, 1222.14, 1222.39 and 1222.40 according to these categories, with hyperlinks to the corresponding narrative documents.

Comments: The sponsor had not provided details on how the Holter subset of subjects had been selected. This will be raised as a clinical question.

In this evaluation, the safety data of the 4 pivotal Phase III studies were evaluated individually, and were found to be consistent among all 4 studies. In addition, the study designs of the 4 pivotal Phase III studies were similar and the baseline demographic and disease characteristics were also comparable across these 4 studies. In view of the above, the combined safety data in the 4 pivotal studies (drawn from the Summary of Clinical Safety supplement) will be presented.

In this evaluation, the safety data of the 6 non pivotal Phase III studies were also evaluated individually, and were found to be consistent among all 6 studies. The study designs of these 6 non pivotal Phase III studies were similar and the baseline demographic characteristics were also comparable across these 6 studies. In view of the above, the combined safety data in the 6 non pivotal studies (drawn from the Summary of Clinical Safety supplement) will be presented.

Summary of patient exposure

For the 4 combined pivotal (48 week, parallel group) Phase III Studies (1222.11, 1222.12, 1222.13, and 1222.14), the overall mean (SD) exposure was 300 (90.6) days. By treatment group the mean (SD) exposure was 287.5 (104.0, 308.4 (78.4) 304.7 (84.8) and 299 (93.1) days in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively. Overall, the majority of subjects (54.5%) had an exposure to study drug of between 282 to 337 days. By treatment group, 51.6%, 56.2%, 56.2% and 53.9% of subjects in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively, had an exposure in this range.

For the 6 combined non pivotal (6 week, cross over) Phase III Studies (1222.24, 1222.25, 1222.37, 1222.38, 1222.39, 1222.40), the overall mean (SD) exposure was 147.4 (34.8) days. By treatment group the mean (SD) exposure to placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg, and formoterol 12 µg was 43.6 (4.6) 44.1 (5.5) 43.9 (5.1) 43.0 (2.6) and 42.8 (3.1) days, respectively. Overall, 75.9%, 74.8%%, 76.7%, 87.4% and 92.5% of subjects were exposed to placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg, and formoterol 12 µg, respectively, for between 23 and 43 days.

With regards to the Phase II studies in COPD patients, in Study 1222.3 (placebo controlled cross over study evaluating single doses of olodaterol 2 µg, 5 µg, 10 µg and 20 µg in the main part of study and single dose open label 40 µg olodaterol in the extension part of study), all 36 subjects in the safety set participated in the main part of the study, and 34 completed the main part of the study. These 34 subjects each had 4 days on treatment with olodaterol (1 day each on each dose level) and one day on treatment with placebo. Of the 36 subjects in the safety set, 14 subjects also participated in the extension period and these subjects had 1 additional day on treatment with olodaterol (40 µg).

In the Phase II Study 1222.5 (placebo controlled, parallel group study evaluating once daily olodaterol 2 µg 5 µg, 10 µg and 20 µg for 4 weeks), the overall mean (SD) exposure was 29.24 (4.52) days. By treatment group, the mean (SD) exposure was 28.95 (4.65), 29.32 (3.32), 28.59 (5.19) 29.16 (3.22) and 30.20 (5.73) days to placebo, olodaterol 2 µg, olodaterol 5 µg, olodaterol 10 µg and olodaterol 20 µg, respectively. Overall, the majority of subjects (89.1%) had an exposure to study drug of greater than 28 days. By treatment group, 84.8%, 92.6%, 86.3%, 88.4% and 93.7% of subjects had an exposure to placebo, olodaterol 2 µg, olodaterol 5 µg, olodaterol 10 µg and olodaterol 20 µg groups, respectively, of greater than 28 days.

In the Phase II Study 1222.26 (a 3 week cross over study evaluating olodaterol 2 µg bid, olodaterol 5 µg bid, olodaterol 5 µg qd, and olodaterol 10 µg qd), a total of 47 subjects received at least 1 dose of study medication, with 47, 46, 47 and 46 subjects receiving

olodaterol 2 µg bid, olodaterol 5 µg bid, olodaterol 5 µg qd, and olodaterol 10 µg qd, respectively. Overall, the mean (SD) exposure to olodaterol 2 µg bid, olodaterol 5 µg bid, olodaterol 5 µg qd, and olodaterol 10 µg qd was 20.7 (1.92) days, 20.98 (0.26) days, 21.0 (0.29) days and 20.98 (0.26) days, respectively with 93.6%, 95.7%, 97.8% and 97.8% of subjects, respectively exposed for 15 and 21 days.

Drug exposure in the Phase II studies in asthma patients (Studies 1222.4, 1222.6, 1222.27, 1222.29) overall, a total of 731 asthma patients were treated across these studies. The overall mean exposure across these studies combined ranged from 22.8 to 29.5 days across the treatment groups.

> Comments: Overall, the study drug exposure is adequate to assess the safety profile of olodaterol.

Post marketing data

This AusPAR describes an application to register a new chemical entity and therefore no postmarketing data were available.

Evaluator's overall conclusions on safety

Overall, the safety results did not raise any major safety concerns for olodaterol. The overall incidences of all causality AEs, treatment related AEs, SAEs and AEs leading to discontinuation were comparable between the olodaterol 5 µg and 10 µg treatment groups and the placebo group in the pivotal Phase III studies. The commonly reported AEs were those expected for a LABA. These results were generally supported by those of the non-pivotal Phase III and Phase II studies.

Analyses of cardiovascular safety and of AEs related to beta 2 adrenergic class effects did not raise major safety concerns. Evaluating the effects of olodaterol on various systemic pharmacodynamic parameters (vital signs, serum potassium, glucose and CPK) also did not raise any major safety concerns. Evaluation of serum potassium in the pivotal studies showed that for both olodaterol doses there was statistically significantly lower serum potassium levels compared to placebo mostly at the Week 6 time points but no statistically significant difference compared to placebo at the Week 12 time points. By comparison, there was no statistically significant difference in mean serum potassium levels between formoterol and placebo at all time points. However, in the pooled pivotal studies, the proportion of subjects in each treatment group with a minimum serum potassium level during the treatment period which was less than the lower limit of normal (LLN) was comparable between the olodaterol groups and the placebo group and between the olodaterol groups and the formoterol group (10.1% to 13.2% across all treatment groups). In addition, across all test time points, the minimum serum potassium recorded was comparable across the pooled treatment groups (2.4 to 3.2 mmol/L). The incidence of AEs of "hypokalaemia" (preferred term) was also low in all treatment groups (0.0% to 0.5%).

Analyses of the incidence of administration related bronchoconstriction (pooled dataset of Studies 1222.11 and 1222.12) showed that it was lower in the pooled olodaterol 5 µg (2.9%) and olodaterol 10 µg groups (4.7%), respectively, compared to the pooled placebo group (13.6%).

First round benefit risk assessment

First round assessment of benefits

The potential benefit of olodaterol in the proposed usage is as a long term, once daily maintenance bronchodilator treatment of airflow obstruction in COPD patients. The selection of the recommended therapeutic dose of olodaterol of olodaterol 5 µg once daily

has been previously discussed and has been found to be appropriate. In view of this, in this section references will be made only to olodaterol 5 µg.

The bronchodilator efficacy of olodaterol was evaluated through effects on FEV1 as well as effects on symptom relief and health related quality of life. The results showed that olodaterol 5 µg once daily had statistically significantly greater mean change from pre-treatment baseline in FEV1 AUC_{0-3h} and in trough FEV1 (co primary endpoints in pivotal studies) compared to placebo, after 12 weeks of treatment and after 24 weeks of treatment. After 12 weeks of treatment there was a difference over placebo of 151 mL to 172 mL in FEV1 AUC_{0-3h} response and of 47 mL to 91 mL in trough FEV1 response. After 24 weeks of treatment there was a difference over placebo of 129 mL to 151 mL in FEV1 AUC_{0-3h} response and of 53 mL to 78 mL in trough FEV1 response.

Comparison between olodaterol and the formoterol (pooled dataset of Studies 1222.13 and 1222.14) showed that there was no statistically significant difference between olodaterol 5 µg qd and the formoterol 12 µg bid for the co primary endpoints of FEV1 AUC_{0-3h} response and trough FEV1 response at Day 169. Mean FEV1 increased within 5 minutes after the administration of olodaterol 5 µg qd, and peaked around 2 to 3 hours post dose. The statistically significantly greater mean trough FEV1 response at Day 85 and at Day 169 with olodaterol 5 µg compared to placebo suggested that the bronchodilator effect of olodaterol was sustained at the end of the 24 hour dosing interval.

Analyses on effects of olodaterol on symptom relief and health related quality of life compared to placebo also yielded results which were generally supportive of the efficacy claim of both doses of olodaterol over placebo. Although the results showed no statistically significant difference between olodaterol 5 µg and placebo for the co primary endpoint of Mahler TDI focal score at Day 169 (in Studies 1222.13 and 1222.14), it is noted that formoterol group also failed to show statistically significant difference. In addition, direct comparison between olodaterol and formoterol group in the pooled dataset of Studies 1222.13 and 1222.14 showed that there was no statistically significant difference between olodaterol 5 µg and formoterol in the Mahler TDI focal score at Day 169.

Analyses of the SGRQ total and component scores at Day 169 in the pooled dataset of Studies 1222.13 and 1222.14 showed that there were statistically significantly lower SGRQ total and component scores (that is, better outcome) at Day 169 for olodaterol 5 µg compared to placebo.

Analyses of rescue medication use and the PGR were also generally supportive of the efficacy claim for olodaterol over placebo.

Results in the replicate non pivotal Phase III Studies 1222.37 and 1222.38 showed that after six weeks of treatment, mean endurance time during constant work rate cycle ergometry was statistically significantly longer for olodaterol 5 µg compared with placebo. Compared to placebo, endurance time was longer by about 12% to14% with olodaterol 5 µg qd.

First round assessment of risks

The risks of olodaterol in the proposed usage are:

- administration related bronchoconstriction
- systemic beta 2 agonist effects

Analyses of the incidence of administration related bronchoconstriction (pooled dataset of Studies 1222.11 and 1222.12) showed that it was lower in the pooled olodaterol 5 µg (2.9%) compared to the pooled placebo group (13.6%).

Evaluating the effects of olodaterol on various systemic beta 2 agonist effects did not reveal any major safety concerns. Analyses of vital signs did not raise any safety concerns in both the pivotal and non-pivotal studies evaluated. The incidence of possible clinically

significant high glucose levels in the pivotal studies was generally comparable between the olodaterol 5 µg and placebo.

Analyses of the CPK levels in the pivotal studies showed that there was an overall mean decrease from baseline in the CPK levels in the olodaterol 5 µg group across 48 weeks, instead of the expected increase.

Evaluation of serum potassium in the pivotal studies showed that for olodaterol 5 µg, there was a statistically significantly lower serum potassium level compared to the pooled placebo group at 1 and 3 hours post dose at Week 6, but no statistically significant difference at 1 and 3 hours post dose at Week 12. However, in the pooled pivotal studies, the proportion of subjects in each treatment group with a minimum serum potassium level during the treatment period which was less than LLN was comparable between the olodaterol 5 µg (10.1%) and placebo (10.2%) groups, and the incidence of AEs of "hypokalaemia" (preferred term) was low (0.3% and 0.5% in the placebo, and olodaterol 5 µg groups, respectively).

Overall, the incidences of all causality adverse events (AEs), treatment related AEs, SAEs and AEs leading to discontinuation were also comparable between olodaterol 5 µg and the placebo in the pivotal studies, and these results were generally supported by those of the non-pivotal Phase III and Phase II studies.

First round assessment of benefit risk balance

The benefit-risk balance of olodaterol, given the proposed usage, is favourable.

Overall, analyses on effects of olodaterol on FEV1 compared to placebo yielded results which were generally supportive of the efficacy claim of olodaterol 5 µg qd over placebo. Analyses on effects of olodaterol on symptom relief and health related quality of life compared to placebo also yielded results which were generally supportive of the efficacy claim of olodaterol 5 µg qd over placebo. Safety results did not raise any major safety concerns.

First round recommendation regarding authorisation

It is recommended that the application for the registration of olodaterol as a long term, once daily maintenance bronchodilator treatment of airflow obstruction in COPD patients be approved.

This is subject to a satisfactory response to the recommendations and clinical questions raised.

Clinical questions

Pharmacokinetics

Not applicable.

Pharmacodynamics

Not applicable.

Efficacy

Question One

Please provide clarification on how the "12 hour PFT set" in Studies 1222.11 and 1222.22 were selected.

Rationale for question: As discussed, it was not clearly explained in the clinical study reports (CSR) or protocols how the "12 hour PFT set" of subpopulation was selected. In the CSR, it was stated that "Based on a regulatory authority request to provide a more complete description of the spirometric profile over time from the large parallel Phase III

studies, a sub group of subjects performed additional serial PFTs up to 12 hours post dose on Day 85 in both Study 1222.11 and the replicate Study 1222.12, with the pre specified intention of describing the results in a separate report based on the pooled dataset and in the sponsor's Clinical Overview, it was stated that "following a US FDA recommendation, lung function was measured up to 12 hours post dose at Day 85 in a subset of patients in 1222.11 (N=241) and 1222.12 (N=321)". These statements clarified that the reason for this subset was an FDA recommendation, and that the analysis of the 12 hour PFT in this subset was pre specified to be performed on the combined dataset rather than the individual studies. However no explanation or clarification was provided regarding how the selection of subjects into this subset was done.

Question Two

Please provide the baseline demographic and disease characteristics of the 12 hour PFT set.

Rationale for question: As discussed in, the baseline demographic and disease characteristics of the 12 hour PFT set were not provided, and hence comparability of these baseline characteristics across the treatment groups in this subset of study population could not be ascertained.

Question Three

Please provide details on the nature of the noncompliance issue in Study 1222.14 involving a study site in Canada.

Rationale for question: As discussed, the sponsor had not provided details on the nature of the noncompliance issue in Study 1222.14 involving a study site in Canada. Although the exclusion of efficacy data at this site from the FAS involved only a single subject and was done prior to database lock and unblinding, and hence was unlikely to have introduced major bias into the efficacy analysis, the lack of information on the nature of the noncompliance issue means nonetheless that the evaluator is unable to determine more definitively if the exclusion of the single subject at this site from the FAS was acceptable.

Question Four

Please provide additional analysis results looking at the potential interaction between smoking status at Weeks 24 and 48 and efficacy, in the 4 pivotal efficacy studies (Studies 1222.11/1222.12 and 1222.13/1222.14).

Rationale for question: As discussed, it is noted that in the subgroup analyses on the co-primary endpoints in Studies 1222.11/1222.12 and 1222.13/1222.14, only the smoking status at baseline was considered in exploring potential interaction between smoking status and efficacy. A look through the study protocols of these studies showed that smoking status of subjects was reviewed at Weeks 24 and 48. However, the potential interaction between smoking status at these time points and efficacy was not explored or presented.

Question Five

Please provide additional information on whether the use of smoking cessation aids such as varenicline was monitored during the conduct of the 4 pivotal studies, and on any known drug-drug interactions between varenicline and olodaterol.

Rationale for question: As smoking cessation is an important part in the overall clinical management of patients with COPD, it is expected that in clinical settings, COPD patients being prescribed olodaterol would also be engaged in smoking cessation programs, which may include the use of varenicline. It would therefore be clinically relevant to explore any potential drug-drug interactions between these 2 medications.

Safety

Please provide details on how the Holter subset of subjects in the 4 pivotal studies had been selected.

Rationale for question: As discussed, in the 4 pivotal studies, Holter monitoring was performed in a subset of subjects at selected sites (50 subjects per treatment group) over a 24 hour period prior to the randomisation visit (Visit 2), and repeated after the completion of all study related tests at Visits 5, 7, 9, and 10. However, the sponsor had not provided details on how the Holter subset of subjects had been selected.

Second round evaluation of clinical data submitted in response to questions

Overall, the sponsor has adequately addressed all the questions posed in the first round of evaluation. The responses by the sponsor did not raise new efficacy or safety concerns.

Pharmacokinetics

Not applicable.

Pharmacodynamics

Not applicable.

Efficacy

Question One

The response by the sponsor adequately clarified the selection of the "12 hour PFT set". According to the sponsor, all participating sites were contacted (prior to study initiation) to determine their capacity to conduct 12 hour post dose spirometry. In sites deemed to have the necessary infrastructure, all patients were given the opportunity to participate in the 12 hour post dose spirometry sub set. The response by the sponsor did not raise additional concerns regarding the study design, data or conclusions.

Question Two

The sponsor clarified that the relevant data, while not available in the individual studies, was available in the combined clinical trial report for Studies 1222.11 and 1222.12, and provided the locations of the relevant tables. These tables are evaluated and showed that the baseline characteristics of the combined 12 hour PFT set were comparable across the treatment groups.

Question Three

The sponsor clarified that following inspections and audit, there was sufficient doubt as to the eligibility of the patients being enrolled into the clinical trials at this site. The response by the sponsor did not raise additional concerns regarding the study data or efficacy analysis conclusions.

Question Four

The sponsor clarified that the number of patients with a documented change in smoking status at Week 24 or at Week 48 was low (1.7% and 2.5% respectively; Table 6), and therefore, subgroup analysis based on smoking status at baseline is considered to be sufficiently representative of smoking status during the study.

It is noted by the evaluator that there is a relatively significant amount of missing data with regards to smoking status at Weeks 24 and 48 (12.9% at Week 24, and 7.6% at Week 48). Hence while the proportion of patients with documented change in smoking status at Week 24 or at Week 48 was low, the actual proportion with a change in smoking status at these time points could potentially be higher. However, the relatively significant amount of missing data at Weeks 24 and 48 also meant that attempts to analyse the potential

interaction between smoking status at these time points and efficacy may not yield meaningful conclusions. Overall, the response by the sponsor did not raise additional concerns regarding the study data or conclusions drawn from the efficacy analysis.

Table 6. Change in smoking status pooled dataset from 1222.11, 1222.12, 1222.13, and 1222.14 (treated set)

		Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol	Total
	N (%)	885 (100)	876 (100)	883 (100)	460 (100)	3104 (100)
Week 24	Missing	150 (16.9)	91 (10.4)	99 (11.2)	60 (13.0)	400 (12.9)
	No change	716 (80.9)	769 (87.8)	772 (87.4)	394 (85.7)	2651 (85.4)
	Change	19 (2.1)	16 (1.8)	12 (1.4)	6 (1.3)	53 (1.7)
Week 48	Missing	69 (7.8)	56 (6.4)	66 (7.5)	45 (9.8)	236 (7.6)
	No change	793 (89.6)	792 (90.4)	799 (90.5)	406 (88.3)	2790 (89.9)
	Change	23 (2.6)	28 (3.2)	18 (2.0)	9 (2.0)	78 (2.5)

Question Five

The sponsor provided a listing of study patients who were on concomitant varenicline which showed that the use of varenicline in the 4 pivotal studies (1222.11, 1222.12, 1222.13, 1222.14) was low (Study 1222.11: 2.4% (5 out of 209), 3.4% (7 out of 208), 1.4% (3 out of 207) in the placebo, olodaterol 5 µg, and olodaterol 10 µg groups, respectively; Study 1222.12: 1.9% (4 out of 216), 2.9% (6 out of 209) and 0.5% (1 out of 217), respectively; Study 1222.13: 0.4% (1 out of 225), 0.9% (2 out of 227), 1.8% (4 out of 225) and 0% (0 out of 227) in the placebo, olodaterol 5 µg, olodaterol 10 µg and formeterol groups, respectively; Study 1222.14: 0.9% (2 out of 235), 1.3% (3 out of 232), 1.7% (4 out of 234) and 0.4% (1 out of 233), respectively). The sponsor also stated that *in vitro* investigations had indicated that olodaterol had no potential to inhibit or induce CYP enzymes at the exposure levels expected to be achieved in clinical practice. According to the sponsor, *in vitro* studies had led to the conclusion that the effects of olodaterol on systemic exposure of other medications were not to be expected and hence these interactions were not investigated in clinical studies. In addition, the sponsor provided a copy of the Product Information for varenicline which stated that varenicline has no known clinically meaningful drug interactions. Based on this information, the sponsor had concluded that a drug-drug interaction between olodaterol and varenicline was not expected.

Safety

The response by the sponsor adequately clarified the selection of the Holter subset of subjects. According to the sponsor, all study sites were given the option to participate in the Holter sub study. If the site declined participation, no patients were enrolled into the sub study at that site. If the site opted to participate, the site was provided with the appropriate Holter monitoring equipment and instructions for use prior to study initiation. The Holter sub study was open to all patients at participating sites. All patients at participating sites who were screened for the study (that is, signed informed consent) was asked if they would be willing to participate in the Holter sub study, and were informed that their participation in the main study would not be impacted if they did not want to participate in the Holter sub study. Recruitment into the Holter sub study was monitored on an ongoing basis during the course of the study, and once the required number of patients had been randomised into the sub study (200 patients for Studies 1222.11 and 1222.12; 250 patients for Studies 1222.13 and 1222.14), recruitment into the Holter sub study was closed. The response by the sponsor did not raise additional concerns regarding the study design, data or conclusions.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of olodaterol in the proposed usage are unchanged from those identified in the First Round assessment.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of olodaterol in the proposed usage are unchanged from those identified in the First Round assessment.

Second round assessment of benefit-risk balance

The benefit-risk balance of olodaterol, given the proposed usage, is considered to be favourable.

Second round recommendation regarding authorisation

It is recommended that the application for the registration of olodaterol as a long term, once daily maintenance bronchodilator treatment of airflow obstruction in COPD patients be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan RMP Version 1.0 (dated 18 April 2012, DLP 11 January 2012) and Australian Specific Annex Version 1.0 (dated 01 August 2012) which was reviewed by the TGA's Office of Product Review (OPR). This RMP was superseded by RMP Version 1.1 (dated 04 April 2013, DLP 11 January 2012) and Australian Specific Annex Version 1.1 (dated 26 April 2013).

All figures and tables in this section that have been copied from the original dossier are considered by the evaluator to be an accurate representation of the reviewed data, unless qualified as such in the commentary of the report.

Table 7. Summary of risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks	Not applicable	Not applicable
Important potential risks		
Cardiac arrhythmia	Routine post-marketing pharmacovigilance Continued evaluation in placebo-controlled clinical trials[1] Labelling in the SmPC Sections 4.4 "Special warnings and precautions" and 4.8 "Undesirable effects"	Not applicable
Myocardial ischaemia	Routine post-marketing pharmacovigilance Continued evaluation in placebo-controlled clinical trials[1] Labelling in the SmPC Sections 4.4 "Special warnings and precautions" and 4.8 "Undesirable effects"	Not applicable
Hypokalemia	Routine post-marketing pharmacovigilance Continued evaluation in placebo-controlled clinical trials[1] Labelling in the SmPC Sections 4.4 "Special warnings and precautions", 4.5 "Interactions" and 4.9 "Overdose"	Not applicable

[1] Continued monitoring and evaluation tasks include ongoing safety assessment in the clinical studies of the ongoing Phase 3 olodaterol + tiotropium fixed dose combination program (1237.5, 1237.6, 1237.13, 1237.14, 1237.15, 1237.20, 1237.22), re-evaluation in the growing integrated olodaterol safety study database, update of exposure and frequency of AEs estimates.

Summary of recommendations

The following table provides a summary of the OPR evaluation of the RMP issues raised with the sponsor, sponsors responses and OPR evaluation of these responses.

Table 8. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	*'Not applicable (there were no questions addressed which were related to clinical safety).'*	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
The sponsor should add the following as safety concerns in the RMP: Hypersensitivity/angioedema (already in the proposed Australian PI);	*'In summary, only rash as an aggregated PV Endpoint occurred more frequently (yet not significantly different) with olodaterol 5 µg (2.2%) compared to placebo (1.1%) (Rate Ratio 1.82 [95% CI 0.85-3.90]). The frequency observed with olodaterol 10 µg was smaller (1.8%) (Rate Ratio 1.52 [95% CI 0.69-3.36]). All reported rash events were non-serious. Two rash cases were reported by the blinded investigator as drug related. In a conservative approach, BI has considered rash as a side effect of olodaterol. None of the rashes observed evolved into a serious hypersensitivity event. Therefore, neither rash nor other types of hypersensitivity have been considered an important risk of olodaterol for the population or the individual and no impact on the risk-benefit balance is considered. Yet, usual considerations that susceptible patients, like with any pharmaceutical product, may develop hypersensitivity to olodaterol should not be neglected.* *As part of the routine pharmacovigilance system BI has a follow-up process in place to systematically collect additional information on any reported cases of hypersensitivity. Moreover, BI's continuous safety screening activities include a weekly review of designated medical events, among which hypersensitivity (including anaphylaxis and severe anaphylactic and cutaneous reactions) is being monitored. Thus, continuous screening and monitoring of any hypersensitivity will be covered by BI's routine pharmacovigilance system.* *In conclusion, BI does not consider hypersensitivity or angioedema as a particular safety concern for Striverdi Respimat which would necessitate inclusion in the RMP, or which would be accessible to particular useful risk minimisation measures beyond appropriate product information, consumer medicine information and routine*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
Cerebrovascular events;	*'Since the incidence of cerebrovascular events in the clinical development of olodaterol comparing 5 µg and 10 µg olodaterol groups to placebo was not different, any effect of therapeutic olodaterol dose with regard to cerebrovascular events is not supported.* *Therefore, BI does not consider cerebrovascular events as a safety concern for Striverdi Respimat and inclusion in the RMP is not considered necessary or justified. Cerebrovascular events will be subject to routine pharmacovigilance.'*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
Granulocytopaenia (a rare, but known class effect); Thrombocytopaenia (a rare, but known class effect);	*'There was no occurrence of granulocytopaenia, thrombocytopenia, or any other blood dyscrasia in any clinical study of the olodaterol development programme. There was also no concern or finding from any non-clinical study or data. There is no mention of granulocytopaenia or thrombocytopenia in the beta agonist product information available in Australia [Attachment 6]. BI is also not aware of any worldwide knowledge or product label indicating a beta agonist class effect with this issue, for either long-acting (salmeterol, formoterol, indacaterol) or short-acting beta agonists (such as salbutamol, fenoterol).* *Therefore, BI does not consider granulocytopaenia and thrombocytopaenia as a particular safety concern for Striverdi Respimat and therefore, inclusion in the RMP is not considered necessary or justified. Granulocytopaenia and thrombocytopaenia will be subject to routine pharmacovigilance. Similar to hypersensitivity (above), BI has a follow-up process within the routine pharmacovigilance system to systematically collect additional information on any reported cases of agranulocytosis or similar. BI's continuous safety screening activities include a weekly review of designated medical events, among which agranulocytosis is being screened.'*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
Cardiovascular events: patients with heart failure (important missing information);	*'BI agrees with the RMP evaluator's assessment of a potential safety concern regarding lack of experience in patients with particular cardiovascular conditions. In particular, patients with a recent history of myocardial infarction, unstable or life threatening cardiac arrhythmia, paroxysmal tachycardia, or decompensated heart failure were not included in olodaterol studies for ethical and individual safety reasons. BI proposes to include the respective cardiovascular conditions in the updated RMP as Important Missing Information and to address the cautionary use of Striverdi Respimat in the product information section on Precautions as an appropriate risk minimisation activity. Precautionary advice to the prescriber will reinforce appropriate cardiovascular assessment and monitoring of these patients. Due to the high prevalence of cardiovascular co-disease in COPD, these conditions comprise a succinct and relevant risk group where further information can be acquired. Beyond routine pharmacovigilance activities, BI proposes the use of a specific follow up form to capture data on patients with cardiovascular disease. See also BI's responses to questions 3 and 4 below.'*	This is considered acceptable. It is noted that the sponsor has made additional changes to the proposed PI to include the following in the 'Precautions' section: *'Patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalised for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (>100 beats per minute) were excluded from the clinical trials. Therefore the experience in these patient groups is limited. Striverdi Respimat should be used with caution in these patient groups.'*
Severe hepatic impairment (no studies performed, important missing information);	*'BI agrees that the risks of severe hepatic impairment could not be extensively studied in the clinical trials and therefore these risks will be included as Important Missing Information in the RMP. Routine pharmacovigilance is considered a sufficient risk minimisation activity. See also BI's response to question 4 below.'*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
Hyperglycaemia (already in the proposed Australian PI);	*'In summary, the incidence of hyperglycaemia events in the clinical development of olodaterol comparing 5 µg and 10 µg olodaterol groups to placebo was not different, which does not support a relevant effect of the therapeutic olodaterol dose with regard to hyperglycaemia. In conclusion, BI does not consider hyperglycaemia as a particular safety concern for Striverdi Respimat which would necessitate inclusion in the RMP, or which would be accessible to particular useful risk minimisation measures. Hyperglycaemia will be adequately described as a potential beta agonist class effect in the Striverdi Respimat product information as a basic risk minimisation measure. Hyperglycaemia will be subject to routine pharmacovigilance.'*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
Deaths due to asthma-related events (in off-label use); and	*'The LABA risks in asthma are fully addressed in the RMP section "Potential for off-label use" along with the worldwide background, scientific experience, assessments, and regulatory labelling and warning recommendations. These labelling and warning recommendations are completely followed for all Striverdi Respimat labels worldwide. In particular, the Striverdi Respimat product information will include the following information:* "STRIVERDI RESPIMAT is a long-acting beta2-agonist indicated for long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema." *And in the Precautions section:* "Striverdi Respimat should not be used in asthma. The long-term efficacy and safety of olodaterol in asthma have not been studied"; and "Striverdi Respimat is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy". *This is clearly and prominently stated in the product information in the Indications and Precautions sections.* *In agreement with the evaluator (as explained in BI's response to question 7 below), an additional statement is proposed in the Precautions section of the product information:* "Long-acting beta2-adrenergic agonists (LABA) may increase the risk of asthma-related hospitalisations and death. Data from a large placebo-controlled study that compared the safety of another long acting beta2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in Striverdi Respimat."'	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
Off-label use (e.g. for asthma) (drug utilisation study recommended).	*'In addition, BI agrees with the RMP evaluator's recommendation to qualify and address offlabel use in asthma as a new additional Important Potential Risk in the RMP. BI also agrees to conduct a drug utilisation study to evaluate the off-label use of Striverdi Respimat (see BI's responses to questions 3 and 5 below).'*	This is considered acceptable.
Given that the sponsor has identified several important potential risks, the sponsor should provide a justification why no additional pharmacovigilance activities have been planned to investigate these further.	The sponsor is planning two additional pharmacogilance items, namely the following post-authorisation studies: *'1. Drug utilisation study to characterise the use of Striverdi Respimat in clinical practice and examine the potential off-label use of Striverdi Respimat in asthma (Observational, cross-sectional, drug utilisation study in Europe). See BI's responses to question 2 i) Off-label use for asthma (above) and question 5 (below).* *2. Post-authorisation Safety Study (PASS) to obtain additional safety data on long-term use and assess adverse cardiovascular outcomes in association with Striverdi Respimat (Observational, longitudinal study in Europe). See BI's response to question 4 below.'*	This is considered acceptable.
The sponsor should consider relevant pharmacovigilance activities for the additional safety concerns recommended above.	See question 3.	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
The sponsor should conduct a drug utilisation study to evaluate the off-label use of olodaterol.	*'BI agrees with the RMP evaluator's recommendation to qualify and address off-label use in asthma as an important potential risk in the RMP (see BI's response to question 2 i) off-label use above). BI agrees to conduct a drug utilisation study to evaluate the off-label use of Striverdi Respimat. The drug utilisation study will characterise the use of Striverdi Respimat in clinical practice and examine the potential off-label use of Striverdi Respimat in asthma with an observational, cross-sectional, drug utilisation study in Europe (see question 3 above) [DUS study plan / synopsis in Attachment 8].'*	This is considered acceptable.
The sponsor should consider relevant risk minimisation activities for the additional safety concerns recommended above.	The sponsor has suggested PI changes in relation to the new Ongoing Safety Concerns included.	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows: In the 'Precautions' section, the PI should include a statement that there have been reports of asthma-related deaths associated with long-acting β_2-adrenergic agonists, such as olodaterol (or a statement to that effect). In the 'Precautions' section, the PI should include a statement that there may be an increased risk of asthma related hospitalisations associated with long-acting β_2-adrenergic agonists, such as olodaterol (or a statement to that effect).	*'In agreement with the evaluator (as explained in BI's response to question 7 below), an additional statement is proposed in the Precautions section of the product information:* "Long-acting beta2-adrenergic agonists (LABA) may increase the risk of asthma-related hospitalisations and death. Data from a large placebo-controlled study that compared the safety of another long acting beta2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in Striverdi Respimat."'	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	Evaluator's comment
In the 'Precautions' section, the PI should include a statement regarding the need for a COPD action plan including the recommendation to seek medical advice if a previously effective dosage regimen fails to control symptoms adequately (or a statement to that effect). In the 'Precautions' section, the PI should include a statement that olodaterol is not indicated to manage acute exacerbations of COPD (or a statement to that effect).	*'The following statement is proposed for inclusion in consideration of the Questions c) and d) as an addition to the section Precautions of the PI (additional text in bold):* Acute bronchospasm Striverdi Respimat is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. Deterioration of disease and acute episodes Striverdi Respimat should not be initiated in patients with acutely deteriorating COPD. In this case, the patient's COPD management plan should direct the patient to seek medical advice immediately, and a re-evaluation of the patient and the COPD treatment regimen should be undertaken. Increasing the daily dosage of Striverdi Respimat beyond the recommended dose is not appropriate.'	This is considered acceptable.
It is recommended the sponsor supply instructions regarding the use of the inhaler with each device to ensure correct usage.	*'In addition to the Consumer Medicine Information leaflet, the Striverdi Respimat device is provided with a detailed and illustrated Instructions for Use document. Further information and an instructive handling video is provided on the internet (www.respimat.com).'*	This is considered acceptable.

Summary and recommendation

There were no outstanding issues except for PI matters. Should the application for registration be approved the OPR recommended implementation of RMP Version 1.1 (dated 04 April 2013, DLP 11 January 2012) and Australian Specific Annex Version 1.1 (dated 26 April 2013).

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

This is a submission for general marketing of a new therapeutic good containing a New Chemical Entity olodaterol hydrochloride (Striverdi Respimat inhalation solution with device for inhalation).

The proposed indication of olodaterol is

> *'long term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and or emphysema.'*

The proposed marketing formulation is the same as used in the clinical studies. The overseas submissions for this product seeking similar use (that is, COPD) are awaiting decision at the time of this Overview. The sponsor is requested to update the status in its pre ACPM response.

It is noted that the sponsor would like to change the trade name from Infortispir Respimat to Striverdi Respimat. This raises the issues of some potential for confusion with the registered Spiriva Respimat containing tiotropium. The sponsor was also invited to comment on this aspect.

Quality

Olodaterol hydrochloride is structurally related to the currently approved eformoterol (formoterol in this submission), salmeterol and indacaterol and is chemically synthesised (R enantiomer).

The inhalation solution contains the active ingredient olodaterol hydrochloride 2.7 µg 11 µL equivalent to olodaterol 2.5 µg 11 µL. The solution also contains benzalkonium chloride, disodium edetate, citric acid and purified water. The use of benzalkonium chloride in nebulising solutions is controversial due to association with risk of bronchoconstriction in some patients with hyperactive airways. The draft PI notes only the presence of benzalkonium chloride. The carton label states *'Contains benzalkonium chloride as preservative'*. The sponsor is invited to provide comments. Please note that benzalkonium chloride in same concentration is present in the registered Spiriva Respimat.

The manufacturing process is stated to have been optimised and the structure well characterised. The suitability of the cartridge container materials and the materials used to manufacture inhaler has previously been found acceptable by TGA for Spiriva Respimat. The product is not claimed to be sterile.

An in use shelf life of 3 months begins when the cartridge is put into the device. Provision is made on the Respimat label for writing the in use expiry date.

The Pharmaceutical Subcommittee (PSC) of ACPM, at its 151st (2013/3) meeting considered olodaterol hydrochloride and advised that the sponsor be asked to:

1. Include a bioburden test prior to the filtration step in the drug product manufacturing process given that the product is delivered into compromised lungs.
2. Disclose the preservative quantitatively on the label in view of the known clinical reactions, including bronchoconstriction in some patients with hyper reactive airways, to inhaled benzalkonium chloride.

However, the TGA subsequently provided opinion that the product is for oral inhalation, is not sterile and has advised that bioburden testing should be left as a GMP issue. The evaluator supports registration. The product labelling will be further reviewed following the ACPM meeting.

Nonclinical

The submitted dossier was considered of high quality; studies were GLP compliant and covered all relevant testing aspects. Pregnancy category B3[19] is proposed. The evaluator supports registration. A number of recommendations for PI have been provided and are supported by the Delegate.

Clinical

A total of 7 pharmacokinetic, 1 pharmacodynamic and 7 dose finding studies were part of the clinical dossier. The 3 Phase II dose finding studies in COPD patients provided rationale for dosing regimen in the subsequent Phase III studies, whereas the 4 Phase II dose finding studies in asthma are relevant for safety only in this submission. There were 4 pivotal Phase III efficacy studies consisting of 2 sets of replicate, randomised, double blind, parallel group trials each of 48 weeks duration. There were 6 other Phase III randomised, double blind studies each of 6 weeks duration as supporting efficacy studies.

Pharmacokinetics

Despite the sensitive bio analytical method, olodaterol was mostly not detectable in plasma after inhaled doses below 5 µg. Peak plasma concentrations of olodaterol were observed within 20 minutes after inhalation indicating rapid absorption from lungs. A slower absorption process appears to determine the terminal half-life (45 hours) of inhaled olodaterol, which is longer than that after IV administration (22 hours). Oral bioavailability of olodaterol is low, so that the fraction of the drug swallowed does not contribute significantly to the plasma concentration profiles after inhalation.

Olodaterol exhibits linear pharmacokinetics with a dose proportional increase in systemic exposure. Steady state is achieved in 8 days on repeated inhalations, with accumulation factors for both Cmax and AUC in the range of 1.1 to 1.8.

Olodaterol is extensively distributed to the tissues (volume of distribution 1110 L). There is moderate plasma protein binding (approximately 60%). Olodaterol undergoes metabolism. About half of drug related material excreted after IV administration is metabolites. The 6 metabolites identified represent one Phase I reaction product with agonistic activity at beta 2 receptors and 5 Phase II reaction products with insignificant pharmacological activity. Olodaterol is the only compound clinically relevant for pharmacological activity. The Phase I metabolism of olodaterol is dependent primarily on CYP2C9, with minor contributions from CYP2C8 and CYP3A4. Inhibition of CYP2C9 with fluconazole did not result in a clinically relevant change in the systemic exposure to olodaterol. Olodaterol is a P-gp substrate *in vitro* and in animal studies. A drug-drug interaction study with ketoconazole was performed. Steady state exposure to olodaterol after inhalation was found to be increased by about 70% on coadministeration with ketoconazole.

Genetic polymorphisms known to be associated with altered activity of the involved uridinediphosphate glucuronosyltransferase isoenzymes (UGT 1A1, 1A7, 1A9 and 2B7) had no obvious impact on systemic exposure to olodaterol and olodaterol glucuronide. A clinical drug-drug interaction study with tiotropium showed that concomitantly inhaled tiotropium and olodaterol did not significantly affect each other's pharmacokinetics.

[19] Pregnancy Category B3. Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

After IV administration of [^{14}C] labelled olodaterol, 53% of the total radioactivity was found in faeces and 38% was in urine. No change in systemic exposure to inhaled olodaterol was observed in subjects with mild and moderate hepatic impairment, and 40% increase was observed in subjects with severe renal impairment.

In various inhalation studies performed with olodaterol, systemic exposure in COPD patients was generally higher than in healthy volunteers. No influence of gender and only moderate influence of age, weight, height and lung function (pre-treatment FEV1) on the systemic exposure to olodaterol was noted.

By comparing dose normalised $AUC_{0-\infty}$ values obtained from healthy volunteers after single inhalation of 30 to 70 µg olodaterol with those obtained after intravenous infusion of 20 µg olodaterol, the absolute bioavailability of olodaterol after inhalation was estimated to be about 30%. The absolute bioavailability of olodaterol administered as an oral solution in was found to be below 1%. It can be concluded that systemic availability of olodaterol after inhalation is mainly determined by lung absorption, while any swallowed portion of the dose only negligibly contributes to systemic exposure.

Pharmacodynamics (PD)

A number of PD outcomes relevant to beta 2 agonists were examined including cardiovascular (blood pressure, heart rate, QT interval) and laboratory (cAMP, serum potassium, glucose) and were consistent with the known profile for this class of drugs.

Dose selection

The dose selection for the Phase III studies was principally based on the following two studies:

- Study 1222.3 single dose study in COPD patients
- Study 1222.5 once daily dosing over 4 weeks in COPD patients

The Study 1222.3 was a single dose, randomised, double blind, placebo controlled, 5 way cross over study evaluating the efficacy and safety of single doses of orally inhaled olodaterol (2 µg, 5 µg, 10 µg and 20 µg) in COPD patients, followed by an optional period of open label olodaterol 40 µg (to characterise PK of metabolites of olodaterol following single inhalation of olodaterol 40 µg). The primary endpoint was FEV1 at 24 hours post dose, that is trough FEV1. Results showed that all single doses of olodaterol had statistically significantly greater FEV1 at 24 hour post dose compared to placebo.

The Study 1222.5 was a 4 week, randomised, double blind, placebo controlled parallel group study evaluating the efficacy and safety after 4 weeks of once daily treatment of orally inhaled olodaterol (2 µg, 5 µg, 10 µg and 20 µg) in COPD patients. The primary endpoint was the trough FEV1 response after 4 weeks of treatment. The results showed that after 4 weeks of treatment, there were statistically significantly greater mean trough FEV1 response and response for all olodaterol doses compared to placebo. The 10 µg and 20 µg doses of olodaterol showed increased efficacy compared to olodaterol 2 µg. The efficacy of olodaterol 10 µg and olodaterol 20 µg was similar. The efficacy of olodaterol 5 µg compared with olodaterol 2 µg and olodaterol 10 µg was variable, such that the position of olodaterol 5 µg on the dose response curve could be characterised as intermediate between suboptimal (2 µg) and plateauing efficacy (10 µg or 20 µg).

In addition, the effects of olodaterol on systemic PD parameters (serum potassium) were used to identify the threshold for the onset of systemic PD activity. The results showed that after the first dose, serum potassium levels with olodaterol 2 µg, 5 µg and 10 µg were similar to placebo, while there were small but statistically significant reductions in serum potassium levels for olodaterol 20 µg compared to placebo. After 4 weeks of treatment,

there were no statistically significant differences in serum potassium levels at any dose compared to placebo. Evaluations of serum creatine phosphokinase showed a similar pattern, suggesting that the threshold for systemic PD activity for olodaterol was about 20 µg in patients with COPD.

Note 5 µg and 10 µg once daily doses were subsequently tested in all Phase III studies.

Study 1222.26

The Study 1222.26 was a 3 week, randomised, double blind, 4 way cross over study to evaluate the 24 hour FEV1 time profile of orally inhaled olodaterol when administered once daily (5 µg and 10 µg) versus twice daily (2 µg twice daily, 5 µg twice daily) in COPD patients. The primary endpoints were FEV1 $AUC_{0\text{-}12h}$ and FEV1 $AUC_{12\text{-}24h}$ after 3 weeks of treatment. The results showed that for all olodaterol dose regimens there were statistically significantly greater FEV1 $AUC_{0\text{-}12h}$ and FEV1 $AUC_{12\text{-}24h}$ responses compared with pre-treatment baseline levels.

The comparison of olodaterol 5 µg once daily versus olodaterol 2 µg twice daily indicated that FEV1 $AUC_{0\text{-}12h}$ for olodaterol 5 µg once daily was significantly higher compared to olodaterol 2 µg twice daily (209 mL versus 155 mL, p = 0.0003). There was no statistically significant difference in FEV1 $AUC_{12\text{-}24h}$ response between olodaterol 5 µg once daily and olodaterol 2 µg twice daily (155 mL versus 167 mL, p = 0.4). With respect to FEV1 $AUC_{0\text{-}24h}$, the treatment difference was not statistically significant between olodaterol 5 µg once daily versus olodaterol 2 µg twice daily (182 mL versus 160 mL, p = 0.1).

The comparison of olodaterol 10 µg once daily versus olodaterol 5 µg twice daily indicated that the FEV1 $AUC_{0\text{-}12h}$ treatment difference was not statistically significant different (204 mL versus 189 mL, p = 0.3). The FEV1 $AUC_{12\text{-}24h}$ response for olodaterol 10 µg once daily was significantly less compared with olodaterol 5 µg twice daily (149 mL versus 201 mL, p = 0.0006). With regard to FEV1 $AUC_{0\text{-}24h}$ there was no statistically significant difference between olodaterol 10 µg once daily and olodaterol 5 µg twice daily (176 mL versus 195 mL, p = 0.175).

The Study 1222.26 was not conducted for the purpose of dose regimen selection for the Phase III studies, but was conducted to evaluate alternative dosing frequencies of olodaterol administration. Note 5 µg twice daily dosing was not tested in the subsequent Phase III COPD studies.

Clinical efficacy

Four pivotal Phase III studies were submitted to support clinical efficacy for the proposed indication in COPD patients. These consisted of 2 sets of replicate, randomised, double blind, parallel group studies, each with 48 weeks of treatment. One set of replicate Studies (1222.11 and 1222.12) was placebo controlled, while the other set (1222.13 and 1222.14) was placebo and active (formoterol) controlled. Both were designed as conventional parallel group superiority trials and aimed to assess improvements in peak and trough lung function as well as symptomatic and quality of life assessments at 12 weeks (Studies 1222.11 and 1222.12) or 24 weeks (Study 1222.13 and 1222.14) and longer term assessment at 48 weeks of treatment (both replicates). In all 4 studies, olodaterol was administered between 7 am and 10 am in the morning.

There were also 6 supporting Phase III efficacy studies in COPD patients. These included 2 sets of replicate, randomised, double blind, placebo and active controlled, crossover studies of 6 weeks duration, evaluating lung function over a 24 hour dosing interval. The first set of replicate Studies (1222.24 and 1222.25) used formoterol as active control, and the second set of replicate Studies (1222.39 and 1222.40) used tiotropium as the active control. In addition, another replicate set (1222.37 and 1222.38) evaluated the effect of olodaterol on exercise tolerance.

Pivotal Studies 1222.11 and 1222.1

These 2 were replicate studies. Both were multicentre, randomised, double blind, placebo controlled, parallel group studies to assess efficacy and safety of once daily treatment of orally inhaled olodaterol (5 µg and 10 µg) delivered by Respimat inhaler, in patients with COPD over 48 weeks compared to placebo. The patients were randomised to 3 treatment groups (olodaterol 5 µg once daily, olodaterol 10 µg once daily, or matching placebo), stratified by use of tiotropium at baseline. The eligible patients were adults (greater than or equal to 40 years) of either sex with a diagnosis of COPD, who had a smoking history of greater than 10 pack years, and had post bronchodilator FEV1 less than 80% predicted normal and post bronchodilator FEV1/forced vital capacity (FVC) less than 70%. History of asthma was an exclusion criterion, among others.

A short acting beta 2 agonist medication (salbutamol) was provided to all patients as rescue bronchodilator agent, and appropriate medications were allowed to control acute exacerbations as medically indicated. Any existing LABAs were withdrawn prior to study, whereas other existing medications were continued during the trial including any long acting anticholinergic (antimuscarinic) agents (LAMA). Patients not LAMA prior to the trial and who subsequently required a new LAMA prior to the Week 12 were discontinued whereas those requiring a new LAMA after Week 12 were permitted to continue.

Total treatment duration was 48 weeks with primary assessment of efficacy was at 12 weeks. There were 2 co primary efficacy endpoints FEV1 AUC_{0-3h} and trough FEV1 (FEV1 at the end of dosing interval (that is, 24 hours) obtained 10 minutes prior to the next study drug inhalation) on Day 85 (12 weeks). The primary efficacy analyses were performed on the Full Analysis Set (FAS). There were a number of secondary outcomes. In this replicate only, a subset of (voluntary) patients (Study 1222.11, n = 241 and Study 1222.12, n = 321) at various centres also undertook pulmonary function tests up to 12 hours post dose on Day 85 (12 hours 'PFT analysis set').

The samples sizes were based on power calculations. In Study 1222.11, a total of 624 patients were randomised and treated (209 placebo, 208 olodaterol 5 µg and 207 olodaterol 10 µg). In Study 1222.12, a total of 642 patients were randomised and treated (216 placebo group, 209 olodaterol 5 µg and 217 olodaterol 10 µg group). Overall the study groups were comparable in both studies and reflective of the target patient population (mean age of 64.9 years and 64.6 years, and mean duration of COPD of 8.4 years and 7.6 years in the studies 11 and 12 respectively). As there were 2 dose levels of olodaterol (5 µg and 10 µg) and 2 co primary endpoints, the primary hypotheses were tested in hierarchical order to maintain overall type 1 error.

Results

In both studies, there was a statistically significant greater mean FEV1 AUC_{0-3h} response at Day 85 compared to placebo for both olodaterol 5 µg (Study 1222.11: treatment difference 172 mL, 95% CI 135 mL to 209 mL, $p < 0.0001$; Study 1222.12: treatment difference 151 mL, 95% CI 116 mL to 185 mL, $p < 0.0001$) and olodaterol 10 µg (Study 1222.11: treatment difference 176 mL, 95% CI 139 mL to 214 mL, $p < 0.0001$; Study 1222.12: treatment difference 143 mL, 95% CI 110 mL to 177 mL, $p < 0.0001$).

There was also statistically significant greater mean trough FEV1 response at Day 85 compared to placebo for both the olodaterol 5 µg (Study 1222.11: treatment difference 91 mL, 95% CI 54 mL to 128 mL, $p < 0.0001$; Study 1222.12: treatment difference 47 mL, 95% CI 11 mL to 84 mL, $p = 0.0116$) and olodaterol 10 µg (Study 1222.11: treatment difference 101 mL, 95% CI 64 mL to 137 mL, $p < 0.0001$; Study 1222.12: treatment difference 48 mL, 95% CI 12 mL to 85 mL, $p = 0.0095$).

The subgroup analyses were consistent with the overall primary efficacy results.

FEV1 AUC_{0-3h} response at Day 85 by baseline tiotropium indicated that both doses (olodaterol 5 µg and 10 µg) had statistically significantly greater effect than placebo with respect to mean FEV1 AUC_{0-3h} response at Day 85 in tiotropium stratum (Study 1222.11: treatment difference 150 mL, 95% CI 71 mL to 229 mL, p = 0.0002 (5 µg) and 113 mL, 95% CI 36 mL to190 mL, p = 0.004 (10 µg); Study 1222.12: treatment difference 107 mL, 95% CI 28 mL to 185 mL, p = 0.0077 (5 µg) and 107 mL, 95% CI 31 mL to 184 mL, p = 0.0057 (10 µg)), as well as in non tiotropium stratum (Study 1222.11: treatment difference 179 mL, 95% CI 136 mL to 221 mL, p < 0.0001 (5 µg) and 196 mL, 95% CI 154 mL to 239 mL, p < 0.0001 (10 µg); Study 1222.12: treatment difference 161 mL, 95% CI 123 mL to 199 mL, p < 0.0001 (5 µg) and 152 mL, 95% CI 114 mL to 190 mL, p < 0.0001 (10 µg)).

Trough FEV1 response at Day 85 by baseline tiotropium indicated that the mean trough FEV1 response at Day 85 was statistically significantly greater than in placebo for both doses of olodaterol only in the non tiotropium stratum (Study 1222.11: treatment difference 96 mL, 95% CI 55 mL to 138 mL, p < 0.0001 (5 µg) and 119 mL, 95% CI 77 mL to 161 mL, p < 0.0001 (10 µg); Study 1222.12: treatment difference 56 mL, 95% CI 15 mL to 95 mL, p = 0.0073 (5 µg) and 50 mL, 9 mL to 91 mL, p = 0.016 (10 µg)), but not in tiotropium stratum (Study 1222.11: treatment difference 72 mL, 95% CI -6 mL to 150 mL, p = 0.07 (5 µg) and 41 mL, 95% CI -3 mL to 117 mL, p = 0.3 (10 µg); Study 1222.12: treatment difference 11 mL, 95% CI -7 mL to 95 mL, p = 0.8 (5 µg) and 39 mL, 95% CI -4 mL to 121 mL, p = 0.3 (10 µg)). Some secondary outcomes were as follows:

- FEV1 AUC_{0-12h} response at Day 85 in the 12 hour 'PFT analysis set' showed a statistically significantly greater mean FEV1 AUC_{0-12h} response at Day 85 compared to the placebo group for both olodaterol dose groups (5 µg and 10 µg).
- Analyses of FVC AUC_{0-12h} at Day 85 in the 12 hour PFT analysis set showed that for both olodaterol doses (5 µg and 10 µg), there was a statistically significantly greater response compared to the placebo group.
- Analyses of mean FEV1 AUC_{0-3h} over 48 weeks showed that for both olodaterol dose groups (5 µg and 10 µg), there were statistically significantly greater mean increase compared to placebo group on all test days (Days 1, 15 [Week 2], 43 [Week 6], 85 [Week 12], 169 [Week 24], and 337 [Week 48]).
- Analyses of mean trough FEV1 over 48 weeks showed that there were statistically significantly greater mean increase compared to placebo on all test days (Days 15, 43, 85, 127, 169, 225, 281, and 337) for both olodaterol dose groups (5 µg and 10 µg), except for olodaterol 10 µg on Day 225 (Week 32) in Study 1222.12.
- Analyses of mean FEV1 $peak_{0-3h}$ and FVC ($peak_{0-3h}$) over 48 weeks showed that for both olodaterol dose groups (5 µg and 10 µg), there was statistically significantly greater increase compared to placebo on all test days (Days 1, 15, 43, 85, 169 and 337).
- Analyses of trough FVC over 48 weeks showed that there was statistically significantly greater response compared to placebo on all test days (Days 15, 43, 85, 127, 169, 225, 281 and 337) in both olodaterol dose groups in Study 1222.11, while the differences from placebo were not statistically significant on most test days in Study 1222.12.
- There were no statistically significant differences in Time to first COPD exacerbation (Study 1222.11: hazard ratio 0.73, 95% CI 0.52 to 1.01 (5 µg) and 0.8, 95% CI 0.58 to 1.1 (10 µg); Study 1222.12: hazard ratio 0.99, 95% CI 0.69 to 1.4 (5 µg) and 1.2, 95% CI 0.87 to 176 (10 µg), Time to first moderate COPD exacerbation or Time to first COPD exacerbation leading to hospitalisation between olodaterol treatment groups and placebo based on Cox regression analysis. There were also no statistically significant differences between both olodaterol groups and placebo treatment group

in the mean number of COPD exacerbations, mean number of moderate COPD exacerbations, or mean number of COPD exacerbations leading to hospitalisation.

The results for the Patient's Global Rating[20] were as follows:

- In Study 1222.11, the mean PGR scores after 6, 12, 24 and 48 weeks ranged from 3.0 to 3.1 in both olodaterol groups and from 3.4 to 3.5 in placebo treatment group. In Study 1222.12, the mean PGR score after 6, 12, 24 and 48 weeks ranged from 2.9 to 3.1 in both olodaterol groups and from 3.2 to 3.3 in the placebo treatment group.
- The smoking status at baseline was considered in subgroup analysis. During the trial, the smoking status was reviewed at Weeks 24 and 48. However, the potential interaction between smoking status at these time points and efficacy was not explored or presented. The sponsor clarified that the number of patients with a documented change in smoking status at Week 24 or at Week 48 was low (1.7% and 2.5% respectively) and therefore, subgroup analysis based on smoking status at baseline is considered to be sufficiently representative of smoking status during the study.

Studies 1222.13 and 1222.14

These 2 were replicate studies. The design was similar to the previous Studies 1222.11 and 1222.12 including the patient enrolment criteria and the efficacy outcomes. There was an additional active comparator arm and the evaluation of primary endpoints was performed after 24 weeks of treatment. Additional clinical endpoints evaluating symptomatic benefit in terms of reduction in dyspnoea (Mahler Transition Dyspnoea Index (TDI) focal score), and improvement of health related quality of life (St. George's Respiratory Questionnaire (SGRQ) total score) were included in the assessment.

The study drugs were olodaterol 5 µg (2 actuations of 2.5 µg once daily), olodaterol 10 µg (2 actuations of 5 µg once daily) administered using the Respimat inhaler, formoterol (12 µg twice daily) administered using the Aerolizer inhaler and matching placebos.

There were 3 co-primary endpoints in these studies (FEV1 $AUC_{0\text{-}3h}$ and trough FEV1 at Day 169 (24 weeks), and the Mahler TDI focal score at Day 169. The analysis of Mahler TDI focal score had been pre specified to be performed only in the combined dataset of Studies 1222.13 and 1222.14.

The sample size was based on power calculations and study hypotheses were tested in hierarchical order, to control overall type 1 error rate. In Study 1222.13, a total of 904 patients were randomised and treated (225 in the placebo group, 227 in olodaterol 5 µg group, 225 in olodaterol 10 µg group, and 227 in formoterol 12 µg group). In Study 1222.14, a total of 934 patients were randomised and treated (235 in placebo group, 232 in olodaterol 5 µg group, 234 in olodaterol 10 µg group, and 233 in formoterol 12 µg group. The treatment groups were comparable and the study population was reflective of the target patient population, with mean age of 64 years in both studies, mean duration of COPD of 6.9 and 6.6 years in Studies 1222.13 and 1222.14 respectively.

Results

In both studies, there was a statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response at Day 169 versus placebo, for both olodaterol 5 µg (Study 1222.13: treatment difference 151 mL, 95% CI 110 mL to 193 mL, $p < 0.0001$; Study 1222.14: treatment difference 129 mL, 95% CI 91 mL to 167 mL, $p<0.0001$) and olodaterol 10 µg (Study 1222.13: treatment difference 165 mL, 95% CI 124 mL to 206 mL, $p < 0.0001$; Study 1222.14: treatment difference 154 mL, 95% CI 116 mL to 191 mL, $p < 0.0001$). The mean FEV1 $AUC_{0\text{-}3h}$ treatment difference against placebo at Day 169 for formoterol 12 µg was also statistically

[20] PGR: patients rate their respiratory condition on a 7 point scale (1 equals very much better, to 7 equals very much worse); thus lower scores indicate better condition

significant (Study 1222.13: treatment difference 177 mL, 95% CI 135 mL to 218 mL, p < 0.0001; Study 1222.14: treatment difference 150 mL, 95% CI 112 mL to 188 mL, p < 0.0001).

There was a statistically significantly greater mean trough FEV1 response at Day 169 versus placebo for both olodaterol 5 µg (Study 1222.13: treatment difference 78 mL, 95% CI 37 mL to 118 mL, p = 0.0002; Study 1222.14: treatment difference 53 mL, 95% CI 15 mL to 90 mL p = 0.0055) and olodaterol 10 µg (Study 1222.13: treatment difference 85 mL, 95% CI 44 mL to 124 mL, p < 0.0001; Study 1222.14: treatment difference 69 mL, 95% CI 32 mL to 106 mL, p = 0.0003). There mean trough FEV1 treatment difference against placebo at Day 169 in formoterol 12 µg group was also statistically significant (Study 1222.13: treatment difference 54 mL, 95% CI 14 mL to 95 mL, p = 0.0088; Study 1222.14: treatment difference 42 mL, 95% CI 5 mL to 80 mL, p = 0.027).

Analysis of mean Mahler TDI focal score at Day 169, analysed using the combined 1222.13 and 1222.14 dataset showed no statistically significant difference compared to placebo group for any of the 3 active treatment groups.

The subgroup analyses were consistent with the overall primary efficacy results. Some secondary outcomes were as follows:

With respect to FEV1 $AUC_{0\text{-}3h}$ both olodaterol groups (5 µg and 10 µg) and formoterol 12 µg group showed mean FEV1 $AUC_{0\text{-}3h}$ responses at Day 169 that were statistically significantly greater than in placebo group in both tiotropium stratum and non tiotropium stratum in both studies.

With respect to mean trough FEV1 response at Day 169 by tiotropium stratum, the analysis showed that response was statistically significantly greater than in placebo for both olodaterol groups and for formoterol group in non tiotropium stratum in both studies. However, in the tiotropium stratum, the treatment difference from placebo group for olodaterol 5 µg group was statistically significant in Study 1222.13 but not in Study 1222.14. For olodaterol 10 µg group in tiotropium stratum, the treatment difference from placebo in mean trough FEV1 at Day 169 was not statistically significant in either study. For formoterol group in tiotropium stratum, the treatment difference in mean trough FEV1 response at Day 169 against placebo group was not statistically significant.

In the combined dataset, there was a statistically significantly lower SGRQ total score, that is, better outcome and its components at Day 169 for both olodaterol dose groups compared to placebo group. There was no statistically significant difference in the SGRQ total score or SGRQ component at Day 169 between the formoterol and the placebo group.

In Study 1222.13, there was a statistically significant lower SGRQ total score at Day 85 (12 weeks) for both olodaterol dose groups compared to the placebo. There was no statistically significant difference in SGRQ total score for formoterol versus placebo at this time point. At Day 85, mean SGRQ scores were statistically significantly lower compared to placebo for olodaterol 10 µg group across all 3 SGRQ components (symptom, activity and impact) but only for the component of 'symptom' for olodaterol 5 µg group. There was no statistically significant difference between formoterol and placebo across the 3 SGRQ components at this time point.

In Study 1222.13, at Day 337 (48 weeks), there was a statistically significantly lower SGRQ total score only for olodaterol 10 µg group compared to placebo group. There was no statistically significant difference in the SGRQ total score between formoterol 12 µg or olodaterol 5 µg and placebo group. There was no statistically significant difference between placebo group and the active treatment groups across the 3 SGRQ components at Day 337, except for the olodaterol 10 µg for the component of 'symptom'.

In Study 14, there was a statistically significantly lower SGRQ total score at Day 85 for the olodaterol 5 µg and formoterol groups compared to placebo but no statistically significant

difference between olodaterol 10 µg group and placebo. The difference between the active treatment groups and placebo across the SGRQ components were mostly not statistically significant at this time point. There was no statistically significant difference in the SGRQ total score as well as the components at Day 337 between olodaterol groups, formoterol and placebo.

In Study 1222.13, the mean PGR score at 6, 12, 24, and 48 weeks ranged from 2.9 to 3.1 in active groups (both olodaterol dose groups and formoterol group) and from 3.1 to 3.4 in placebo group. The lower (better) scores in olodaterol treatment groups compared to placebo were statistically significant at all time points up to 24 weeks but not at Week 48. The lower (better) scores in formoterol groups compared to placebo were statistically significant at Weeks 6 and 12 only but not at Weeks 24 and 48.

In Study 1222.14, the mean PGR score after 6, 12, 24, and 48 weeks ranged from 3.0 to 3.2 in the active groups (both olodaterol groups and formoterol group) and from 3.2 to 3.4 in placebo group. The lower scores in the olodaterol 5 µg group compared to placebo group were statistically significant at Weeks 6 and 12 only, while those for the olodaterol 10 µg and for formoterol group were statistically significant at time points up to Week 24.

In the combined analyses, the mean PGR scores at 6, 12, 24 and 48 weeks ranged from 2.9 to 3.1 in pooled olodaterol groups (5 and 10 µg), from 3.0 to 3.1 in the pooled formoterol group, and from 3.1 to 3.4 in the pooled placebo group. The lower scores in the pooled olodaterol 10 µg group compared to pooled placebo group were statistically significant at all time points up to 48 weeks, while those for the pooled olodaterol 5 µg group and for the pooled formoterol group were statistically significant at time points up to Week 24.

Analysis of FEV1 $AUC_{0\text{-}3h}$ over 48 weeks showed that for both olodaterol groups (5 µg and 10 µg) as well as for the formoterol group, there was statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response compared to placebo group on all test days (Days 1, 15, 43, 85, 169 and 337 of the studies) in both studies and that effect was mostly maintained at Week 48.

Analyses of trough FEV1 response over 48 weeks showed that there was statistically significantly greater mean trough FEV1 response compared to placebo on all test days (Days 15, 43, 85, 127, 169, 225, 281, 337) in both olodaterol groups (5 µg and 10 µg) as well as in formoterol group in both individual studies, except for olodaterol 5 µg group on Day 281 and formoterol on Day 281 in Study 1222.13, and in formoterol group on Day 337 in Study 1222.14. The treatment effect at Week 48 was similar to that at Week 24.

Analyses of FEV1 ($peak_{0\text{-}3h}$) response over 48 weeks showed that for both olodaterol groups (5 and 10 µg) as well as for formoterol group, there were statistically significantly greater responses compared to placebo on all test days (Days 1, 15, 43, 85, 169 and 337), in both studies.

Analyses of FEV1 at individual time points up to 3 hour post dose over 48 weeks (at 5, 15, and 30 minutes, and at 1, 2 and 3 hours after inhalation on Day 1 and at 2, 6, 12, 24 and 48 weeks) showed that differences from placebo were statistically significant for both olodaterol groups (5 and 10 µg) as well as for formoterol at all time points in both studies.

Analyses of FVC $AUC_{0\text{-}3h}$ over 48 weeks showed that for both olodaterol groups (5 µg and 10 µg) as well as for formoterol group, there were statistically significantly greater mean FVC $AUC_{0\text{-}3h}$ responses compared to placebo on all test days (Days 1, 15, 43, 85, 169 and 337), in both studies.

Analyses of trough FVC response over 48 weeks was studied on Days 15, 43, 85, 127, 169, 225, 281 and 337. In Study 1222.13, there was statistically significantly greater mean trough FVC responses compared to placebo in olodaterol 10 µg group only on Days 15, 43, 85 and 169. For olodaterol 5 µg group statistically significant response was noted on Days 43, 85 and 337. For formoterol statistically significant response was noted on only on Days

15, 43 and 85. In Study 1222.14, there were statistically significantly greater mean trough FVC responses compared to placebo on most test days (Days 15, 43, 85, 127, 281, and 337 for both the olodaterol groups, and also Day 225 in olodaterol 5 µg group). There was statistically significantly greater mean trough FVC responses compared to placebo in formoterol 12 group on Days 15, 43, 85 and 127.

Analyses of FVC ($peak_{0-3h}$) response over 48 weeks showed that for both olodaterol groups as well as for formoterol group, there were statistically significantly greater mean FVC $peak_{0-3h}$ responses compared to placebo on all test days (Days 1, 15, 43, 85, 169 and 337) in both studies.

The Cox proportional hazards regression analysis showed that there was no statistically significant difference in Time to first COPD exacerbation (hazard ratios: Study 1222.13: 1.16, 95% CI 0.84 to 1.6 (5 µg); 1.18, 95% CI 0.86 to 1.6 (10 µg); 0.85, 95% CI 0.61 to 1.2 (formoterol); Study 1222.14: 0.80, 95% CI 0.58 to 1.1 (5 µg); 0.87, 95% CI 0.63 to 1.2 (10 µg); 0.92, 95% CI 0.67 to 1.3 (formoterol)), first moderate COPD exacerbation, or first COPD exacerbation leading to hospitalisation between the olodaterol groups and placebo and between formoterol and placebo in both studies. There were also no statistically significant differences between the olodaterol groups and placebo and between formoterol and placebo for the mean number of COPD exacerbations, mean number of moderate COPD exacerbations, or mean number of COPD exacerbations leading to hospitalisation in both studies.

Studies 1222.24 and 1222.25

Replicate Studies 1222.24 and 1222.25 were multi centre, randomised, double blind, placebo controlled, four way cross over studies to characterise the 24 hour FEV1 time profiles of orally inhaled olodaterol 5 µg and 10 µg, administered once daily with Respimat Inhaler, and of orally inhaled formoterol 12 µg, administered twice daily with Aerolizer Inhaler, after 6 weeks of treatment in patients with COPD. The patient selection criteria were similar to Studies 1222.11, 1222.12, 1222.13 and 1222. The patients underwent four 6 week treatment periods, each separated by a 2 week wash out interval. A total of 99 and 100 patients were randomised in Studies 1222.24 and 25 respectively. Baseline demographic characteristics were comparable. There was a statistically significant greater mean FEV1 AUC_{0-12h} response and greater FEV1 AUC_{12-24h} response at Day 43 (Week 6) for all 3 active groups compared to placebo in both studies. There was also a statistically significant greater mean FEV1 AUC_{0-24h} response at Day 43 for all 3 active groups compared to placebo in both studies. FEV1time profiles on Day 43 showed that FEV1 increased within 30 minutes following the morning dose for both olodaterol doses, peaked at around 2 hours post dose and then reduced progressively towards baseline.

Pooled analyses (1222.23 and 1222.24) comparing olodaterol 5 µg and olodaterol 10 µg with formoterol showed that for mean FEV1 AUC_{0-12h} response at Day 43, there was no statistically significant difference between either dose of olodaterol and formoterol. However, the mean FEV1 AUC_{12-24h} response for formoterol was statistically significantly greater than that for olodaterol 10 µg (treatment difference -40 mL, p = 0.0024) and for olodaterol 5 µg (treatment difference -50 mL, p = 0.0001).

Overall mean FEV1 AUC_{0-24h} response at Day 43 showed no statistically significant difference between either dose of olodaterol and formoterol. There were no statistically significant differences in mean trough FEV1 response between olodaterol dose groups and formoterol.

Studies 1222.39 and 1222.40

Replicate Studies 1222.39 and 1222.40 were also multi centre, randomised, double blind, placebo controlled, four way cross over studies to characterise the 24 hour FEV1 time profiles of orally inhaled olodaterol (5 and 10 µg) administered once daily with the

Respimat Inhaler, and of orally inhaled tiotropium bromide (18 µg) administered once daily with the Handihaler, after 6 weeks of treatment in patients with COPD. The patient selection criteria were similar to Studies 1222.11, 1222.12, 1222.13 and 1222.14. The washout intervals in these studies were 3 weeks between each of the treatment periods. A total of 108 and 122 patients were randomised in Studies 1222.39 and 1222.40 respectively. Baseline features were comparable.

There was a statistically significant greater mean FEV1 $AUC_{0\text{-}12h}$ response and greater FEV1 $AUC_{12\text{-}24h}$ response at Day 43 (Week 6) for the 3 active groups compared to placebo in both studies. There was also a statistically significant greater mean FEV1 $AUC_{0\text{-}24h}$ response at Day 43 for the 3 active groups compared to placebo in both studies. The FEV1 time profiles on Day 43 showed that FEV1 increased within 30 minutes following the morning dose for both olodaterol doses, peaked around 2 hours post dose and then reduced progressively towards baseline. Tiotropium showed similar FEV1 time profile.

Analyses in the combined dataset (1222.39 and 1222.40) comparing olodaterol 5 µg and olodaterol 10 µg with tiotropium showed that for mean FEV1 $AUC_{0\text{-}12h}$ response at Day 43, there were no statistically significant differences between either dose of olodaterol and tiotropium. The mean FEV1 $AUC_{12\text{-}24h}$ response for tiotropium was statistically significantly less than that for olodaterol 10 µg (treatment difference 30 mL, $p = 0.0306$). There was no statistically significant difference in mean FEV1 $AUC_{12\text{-}24h}$ response between olodaterol 5 µg and tiotropium. Overall, mean FEV1 $AUC_{0\text{-}24h}$ response at Day 43 showed no statistically significant differences between either dose of olodaterol and tiotropium.

Studies 1222.37 and 1222.38

Replicate Studies 1222.37 and 1222.38 were multi centre, randomised, double blind, placebo controlled, 3 way cross over studies to determine the effect of 6 weeks treatment of orally inhaled olodaterol (5 and 10 µg) administered once daily with Respimat inhaler, on exercise endurance time in patients with COPD. The patient selection criteria were similar to Studies 1222.11, 1222.12, 1222.13 and 1222.14. A total of 151 and 157 patients respectively were randomised in the two studies. The baseline characteristics were comparable.

The patients underwent three 6 week treatment periods, each separated by a 2 week wash out interval. The primary efficacy endpoint in both studies was the endurance time during constant work rate cycle ergometry to symptom limitation at 75% maximal work capacity (Wcap)[21] after 6 weeks of treatment.

After 6 weeks of treatment, mean endurance time (during constant work rate cycle ergometry) was statistically significantly longer for both olodaterol doses compared to placebo in both studies. The endurance time was longer by 14% with olodaterol 5 µg ($p = 0.0002$) and 13.8% with olodaterol 10 µg ($p = 0.0003$) in Study 1222.37 and by 11.8% with olodaterol 5 µg ($p = 0.0018$) and 10.5% with olodaterol 10 µg ($p = 0.0052$) in Study 1222.38 versus placebo. The difference in treatment means between olodaterol 5 µg and placebo was 42 to 52 seconds, and that between olodaterol 10 µg and placebo was 37 to 51 seconds.

Mean Inspiratory Capacity (IC) at isotime (endurance time of the constant work rate exercise test of shortest duration at screening and at Week 6 of each first, second and third treatment periods) was statistically significantly greater (indicating a lower end expiratory lung volume) compared to placebo for both olodaterol 5 µg (Study 1222.37: 2.099L versus 1.917 L in placebo, $p < 0.0001$; Study 1222.38: 2.246 L versus 2.162 L in placebo, $p = 0.0155$) and olodaterol 10 µg (Study 1222.37: 2.091 L versus 1.917 L in placebo, $p < 0.0001$, Study 1222.38: 2.328 L versus 2.162 L in placebo, $p < 0.0001$).

[21] Maximum work rate achieved for at least 30 seconds during the incremental cycle ergometry performed at Visit 1.

In Study 1222.37, Intensity of breathing discomfort (Borg Category Ratio Scale) at isotime showed was statistically significantly for both olodaterol 5 µg and 10 µg groups compared to placebo. In Study 1222.38, the differences intensity of breathing discomfort at isotime for olodaterol 5 µg and for 10 µg compared to placebo was not statistically significant.

Clinical safety

The mean (SD) exposure in the 4 combined pivotal Phase III studies (1222.11, 1222.12, 1222.13 and 1222.14) was 300 (90.6) days. The mean exposure was 287, 308, 304 and 299 days in placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol groups respectively in these 4 studies combined. Overall, 54.5% had an exposure to study drug of between 282 to 337 days. The percentages of patients with any adverse event (AE) were comparable among treatment groups. The most commonly reported AE was COPD (28.8%, 25.9%, 30.1%, and 28.5% in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol groups respectively). The most commonly reported AE in supportive 6 week crossover Phase III studies was also COPD (6.2%, 6.3%, 4.2%, 2.8% and 4.8% in placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups respectively).

The most commonly reported treatment related AEs (ADRs) in the 4 pivotal Phase III studies were COPD (0.6%, 1.4%, 1.4% and 2.8% in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups respectively) and headache (1.1%, 0.3%, 0.7% and 0.7% in respective groups). The most commonly reported ADRs in supportive 6 week crossover phase trials were cough (0.3%, 0.4%, 0.0%, 0.5% and 0.0% in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups respectively).

Overall there were 53 on treatment deaths, 7 post treatment deaths and 16 post study deaths in the four pivotal Phase III studies. The incidence of on treatment deaths was 1.5% (13 out of 885), 1.5% (13 out of 876), 1.9% (17 out of 883) and 2.2% (10 out of 460) in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups respectively. The most frequently reported cause of death in olodaterol 5 µg group was COPD. The most frequently reported cause of deaths in olodaterol 10 µg group was pneumonia. Of the 23 post treatment/post study deaths, 10, 6, 4 and 3 deaths occurred in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups respectively.

In the 4 pivotal Phase III efficacy studies, the incidence of Serious AEs (SAEs) was 16.4% (145 out of 885), 15.8% (138 out of 876), 16.6% (147 out of 883) and 15.0% (69 out of 460) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups respectively) The most frequently reported SAEs were COPD (6.0%, 4.7%, 6.9% and 5.9% in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups respectively) and pneumonia (1.5%, 1.6%, 2.5% and 1.5% in the respective groups). The incidence of SAEs in "Neoplasms benign, malignant and unspecified (including cysts and polyps)" category was: olodaterol 5 µg (1.6%; 14 out of 876); olodaterol 10 µg (2.2%; 19 out of 883; formoterol 12 µg (1.7%; 8 out of 460); placebo (1.0%; 9 out of 885).

In the supportive 6 week crossover Phase III studies, three deaths were reported (1 in olodaterol 5 µg group (Study 1222.24) and 2 in olodaterol 10 µg group (1 each in studies 1222.25 and 1222.38). The cause of death for the patient in olodaterol 5 µg group was cardiopulmonary arrest, while that for the patient in olodaterol 10 µg group in study 1222.25 was COPD. The cause of death for patient in olodaterol 10 µg in Study 1222.38 was not known. The incidence of SAEs in these crossover studies was 3.3% (23 out of 693), 3.3% (23 out of 701), 2.7% (19 out of 691), 3.3% (7 out of 214) and 3.2% (6 out of 186) in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups respectively. The most frequently reported SAEs were COPD (1.2%, 0.4%, 1.0%, 0.9% and 2.2% respectively). One patient each in olodaterol 5 µg group and olodaterol 10 µg group had a treatment related SAE of atrial fibrillation.

No deaths were reported in Phase II studies (1222.3, 1222.5 and 1222.26). In Study 1222.3 the incidence of SAEs was 2.9% (1 out of 35), 2.9% (1 out of 35), 5.7% (2 out of 35), 0.0% (0 out of 34) and 0.0% (0 out of 35) for placebo, olodaterol 2 µg, 5 µg, 10 µg and 20 µg groups respectively. In Study 1222.5, the incidence of SAEs was 2.5% (2 out of 81), 2.5% (2 out of 80), 2.3% (2 out of 86), 2.5% (2 out of 79) and 0.0% (0 out of 79) for olodaterol 2 µg, 5 µg, 10 µg, and 20 µg groups respectively. In Study 1222.26, one patient was reported with an SAE (COPD exacerbation) during treatment with olodaterol 5 µg.

No deaths were reported in asthma Studies (1222.4, 1222.6, 1222.27 and 1222.29) included in this dossier. The incidence of SAEs was 1.0% (7 out of 731; 2 placebo; 1 olodaterol 2.5 µg twice daily; 1 olodaterol 5 µg twice daily; 2 olodaterol 10 µg; 1 olodaterol 20 µg).

Laboratory outcomes

In the 4 pivotal studies, the reported incidence of possible clinically significant high glucose levels was 2.6%, 3.7%, 2.8% and 1.7% in pooled placebo, olodaterol 5 µg, olodaterol 1 µg, and formoterol groups respectively.

Change in CPK levels from baseline to Days 85, 169 and 337 was assessed in the 4 pivotal studies. Overall, there was a mean decrease from baseline in CPK levels at Days 85, 169 and 337 in placebo and olodaterol 5 µg groups, and an increase from baseline in formoterol group. In the olodaterol 10 µg group, the trend was variable with slight increase from baseline at Day 85, and slight decreases from baseline at Days 169 and 337.

The serum potassium levels were evaluated in the 4 pivotal studies at 1 and 3 hours post dose at Week 6 (Day 43) and Week 12 (Day 85). For the pooled olodaterol 5 µg group, there was a statistically significantly lower serum potassium level compared to pooled placebo group at 1 and 3 hours post dose on Day 43 (1 hour post dose: treatment difference -0.044mmol/L from placebo, p = 0.03; 3 hours post dose: treatment difference -0.040mmol/L from placebo, p =0.04) but the difference between pooled olodaterol 5 µg group and placebo group was not statistically significant at 1 hour and 3 hours post dose on Day 85. For the pooled olodaterol 10 µg group, there was no statistically significant difference in mean serum potassium levels compared to placebo at all time points except at 1 hour post dose on Day 43 (treatment difference -0.042mmol/L from placebo, p = 0.04). There was no statistically significant difference in mean serum potassium levels between pooled formoterol group and pooled placebo group at all time points. Across the 4 test time points, the minimum serum potassium recorded was 2.8 mmol/L, 2.4mmol/L, 2.8 mmol/L and 3.2 mmol/L in pooled placebo, olodaterol 5 µg, olodaterol 10 µg and formoterol 12 µg groups respectively in the 4 pivotal studies. The proportion of patients in each pooled treatment group with a minimum serum potassium level during the treatment period below lower limit normal (less than LLN) was 10.2%, 10.1%, 10.1% and 13.2% in placebo, olodaterol 5 µg, olodaterol 10 µg and formoterol 12 µg groups respectively.

In the supportive 6 week crossover studies, the incidence of possible clinically significant high glucose levels was 2.7%, 3.7%, 2.4%, 4.9% and 1.8% in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups respectively. The incidence of possible clinically significant low potassium levels was 0% across all treatment groups in these studies. The mean last potassium value on treatment was 4.2 mmol/L, 4.2 mmol/L, 4.2 mmol/L, 4.2 mmol/L and 4.1 mmol/L in pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups respectively. The change from baseline in mean last potassium value on treatment was 0.0mmol/L in all treatment groups. The proportion of patients in each pooled treatment group with a minimum serum potassium level during the treatment period less than LLL was 1.2%, 1.3%, 0.9%, 0.5% and 1.1% in placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups respectively.

Serum potassium was also assessed in Phase II studies (1222.3, 1222. 5 and 1222.26).

In Study 1222.3, there was a trend for lower potassium levels with higher doses of olodaterol at 1 hour and 2 hour post dose. At 1 hour post dose, the difference in geometric mean compared to placebo was statistically significant for olodaterol 20 µg, but not for other doses. At 2 hour post dose, the difference in geometric mean compared to placebo was statistically significant for olodaterol 5 µg, 10 µg, and 20 µg but not for 2 µg. At 4 hour post dose, there was no statistically significant difference in the potassium geometric mean between placebo and any of the olodaterol groups. For the single dose olodaterol 40 µg in this study, the difference in geometric mean compared to placebo was statistically significant at 1 hour, 2 hours and 4 hours post dose.

In Study 5, after the first dose (Day 1) and after 1 week of treatment (Day 8), the difference in the maximum decrease from baseline in serum potassium compared to placebo was statistically significant only for olodaterol 20 µg, but not for other doses. At Days 15 and 29, there was no statistically significant difference between placebo and any olodaterol dose group.

There were no distinguishing features between the dose groups with respect to ECG recording, Holter monitoring or vital signs.

Administration related bronchoconstriction (ARB)

ARB (drop in FEV1 greater than or equal to 15%; use of rescue medication; symptoms such as cough, wheeze or dyspnoea within 30 minutes of inhaling a study drug on a test day) was assessed in replicate pivotal Studies 11 and 12. The overall incidence in pooled groups was: 2.9% (12 out of 417) olodaterol 5 µg; 4.7% (20 out of 424) olodaterol 10 µg; 13.6% (58 out of 425) placebo.

Adjudicated SAEs

An analysis of respiratory related, composite outcome and its components (death; hospitalisation; intubation) was carried out, with independent adjudication for relationship of SAEs to asthma, COPD, pneumonia or another respiratory condition. The safety database consisted of 5387 patients across 18 studies of which 3380 were olodaterol treated, 1409 placebo, 541 formoterol treated and 57 tiotropium treated. Majority were COPD patients (87.0%; 4687 out of 5387) from 15 studies, the remainder from the 3 asthma studies.

Overall incidence of adjudicated events (composite) was 8.6% (292 out of 3380) in the combined olodaterol group compared to 10.4% (146 out of 1409) in placebo, 11.8% (64 out of 541) in formoterol group and 3.5% (2 out of 57) in tiotropium group. The incidence of respiratory related events was 4.6% (156 out of 3380), 5.3% (74 out of 1409), 7.2% (39 out of 541) and 1.8% (1 out of 57) for the combined olodaterol, placebo, formoterol and tiotropium groups respectively. The incidence of individual components was: Respiratory related deaths [(0.6% (21 out of 3380) versus 0.4% (5 out of 1409) versus 0.7% (4 out of 541) versus 0.00% (0 out of 57)], Respiratory related hospitalisations [(4.4% (148 out of 3380) versus 5.1% (72 out of 1409) versus 6.7% (36 out of 541) versus 1.8% (1 out of 57)] and Respiratory related intubations [(0.5% (17 out of 3380) versus 0.6% (8 out of 1409) versus 0.7% (4 out of 541) versus 0.0% (0 out of 57)} in the combined olodaterol, placebo, formoterol and tiotropium groups respectively.

Cardiovascular safety

Cardiac related endpoints on the combined dataset of the 4 pivotal Studies (1222.11, 1222.12, 1222.13 and 1222.14) were also analysed. The overall incidence of cardiovascular AEs was 70.8% (627 out of 885), 71.0% (622 out of 876), 72.7% (642 out of 883) and 69.1% (318 out of 460) in placebo, olodaterol 5 µg, olodaterol 10 µg and formoterol groups respectively. Specific incidences were as follows for the placebo, olodaterol 5 µg, olodaterol 10 µg and formoterol groups respectively:

- Cardiac arrhythmias: 4.2% versus 5.6% versus 4.4% versus 4.3%

- Tachyarrhythmias: 3.4% versus 3.5% versus 2.9% versus 3.3%
- Palpitations: 1.5% versus 1.6% versus 2.2% versus 2.2%
- Ventricular tachyarrhythmias: 1.0% versus 1.9% versus 1.4% versus 2.0%

Analysis of major adverse cardiac events (MACE) was undertaken on the combined dataset of the 4 pivotal 48 weeks studies 11 out of 12 out of 13 out of 14. Overall, the incidence of "Fatal AE" was 1.5% (15 out of 885), 1.5% (13 out of 876), 1.9% (17 out of 883) and 2.2% (10 out of 460) in placebo, olodaterol 5µg, olodaterol 10µg and formoterol groups respectively.

The clinical evaluator recommends approval. The recommendations with regard to PI are supported.

Risk management plan

There are no outstanding issues following the evaluation of sponsor's response. The PI modifications accepted or proposed by the sponsor were considered acceptable. Advice from ACSOM was not sought for this submission.

The updated RMP Version 1.1 (dated 04 April 2013, DLP 11 January 2012) and Australian Specific Annex Version 1.1 (dated 26 April 2013) and any future updates are proposed as a condition of registration.

Risk-benefit analysis

Delegate considerations

Quality

There are no outstanding issues. The product labelling will be reviewed post ACPM especially with respect to benzalkonium chloride information on the label.

Nonclinical

There are no outstanding issues. Any recommendations with regard to PI are supported.

Clinical

There are no outstanding issues. Recommendations with respect to PI are supported by the Delegate.

Olodaterol is a New Chemical Entity. The clinical development program was comprehensive and the drug appears to have been thoroughly investigated.

Olodaterol, a long acting beta 2 adrenergic agent, is orally inhaled and acts locally in the lungs. The absorption from lungs is rapid and about 30% of intravenous dose but in the proposed clinical dose (5 µg per day) low systemic effects are expected in the short term. Any ingested amount is not likely to contribute further to systemic exposure. The drug is metabolised in liver, although some active renal secretion probably also takes place. The pharmacokinetics were linear, dose proportional and not likely to lead to accumulation except in the presence of significant liver or renal impairment. Olodaterol has expected systemic effects profile known for beta 2 agonist agents, including tendency to cause hypokalaemia and cardio stimulatory effects. The pharmacokinetic and pharmacodynamic information generated to support the drug is considered adequate. However, population pharmacokinetics was not provided and this is considered a deficiency.

Dose finding was investigated in two Phase II studies and supported 5 µg and 10 µg once daily for further testing in Phase III setting. The 2 µg daily dose was shown to be

sub-therapeutic and 20 µg daily dose as providing no further increase in efficacy over 10 µg daily dose. Another Study (1222.26) showed advantage for 5 µg twice daily dosing compared with 10 µg once daily dosing with respect to FEV1 $AUC_{12\text{-}24h}$ but not for FEV1 $AUC_{0\text{-}12h}$ or FEV1 $AUC_{0\text{-}24}$ responses. However, given that a lower dose (5 µg once daily) was tested subsequently (along with 10 µg once daily dose) in Phase III studies and is also the proposed clinical dose, the twice daily dosing is not considered an issue. The 2 µg twice daily dose examined in the same study was shown to be sub-therapeutic.

The Phase III program was particularly well planned with 2 sets of replicate studies providing confirmatory evidence in COPD patient population, against placebo and against an appropriate active comparator (formoterol 12 µg twice daily; note indacaterol which is a recently registered LABA with once daily dosing would not have been available at the time as an approved comparator). There were additional Phase III studies characterising olodaterol effect over 24 hours and in relation to exercise.

All 4 confirmatory efficacy trials showed consistent bronchodilator, placebo corrected, treatment effect (FEV1 $AUC_{0\text{-}3h}$ and trough FEV1) roughly ranging from 50 mL to 150 mL for both 5 µg and 10 µg once daily olodaterol doses. The two olodaterol doses had similar clinical effect. The effect with formoterol treatment was not different effect with olodaterol treatment. The primary effects were assessed at 12 and 24 weeks and were shown to have been maintained at 48 weeks. The effect was homogenous across demographic and prognostic subgroups but less so in patients currently on tiotropium (LAMA).

However, none of the patient assessed/perceived measures of improvement, symptom relief measures or quality of life measures showed clinically meaningful improvement and were also mostly statistically not significantly different from placebo. There was also no improvement shown with respect to use of rescue medications or episodes of disease exacerbation. The exercise/endurance tested in another set of Studies (1222.37 and 1222.38) also did not indicate any benefit.

The adverse effects data collected in the clinical trials program indicated safety profile consistent with an inhaled beta 2 adrenergic agonist agent and generally comparable with formoterol. Special analyses were done with respect to administration related bronchoconstriction, respiratory related serious adverse outcomes and cardiovascular safety. The occurrences were low in many cases and in all groups (especially cardiovascular/MACE endpoints) and inconclusive for determining differences between the groups based on this small dataset. Long term effects on mortality, beneficial or otherwise, are unknowable from this dataset. Long term, post market surveillance will, therefore, be of significant importance.

Risk management plan

There are no outstanding issues. The recommendations with respect to PI are supported by the Delegate.

Proposed action

Pending advice from the ACPM, the dataset is considered to be adequate to support the proposed use in COPD.

The proposed indication includes the term '*long term'* and patients *'including chronic bronchitis and or emphysema*'. The former is poorly defined and superfluous (in the presence of another term '*maintenance bronchodilator treatment'* although both are included in the currently approved indication for indacaterol) while the latter is not supported by patient population definition in the clinical trials, although the three coexist.

In addition, the olodaterol treatment was an add on to patients on existing COPD treatments (except any LABA) including LAMA. However, it is understood that this need

not be reflected in the indication as clinical guidelines for COPD are clear and well understood. The description of participating patients in the clinical trials section should therefore suffice.

An issue was raised with respect to the timing of the daily dose ('*at the same time of the day'* or '*same time in the morning'*, the latter is strictly based on the clinical trial data). The Delegate accepts the argument that time of dosing may be more appropriately left to the judgement of prescribing physicians based on knowledge of individual patients. It is also likely to be less relevant in COPD than in asthma. The clinical trials description in the PI should note that drugs were delivered in the morning in pivotal clinical trials.

The following modified indication is proposed:

> *'Striverdi Respimat is a long acting beta 2 agonist indicated as once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) (see Clinical Trials)'*

The dosing as proposed (two 2.5 µg actuations daily), including recommendations in special populations (no change required in elderly, (any) renal impairment, or mild and moderate hepatic impairment) is also supported.

The PI will require further modifications. No effect on COPD symptoms, exacerbations, exercise and quality of life needs to be noted. The sponsor is requested to provide update copies (annotated and clean) including all amendments requested by various evaluation areas of the TGA including any in this Overview, using the draft PI at the time of submission as the base document. Further PI negotiations are expected post ACPM.

Request for ACPM advice

The Committee is requested to provide advice on the following issues:

- Adequacy of dataset for the proposed use and advice on wording of therapeutic indication.
- Any other issue that the Committee considers relevant to a decision on general marketing of this drug.

Response from sponsor

Presented here is Boehringer Ingelheim (BI) Pre ACPM Response to the TGA Delegate's proposed action and comments in relation to the application for registration of Striverdi Respimat olodaterol (as hydrochloride) 2.5 microgram/actuation solution for inhalation cartridge for the long term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and or emphysema.

Indications and dosage

Boehringer Ingelheim (BI) welcomes the TGA Delegate's recommendation to approve the application to register olodaterol for the treatment of patients with COPD. BI accepts the Delegate's proposed modified indication as shown below.

> *'Infortispir Respimat[22] is a long acting beta 2 agonist indicated as once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).'*

BI also agrees with the Delegate that there is no need to specify in the indication that Striverdi Respimat be used as add on therapy to existing COPD treatments (except any

[22] The trade name "Infortispir Respimat" was later altered to "Striverdi Respimat".

LABA), including LAMA, as the clinical guidelines for COPD are clear and well understood, and the description of the patients studied in the clinical trials section of the Product Information (PI) should suffice. BI also agrees with the Delegate for the proposed dosing (two 2.5 µg actuations once daily) with recommendations in special populations.

Clinical trials

Pharmacokinetics

The Delegate states '*The pharmacokinetic and pharmacodynamic information generated to support the drug is considered adequate. However, population pharmacokinetics was not performed and this is considered a deficiency*'.

Clinical pharmacokinetic (PK) information for olodaterol was obtained from a total of 23 clinical studies. The vast majority of these studies included frequent PK blood sampling, thus allowing thorough assessment of the general PK properties of olodaterol as well as the PK in the target population. The influence of extrinsic and intrinsic factors, such as age, weight, lung function etc., was comprehensively investigated by a meta-analysis using data from the Phase II trials with COPD patients and asthma patients. Each of the two included studies provided single dose as well as steady state PK parameters from an adequate number of patients (N=405 and 296, respectively) to identify relevant covariates. Dedicated Phase I studies additionally provided information on the effects of renal and hepatic impairment, and of CYP and P-gp inhibiting co-medications. A population PK analysis would not have provided any additional information relevant for the clinical use of olodaterol, and hence was not performed.

Clinical efficacy

BI would like to address the Delegate's assessment of COPD symptoms, exacerbations, exercise and quality of life. BI's response is summarised as follows:

Symptomatic benefit (TDI, SGRQ, rescue use, PGR): Symptomatic benefit was assessed in a number of ways within the Phase III program for olodaterol:

- Assessment of effects of olodaterol (and the active control, twice daily formoterol) on dyspnoea (TDI focal score; co-primary endpoint) and health related quality of life (SGRQ total score; key secondary endpoint), based on an analysis of the combined dataset from Studies 1222.13 and 1222.14.
- Assessment of daytime and night time use of rescue medication (as needed salbutamol) on a daily basis (using an electronic diary) throughout the 48 weeks of treatment in each of the four 48 week Studies (1222.11, 1222.12; 1222.13, 1222.14).
- Assessment of the patient's global rating of benefit, using a Patient Global Rating, in each of the four 48 week Studies (1222.11, 1222.12; 1222.13, 1222.14).

Transition Dyspnoea Index (TDI)

The TDI focal score after 24 weeks (Day 169) was included as a co-primary endpoint in the replicate, placebo and active controlled, 48 week trials (1222.13, 1222.14; pre specified to be conducted on the combined dataset). At the first measurement time point (Day 43) in both studies, there was a consistent improvement in TDI focal score for olodaterol 5 µg, olodaterol 10 µg and formoterol 12 µg compared to placebo. At the next measurement time point (Day 85), improvements in TDI focal score for olodaterol 5 µg, olodaterol 10 µg and formoterol 12 µg compared to placebo were also demonstrated. However, in one Study (1222.13) there was a notable increase in the TDI focal score in the placebo group compared to Day 43, with a further increase at the next measurement time points (Day 127, Day 169). The TDI focal score in the active treatment groups remained consistent from Day 43 to Day 169, such that the placebo TDI focal score at Day 169 was similar to the TDI focal score in the three active treatment arms. This unexpected observation in the

placebo group was not observed in 1222.14, in which the placebo response was consistent from Day 43 to Day 169. As a consequence, the pre specified co primary analysis of TDI focal score at Day 169 based on the combined dataset from 1222.13 and 1222.14 cannot provide a reliable estimate of the effect size (compared to placebo) for olodaterol or formoterol. While the unexpected placebo response over time does not permit formal conclusions of a benefit of olodaterol for the TDI focal score, based on the pre specified co primary endpoint, other aspects of the TDI assessment do provide convincing evidence of benefit following olodaterol treatment nevertheless:

- The TDI focal score in the active and placebo arms at Day 43 are consistent in the two studies, with statistical significance being achieved for comparisons to placebo for all three active treatment arms in the combined dataset.
- A statistically significant improvement in TDI focal score for both olodaterol 5 µg and olodaterol 10 µg compared to placebo was also achieved at Day 85, even though an unusual placebo response was already apparent in 1222.13.
- TDI focal scores for olodaterol and formoterol are comparable from Day 43 to Day 169 in both studies; a pre specified key secondary analysis revealed no significant difference between olodaterol and formoterol at Day 169 (two sided superiority testing).

To address the unusual placebo response and a potential influence of missing values due to early discontinuations, post hoc sensitivity analyses on the combined dataset were conducted using pattern mixture models[23] (PMM), based on the methods described by Hogan *et al*,[24] which revealed that there was a linear response for TDI focal score over log transformed days on treatment. The analyses showed a statistically significant increase in TDI focal score at Day 169 for both olodaterol 5 µg and olodaterol 10 µg compared to placebo. In conclusion, the PMM can correct the unusual placebo response by providing more appropriate imputation for missing values.

St. George's respiratory questionnaire (SGRQ)

The SGRQ total score at Day 169 was included as a key secondary endpoint in the replicate, placebo and active controlled, 48 week trials (1222.13, 1222.14; pre specified to be conducted on the combined dataset). Notwithstanding the lack of alpha protection as a result of the failure to achieve statistical significance for the TDI focal score, the results of the SGRQ analyses do provide convincing evidence of a symptomatic benefit of olodaterol 5 µg and olodaterol 10 µg (p values for the comparisons to placebo were less than 0.0035, well below the prespecified threshold (p=0.05)). In the combined dataset, statistically significant improvements in SGRQ total score compared to placebo were demonstrated for both olodaterol 5 µg (-2.8 units, p=0.0034) and olodaterol 10 µg (-3.4 units, p=0.0004) at the pre specified time point Day 169; significant improvements were seen in all 3 SGRQ domains (symptoms, activities, impact). A statistically significant improvement in SGRQ total score compared to placebo was also demonstrated for formoterol 12 µg at Day 85 (-2.5 units, p=0.01), but not at Day 169 (-1.2 units, p=0.2009). At Day 169, the SGRQ total score for olodaterol 10 µg was significantly improved compared to formoterol 12 µg (-2.2 units, p=0.0224), with no significant difference between olodaterol 5 µg and formoterol 12 µg (-1.6 units, p=0.0945) or between olodaterol 10 µg and olodaterol 5 µg (-0.6 units, p=0.5370)).

In addition a responder analysis showed that more patients treated with olodaterol had an improvement in SGRQ total score greater than the MCID (4 units) compared to placebo

[23] This type of sensitivity analysis for handling of missing data in clinical trials is one of the recommendations of the US National Research Council Committee on National Statistics.
[24] Hogan JW, Roy J, Korkontzelou C. Tutorial in biostatistics: handling drop-out in longitudinal studies. *Stat Med* 23, 1455 to 1497 (2004).

(50.2% for olodaterol 5 µg, 49.1% for olodaterol 10 µg versus 36.4% for placebo, $p < 0.001$; combined dataset). For formoterol 12 µg, there was no significant difference compared to placebo in the number of patients with an improvement in SGRQ total score greater than the MCID (39.1% for formoterol 12 µg versus 36.4% for placebo, $p = 0.4621$; combined dataset).

Rescue medication use

Both daytime and night time rescue medication use was recorded on a daily basis throughout the 48 week treatment period in each of the 48 week studies. In all studies, once daily treatment (morning dosing) with olodaterol 5 µg and olodaterol 10 µg resulted in statistically significant reductions in both daytime and night time rescue medication use compared to placebo. The reduction in daytime and night time rescue medication with olodaterol was comparable to twice daily (morning and evening) treatment with formoterol (1222.13, 1222.14), providing additional support that once daily morning administration of olodaterol offers meaningful bronchodilatory effects over the entire dosing interval.

Patient's global rating (PGR)

In the combined datasets for the 48 weeks Studies (1222.11, 1222.12, 1222.13 and 1222.14), patients consistently rated their respiratory condition as "a little better" (score of 2.9 to 3.1) following treatment with olodaterol 5 µg and olodaterol 10 µg, which compares with a rating of 3.1 to 3.4 with placebo (between "no change" (score of 4) and "a little better" (score of 3)); the difference in PGR for olodaterol compared to placebo was statistically significant at all time points up to Day 169.

Conclusions

Although the pre specified co primary symptomatic endpoint (Mahler TDI focal score at Day 169 compared to placebo) missed statistical significance due to an unusual placebo response in one study, substantial evidence of symptomatic benefit has been demonstrated by nominally significant improvements compared to placebo in the TDI focal score at earlier time points for both olodaterol 5 µg once daily and olodaterol 10 µg once daily, by post hoc analysis of the TDI focal score using imputation methods for discontinued patients that do not assume missing at random (PPM), and by consistent improvements in health status as assessed by SGRQ and several other patient centred outcomes such as reduction in rescue medication use. The effect of olodaterol 5 µg is similar or numerically better than the active comparator formoterol. These results indicate that the increase in FEV1 response seen in the 48 week studies has been translated into improvement in symptoms and health status, thereby supporting the clinical relevance of the effect sizes seen for the bronchodilator response. Furthermore, these benefits on symptoms and health status have been demonstrated in a study population allowed usual care maintenance pulmonary therapies, a factor of influence on effect size.

Symptom limited exercise tolerance

Studies 1222.37 and 1222.38 were specifically included in the Phase III clinical program to evaluate the effects of olodaterol on symptom limited exercise tolerance. The trial design for these studies was founded on the hypothesis that olodaterol reduces the degree of airflow limitation in patients with COPD during tidal breathing, allowing for a reduction in lung hyperinflation; this reduced lung hyperinflation leads to a reduction in the intensity of breathing discomfort experienced during exercise and a consequent improvement in symptom limited exercise tolerance. Based on this hypothesis, the primary endpoint was specified as endurance time during constant work rate cycle ergometry at 75% maximal work capacity, while IC at isotime (standard time during exercise) and the intensity of breathing discomfort at isotime were identified as key secondary endpoints.

In each study, olodaterol 5 µg and olodaterol 10 µg demonstrated statistically significant increases compared to placebo in endurance time during constant work rate cycle ergometry at 75% maximal work capacity (14% (p = 0.0002; 1222.37) and 11.8% (p = 0.0018; 1222.38) improvement for olodaterol 5 µg; 14% (p=0.0003; 1222.37) and 10.5% (p=0.0052; 1222.38) improvement for olodaterol 10 µg). In both studies, olodaterol 5 µg and olodaterol 10 µg demonstrated statistically significant increases in IC at isotime (key secondary endpoint). In 1222.37, olodaterol 5 µg and olodaterol 10 µg demonstrated statistically significant decreases in the intensity of breathing discomfort at isotime (key secondary endpoint); in 1222.38, the decrease in the intensity of breathing discomfort at isotime for olodaterol 5 µg compared to placebo was not statistically significant (there was no reduction for olodaterol 10 µg).

Conclusions

The results from Studies 1222.37 and 1222.38 confirm that the improvements in airflow following treatment with olodaterol, as measured by FEV1, translated into reductions in lung hyperinflation at rest and during exercise, with a consequent improvement in exercise endurance time. When expressed as a relative improvement compared to placebo, there was a consistency in improvements for FEV1, IC and exercise endurance time, and also with significant improvements in breathing discomfort during exercise in Study 1222.37. As such, the results from the exercise studies have clinical relevance by providing an important further characterisation of the bronchodilator efficacy of olodaterol at the impairment disability interface.

Exacerbations

The pivotal studies were not designed for demonstrating an effect on COPD exacerbations. For example, (i) eligible patients were not selected on the presence of a previous exacerbation in the preceding year and or stratified according to the number of exacerbations in the previous year, (ii) the studies were not powered to demonstrate differences in the incidence of exacerbations.[25] Also of high relevance, there was a very low incidence of exacerbations in the placebo group in the studies, which precluded any opportunity to evaluate the effects of olodaterol (and formoterol) on exacerbations beyond a purely exploratory analysis. This was foreseen by BI during the planning of the studies. BI had identified "COPD exacerbations" as a safety endpoint but based on FDA recommendations COPD exacerbations were finally identified as a secondary efficacy endpoint. The low incidence of exacerbations in the placebo group is highlighted by a comparison with the Phase III studies conducted with tiotropium Respimat (replicate Studies 205.254/205.255; 205.372). Both the proportion of patients with at least one moderate to severe exacerbation and the rate of moderate to severe exacerbations in the placebo group is considerably less in the olodaterol studies compared to the tiotropium studies (29.6% and 0.58 per year in the olodaterol studies; 44.1% and 1.91 per year in 205.254/255; 43.1% and 0.87 per year in 205.372). Indeed, the proportion of patients with at least one moderate to severe exacerbation in the placebo group in the olodaterol studies (approximately 30%) was noticeably less than the proportion of patients with at least one moderate to severe exacerbation in the tiotropium groups in 205.254/255 (approximately 37%) and 205.372 (approximately 35%).

Conclusion

In exploratory analyses based on both efficacy and safety evaluations, there is a trend towards a reduction in COPD exacerbations in patients treated with olodaterol compared to patients treated with placebo. However, no formal conclusions can be drawn from these

[25] For HR = 0.9, with 900 patients per group the power is 22% to detect 5% level of significance; for HR = 0.85, the power is 44%.

analyses. Further studies are required with design features that allow for a rigorous evaluation of the effects of olodaterol on COPD exacerbations in a confirmatory manner.

Trade name

BI requested modification of the trade name from Infortispir Respimat to Striverdi Respimat. BI disagrees with the Delegate's concerns regarding potential confusion with the registered Spiriva Respimat (tiotropium) and gave the following reasons why the risk for potential confusion is minimal:

- Trade name
  - While both names begin with "S" and contain the letters "r" and "i" in the infix, the remaining letters of the names are orthographically differentiated ("-verdi" versys "-iva")
  - Additionally, Striverdi contains an ascending letter in the second position ("t") whereas Spiriva contains a descending letter in the second position ("p")
  - Furthermore, Striverdi is a longer name with nine letters whilst Spiriva has seven, making the names appear differently.
- Active ingredient: the active ingredients do not look alike or sound alike: olodaterol (as hydrochloride); tiotropium
- Packaging design: the packaging colours for Striverdi Respimat are yellow compared to Spiriva Respimat, which are green
- Physical appearance: Striverdi Respimat has a yellow cap, in contrast to Spiriva Respimat, which has a green cap
- Description in PI & CMI: both the PI and CMI proposed for Striverdi Respimat contain the identifying description 'with a yellow cap' to enhance ease of differentiation between the products.

In a complex health care system, no trade name is completely free of possible confusion with another trade name. Therefore, a trade name by itself does not eliminate the potential risk of human error. In general, to avoid patients being dispensed incorrect medication, it is important that pharmacists implement procedures to ensure that patients are dispensed the correct medications.

Upon the request of some authorities (for example US FDA; Health Authority in Norway), BI has withdrawn the trade name Infortispir and developed the trade name Striverdi, which has been authorised by health authorities in the USA, Europe and Canada. None of these health authorities have objected to the trade name Striverdi, thus giving patients the convenience of a global brand. Maintaining the name Striverdi is of major importance in order to preserve the global name which in today's world is a major concern with health agencies, healthcare professionals and patients.

In summary, the risk for potential confusion between Striverdi Respimat and Spiriva Respimat is limited for the specific reasons mentioned above (trade name differentiation, active ingredient names do not look alike or sound alike, packaging designs are different, physical appearance and description in PI and CMI).

Quality

Benzalkonium chloride (BAC), a preservative in the proposed Striverdi Respimat product is not a novel excipient in inhalational products and the anticipated daily doses achieved at the MRHDs is lower for Striverdi Respimat than that achieved for other registered inhalational products.

The PSC of ACPM at its 151st (2013/3) meeting has recommended that the preservative BAC be quantitatively disclosed on the label in view of *'…known clinical reactions, including*

bronchoconstriction in some patients with hyper reactive airways…' This observation has been made when bronchodilator drugs are delivered from nebulizers, which provide much higher doses of this excipient.[26]

However, administration related bronchoconstriction (ARB) that occurred within 30 minutes of inhaling trial medications were examined in two trials (SUB 1222.11 and 1222.12,at various time points. The frequency of ARB was found to be very low. There were 13.6% patients who had any defined symptom of ARB at any time point in the placebo group, followed by the olodaterol 10 µg (4.7%) and olodaterol 5 µg (2.9%) groups. The most commonly occurring event was an asymptomatic fall in FEV1 of equal or greater than 15% below test day pre dose FEV1. The frequency of patients who had a drop in FEV1 of greater than or equal to 15% was highest in the placebo group (11.8%) compared to the olodaterol 5 µg (2.6%) and 10 µg (3.8%) groups. A fall in FEV1 without symptoms might not reflect an adverse response to an inhaled substance, but rather may be the result of the forced expiration manoeuvre itself. Consequently, the incidence of asymptomatic falls in FEV1 alone is the least suggestive category of ARB. Rescue medication use was highest in the placebo group (2.1%) compared to the olodaterol 5 µg (0.2%) and olodaterol 10 µg (0.9%) groups. Coughing, wheezing or dyspnoea within 30 minutes of inhaling study medication did not occur in any patient. Thus, no evidence of paradoxical bronchospasm was observed in the two 48 week trials (1222.11 and 1222.12,) following administration of olodaterol using in the Striverdi Respimat clinical trial program.

In addition, in accordance with the Therapeutic Goods Order No. 69 General requirements for labels for medicines subsection 3(9) Preparations for use on skin or mucous membranes, both the proposed PI and labels qualitatively disclose the presence of BAC. This is consistent with the approach taken for other products registered containing BAC.

In summary, it is not considered necessary from a nonclinical or clinical perspective to include the quantity of BAC on the product labelling or PI for Striverdi Respimat. Further, the qualitative disclosure on the proposed product labelling is consistent with the TGO 69 and other currently registered products.

Conclusion

In conclusion, Boehringer Ingelheim welcomed the TGA Delegate's recommendation to approve the registration of Striverdi Respimat olodaterol for the following indication:

> *'Infortispir Respimat[27] is a long acting beta 2 agonist indicated as once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).'*

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Infortispir Respimat inhalation containing 2.5 µg per actuation of olodaterol (as hydrochloride) to have an overall positive benefit risk profile for the Delegate's amended indication;

[26] Beasley CRW, Rafferty P, Holgate ST. The role of preservatives in Atrovent induced bronchoconstriction. *Thorax* 42:230-231 (1987); Rafferty P, Beasley R, Holgate ST. Comparison of the efficacy of preservative free ipratropium bromide and Atrovent nebuliser solution. *Thorax* 43:446-450 (1988)
[27] The trade name "Infortispir Respimat" was later altered to "Striverdi Respimat".

> *'Infortispir Respimat[28] is a long acting beta 2 agonist indicated as once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)' (see Clinical Trials)*

In making this recommendation the ACPM noted the trade name change and found it somewhat perplexing but unlikely to cause confusion.

The Committee was requested to provide advice on the following issues:

- Adequacy of dataset for the proposed use and advice on wording of therapeutic indication.

The ACPM advised these were well conducted studies which provided evidence of bronchodilation similar to other long acting beta agonists. The dataset was adequate to demonstrate both safety and efficacy.

The trials provided some evidence of symptom improvement but the studies were not sufficiently powered for full exploration of this. The Committee did not support inclusion of post hoc analysis in the PI.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI).

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Striverdi Respimat solution for inhalation delivering 2.5 micrograms of olodaterol (as hydrochloride) per actuation cartridge, indicated for:

> *'Striverdi Respimat is a long acting beta 2 agonist indicated for once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).'*

Specific conditions of registration applying to these therapeutic goods

Striverdi Respimat (olodaterol hydrochloride) Risk Management Plan (RMP) Version 1.1 dated 4 April 2013 (data lock point (DLP) 11 January 2012) and Australian Specific Annex Version 1.1 (dated 26 April 2013), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

[28] The trade name "Infortispir Respimat" was subsequently altered to "Striverdi Respimat".

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au