Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Umeclidinium bromide and Vilanterol trifenatate

Proprietary Product Name: Anoro Ellipta

Sponsor: GlaxoSmithKline Australia Pty Ltd

April 2015

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 <https://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

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	adverse event
AESI	adverse event of special interest
ASA	Australian specific annex (of the RMP)
$AUC_{0\text{-}24\ h}$	Area under the concentration time curve for 0 to 24 hours
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CYP	cytochrome P450
CYP1A1	P450 1A1
CYP2D6	P450 2D6
CYP3A4	P450 3A4
ECG	electrocardiogram
ED_{50}	estimated dose that would yield 50% of effective dose
EET	exercise endurance time
EMA	European Medicines Agency
E_{max}	maximum effect
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FF	fluticasone furoate
FVC	forced vital capacity
GCP	Good Clinical Practice

Abbreviation	Meaning
GOLD	Global Initiative for Obstructive Lung Disease
GSK	GlaxoSmithKline
GSK573719	umeclidinium bromide (UMEC)
h	hour(s)
hERG K^+	human ether-à-go-go-related gene potassium channel
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	inhaled corticosteroid
IH	inhalation
ITT	intent-to-treat
IV	intravenous(ly)
Ki	Affinity (binding) constant
L	litre
LABA	long acting $beta_2$-agonist
LAMA	long acting muscarinic antagonist
LS	least squares
LSM	Least squares mean
MACE	Major Adverse Cardiac Event
µg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
mL	millilitre
NOAEL	no observed adverse effect level
NOEL	no observable effect level
OCT	organic cation transporter
PASS	post authorisation safety studies

Abbreviation	Meaning
PBRER	Periodic Benefit-Risk Evaluation Reports
PD	pharmacodynamic
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PMSB	TGA's Post-Market Surveillance Branch
PSURs	Periodic Safety Update Reports
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
SMQ(s)	Standardised MedRA Querie(s)
SOBDA	shortness of breath with daily activities
SS	safety specifications
TDI	Transition Dyspnoea Index
TFH	Twenty four hour
TIO	tiotropium (bromide)
t_{max}	time of occurrence of C_{max}
UK	United Kingdom
UMEC	umeclidinium bromide (GSK573719)
USA	United States of America
VI	vilanterol (GW642444)

I. Introduction to product submission

Submission details

Type of submission:	New fixed dose combination
Decision:	Approved
Date of decision:	3 July 2014
Active ingredients:	Umeclidinium bromide and vilanterol trifenatate
Product name:	Anoro Ellipta
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd PO Box 18095 Melbourne VIC 8003
Dose form:	Powder for Inhalation
Strengths:	62.5 µg umeclidinium bromide/25 µg vilanterol trifenatate
Container:	Inhaler - dry powder
Pack sizes:	7 (physicians sample pack), 30
Approved therapeutic use:	*Anoro Ellipta is indicated as a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).*
Route of administration:	Inhalation
Dosage:	Adults: Anoro Ellipta (umeclidinium bromide/vilanterol trifenatate 62.5/25 micrograms) should be taken as one inhalation once daily by the orally inhaled route. Anoro Ellipta should be taken at the same time every day. This product should not be used in children. Further details regarding dosage are provided in the Product Information (PI, attachment 1).
ARTG number:	207529

Product background

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (the sponsor) to register Anoro Ellipta dry powder for inhalation containing umeclidinium bromide (UMEC)[1] and vilanterol trifenatate (VI)[2] for the following indication:

[1] Umeclidinium bromide is referred to by the abbreviation UMEC or umeclidinium throughout this document and is also sometimes referred to by the company abbreviation GSK573719.
[2] Vilanterol trifenatate is referred to by the abbreviation VI or vilanterol throughout this document and is also sometimes referred to by the company abbreviation GW642444.

Anoro Ellipta is indicated as a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Vilanterol trifenatate (VI) is a selective long acting beta$_2$-agonist (LABA). It has been considered recently (as a new chemical entity) by the TGA as part of an application by the sponsor to register a dry powder inhaler that also contains fluticasone furoate (Breo Ellipta). Vilanterol is not marketed as a mono product.

Umeclidinium bromide(UMEC) is a new chemical entity, a long acting muscarinic antagonist (LAMA) that exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic acetylcholine receptors on airway smooth muscle. The registration of UMEC as a new chemical entity was considered at the same time the TGA considered the registration of the fixed dose combination product Anoro Ellipta.

Two strengths of Anoro Ellipta were initially proposed for registration: 125 µg UMEC/25 µg VI, and 62.5 µg UMEC/25 µg VI. The sponsor withdrew the application for the 125 µg UMEC/25 µg VI strength on 7 January 2014 following discussions with the United States (US), European Union (EU) and Canadian regulatory authorities, as "[the sponsor] believes additional data are needed to further characterise the subpopulation which could derive most benefit from the higher strength (125/25 µg)."

Chronic obstructive pulmonary disease (COPD) is a serious, progressive and disabling condition that limits airflow in the lungs. People with COPD are prone to severe episodes of shortness of breath, with fits of coughing. Current pharmacological treatment of COPD includes 2 classes of inhaled bronchodilators: beta$_2$-adrenergic receptor agonists (beta$_2$-agonists) and muscarinic antagonists (also referred to as anticholinergics). Inhaled LABAs and LAMAs, are currently recommended for the treatment of symptomatic patients with moderate to very severe COPD and are considered to be more efficacious than short acting bronchodilators.

Co-administration of LAMAs and LABAs is considered to be more effective than either drug class alone in managing stable COPD. At the time of the submission no LAMA/LABA combination products were currently licensed for COPD treatment.[3] A LAMA/LABA combination product could potentially optimise bronchodilator therapy of COPD while avoiding the risk of side effects associated with increasing the dose of a single bronchodilator class.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 4 July 2014.

At the time the TGA considered this application, a similar application had been approved in the USA (18 December 2013), Canada (23 December 2013), EU (8 May 2014), New Zealand (20 March 2014) and Chile (11 March 2014), and was under consideration in 13 other counties including Switzerland.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[3] Ultibro Breezhaler was registered in Australia on 21 March 2014.

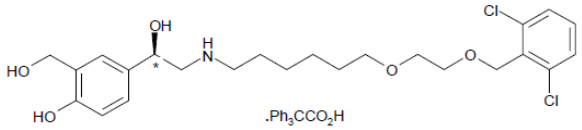
II. Quality findings

Drug substances (active ingredient)

Vilanterol trifenatate

Vilanterol trifenatate (VI) (structure shown in Figure 1) is a white non solvated anhydrous crystalline solid. It is structurally related to other beta$_2$-agonists such as indacaterol and olodaterol. Although VI is practically insoluble in water, fine particles of the substance have been shown to dissolve rapidly in simulated lung fluid.

Figure 1. Structure of vilanterol trifenatate.



* = chiral centre

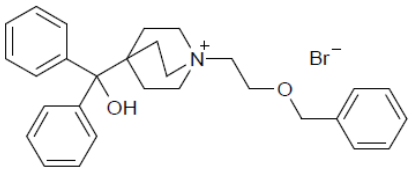
Its manufacture, quality control and stability were described in a recent submission by the sponsor to register Breo Ellipta a powder for inhalation product containing fluticasone furoate and VI.

The drug substance specification includes limits and tests for identification, assay and residual solvents. The limits for most of the specified impurities lie outside the qualification limits specified in CPMP/ICH/2737/99[4] but they are acceptable on the basis that at the maximum recommended VI dose (25 µg) the impurity levels are well below the standard threshold of toxicological concern (1.5 µg/day). The particle size limits are the same as those described in the recent submission and are based upon a physical characterisation of the drug substance used in clinical and stability batches.

Umeclidinium bromide

Umeclidinium bromide (UMEC) (structure shown in Figure 2) is a white anhydrous solid. It is manufactured and micronised at the same sites used in the manufacture of VI. Like VI, UMEC is not very soluble in water but fine particles of the drug substance dissolve rapidly in simulated lung fluid.

Figure 2. Structure of umeclidinium bromide.



The drug substance quality is controlled by a specification that includes appropriate limits for assay and residual solvents. The specified impurity limits, which all lie outside that specified in CPMP/ICH/2737/99, are considered justified on the basis that at the maximum recommended UMEC dose (62.5 µg) the impurity levels are well below the standard threshold of toxicological concern (1.5 µg/day). The particle size limits are based on the drug substance batches used in the key clinical and stability trials.

[4] CPMP/ICH/2737/99. ICH Topic Q 3 A (R2) Impurities in new Drug Substances. Note for Guidance on Impurities Testing: Impurities in New Drug Substances.

Drug product

The same inhaler device as approved for the Breo Ellipta powder is to be used for Anoro Ellipta. It simultaneously delivers the powdered contents of two blister strips. One of the blister strips contains a powdered blend of UMEC, magnesium stearate and lactose monohydrate. The other contains a blend of VI, lactose monohydrate and magnesium stearate. Each inhaler is contained within a secondary pack comprising a sealed foil laminate tray which also contains a silica gel desiccant packet.

The blisters contain 62.5 µg of UMEC and 25 µg of VI respectively for the two blisters. This corresponds to a delivered dose of 55/22 µg UMEC/VI. As a blister inhaler product, the label quantity is expressed in terms of the amounts of active substances in the blister.

The formulation and manufacturing process were developed using a quality by design approach. For both powders the addition of magnesium stearate was found to improve the stability of the aerodynamic particle size distribution of the emitted dose. It also improved the chemical stability of the VI powder.

The manufacturing process comprises four unit operations: blending and filling (for each drug substance mixture), assembly and packing.

The drug product specification includes limits for mean UMEC and VI content per blister. Blister content uniformity is included as an in-process control. Appropriate tests and limits are also included to control the uniformity of the delivered dose and the mean delivered dose. The fine particle mass limits are based on tolerance intervals calculated from clinical and stability drug product batches. Impurities and microbial content are appropriately controlled.

The analytical methods used to test the drug product were adequately validated.

Stability data were provided to support a shelf life for the unopened product of 24 months when it is stored below 30°C. Following removal of the secondary packaging and desiccant packet from the inhaler, the product may be stored for a maximum period of 6 weeks (below 30°C).

Biopharmaceutics

Studies were submitted in which the absolute bioavailabilities and pharmacokinetic (PK) profiles of UMEC and VI were determined. These studies were summarised as part of the chemistry and quality assessment but have not been assessed in detail due to the locally acting nature of the product.

Following inhalation the maximum concentration (C_{max}) of both drug substances occurs at 5 to 15 minutes. The absolute bio availabilities are 13% (UMEC) and 27% (VI). The mean volume of distribution for UMEC is 86 L and 165 L for VI. Both VI and UMEC are metabolised oxidatively to produce compounds with reduced pharmacological activity. The half-lives of each drug substance following repeated inhalation dosing were in the range 11 to 19 hours.

A food interaction study was not conducted on the basis that the oral bioavailability of UMEC is negligible (< 1%) and VI from the swallowed portion undergoes extensive first pass metabolism.

Advisory committee considerations

No significant issues were raised during the chemistry and quality assessment and consequently the product was not referred for consideration by the Pharmaceutical Sub-Committee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

The chemistry, manufacturing and quality aspects of the submission are acceptable and approval is recommended.

III. Nonclinical findings

Introduction

The nonclinical dossier was comprised of data previously submitted and evaluated in the original application to register vilanterol trifenatate as a new chemical entity (in combination with fluticasone furoate as Breo Ellipta) plus new data for umeclidinium (alone, or in combination with vilanterol). The nonclinical report focused on the data relating to umeclidinium as a new chemical entity and for the novel combination; detailed assessment of previous studies relating to vilanterol as a new chemical entity were considered in the nonclinical evaluation report for the application to register vilanterol in combination with fluticasone furoate (Breo Ellipta) (for details regarding studies relating to vilanterol please see the Breo Ellipta AusPAR).

The nonclinical dataset was of high quality. All pivotal safety related studies were conducted under Good Laboratory Practice (GLP) conditions.

Pharmacology

Primary pharmacology

Umeclidinium is a LAMA, anticipated to inhibit acetylcholine induced bronchoconstriction (principally mediated by M_3 receptors on bronchial smooth muscle cells; Gosens et al., 2006[5]). Vilanterol is a LABA, anticipated to produce direct relaxation of airway smooth muscle.

Umeclidinium was shown to possess high affinity for all five human muscarinic receptor subtypes (affinity (binding) constant, Ki, 0.05 to 0.16 nM; 0.062 nM at the M_3 subtype) where it acted as a competitive inhibitor. The rate of dissociation of the drug from the M_3 receptor was slow (half-life, 82 minutes). Umeclidinium inhibited contractions induced by carbachol (cholinergic agonist) in isolated human bronchial and guinea pig tracheal strips, acting with a long duration of action (offset half times following washout, > 10 hours).

In vivo, intranasal administration of UMEC in mice and intratracheal instillation in guinea pigs produced dose dependent inhibition of bronchoconstriction induced by cholinergic agonists. Inhibition of ≥ 50% was maintained for up to 72 hours post dose in mice (0.05 µg intranasal) and for more than 48 hours (2.5 µg intratracheal) or 5 days (25 µg intra tracheal) in guinea pigs.

The two principal human metabolites of UMEC showed either negligible activity (M14; GSK339067) or almost 6 times lower activity compared to the parent (M33; GSK1761002) in cell based functional assays examining antagonism of the recombinant human M_3 receptor.

No primary pharmacology studies were conducted with UMEC and VI in combination. The use of the two pharmacological classes in combination is well established clinically.

[5] Gosens R., et al. Muscarinic receptor signalling in the pathophysiology of asthma and COPD. *Respir. Res*. 2006:7;73.

Secondary pharmacodynamics and safety pharmacology

Umeclidinium was screened for secondary activity against a panel of 50 other receptors, ion channels and transporters. The kappa opioid receptor was identified as the highest affinity secondary target, with UMEC inhibiting radio ligand binding with a Ki of 69 nM (that is, > 1000 times less potent compared to the primary pharmacological target). Given that the observed Ki value is > 425 times higher than the plasma C_{max} for UMEC in patients at the maximum recommended dose of 62.5 µg/day (that is, 0.0693 ng/mL (= 0.162 nM)), the finding is not considered to be of clinical relevance.

Specialised safety pharmacology studies with UMEC covered the core battery of systems (central nervous system (CNS), cardiovascular and respiratory). No adverse effects on CNS function were observed in rats at inhalational doses ≤ 1994 µg/kg; effects observed in the study were limited to moderately dilated pupils (≥ 322 µg/kg; consistent with antimuscarinic activity). Umeclidinium was shown to be able to inhibit the human ether-à-go-go-related gene (hERG) potassium (K^+) channel current in transfected mammalian cells, but only very weakly; the half maximal inhibitory concentration (IC_{50}) value (9.41 µM) is > 58000 times greater than the plasma C_{max} in patients at the maximum recommended dose of 62.5 µg/day (and an even larger margin exists when considering the free plasma concentration), indicating no clinical significance. In dogs, a 10 µg/kg intravenous (IV) dose caused a small decrease in pulse pressure, an increase in heart rate, an increase in the electrocardiogram (ECG) PR interval, a decrease in the RR interval, and second degree atrioventricular block (isolated P waves in the absence of QRS complexes) effects consistent with antimuscarinic activity. There were no cardiovascular effects in dogs at 3 µg/kg IV, a dose yielding almost 330 times the plasma $C_{max,}$ in patients treated with UMEC at 62.5 µg/day.

In a cardiovascular safety study conducted with UMEC and VI in combination in dogs, single IV administration of the two drugs (0.3/0.3 µg/kg) caused a small increase in mean, systolic and diastolic blood pressure that was not seen with the individual agents; UMEC did not exacerbate the increase in heart rate induced by VI. Increased pulse rates/heart rates were observed in the general repeat dose inhalational toxicity studies conducted with UMEC (alone and in combination with VI) in dogs, generally accompanied by the loss of respiratory sinus arrhythmia (the physiological modulation of heart rate in time with breathing). No further ECG changes related to UMEC were evident in these studies.

Respiratory parameters were examined in rats during and after inhalational exposure to UMEC, with an increase in respiratory rate and a decrease in tidal volume observed at ≥ 215 µg/kg; there was no effect at 36 µg/kg. These changes may relate to the pharmacologically mediated bronchodilation.

Pharmacokinetics

Absorption of UMEC after inhalation was shown to be rapid in mice, rats, rabbits and dogs, with peak plasma concentrations generally observed at the first sampling time point (0.17 to 1 hours post dose). Similarly, the plasma C_{max} was achieved within 5 to 15 minutes of inhalational administration in COPD patients. Plasma C_{max} and area under the concentration-time curve (AUC) were generally dose proportional with inhalational administration in the laboratory animal species and in humans. Accumulation with repeated dosing was generally not seen or was only limited. No consistent sex differences were observed. Oral bioavailability was found to be negligible in rats, dogs and humans.

Co-administration of inhaled VI did not affect the PKs of UMEC in rats, dogs or humans. Evidence of an effect of UMEC on the PKs of VI in the three species was limited to rats, where co-administration of inhaled UMEC was seen to reduce exposure to VI.

Tissue distribution of radioactivity after IV administration of radiolabelled (^{14}C)-UMEC in rats was rapid and wide, with highest concentrations of radioactivity detected in the kidney and liver. Penetration of the blood brain barrier was poor, with peak concentrations of ^{14}C-UMEC derived radioactivity approximately 44 times lower than in blood. Some association of drug related material with melanin was seen. Plasma protein binding by UMEC was moderate in all species (75 to 89% in mouse, rat, rabbit and dog; 89% in human) and independent of concentration. Severe renal impairment and hepatic impairment did not alter the extent of plasma protein binding compared to that in healthy human volunteers. Human serum albumin, gamma globulin and α1-acid glycoprotein contributed to binding (67%, 65% and 85% binding, respectively). Blood cell association was low in all species.

Metabolism of UMEC chiefly involved O-dealkylation (generating metabolite M14), hydroxylation (M33 and other metabolites) and glucuronidation. Unchanged UMEC was by far the dominant circulating species in laboratory animals (mouse, rat and dog) and humans (following IV administration in all species, and additionally inhalational administration in humans). Cytochrome P450 (CYP) 2D6 was identified as the P450 isoform chiefly responsible for the metabolism of the drug in in vitro experiments, with additional minor contributions from CYP1A1 and CYP3A4. All major human metabolites were also formed in one or both of the species (rats and dogs) used in the pivotal repeat dose toxicity studies with the exception of a dihydroxylated metabolite (M61), which accounted for approximately 20% of drug related material in plasma in humans after IV administration.

Excretion of radioactivity following dosing with ^{14}C-UMEC was primarily via the faeces after IV (mouse, rat, dog and human) and oral administration (rat, dog and human). Biliary excretion was demonstrated in rats and dogs.

Comparisons of the PK profiles of UMEC in the laboratory animal species used in the pivotal repeat dose toxicity studies (rats and dogs) indicate sufficient similarities exist to allow them to serve as appropriate models for the assessment of UMEC toxicity in humans. Notably though, these animal species are unable to model potential toxicity related to the unique human metabolite M61. This is not considered a major deficiency, however, in light of the relatively low systemic exposure to this metabolite in patients.

Pharmacokinetic drug interactions

Umeclidinium was shown to be able to inhibit CYP2D6 (IC_{50}), 0.1 μM), CYP3A4 (IC_{50}, 1.0 or 8.0 μM depending on the substrate) and CYP2C19 (IC_{50}, 14 μM), but not CYPs 1A2 or 2C9 (IC_{50} > 33 μM), in experiments with human liver microsomes. Given these IC_{50} values are > 600 times higher than the drug's peak plasma concentration in humans at the maximum recommended dose of 62.5 μg/day, no relevant CYP inhibition is expected in patients.

In an in vivo enzyme induction study in rats (involving 4 weeks treatment by inhalation), mean CYP1A1 messenger ribonucleic acid (mRNA) was increased to approximately 8 times the control level in females with treatment at 1829 μg/kg/day (due to one animal) (no effect in males or at ≤ 243 μg/kg/day) and CYP4A1 mRNA was increased to approximately 2 and approximately 4 times the level of controls in males at 26.1 and 243 μg/kg/day; levels of CYP1A2, 2B1, 2B2, 2E1, 3A2 and 3A23 mRNA were unaffected. Given the magnitude of the changes and the large associated relative exposure levels (animal: human plasma AUC ratios at doses producing changes, 10.5 to 621), no clinically significant enzyme induction is expected to be produced by UMEC in patients.

Umeclidinium was shown to be a substrate for P-glycoprotein (P-gp) in experiments with transfected mammalian cells. Demonstrating the significant role P-gp plays in limiting absorption, the oral bioavailability of ^{14}C-UMEC derived radioactivity was markedly higher in P-gp knockout mice compared to wild type ones (14% compared to 1.1%).

Umeclidinium (≤ 100 μM) did not act as an inhibitor of P-gp. Experiments with recombinant human cation transporters showed that the drug is a substrate for organic cation transporter (OCT) OCT1 (Km, 4.42 μM) and OCT2 (Km, 0.157 μM), but not for OCT3, OCTN1 or OCTN2.

Toxicology

Toxicity

Single-dose toxicity

No conventional single dose toxicity study was conducted for UMEC; information on the drug's acute toxicity was instead obtained from other studies (in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline M3(R2)[6]). No mortality or overt signs of toxicity were observed with UMEC in rats after a single inhalational dose of up to 2260 μg/kg (in safety pharmacology studies) or with subcutaneous (SC) administration at 60 μg/kg (local tolerance/toxicokinetic study), nor following two 20 mg/kg IV doses 24 hours apart (in a genotoxicity study); animals were monitored for up to 24 hours (inhalation, SC) or 48 hours (IV) after dosing/the commencement of treatment. In general repeat dose toxicity studies where animals were treated for at least 14 days; that is, where the period of monitoring met the recommended minimum observation period after a single dose recommended in the EU Guideline on Single Dose Toxicity (3BS1a), no treatment related mortality was observed at dose levels of up to 2850 μg/kg/day by inhalation in mice, 1828.5 μg/kg/day by inhalation and 1600 μg/kg/day by the SC route in rats, and 2758 μg/kg/day by inhalation in dogs. These data support that UMEC has a low order of acute toxicity. Similarly, previously evaluated studies indicated a low order of acute toxicity by the inhalational route for VI.

Repeat dose toxicity

Studies with UMEC by the inhalational route of up to 3 months duration were conducted in mice, 6 months in rats and 9 months in dogs. Other routes were used in studies in mice (oral up to 3 months) and rats (SC up to 2 weeks). The duration of the pivotal studies, the species used (rats and dogs), group sizes and the use of both sexes were consistent with EU guidelines. Umeclidinium was formulated in lactose and magnesium stearate in the pivotal and most of the other inhalational studies, resembling the proposed commercial product.

The repeat dose toxicity of UMEC and VI in combination was examined in inhalational studies in rats (4 weeks duration) and dogs (up to 3 months). The conduct of a 3 month study in a single species meets recommendations in the EU Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005).

Relative exposure

Exposure ratios have been calculated based on animal: human plasma $AUC_{0-24\,h}$ values (for consideration of systemic effects) and animal: human lung deposited dose adjusted for lung weight (for consideration of local toxicity). Lung deposited doses were calculated assuming 10%, 25% and 100% deposition in rodents, dogs and humans, respectively; lung weights of 0.2, 1.5, 110 and 1000 g in mice, rats, dogs and humans, respectively; and body weights of 0.03, 0.25 and 10 kg for mice, rats and dogs, respectively. High local and

[6] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. December 2009 EMA/CPMP/ICH/286/1995.

systemic exposure ratios were obtained in the animal studies. Human AUC values are from the sponsor's summary of the population PK analyses.

Table 1. Relative local and systemic exposure achieved in selected inhalational toxicity studies with umeclidinium.

Species	Study	Achieved dose (µg/kg/day)	Lung deposited dose (µg/g tissue)	Plasma AUC_{0-24h} (ng h/mL)	Exposure ratio	
					Local	Systemic
Mouse (CD-1)	WD2007/01600 [13 weeks]	92	1.38	5.17	22	17
		287	4.31	5.70	69	18
		1060	15.9	36.8	254	118
		2850	42.8	114	684	365
	2012N131664 [carcinogenicity]	♂ 58.6→32.2	0.88 / 0.48	2.08 / 1.53	14 / 7.7	6.7 / 4.9
		♂ 188→102	2.82 / 1.53	1.64 / 3.28	45 / 24	5.2 / 10
		♂ 533→295	8.00 / 4.43	12.2 / 8.21	128 / 71	39 / 26
		♀ 20.8	0.31	0.505	5.0	1.6
		♀ 63.7	0.96	4.31	15	14
		♀ 200	3.00	8.26	48	26
Rat (SD)	WD2007/02012 [13 weeks]	38	0.63	2.10	10	6.7
		102	1.70	6.09	27	19
		288	4.80	16.2	77	52
		924	15.4	40.1	246	128
	FD2009/00467 [26 weeks; pivotal]	87.1	1.45	8.08	23	26
		289	4.82	27.1	77	87
		987	16.45	65.4	263	209
	2012N131619 [carcinogenicity]	30.1→14.7	0.50 / 0.25	0.113 / 0.637	8.0 / 3.9	0.4 / 2.0
		101→45	1.68 / 0.75	4.05 / 2.10	27 / 12	13 / 6.7
		276→137	4.60 / 2.28	13.5 / 6.75	74 / 37	43 / 22
Dog (Beagle)	WD2007/01512 [13 weeks]	40.7	0.93	0.684	15	2.2
		187	4.25	3.93	68	13
		1070	24.3	22.5	389	72
	FD2009/00466 [39 weeks; pivotal]	109	2.48	11.2	40	36
		421	9.57	36.3	153	116
		1002	22.8	76.2	364	244
Human (COPD patients)	Population PK analysis	[62.5 µg/day]	0.0625	0.3124	–	–

Table 2. Relative local and systemic exposure achieved in combination toxicity studies.

Species, study		Achieved dose (µg/kg/day)		Lung deposited dose (µg/g tissue)		Plasma AUC_{0-24h} (ng h/mL)		Exposure ratio			
								Local		Systemic	
		umec	vilant	umec	vilant	umec	vilant	umec	vilant	umec	vilant
Rat (SD)	FD2009/00392 [4 weeks]	817	4.37	13.6	0.073	27.0	–	218	2.9	86	–
		1200	60.7	20.0	1.01	29.6	3.81	320	40	95	6.2
		1060	1040	17.7	17.3	35.2	76.6	283	693	113	125
		757	0	12.6	–	26.6	–	202	–	85	–
		0	869	–	14.5	–	115	–	579	–	187
Dog (Beagle)	FD2009/00391 [4 weeks]	996	6.46	22.6	0.15	74.3	12.4	362	5.9	238	20
		190	205	4.32	4.66	9.85	192	69	186	32	312
		997	0	22.7	–	70.4	–	363	–	225	–
		0	174	–	3.95	–	181	–	158	–	294
	WD2010/00677 [13 weeks; pivotal]	1070	7.5	24.3	0.17	61.4	10.7	389	6.8	197	17
		23	29	0.52	0.66	1.45	74.9	8.4	26	4.6	122
		60	72	1.36	1.64	5.92	156	22	65	19	254
		177	183	4.02	4.16	9.71	192	64	166	31	312
		1048	0	23.8	–	79.6	–	381	–	255	–
		0	180	–	4.09	–	231	–	164	–	376
Human (COPD patients) [Population PK analysis]		[62.5/25 µg/day]		0.0625	0.025	0.3124	0.6147	–		–	

umec = umeclidinium; vilant = vilanterol

Major toxicities

The major target organs for toxicity in inhalational studies with UMEC were respiratory tract tissues and the cardiovascular system. The gastrointestinal (GI) tract was identified as an additional target in oral studies.

Umeclidinium was seen to act as an irritant of the upper respiratory tract in all three laboratory animal species (mouse, rat and dog). Corresponding histopathological findings in affected tissues (nasal turbinates, nasopharynx, larynx and tracheal bifurcation) included epithelial degeneration/regeneration, hyperplasia, squamous metaplasia, inflammatory cell infiltration and erosion/ulceration. These effects may have been exacerbated by drying of the mucosa due to the drug's antimuscarinic activity. In the pivotal studies, such respiratory tract findings were observed at all dose levels in rats (≥ 87.1 µg/kg/day by inhalation; relative local exposure, 23) and at ≥ 421 µg/kg/day in dogs (relative local exposure, 153). No histopathological changes were observed in the respiratory tract of dogs treated for 9 months at 109 µg/kg/day, yielding a high multiple of the local clinical dose, (relative local exposure, 40).

Oral administration of UMEC at high doses in mice (≥ 30 mg/kg/day) was also associated with nasal cavity changes consistent with local irritation (epithelial atrophy/degeneration and fluid/ inflammatory exudates in nasal airways), most likely due to gastro oesophageal reflux. Breathing difficulties, abdominal distension, fundic degeneration of the stomach (≥ 30 mg/kg/day) and elongation of the caecum and epithelial hyperplasia in the colon (at 100 mg/kg/day) were additionally seen; these are considered related to a mix of local irritant and antimuscarinic activity (to cause smooth muscle relaxation). The GI tract was not a target for toxicity with administration by the inhalational route at doses yielding very large multiples of the clinical exposure.

Lung macrophage accumulation was increased in incidence and severity (up to slight) in male rats treated with UMEC at 987 µg/kg/day by inhalation for 6 months (relative local exposure, 263). This was not apparent at ≤ 289 µg/kg/day (relative local exposure, 77).

Dogs treated with UMEC showed tachycardia and other clinical signs (dry eyes, nose and mouth) consistent with the drug's antimuscarinic activity. Moderate subacute inflammation in the extramural coronary arteries was seen in the heart of single animals at 421 and 1002 µg/kg/day (relative systemic exposure, 116 to 244), and subacute inflammation was seen in a pulmonary arteriole in another animal at 1002 µg/kg/day (relative systemic exposure, 244), in the pivotal 9 month dog study. Treatment with UMEC did not produce cardiovascular lesions in rats. No observable effect levels (NOELs) for cardiovascular lesions by UMEC are 109 µg/kg/day in dogs (relative systemic exposure 36) and 987 µg/kg/day in rats (relative systemic exposure, 209).

Toxicity of umeclidinium and vilanterol in combination

Previously evaluated studies with VI identified the respiratory tract, cardiovascular system, liver, female reproductive tract and mammary gland as the chief target organs for toxicity; the drug having a toxicity profile typical of an inhaled $beta_2$-agonist.

Repeat dose toxicity studies with UMEC and VI in combination revealed no novel toxicities compared to the single agents. Evidence of exacerbated toxicity with co-administration was limited to a modest increase in the local irritant effects of both drugs in the upper respiratory tract, seen in a 4 week study in rats.

Genotoxicity

The potential genotoxicity of UMEC was investigated in the standard battery of tests (bacterial mutagenicity, mouse lymphoma thymidine kinase (tk) assay and bone marrow micronucleus test). The conduct of the studies was in accordance with ICH guidelines. Concentrations and doses were appropriate. A suitable set of *Salmonella typhimurium* and *Escherichia coli* strains were used in the bacterial mutation assays. The in vivo assay for clastogenicity was conducted in rats and involved IV administration (20 mg/kg/day × 2 days), yielding a very high multiple (approximately 8000 fold) of the plasma C_{max} in patients at the maximum recommended human dose of 62.5 µg/day. All studies returned negative results for UMEC. Previously evaluated studies established that VI is also not genotoxic.

Carcinogenicity

The carcinogenic potential of UMEC by the inhalational route was investigated in 2 year studies in mice and rats. Group sizes were adequate. Appropriate doses were tested, albeit requiring reduction in male mice and rats of both sexes during the course of the studies due to excessive suppression of body weight gain. There was no adverse effect on survival. No carcinogenic effect was seen with the drug in either species. NOELs for carcinogenicity are 295 µg/kg/day in male mice (relative systemic exposure, 26; relative local exposure, 71), 200 µg/kg/day in female mice (relative systemic exposure, 26; relative local exposure, 48) and 137 µg/kg/day in rats (relative systemic exposure, 22; relative local exposure, 37).

In previously evaluated 2 year inhalational carcinogenicity studies conducted with VI, treatment was associated with increased incidences of ovarian tubulostromal adenoma (at 29500 µg/kg/day), sex cord stromal adenoma (≥ 62 µg/kg/day), and uterine leiomyoma and leiomyosarcoma (≥ 62 µg/kg/day) in mice, and mesovarian leiomyoma and pituitary adenoma (≥ 84.4 µg/kg/day) in rats. These findings are consistent with those for other $beta_2$-agonists in rodents and are considered to be pharmacologically mediated and not clinically relevant. NOELs for carcinogenicity with VI were 6.4 µg/kg/day in mice and 10.5 µg/kg/day in rats. The plasma area under the concentration time curve for 0 to 24 hours ($AUC_{0\text{-}24\,h}$) values at these doses (7.94 and 0.317 ng·h/mL in the respective species) are 13

and 0.5 times that in patients at the maximum recommended human dose of 25 µg/day (based on a human reference $AUC_{0\text{-}24\,h}$ value of 0.6147 ng·h/mL).

No carcinogenicity study has been conducted with UMEC and VI in combination.

Reproductive toxicity

Submitted studies with UMEC covered all stages (fertility and early embryonic development, embryofetal development, and pre/postnatal development). The studies were appropriately designed with regard to the numbers of animals, the timing/duration of treatment, the range of species and the route of administration (inhalation and/or SC).

Relative exposure

Very high multiples of the clinical plasma AUC were obtained in animals at the upper dose levels in the studies.

Table 3 Relative exposure in reproductive toxicity studies with umeclidinium

Species	Study		Route	Dose (µg/kg/day)	$AUC_{0\text{-}24\,h}$ (ng h/mL)	Exposure ratio
Rat (SD)	Fertility	♂	SC	180	24.9[a]	80
		♀	inhalation	294	16.5[b]	53
	Embryofetal development		inhalation	278	15.6[b]	50
	Pre-/postnatal development		SC	60	8.07	26
				180	24.9	80
Rabbit (NZW)	Embryofetal development		inhalation	306	10.9	35
			SC	180	61.4	197
Human (COPD patients)	Population PK analysis		inhalation	[62.5 µg/day]	0.3124	–

Only data for the highest dose levels and NOELs are shown;
a = based on data obtained in Study 2011N118595 (rat pre-/postnatal development study);
b = estimated based on extrapolation of data from Study WD2007/02012 (rat 13-week general repeat-dose toxicity)

Fertility and early embryonic development were unaffected by UMEC in male (≤ 180 µg/kg/day SC; estimated relative exposure, 80) and female rats (≤ 294 µg/kg/day by inhalation; estimated relative exposure, 53). No adverse effects on embryofetal development were observed with the drug in either rats (≤ 278 µg/kg/day by inhalation; estimated relative exposure, 50) or rabbits (≤ 306 µg/kg/day by inhalation (relative exposure, 35) or ≤ 180 µg/kg/day SC (relative exposure, 197)). Placental transfer of UMEC was not investigated.

A pilot, non GLP compliant embryofetal development study was conducted with UMEC and VI in combination in rabbits (100/100 µg/kg/day SC). While no adverse effects on embryofetal development were observed, the study is of very limited predictive value given the very small number of animals used and the limited extent of the fetal examination (external only; no visceral or skeletal examination), and no definitive NOEL is considered to have been established.

In a pre/postnatal study, pre weaning body weight was reduced in pups of rats treated with UMEC at 180 µg/kg/day SC during gestation and lactation (relative exposure, 80); no other effects on development were noted. The NOEL for effects on pre/postnatal development in the rat was 60 µg/kg/day SC (relative exposure, 26). While there were no specific studies investigating excretion of UMEC in milk in animals, the drug was detected in the plasma of 2/54 suckling pups in the pre/postnatal development study, suggesting some possible transfer.

In previously evaluated studies, VI was found to not affect male or female fertility in rats (≤ 31500 and ≤ 37100 µg/kg/day by inhalation in the respective sexes; estimated relative exposure, 1950 and 2310 (based on plasma $AUC_{0\text{-}24\,h}$ values of 1200 and 1420 ng·h/mL in animals, extrapolated from data obtained in Study WD2006/01716 (rat 13 week general repeat dose toxicity study))). Slight delays in ossification were observed in fetuses of rats treated with the drug at ≥ 613 µg/kg/day by inhalation (estimated relative exposure, 59 (based on a plasma $AUC_{0\text{-}24\,h}$ of 36.5 ng·h/mL, extrapolated from data obtained in Study WD2006/01716), occurring in conjunction with maternal toxicity; relative exposure at the NOEL (45.4 µg/kg/day) is estimated to be approximately 4. Various abnormalities, including cleft palate, open eyelids and limb malrotation, were observed in fetuses of rabbits treated with VI by inhalation (≥ 62.7 µg/kg/day; relative exposure, 6 (based on an animal plasma $AUC_{0\text{-}24\,h}$ of 3.76 ng·h/mL)). Fetal malformations were also seen in the rabbit with SC administration of VI at 300 µg/kg/day (relative exposure, 498 (based on an animal plasma $AUC_{0\text{-}24\,h}$ of 306 ng·h/mL)), but no adverse effects on embryofetal development were evident in the rabbit at 30 µg/kg/day SC (relative exposure, 36 (based on an animal plasma $AUC_{0\text{-}24\,h}$ of 22.4 ng·h/mL)). Effects on pre/postnatal development in rats treated with VI were limited to a slight decrease in pup body weight (at 3 to 10 mg/kg/day oral).

Pregnancy classification

The sponsor has proposed Pregnancy Category B3[7] for the use of Anoro Ellipta in pregnancy. This category is considered appropriate given the available data from animal studies which showed fetal damage (including malformations) with VI, albeit mostly at high relative exposure margins.

Immunotoxicity

No specialised immunotoxicity study was conducted. This is acceptable given the absence of findings to suggest immunotoxicity in the general repeat dose toxicity studies.

Local tolerance and antigenicity

Consistent with findings showing local irritant activity with inhalational and oral administration in the general repeat dose toxicity studies, UMEC was found to be a mild to moderate skin irritant (rabbit in vivo; human in vitro) and a mild to moderate ocular irritant (human in vitro). Umeclidinium was shown to not be a skin sensitiser (mouse local lymph node assay).

Paediatric use

Anoro Ellipta is not proposed for paediatric use and no specific studies in juvenile animals with UMEC alone or in combination with VI were submitted.

Impurities

Proposed impurity limits are considered to be acceptable from a toxicological perspective, based on application of the TTC (threshold of toxicological concern) principle.

Excipient: magnesium stearate

Magnesium stearate is included as an excipient in the product. The dose of magnesium stearate provided by Anoro Ellipta therapy of 200 µg/day, is higher than for existing

[7] Category B3 for the use of medicines in pregnancy is defined as: *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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*

inhalational products (37 µg/day with Seebri/Tovanor Breezhaler; 125 µg/day with Breo Ellipta). Previously evaluated studies have established no observed adverse effect levels (NOAELs) of 1.648 mg/kg/day for magnesium stearate by the inhalational route in rats (6 month study; featuring microscopic examination of respiratory tract tissues) and 10 mg/kg/day for dogs (12 month study; microscopic examination of respiratory and other tissues). Using the same lung weight, body weight and deposition factors assumed for UMEC earlier, these doses yield local exposure to magnesium stearate almost 140 times (rats) and 1140 times (dogs) higher than the clinical dose. Accordingly, no safety concern is considered to be posed by magnesium stearate at a dose of 200 µg/day by inhalation in humans.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for UMEC/VI detailed in the sponsor's draft Risk Management Plan (Part II, Module SII (version 2.0)) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

Summary

- Umeclidinium bromide is a new chemical entity. Vilanterol trifenatate was not yet registered at the time this report was prepared, but has been evaluated in an earlier application to register it in combination with fluticasone furoate (in COPD and asthma patients at the same dose as proposed here). While previously evaluated data for VI were included in the current dossier, the non clinical evaluation report focuses on the data relating to UMEC as a new chemical entity and for the novel combination.
- The nonclinical dossier was of high quality. All pivotal safety related studies were conducted under GLP conditions.
- Umeclidinium is a competitive muscarinic receptor antagonist with sub nanomolar affinity across all five human muscarinic receptor subtypes. The rate of dissociation from the M_3 receptor (the muscarinic subtype mainly mediating bronchoconstriction) was slow. Long lasting antagonism of cholinergic agonist induced contraction was shown for the drug in vitro in isolated human bronchial and guinea pig tracheal strips, and in vivo in mice (intranasal administration) and guinea pigs (intratracheal administration). Vilanterol is a long-acting beta$_2$-agonist.
- No clinically significant off target activity was found for UMEC in secondary pharmacodynamic (PD) studies. Safety pharmacology studies with UMEC covered the CNS, cardiovascular and respiratory systems, with limited classic anticholinergic effects observed (most notably tachycardia). Inhibition of the hERG K^+ channel did not occur at clinically relevant concentrations.
- Rapid absorption of UMEC after inhalation was shown in laboratory animal species and humans, with oral bioavailability negligible. Tissue distribution of radioactivity following IV administration of ^{14}C-UMEC was rapid and wide in the rat; penetration of the blood brain barrier was poor. Plasma protein binding by UMEC was moderate in all species. Co administration of inhaled VI did not affect the PKs of UMEC in rats, dogs or humans, nor vice versa except in rats, where UMEC was seen to reduce exposure to VI.
- Metabolism of UMEC chiefly involved O-dealkylation, hydroxylation and glucuronidation. A major role for CYP2D6 and additional minor roles for CYP1A1 and CYP3A4 were shown. Excretion was predominantly via the faeces in all species. The drug is a substrate for P-gp, OCT1 and OCT2. CYP inhibition (2D6, 3A4, 2C19, 1A2 and

2C9) and induction (1A1, 1A2, 2B1, 2B2, 2E1, 3A2, 3A23 and 4A1) by UMEC were not seen at clinically relevant concentrations/exposure levels.

- Umeclidinium displayed a low order of acute toxicity in laboratory animal species.
- The repeat dose toxicity of UMEC by the inhalational route was investigated in studies in mice, rats and dogs; the pivotal studies were conducted in rats (6 months) and dogs (9 months). The major target organs for toxicity identified in inhalational studies were the respiratory tract (irritation of nasal turbinates, nasopharynx, larynx and tracheal bifurcation; increased lung macrophage accumulation) and the cardiovascular system (inflammation in extramural coronary arteries and pulmonary arteriole, as well as tachycardia), with such effects seen at very large multiples of the clinical exposure level.
- Repeat dose toxicity studies with UMEC and VI in combination, conducted by the inhalational route in rats (4 weeks) and dogs (up to 3 months), revealed no novel toxicities but some exacerbation of the local irritant effects of both drugs in the upper respiratory tract.
- Umeclidinium was examined for potential genotoxicity in bacterial mutagenicity assays, the mouse lymphoma tk assay and the bone marrow micronucleus test, with universally negative results returned. Two year inhalational studies with UMEC in mice and rats revealed no carcinogenic effect.
- Umeclidinium did not affect male or female fertility in rats, and had no adverse effect on embryofetal development in rats or rabbits. Reduced pre weaning body weight was observed in pups of rats treated with UMEC during gestation and lactation, but only at a very large multiple of the clinical exposure level.

Conclusions and recommendation

- The nonclinical dossier contained no major deficiencies.
- Primary pharmacology studies with UMEC, showing potent and long lasting antimuscarinic activity/inhibition of bronchoconstriction, support the drug's use for the proposed indication.
- Secondary PD studies revealed no clinical significant activities for UMEC. Safety pharmacology studies identified a classic antimuscarinic profile for the drug, with limited clinical relevance predicted.
- The respiratory tract (principally upper and was related to local irritation) and the cardiovascular system were identified as the main targets for toxicity by UMEC. Given the nature of the findings and with very large exposure margins evident at the NOELs established in the pivotal rat and/or dog studies, limited clinical significance is predicted.
- Repeat dose toxicity studies with UMEC and VI in combination showed no serious toxicological interaction. The dose of magnesium stearate (excipient) provided by Anoro Ellipta therapy (200 µg/day) is higher than for existing inhalational products, but its safety is supported by previously evaluated studies in rats and dogs.
- Umeclidinium and VI are not considered to pose a genotoxic or carcinogenic hazard to patients.
- While no adverse effects on embryofetal development were observed with UMEC alone, previously evaluated studies with VI showed fetal damage (including malformations). Placement in Pregnancy Category B3, as the sponsor proposes, is supported.

- There are no nonclinical objections to the registration of Anoro Ellipta for the proposed indication.
- The nonclinical evaluator also recommended amendments to nonclinical statements in the draft PI document. Details of these are beyond the scope of this AusPAR.

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

Clinical rationale

COPD is a major cause of poor health, resulting in millions of deaths annually worldwide and contributing significantly to health care costs and morbidity. Current pharmacological treatment of COPD includes 2 classes of inhaled bronchodilators: beta$_2$-agonists and muscarinic antagonist (that is, anticholinergics). Inhaled LABAs (for example, salmeterol and indacaterol) and LAMAs (for example, tiotropium (TIO) and aclidinium), are currently recommended for the treatment of symptomatic patients with moderate to very severe COPD and are considered to be more efficacious than short acting bronchodilators. There are no prescribing information restrictions on the concomitant use of a LABA and a LAMA in the COPD population, and co administration of LAMAs and LABAs is considered in clinical practice to be more effective than either drug class alone in managing stable COPD. At the time of this submission no LAMA/LABA combination products were currently licensed for COPD treatment. By targeting 2 different pharmacologic mechanisms, a LAMA/LABA combination product could potentially optimise bronchodilator therapy of COPD while avoiding the risk of side effects associated with increasing the dose of a single bronchodilator class. The development of a LAMA/LABA combination product could be a beneficial addition to the treatment options in COPD.

Evaluator's comments: The clinical rationale is sound and logical.

Guidance

According to the sponsor, the development program of Anoro Ellipta complied with the following guidances and regulations:

- European Medicines Agency (EMA), Note for Guidance on Fixed Dose Combination Medicinal Products. 19 February 2009.
- EMA, Points to consider on the clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). 19 May 1999.
- Food and Drug Administration, Guidance for Industry- Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November 2007.
- Food and Drug Administration, CFR300.50 regulations on Fixed Dose Combination Prescription Drugs for Human Use. 1999.

Contents of the clinical dossier

The submission contained the following clinical information:

- 39 clinical pharmacology studies, including 27 that provided PK data and 5 that provided PD data

- 3 population PK analyses
- 7 dose finding studies. These included 4 dose ranging studies on umeclidinium in COPD patients (3 Phase II studies (AC4113589, AC4113073 and AC4115321) and 1 Phase IIIa study (AC4115408)), and 3 dose ranging studies on vilanterol (1 in COPD patients (B2C111045) and 2 on asthma patients (B2C109575 and HZA113310))
- 4 pivotal efficacy/safety studies. These 4 pivotal Phase III studies consisted of 2 sets of randomised, double blind, parallel group studies, each with a 24 week treatment duration. One set of studies (DB2113361 and DB2113373) was placebo controlled, while the other set (DB2113360 and DB2113374) was active controlled (active control: TIO). Studies DB2113361 and DB2113373 were identical except for the doses of UMEC/VI and UMEC investigated. Study DB2113361 evaluated UMEC/VI, UMEC and VI doses of 125/25 µg, 125 µg and 25 µg once daily respectively, while Study DB2113373 evaluated doses of 62.5/25 µg, 62.5 µg and 25 µg, once daily, respectively. Studies DB2113360 and DB2113374 were also identical except for the study drugs used. Study DB2113360 evaluated once daily doses of UMEC/VI 125/25 µg, UMEC/VI 62.5/25 µg, and VI 25 µg, while Study DB2113374 evaluated once daily doses of UMEC/VI 125/25 µg, UMEC/VI 62.5/25 µg, and UMEC 125 µg
- 3 other efficacy/safety studies. These included two 12-week exercise tolerance studies (DB2114417 and DB2114418) and one 12 month long term safety study (DB2113359)
- Other reports. These included 1 Phase IIa safety/tolerability study of UMEC/VI (500/25 µg) in COPD patients (DB2113120), and 2 combined/pooled analyses reports. These 2 reports consisted of the meta-analyses of 2 of the pivotal efficacy studies DB2113360 and DB2113374 (report DB2116844), and of 2 of the dose ranging studies AC4113073 and AC4115321 (report AC4116689). In addition, the sponsor had submitted six other studies in COPD patients evaluating a fluticasone furoate /VI combined product and VI, 10 studies in asthma patients evaluating fluticasone furoate /VI and VI, 7 ongoing studies, and 2 reports on the development and validation of the Shortness of Breath with Daily Activities (SOBDA) questionnaire
- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

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.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 shows the studies relating to each pharmacokinetic (PK) topic.

Table 4. Submitted pharmacokinetic studies.

PK topic	Subtopic		Study ID
PK in healthy adults	General PK		
	Single dose	UMEC	AC4112008
		VI	B2C106180
		UMEC	AC4115487
		UMEC	AC4106889
		UMEC	AC4105209
		VI/GSK233705	DB1111509
		VI	B2C10001
		VI/GW85698X	HZA105871
	Multi-dose	VI	B2CC10878
	Absolute Bioavailability	Single dose FF/VI	HZA102934
	Food effect		No studies conducted
	Mass Balance Study	UMEC	AC4112014
		VI	B2C106181
PK in special populations			
Target population §	Single dose	UMEC	AC4108123
		VI	B2C110165
	Multi-dose	UMEC	AC4105211
		UMEC	AC4113589
		UMEC	AC4115321
		UMEC	AC4113073
		UMEC	AC4115408
		UMEC/VI	DB2113361

PK topic	Subtopic		Study ID
		UMEC/VI	DB2113373
		FF/VI	HZC111348
		FF/VI	HZC110946
		UMEC/VI	DB2113120
		VI	B2C111045
		VI	B2C108562
Hepatic impairment		UMEC/VI; UMEC	DB2114637
		FF/VI	H2A111789
Renal impairment		UMEC/VI; UMEC	DB2114636
		FF/VI	H2A111789
Neonates/infants/children/adolescents			No studies
Elderly			No studies
Japanese Subjects		UMEC, UMEC/VI	DB2113208
		UMEC	AC4113377
		VI	DB1112146
		VI	DB1112017
		VI/GW85698X	HZA102940
Genetic/gender-related PK			
	Males vs. females		No studies
	CYP2D6	UMEC	AC4110106
PK interactions			
	Verapamil		DB2113950
	Ketoconazole		B2C112205
	Ketoconazole		H2A105548

PK topic	Subtopic		Study ID
Population PK analyses			
			DB2116975 2011N122282 2011N130718

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

Evaluator's summary and conclusions on pharmacokinetics

Pharmacokinetic studies presented appear to have been carefully conducted with appropriate methodological considerations using validated analytical methods. There were no specific studies conducted with respect to the effect of age on PK parameters. The sponsor has relied on a population PK study to gauge any clinically relevant effects. Similarly it is not clear that the sponsor has fulfilled the guidelines with respect to evaluating the bioequivalence requirements of the guidelines with respect to comparing each component medication alone with the values obtained with administering the combination.

Three studies were conducted which allowed for the evaluation of a potential PK interaction between UMEC and VI (DB2114635; DB2113208; DB2113950) although none were specifically designed for this purpose. When UMEC and VI were administered in combination by the inhalation route, the PK parameters for each component were similar to those observed when each active substance was administered separately. Similar results were observed in population PK analyses (DB2116975) at the proposed therapeutic doses.

Inhaled UMEC is rapidly absorbed, with median time of occurrence of C_{max} (t_{max}) of 5 to 15 minutes, followed by rapid disposition from the systemic circulation. Both plasma and urine data demonstrated approximately 2 fold accumulation in UMEC systemic exposure following 7 days of dosing. At the proposed therapeutic doses of 62.5 µg and 125 µg, UMEC exposure was dose proportional. Following repeat dose UMEC/VI 125/25 µg to healthy subjects, plasma elimination half-life of UMEC averaged 19 hours (95% confidence interval (CI): 13 to 29 hours), with 3% to 4% of drug excreted unchanged in urine at steady state. Inhaled VI is rapidly absorbed, with t_{max} values of 7 to 10 minutes, followed by rapid disappearance from the systemic circulation attributed to both moderate to high clearance and wide distribution in tissue compartments. Plasma data suggested an up to 2 fold accumulation following 28 days of repeat dosing. Following repeat dose UMEC/VI 125/25 µg to healthy subjects, plasma elimination half-life of VI averaged 11 hours (95% CI: 8 to 13 hours) with no detectable VI excreted in urine.

Weight and age were statistically significant covariates on apparent clearance of inhaled UMEC and VI; and weight was a significant covariate on UMEC apparent volume of distribution. The magnitude of effect of these covariates on UMEC and VI exposure was small and does not warrant dose adjustment. Gender, post salbutamol reversibility, post salbutamol and ipratropium reversibility, use of inhaled corticosteroid (ICS) at screening, smoking status, race, and percent predicted baseline forced expiratory volume in 1 second (FEV1) did not significantly affect UMEC and VI PK.

Neither UMEC 125 µg nor UMEC/VI 125/25 µg administered to subjects with severe renal impairment resulted in clinically significant increases in either UMEC or VI systemic exposure. Therefore, no dose adjustment is recommended in patients with impaired renal function. Both UMEC 125 µg and UMEC/VI 125/25 µg administered to subjects with

moderate hepatic impairment led to UMEC and VI systemic exposures that were on average lower in the subjects with moderate hepatic impairment compared to healthy subjects. Therefore, no dose adjustment is recommended in patients with moderate hepatic impairment. UMEC/VI has not been studied in subjects with severe hepatic impairment.

UMEC is metabolised principally by CYP2D6. There was no clinically significant difference in the systemic exposure to UMEC following 7 days of repeat inhaled dosing with UMEC doses up to 1000 µg in a population of CYP2D6 poor metabolisers. No dose adjustment is recommended in patients using concomitant CYP2D6 inhibitors or subjects with genetic polymorphisms of CYP2D6 metabolism. The major routes of metabolism of VI in humans are mediated primarily by CYP3A4. Results from clinical drug interaction studies support the position that caution is advised when administering VI in the presence of strong CYP3A4 inhibitors. Both UMEC and VI are substrates of the P-gp transporter. Results from a clinical drug interaction study support the position that no dose adjustment is recommended in patients using concomitant P-gp transporter inhibitors.

Pharmacodynamics

Studies providing pharmacodynamic (PD) data

Table 5 shows the studies relating to each PD topic.

Table 5 Studies relating to each pharmacodynamic topic.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on sGaw	AC4105209 AC4108123 B2C10001
	Effect on FEV1	B2C110165 DB2113361 DB2113373
Secondary Pharmacology	Effect on QTc[8] Interval	DB2114635
		H2A102963
	Blood Glucose	B2C108784
		B2C110165
	Blood Potassium	DB2113208
		DB2113950
Gender, other genetic and	Effect of Gender	N/A

[8] QT interval of the ECG. The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death. QTc: Corrected QT interval. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated.

PD Topic	Subtopic	Study ID
Age related differences in PD Response		
PD Interactions	VI and ketaconazole	B2C112205
Population PD and PK-PD analysis		None

Evaluator's conclusions on pharmacodynamics

Early phase healthy subject studies and studies in subjects with COPD demonstrated a clear bronchodilatory effect of both UMEC and VI. Bronchodilation was assessed by changes in specific airway conductance and forced expiratory volume. Evidence from these studies confirms bronchodilation as the therapeutic mechanism of action for UMEC/VI. In healthy subjects, UMEC 100 to 350 µg significantly increased bronchodilation compared with placebo up to 12 hours post dose, and to 24 hours post dose with 350 µg. In COPD patients 250 to 1000 µg provided superior bronchodilation compared to placebo up to 24 hours post dose. For VI doses from 25 to 100 µg significantly increased bronchodilation compared with placebo to 24 hours post dose in both healthy subjects and patients with COPD.

There was no evidence of an effect on QT interval corrected for heart rate using Fridericia's formula (QTcF) following 10 days of inhalation dosing with UMEC/VI 125/25 µg or UMEC 500 µg compared with placebo. A dose representing 4 times the proposed upper therapeutic UMEC/VI dose (UMEC/VI 500/100 µg) increased QTcF 8.2 millisecond at 30 minutes only, which was the largest increase observed. Data from clinical pharmacology studies in healthy subjects and subjects with COPD suggest that small, transient changes in systolic blood pressure and diastolic blood pressure following both UMEC and VI. Studies in healthy subjects and subjects with COPD suggest no clinically relevant changes in blood potassium or glucose following both UMEC and VI.

A physiological maximum effect (E_{max}) model adequately characterised the dose trough FEV1 response for UMEC over the once daily dose range of 15.6 to 1000 µg in subjects with COPD, with an estimated 50% effective dose (ED_{50}) of 33 µg.

The once daily proposed UMEC doses of 62.5 µg and 125 µg have shown dose related increases in trough FEV1. There was no marked difference between the once daily versus twice daily regimen for UMEC. The VI dose of 25 µg has also shown consistent clinically relevant changes in trough FEV1. The trough FEV1 responses obtained for each dose of the combination (UMEC/VI 62.5/25 µg and 125/25 µg) appeared to be sub additive when compared to the addition of FEV1 responses from the individual components. There was no apparent dose or concentration dependent change in cardiovascular (heart rate) effects for UMEC over the dose range 15.6 to 1000 µg.

Dosage selection for the pivotal studies

Dose selection of UMEC for the pivotal studies was based on the results of two Phase IIb dose ranging studies in COPD subjects (AC4113073 and AC4113589). Two other studies, AC4115321 and AC4115408, were conducted after the commencement of the Phase III studies, and their results were used to further support the dose selection of UMEC for the pivotal studies. Dose selection of VI for the pivotal studies was based on the results of a Phase IIb dose ranging study in COPD subjects (B2C111045). A summary of the study design and dose tested in these studies is presented in Table 6.

Table 6. Studies to support doses and dosing interval of UMEC and VI used in the UMEC/VI Phase III COPD studies.

Study Number	Study Objective	Study Design and Duration	Relevant Treatment Arms (µg)	Population
UMEC Dose selection				
AC4113589	Dose ranging	R, DB, PG, PC 28 Days	UMEC 125 QD UMEC 250 QD UMEC 500 QD PLA QD	COPD
AC4113073	Dose ranging, dosing interval and PK	R, DB, XO, PC Incomplete block 3 periods per subject, 14 days per period	UMEC 62.5 QD UMEC 125 QD UMEC 250 QD UMEC 500 QD UMEC 1000 QD TIO 18 OL QD PLA QD UMEC 62.5 BD UMEC 125 BD UMEC 250 BD PLA BD	COPD
AC4115321	Dose ranging and dosing interval	R, DB, XO, PC Incomplete block 3 periods per subject, 7 days per period	UMEC 15.6 QD UMEC 31.25 QD UMEC 62.5 QD UMEC 125 QD TIO 18 OL QD PLA QD UMEC 15.6 BD UMEC 31.25 BD PLA BD	COPD
AC4115408	Efficacy and Safety	R, DB, PG, PC 12 weeks	UMEC 125 QD UMEC 62.5 QD PLA QD	COPD
VI dose selection				
B2C111045	Dose ranging	R, DB, PG, PC Stratified [a] 28 dyas	VI 3 QD VI 6.25 QD VI 12.5 QD VI 25 QD VI 50 QD PLA QD	COPD

Abbreviations DB double blind, OL open label, PC placebo controlled, PG parallel group, PLA placebo, r randomized, XO cross over. (a). Subjects reversibility to salbutamol was used to stratify the randomisation.

According to the sponsor the efficacy and safety results from Studies AC4113073 and AC4113589 indicated that the 62.5 and 125 µg once daily doses of UMEC were the most appropriate doses for further clinical development. The selection of one single dose of UMEC for Phase III clinical development was not apparent due to a lack of clear separation in FEV1 response between the two doses, and hence, both 62.5 µg and 125 µg once daily

doses of UMEC were evaluated (as monotherapy and as a component of UMEC/VI) in the Phase III studies.

Based upon the efficacy and safety data 25 µg once daily of VI was selected as the optimal dose to be assessed in the pivotal Phase III studies.

Evaluator's comments: 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 randomised, double blind, parallel group studies (Studies DB2113361/DB2113373, and Studies DB2113360/DB2113374), each with a 24 week treatment duration. Within each set, the studies were identical except for the study drugs or doses tested. In addition, the sponsor had performed a meta-analysis of Studies DB2113360 and DB2113374, comparing UMEC/VI and TIO for the endpoint of the Transition Dyspnoea Index (TDI) score[9].

Details of these studies are presented in the CER Extract (see Attachment 2).

Evaluator's conclusions on efficacy

The efficacy of Anoro Ellipta (UMEC/VI) was evaluated in 2 sets of randomised, double blind, parallel group studies, where 1 set of studies was placebo controlled, while the other set was active controlled (active control: TIO). The study designs, study inclusion and exclusion criteria and the primary and secondary endpoints are consistent with the recommendations in the EMA guidelines on clinical investigation of medicinal products in the treatment of COPD [10], as well as the Food and Drug Administration (FDA) Guidance for Industry - Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. Overall, 1493 and 1536 subjects with COPD were randomised in the 2 placebo controlled studies (DB2113361 and DB2113373, respectively), while 826 and 872 subjects with COPD were randomised in the 2 active controlled studies (DB2113360 and DB2113374, respectively). Baseline demographic and disease characteristics of the study populations in these studies showed that they were reflective of the target patient population.

In these 4 pivotal studies, the efficacy of UMEC/VI was evaluated through effects on FEV1 as well as effects on symptom relief and health outcomes. Overall, analyses on the effects of UMEC/VI on FEV1 compared to placebo yielded results which were supportive of the efficacy claim of both doses of UMEC/VI (125/25 µg and 62.5/25 µg) as well as of its components (UMEC 125 µg, UMEC 62.5 µg and VI 25 µg) over placebo. Analyses on the effects of UMEC/VI on FEV1 compared to an active comparator, TIO, also yielded results which were generally supportive of the efficacy claim of both doses of UMEC/VI (125/25 µg and 62.5/25 µg) over TIO. Analyses on the effects of UMEC/VI on symptom relief and health outcomes compared to placebo yielded results which were generally supportive of the efficacy claim of both doses of UMEC/VI over placebo. However, comparisons between UMEC/VI and TIO with regards to effects on symptom relief and

[9] TDI is an interview-based measurements of breathlessness related to activities of daily living. The TDI is an evaluative instrument that includes specific criteria for each of three components to measure changes from a baseline state.
[10] Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). EMA/CHMP/483572/2012 –corr1.

health outcomes yielded results that largely showed no statistically significant treatment differences between either dose of UMEC/VI and TIO.

With regards to bronchodilatory effects at the end of a 24 hour dosing interval (as measured by trough FEV1) in the two pivotal 24 week placebo controlled studies (DB2113361 and DB213373), both doses of UMEC/VI showed statistically significant improvements over placebo in trough FEV1 at Day 169 (difference over placebo of 167 mL and 238 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively; $p < 0.001$). Improvements over placebo were also observed in the 12 week exercise studies (DB2114417 and DB2114418); difference over placebo of 211 to 243 mL and 169 to 261 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively; $p < 0.001$, although statistical significance could not be claimed for the comparisons in Study DB2114417 under the terms of the testing hierarchy in the study. In the two pivotal 24 week active controlled studies (DB2113360 and DB213374), both doses of UMEC/VI showed statistically significant improvements over TIO in trough FEV1 at Day 169 (difference over TIO of 60 to 90 mL and 74 to 88 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively; $p \leq 0.018$), although statistical significance could not be claimed for the comparison between UMEC/VI 62.5/25 µg and TIO in Study DB213374 as a result of a prior test in the predefined testing hierarchy not achieving statistical significance in this study. Comparisons between UMEC/VI 62.5/25 µg with its individual components in the pivotal studies showed statistically significant improvements of the combination product over the individual components in trough FEV1 at Day 169 (improvement over UMEC 62.5 µg of 52 mL ($p = 0.004$; Study DB213373); improvement over VI 25 µg of 95 mL ($p < 0.001$; Study DB213373) and of 90 mL ($p < 0.001$; Study DB213360)). Comparisons between UMEC/VI 125/25 µg with its individual components in the pivotal studies also showed statistically significant improvements of the combination product over the individual components in trough FEV1 at Day 169, except for that between UMEC/VI 125/25 µg and UMEC 125 µg in Study DB213374 (improvement over UMEC 125 µg of 79 mL ($p < 0.001$; Study DB213361) and of 37 mL ($p = 0.142$; Study DB213374); improvement over VI 25 µg of 114 mL ($p < 0.001$; Study DB213361) and of 88 mL ($p < 0.001$; Study DB213360)).

Analyses of the bronchodilatory effects in the first 6 hours after dosing, after 24 weeks of treatment (weighted mean FEV1 over 0 to 6 hours post dose at Day 168) showed that in the two 24 week placebo controlled studies (DB2113361 and DB213373), both doses of UMEC/VI showed improvements over placebo in weighted mean FEV1 over 0 to 6 hours post dose at Day 168 (difference over placebo of 242 mL and 287 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively; $p < 0.001$)[11]. In one of the 24 week active controlled studies (DB2113360), both doses of UMEC/VI showed statistically significant improvements over TIO in weighted mean FEV1 over 0 to 6 hours post dose at Day 168 (difference over TIO of 74 mL and 83 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively; $p \leq 0.005$). In the other 24 week active controlled studies (DB2113374), both doses of UMEC/VI also showed improvements over TIO in weighted mean FEV1 over 0 to 6 hours post dose at Day 168 (difference over TIO of 96 mL and 101 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively; $p \leq 0.003$), although statistical significance could not be claimed for these comparisons as a result of a prior test in the predefined testing hierarchy not achieving statistical significance in Study DB2113374.

With regards to bronchodilatory effects over 24 week treatment period (as measured by serial trough FEV1 and weighted mean FEV1 over 0 to6 hours across the 24 week

[11] For regulatory agencies that consider the TDI score as a key secondary efficacy endpoint, these improvements in weighted mean FEV1 over 0 to 6 hours observed in both studies were not considered inferential as a prior comparison in the testing hierarchy did not achieve significance. For regulatory agencies that do not consider the TDI as a key secondary endpoint, these improvements were considered statistically significant.

treatment period), results in the 4 pivotal studies showed that improvements with both doses of UMEC/VI in trough FEV1 compared to placebo and TIO were observed early (at Day 2) and then maintained across the 24 week treatment period. Improvements with both doses of UMEC/VI in weighted mean FEV1 over 0 to 6 hours compared to placebo and TIO were also observed early and then maintained across the 24 week treatment.

Characterisation of bronchodilatory effects over the 24 hour dosing period was done by analyses of data in the twenty four hour (TFH) Population in Studies DB2113361 and DB2113373. Results showed that there were statistically significantly greater least squares mean (LSM) changes from baseline in 0 to 24 hour weighted mean FEV1 compared to placebo for both UMEC/VI 62.5/25 µg (Study DB2113373) and UMEC/VI 125/25 µg (DB2113361) at Days 1, 84 and 168 (UMEC/VI 62.5/25 µg: differences over placebo of 212 mL, 254 mL and 219 mL at Days 1, 84 and 168, respectively ($p < 0.001$); UMEC/VI 125/25 µg: differences over placebo of 253 mL, 309 mL and 312 mL, respectively ($p < 0.001$)). Analyses of serial FEV1 at Days 1, 84, and 168 in the TFH population in Studies DB2113361 and DB2113373 showed that there were statistically significantly greater post dose improvements in FEV1 from baseline compared to placebo for both doses of UMEC/VI.

With regards to effects on symptom relief and health outcomes, results were generally supportive of improvements over placebo for both doses of UMEC/VI, but not over TIO for either dose of UMEC/VI. In the pivotal 24 week placebo controlled studies (DB2113361 and DB213373), both doses of UMEC/VI showed statistically significant improvements over placebo in TDI focal scores at Days 28, 84 and 168 (difference over placebo at Day 168 of 1.2 and 1.0 with UMEC/VI 62.5/25 µg and 125/25 µg, respectively; $p < 0.001$). The proportion of TDI responders (as defined by a ≥ 1 unit value) at Day 168 was greater for UMEC/VI 62.5/25 µg compared with placebo (Study DB2113373; 58% versus 41%) and for UMEC/VI 125/25 µg compared with placebo (Study DB2113361; 49% versus 30%). The ratio of the odds of being a TDI responder versus a non responder was greater for both doses of UMEC/VI compared with placebo at all assessed time points (odds ratio of 2.0 to 3.1 ($p < 0.001$) and2.5 to 3.7 ($p < 0.001$) with UMEC/VI 62.5/25 µg and 125/25 µg, respectively. However, in the pivotal 24 week active controlled studies (DB2113360 and DB213374), the treatment differences between either dose of UMEC/VI and TIO for TDI focal score at Day 168 were not statistically significant in both the individual studies as well as the meta-analysis of the two studies. Statistically significant improvements over TIO with both doses of UMEC/VI were seen at Days 28 and 84 only in Study DB2113360 and the meta-analysis, but not in Study DB2113374. The odds of being a responder versus a non responder based on TDI score was also not statistically significant for either dose of UMEC/VI compared with TIO at Day 168 in both the individual studies as well as the meta-analysis of the two studies.

Analyses of other endpoints of symptomatic benefit and health outcomes (rescue salbutamol use, SOBDA score and proportion of SOBDA responders, COPD exacerbation, St. George's Respiratory Questionnaire (SGRQ) [12][13]score and proportion of SGRQ responders, and evaluation of healthcare resource utilisation) gave similar results, showing improvements with both doses of UMEC/VI over placebo, but not over TIO. In the pivotal 24 week placebo controlled studies (DB2113361 and DB213373), both doses of UMEC/VI showed statistically significantly greater reductions from baseline in LSM rescue salbutamol use over Weeks 1 to 24 compared to placebo (reduced by 0.8 and 1.5 puffs per day compared to placebo with UMEC/VI 62.5/25 µg ($p < 0.001$) and UMEC/VI 125/25 µg ($p=0.001$), respectively), and larger changes from baseline in percentage of rescue free

[12] Jones PW et al A self-complete measure for chronic airflow limitation, the St George's Respiratory Questionnaire. 1992 *Am Rev Respir Dis* 145 1321-1327.
[13] The St George's Respiratory Questionnaire (SGRQ) is an index designed to measure and to quantify health related health status in patients with chronic airflow limitation.

days over Weeks 1 to 24 compared with placebo for both doses of UMEC/VI (11.1% for UMEC/VI 62.5/25 µg versus -0.9% for placebo and 17.2% for UMEC/VI 125/25 µg versus 0.4% for placebo). There was statistically significantly greater LSM SOBDA score improvement from baseline with both doses of UMEC/VI compared with placebo at Week 24 (difference over placebo of -0.17 and-0.15 with UMEC/VI 62.5/25 µg ($p < 0.001$) and UMEC/VI 125/25 µg ($p = 0.002$), respectively). The proportion of SOBDA responders at Week 24 was greater for UMEC/VI 62.5/25 µg compared with placebo (using responder threshold of -0.1: 32% versus 21% ($p = 0.002$); using responder threshold of -0.2: 28% versus 16% ($p < 0.001$)) and for UMEC/VI 125/25 µg compared with placebo (using responder threshold of -0.1: 34% versus 22% ($p = 0.002$); using responder threshold of - 0.2: 28% versus 16% ($p < 0.001$)). Both doses of UMEC/VI also showed a lower risk of COPD exacerbation compared with placebo (hazard ratios of 0.5 ($p = 0.004$) and 0.4 ($p < 0.001$) with UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively). In terms of health outcomes, there were statistically significant greater LSM decreases from baseline in SGRQ total score at Day 168 compared to placebo for both doses of UMEC/VI (difference over placebo of -5.51 ($p < 0.001$) and -3.60 ($p = 0.001$) with UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively). The proportion of SGRQ responders (defined as having a SGRQ total score of 4 units below baseline or lower) at Day 168 was greater for UMEC/VI 62.5/25 µg compared with placebo (Study DB2113373: 49% versus 34%, $p < 0.001$) and for UMEC/VI 125/25 µg compared with placebo (Study DB2113361; 49% versus. 37%, $p = 0.002$). However, analysis of healthcare resource utilisation in Studies DB2113361 and DB2113373 yielded results that were comparable between the placebo and UMEC/VI treatment groups.

In the pivotal 24 week active-controlled studies (DB2113360 and DB213374), UMEC/VI 125/25 µg showed statistically significantly greater reductions from baseline in LSM rescue salbutamol use over Weeks 1 to 24 compared to TIO (reduced by 0.6 and1.1 puffs per day compared to TIO in studies DB2113360 and DB213374, respectively; $p \leq 0.031$). However, statistically significantly greater reductions from baseline in LSM rescue salbutamol use over Weeks 1 to 24 compared to TIO for UMEC/VI 62.5/25 µg was only observed in Study DB2113360 (reduced by 0.7 puffs per day compared to TIO; $p = 0.022$). There were larger changes from baseline in percentage of rescue free days over Weeks 1 to 24 compared with TIO with both doses of UMEC/VI (Study DB2113360: 18.6% and 18.8% with UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively versus 11.7% with TIO; Study DB213374: 17.6% and 26.9%, respectively versus 13.4%). However, analyses of the SOBDA score, proportion of SOBDA responders at Week 24, COPD exacerbations, SGRQ total score at Day 168 and proportion of SGRQ responders at Day 168 yielded results that were not statistically significant for the comparison between either dose of UMEC/VI and TIO.

With regards to effects on exercise tolerance, analyses in one of the 2 exercise studies (DB2114417) showed that there were no statistically significant difference in 3 hour post dose exercise endurance time (EET) at Week 12 between either doses of UMEC/VI and placebo (EET change from baseline of 58.6, 69.1 and 36.7 seconds with UMEC/VI 62.5/25 µg, UMEC/VI 125/25 µg and placebo, respectively; UMEC/VI 62.5/25 µg versus placebo: $p = 0.234$; UMEC/VI 125/25 µg versus placebo: $p = 0.08$). However, in the other exercise Study (DB2114418), there were statistically significantly greater LSM changes from baseline in the 3 hour post dose EET at Week 12 compared with placebo for both doses of UMEC/VI (UMEC/VI 62.5/25 µg: difference of 69.4 seconds over placebo (69.5 versus 0.1 seconds), $p = 0.003$; UMEC/VI 125/25 µg: difference of 65.8 seconds over placebo (65.9 versus 0.1 seconds), $p = 0.005$). Detailed analysis shows that the changes in EET from baseline were similar with both doses of UMEC/VI between both studies, but there was a greater placebo response in Study DB2114417 (EET change from baseline of 36.7 seconds) than was observed in the DB2114418 study (EET change from baseline of

0.1 seconds). The sponsor had stated that no obvious reason for this difference between the studies was found.

The individual components of UMEC/VI (UMEC 62.5 µg, UMEC 125 µg and VI 25 µg) were all new chemical entities at the time the CER was prepared and had not been approved as monotherapies. The bronchodilatory efficacy of the individual components was investigated against placebo in the two pivotal 24 week placebo controlled studies (DB2113361 and DB213373). Results in these 2 studies showed that there were statistically significant improvements over placebo in trough FEV1 at Day 169 with both doses of UMEC and with VI 25 µg (difference over placebo of 115 mL, 160 mL and 72 to 124 mL with UMEC 62.5 µg, UMEC 125 µg and VI 25 µg, respectively ($p < 0.001$)). There were also improvements over placebo in weighted mean FEV1 over 0 to 6 hours post dose at Day 168 with both doses of UMEC and with VI 25 µg (difference over placebo of 150 mL, 178 mL and 122 to 145 mL with UMEC 62.5 µg, UMEC 125 µg and VI 25 µg, respectively ($p < 0.001$))[14]. These results were generally supported by results in the two exercise studies (DB2114417 and DB2114418). In Study DB2114418, there were statistically significant improvements over placebo in trough FEV1 at Week 12 with both doses of UMEC and with VI 25 µg (difference over placebo of 144 mL, 255 mL and 112 mL with UMEC 62.5 µg, UMEC 125 µg and VI 25 µg, respectively ($p < 0.001$)). In Study DB2114417, there were also improvements over placebo in trough FEV1 at Week 12 with both doses of UMEC and with VI 25 µg (difference over placebo of 87 mL, 140 mL and 99 mL with UMEC 62.5 µg, UMEC 125 µg and VI 25 µg, respectively ($p \leq 0.003$)), although statistical significance could not be claimed for these comparisons as a result of a prior test in the predefined testing hierarchy not achieving statistical significance in Study DB2114417. In the two pivotal 24 week active controlled studies (DB2113360 and DB213374), direct statistical comparisons of UMEC or VI with TIO was not performed, but FEV1 results of UMEC and VI were numerically similar to or greater than those of TIO (change from baseline in trough FEV1 at Day 169: 186 mL (standard error (SE):17.8 mL) for UMEC 125 µg versus 149 mL (SE: 17.6 mL) for TIO; 121 mL (SE:18.9 mL) for VI 25 µg versus 121 mL (SE: 18.6 mL) for TIO; change from baseline in weighted mean FEV1 over 0 to 6 hours on Day 168: 206 mL (SE:16.7 mL) for UMEC 125 µg versus 180 mL (SE: 16.5 mL) for TIO; 178 mL (SE:18.9 mL) for VI 25 µg versus 181 mL (SE: 18.7 mL) for TIO).

Although 2 doses of UMEC/VI were tested in the Phase III studies and both were proposed for registration, the recommended dose in the proposed PI was one oral inhalation of UMEC/VI 62.5/25 µg once daily, with additional note that "the use of Anoro Ellipta 125/25 micrograms once daily in some patients has been shown to provide additional clinical benefit with regard to lung function and rescue medication use".[15] The sponsor provided the rationale that efficacy results in the pivotal studies showed no clear differentiation between the 2 doses. Studies DB2113360 and DB2113374 allowed within study comparisons of the 2 doses and showed that in Study DB2113360, there was a treatment difference over TIO in trough FEV1 at Day 169 of 90 mL and 88 mL with UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively, and in Study DB2113374, there was a treatment difference over TIO in trough FEV1 at Day 169 of 60 mL and 74 mL with UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively. In Study DB2113360, the treatment difference over TIO in weighted mean FEV1 over 0 to 6 hours post dose at Day 168 was 74 mL and 83 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively, while in Study DB2113374, the treatment difference over TIO for this endpoint was 96 mL and 101 mL, respectively. Results in the 2 pivotal placebo controlled studies (DB2113361 and

[14] For regulatory agencies that consider the TDI score as a key secondary efficacy endpoint, these improvements in weighted mean FEV1 over 0 to 6 hours observed in both studies were not considered inferential as a prior comparison in the testing hierarchy did not achieve significance. For regulatory agencies that do not consider the TDI as a key secondary endpoint, these improvements were considered statistically significant.

[15] The application for the higher strength UMEC/VI 125/25 µg was withdrawn.

DB213373) and the 2 exercise studies (DB2114417 and DB2114418) were also generally supportive of this. Hence, the sponsor had concluded that the UMEC/VI dose of 62.5/25 µg would be appropriate for the majority of COPD patients.

Subgroup analyses on integrated data of the 4 pivotal efficacy studies showed that in the subgroup of subjects reversible to salbutamol[16] at screening, there were greater improvements in bronchodilatation as measured by trough FEV1 at Day 169 with UMEC/VI 125/25 µg (282 mL improvement over placebo; $p < 0.001$) compared with UMEC/VI 62.5/25 µg (225 mL over placebo; $p < 0.001$), a pattern that was not observed in the non reversible subjects (UMEC/VI 125/25 µg: 181 mL improvement over placebo, $p < 0.001$; UMEC/VI 62.5/25 µg: 188 mL improvement over placebo, $p < 0.001$). Greater treatment response with the 125/25 µg than with 62.5/25 µg in the reversible subgroup was also observed for the TDI focal scores, SGRQ scores, and rescue salbutamol use. Hence, the sponsor had concluded that in some COPD patients who had salbutamol reversibility, UMEC/VI 125/25 µg could potentially offer additional benefit.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

In the pivotal efficacy studies (Studies DB2113361, DB2113373, DB2113360 and DB2113374), 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 special interest included cardiovascular effects, effects on glucose, and effects on potassium, tremor, urinary retention, ocular effects, gallbladder disorders, pneumonia, intestinal obstruction, and anticholinergic syndrome.
- Laboratory tests performed included haematology, and routine non fasting blood chemistry (alkaline phosphatase, gamma-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, total, direct and indirect bilirubin, total protein, albumin, serum potassium, sodium, chloride, bicarbonate, creatinine, blood urea nitrogen, glucose, calcium, phosphorus, uric acid, creatine phosphokinase). Laboratory tests were performed according to the schedule provided.
- Other safety endpoints included vital signs (pulse rate and systolic and diastolic blood pressure) and 12 lead ECG performed according to the schedule provided. In addition, in Studies DB2113361 and DB2113373, 24 hour Holter monitoring was performed in a subset of subjects (TFH population subset[17]) over a 24 hour period at screening, and Days 1, 84 and 168. Across these 2 studies, Holter monitoring was done in 396 subjects: 73, 53, 55, 54, 53 and 108 subjects in the pooled placebo, UMEC/VI 62.5/25 µg, UMEC/VI 125/25 µg, UMEC 62.5 µg, UMEC 125 µg and VI 25 µg groups, respectively.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

[16] Defined as an increase in FEV1 of ≥ 12% and ≥ 200 mL following administration of 4 puffs of salbutamol.
[17] The Twenty Four Hour (TFH) population comprised of a subset of subjects from the ITT population for whom 24-hour data were collected for spirometry and Holter monitoring. (Studies DB2113361 and DB2113373)

Dose response and non pivotal efficacy studies

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

- The two 12 week exercise tolerance studies (DB2114417 and DB2114418) provided data on AEs, vital signs, routine laboratory evaluations and 12 lead ECG.
- The 12 month long term safety study (DB2113359) provided data on AEs, AEs of special interest (cardiovascular, effects on glucose, effects on potassium, tremor, urinary retention, ocular effects, gallbladder disorders, pneumonia, intestinal obstruction, and anticholinergic syndrome), vital signs, routine laboratory evaluations,12 lead ECG, and 24 hour Holter ECGs.
- The five dose finding studies in COPD patients (Studies AC4113589, AC4113073, AC4115321, AC4115408 and B2C111045) provided data on AEs, COPD exacerbations, vital signs, routine laboratory evaluations and 12 lead ECG.
- The Phase IIa safety/tolerability study of UMEC/VI 500/25 µg in COPD patients (DB2113120) assessed safety through its primary endpoint of change from baseline in weighted mean pulse rate over 0 to 6 hours post dose at Day 28, and the secondary endpoints of weighted mean pulse rate over 0 to 6 hours post dose on Days 1 and 14, and maximum and minimum pulse rate over 0 to 6 hours post dose on Days 1, 14, and 28. In addition the study provided data on AEs, COPD exacerbations, vital signs, routine laboratory evaluations and 12 lead ECG.

Evaluator's comments

- The safety evaluation parameters were appropriate. UMEC is a LAMA and VI is a LABA, and hence the main safety concerns with UMEC/VI will relate to known LAMA and LABA effects. The AEs of special interest addressed the known pharmacologic class effects of LAMA (for example, cardiovascular effects, ocular disorders (for example, blurred vision), urinary retention, gastrointestinal and gallbladder disorders, and anticholinergic effects) and of LABA (for example, cardiovascular effects, metabolic effects (low potassium and elevated glucose) and tremors).
- In the CER, 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 inclusion/exclusion criteria of the 4 pivotal Phase III studies were similar and the baseline demographic and disease characteristics were also comparable across these 4 studies.
- The safety data of the 2 non pivotal exercise tolerance studies were also evaluated individually, and were found to be consistent between both studies. The study design of these 2 non pivotal Phase III studies was similar and the baseline demographic characteristics were also comparable across these 2 studies.
- The five dose finding studies in COPD patients and the Phase IIa safety/tolerability study of UMEC/VI in COPD patients (DB2113120) were evaluated with regards to dose selection for the pivotal Phase III studies and whether the safety results were consistent with those of the pivotal studies. The safety data of these 6 Phase II studies were found to be generally consistent with the safety results of the pivotal studies and no major safety concerns were raised.

Patient exposure

For the 4 combined pivotal Phase III studies, the mean (standard deviation (SD)) exposure was 136.6 (55.39), 150.1 (44.11), 147.6 (46.97), 146.7 (47.03), 144.5 (48.53), 145.3 (47.85) and 149.5 (45.74) days in the pooled placebo, UMEC/VI 62.5/25 µg, UMEC/VI

125/25 µg, UMEC 62.5 µg, UMEC 125 µg, VI 25 µg and TIO 18 µg groups, respectively (Table 7). Overall, 73%, 84%, 82%, 82%, 79%, 79% and 85% of subjects in these respective groups had an exposure to study drug of > 20 weeks.

Table 7. Summary of Exposure (DB2113361, DB2113373, DB2113360, and DB2113374 ITT Population).

	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Exposure (days)							
n	555	842	832	418	629	1034	423
Mean	136.6	150.1	147.6	146.7	144.5	145.3	149.5
SD	55.39	44.11	46.97	47.03	48.53	47.85	45.75
Median	167.0	168.0	168.0	168.0	167.0	168.0	167.0
Min	1	1	1	1	1	1	1
Max	192	177	179	179	183	206	176
Total Subject-years Exposure	207.52	345.92	336.27	167.88	248.89	411.20	173.09
Range of Exposure							
n	555	842	832	418	629	1034	423
≥1 day	555 (100)	842 (100)	832 (100)	418 (100)	629 (100)	1034 (100)	423 (100)
>4 weeks	495 (89)	793 (94)	782 (94)	395 (94)	585 (93)	961 (93)	395 (93)
>8 weeks	468 (84)	774 (92)	747 (90)	377 (90)	558 (89)	927 (90)	382 (90)
>12 weeks	452 (81)	749 (89)	729 (88)	364 (87)	538 (86)	897 (87)	374 (88)
>16 weeks	415 (75)	722 (86)	698 (84)	345 (83)	509 (81)	844 (82)	365 (86)
>20 weeks	405 (73)	705 (84)	684 (82)	341 (82)	498 (79)	822 (79)	359 (85)
>24 weeks	169 (30)	326 (39)	281 (34)	154 (37)	200 (32)	343 (33)	116 (27)

Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

For the 2 combined exercise tolerance studies, the mean (SD) exposure was 77.8 (20.17), 80.5 (16.23), 80.4 (16.50), 81.4 (12.73), 77.7 (21.07) and 78.5 (19.39) days in the pooled placebo, UMEC/VI 62.5/25 µg, UMEC/VI 125/25 µg, UMEC 62.5 µg, UMEC 125 µg, and VI 25 µg groups, respectively. Overall, 62%, 65%, 69%, 67%, 63% and 66% of subjects in these respective groups had an exposure to study drug of > 12 weeks.

In the 12 month long term safety study (DB2113359), the mean (SD) exposure was 269.4 (127.54), 269.0 (125.52) and 285.3 (114.18) days in the placebo, UMEC 125 µg and UMEC/VI 125/25 µg groups, respectively. Overall, 65%, 64% and 66% of subjects in these respective groups had an exposure to study drug of ≥ 274 days.

Evaluator's comments: Overall, the study drug exposure is adequate to assess the safety profile of UMEC/VI.

Safety issues with the potential for major regulatory impact

Muscarinic antagonist class effects

Muscarinic antagonist pharmacological class effects include cardiovascular effects, ocular disorders, urinary retention, intestinal obstruction, gallbladder disorders, and anticholinergic effects. The results did not raise any particular safety concerns.

Beta$_2$-agonist class effects

Beta$_2$-agonist pharmacological class effects include cardiovascular effects, hypokalaemia, elevated glucose and tremors. The results did not raise any particular safety concerns.

Post marketing data

Not applicable.

Evaluator's conclusions on safety

Overall, the safety results did not raise any major safety concerns for either dose of UMEC/VI or its individual components. The overall incidences of all causality AEs, treatment related AEs, serious adverse events (SAEs) and AEs leading to discontinuation were comparable between both doses of UMEC/VI and placebo or TIO in the pivotal Phase III studies. These results were generally supported by those of the non-pivotal exercise tolerance studies and the long term safety study. The commonly reported treatment related AEs were those expected for a LABA and LAMA. Analyses of cardiovascular safety and of AEs related to muscarinic antagonist and beta$_2$-agonist pharmacological class effects did not raise major safety concerns. The incidences of these AEs were generally low and comparable between placebo and active treatment groups, with no obvious dose or treatment related trends detected.

With regards to potential drug/drug interactions with known pharmacological smoking cessation agents, such as varenicline, the sponsor had not provided any analyses regarding potential drug/drug interactions between UMEC/VI and varenicline, or incidence of AEs with and without concomitant use of varenicline. As smoking cessation plays an important role in the overall clinical management of patients with COPD, it is expected that in clinical settings, COPD patients being prescribed UMEC/VI 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 safety issues with concomitant use of these 2 medications in the 4 pivotal studies. However, a look through the data of the 4 pivotal studies showed that the incidence of concomitant use of varenicline during the studies was very low (1% in each study). In view of this, additional safety analyses comparing results with and without concomitant use of varenicline in the 4 pivotal studies are not considered to be able to allow meaningful interpretation.

First round benefit-risk assessment

First round assessment of benefits

The potential benefit of UMEC/VI in the proposed usage is as a once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Overall, efficacy results were supportive of the efficacy claim of both doses of UMEC/VI (125/25 µg and 62.5/25 µg) over placebo in terms of lung function as well as symptom relief.

The efficacy of UMEC/VI was evaluated through effects on lung function, FEV1, as well as effects on symptom relief and health outcomes, compared to placebo and to TIO. Analyses on the effects of UMEC/VI on FEV1 compared to placebo in the two pivotal 24 week placebo controlled studies showed that after 24 weeks of treatment, both doses of UMEC/VI had statistically significant improvements over placebo in trough FEV1 (difference over placebo of 167 mL and 238 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively) and in weighted mean FEV1 over 0 to 6 hours post dose (difference over placebo of 242 mL and 287 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively). Over the 24 week treatment period, improvements with both doses of UMEC/VI in trough FEV1 and weighted mean FEV1 over 0 to 6 hours post dose compared to placebo were observed early and then maintained across the 24 week treatment period.

Analyses on the effects of UMEC/VI on FEV1 compared to TIO in the two pivotal 24 week active controlled studies showed that after 24 weeks of treatment, both doses of UMEC/VI had improvements over placebo in trough FEV1 (difference over TIO of 60 to 90 mL and 74 to 88 mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively) and in weighted mean FEV1 over 0 to 6 hours post dose (difference over TIO of 74 to 96 mL and 83 to 101

mL with UMEC/VI 62.5/25 µg and 125/25 µg, respectively)[18]. Over the 24 week treatment period, improvements with both doses of UMEC/VI in trough FEV1 and weighted mean FEV1 over 0 to 6 hours post dose compared to TIO were observed early and then maintained across the 24 week treatment period.

Analyses on the effects of UMEC/VI on symptom relief and health outcomes compared to placebo in the two pivotal 24 week placebo controlled studies showed that after 24 weeks of treatment, both doses of UMEC/VI had statistically significant improvements over placebo in TDI focal scores (difference over placebo of 1.2 and 1.0 with UMEC/VI 62.5/25 µg and 125/25 µg, respectively), and there were greater proportions of TDI responders (as defined by a ≥ 1 unit value) compared with placebo for UMEC/VI 62.5/25 µg (58% versus 41% with placebo) and for UMEC/VI 125/25 µg (49% versus 30% with placebo). There were also statistically significantly greater reductions from baseline in rescue salbutamol use over Weeks 1 to 24 compared to placebo as well as greater changes from baseline in percentage of rescue free days over Weeks 1 to 24 compared with placebo. Both doses of UMEC/VI also showed statistically significantly lower risk of COPD exacerbation compared with placebo.

With regards to effects on exercise tolerance, analyses in one of the 2 exercise studies (DB2114418) showed statistically significantly greater changes from baseline in the 3 hour post dose EET at Week 12 compared with placebo for both doses of UMEC/VI (difference over placebo of 69.4 seconds and 65.8 seconds for UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively), while results in the other exercise study (DB2114417) showed no statistically significant difference in 3 hour post dose EET at Week 12 between either doses of UMEC/VI and placebo. However, further analysis shows that this was due to a greater placebo response in Study DB2114417 than was observed in the DB2114418 study, and the changes in EET from baseline were similar with both doses of UMEC/VI between both studies.

Efficacy results in the pivotal studies showed no clear differentiation between the 2 doses of UMEC/VI. The two pivotal 24 week active controlled studies (DB2113360 and DB2113374) allowed within study comparisons of the 2 doses and showed that in Study DB2113360, change from baseline in trough FEV1 at Day 169 was 211 mL and 209 mL with UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively (treatment difference over TIO of 90 mL and 88 mL, respectively), while in Study DB2113374, change from baseline in trough FEV1 at Day 169 was 208 mL and 223 mL with UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively (treatment difference over TIO of 60 mL and 74 mL, respectively).

Additional subgroup analyses on integrated data of the 4 pivotal efficacy studies showed that in the subgroup of subjects reversible to salbutamol at screening, there were greater improvements in bronchodilatation with UMEC/VI 125/25 µg (improvement over placebo in trough FEV1 at Day 169 of 282 mL) compared with UMEC/VI 62.5/25 µg (improvement over placebo of 225 mL), a pattern that was not observed in the non reversible subjects (improvement over placebo of 181 mL and 188 mL with UMEC/VI 125/25 µg and UMEC/VI 62.5/25 µg, respectively). This greater treatment response with UMEC/VI 125/25 µg than with UMEC/VI 62.5/25 µg in the reversible subgroup was also observed for the TDI focal scores, SGRQ scores, and rescue salbutamol use. The sponsor's conclusions that the UMEC/VI dose of 62.5/25 µg would be appropriate for the majority of COPD patients, and that UMEC/VI 125/25 µg could potentially offer additional benefit in some COPD patients who had salbutamol reversibility, were sound.

[18] statistical significance could not be claimed for these comparisons in Study DB2113374 as a result of a prior test in the predefined testing hierarchy not achieving statistical significance in Study DB2113374

First round assessment of risks

The risks of UMEC/VI in the proposed usage are:

- Muscarinic antagonist pharmacological class effects.
- $Beta_2$-agonist pharmacological class effects.

In particular, as both LAMA and LABA have potential cardiovascular effects, and UMEC/VI consists of a combination of a LAMA and a LABA, adverse effects on the cardiovascular system needs to be assessed.

Overall, analyses of cardiovascular safety and of AEs related to muscarinic antagonist and $beta_2$-agonist pharmacological class effects did not raise major safety concerns. In the pivotal studies, the incidence of on treatment events in the cardiovascular special interest group was generally comparable across the pooled treatment groups (6% to 10%). The overall most commonly reported subgroup of on treatment cardiovascular adverse event of special interest (AESI) was cardiac arrhythmias, but the incidence was low and comparable across treatment groups (2% to 5% across treatment groups; 3% and 2% with UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg, respectively compared with 3% with placebo and 2% with TIO). There were no obvious dose or treatment related trends. Results in the 2 exercise studies and the long term safety studies were consistent with those in the pivotal studies. Cardiovascular effects were assessed via Holter monitoring in a subset of subjects in the 2 placebo controlled pivotal studies and in the long term safety study. Results did not raise major cardiovascular safety concerns for either dose of UMEC/VI. The proportion of subjects with one or more abnormal, clinically significant Holter ECG interpretation at any time post baseline was 53% and 45% in the UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg groups, respectively, versus 60% in the placebo group, in the 2 pivotal studies, while that in the long term safety study was 55% in the UMEC/VI 125/25 µg group versus 52% in the placebo group. The incidences of other AEs of special interest relating to muscarinic antagonist and $beta_2$-agonist pharmacological class effects were generally low and comparable between placebo and active treatment groups, with no obvious dose or treatment related trends detected.

First round assessment of benefit-risk balance

The benefit-risk balance of UMEC/VI, given the proposed usage, is favourable.

Overall, analyses on effects of UMEC/VI on FEV1 compared to placebo yielded results which were generally supportive of the efficacy claim of both doses of UMEC/VI (62.5/25 µg and 125/25 µg) over placebo. Analyses on effects of UMEC/VI on symptom relief compared to placebo also yielded results which were generally supportive of the efficacy claim of both doses of UMEC/VI 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 UMEC/VI 62.5/25 µg and 125/25 µg as a long term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD be approved.

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

Clinical questions

Efficacy

1. Please provide clarification on how the twenty four hour (TFH) population subsets in Studies DB2113361 and DB2113373 were selected.
2. Please provide the baseline demographic and disease characteristics of the TFH population in Studies DB2113361, DB2113373.
3. Please elaborate on the sample size calculations for Studies DB2113360 and DB2113374, with regards to the increased in the planned number of evaluable subjects in each arm from the calculated 111 to 146 subjects.

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. In this section on the evaluation of the sponsor's responses to the questions posed in the first round of evaluation, each question will be re-stated for ease of reference, followed by the evaluation.

Question 1

Please provide clarification on how the twenty four hour population subsets in Studies DB2113361 and DB2113373 were selected.

The sponsor provided explanation that subset specific investigational sites were used in Studies DB2113373 and DB2113361 in order to limit selection bias. A feasibility analysis was conducted to identify sites with the ability to conduct 24 hour serial spirometry assessments. The majority of these subset sites were restricted to enrolling all patients into the TFH subset, and this reduced selection bias as there was no option for them to enrol a patient into the non subset group. In Study DB2113361, nine of the 14 sites (65%) that enrolled subset patients were subset specific and in Study DB2113373, nine of the 13 sites (69%) were subset specific. Overall, the majority of patients in the 24 hour subset were enrolled at the subset specific sites (subset specific sites enrolled 165 of 199 (83%) of subset subjects in Study DB2113361 and 155 of 197 (79%) of subset subjects in Study DB21133373), thus minimising the risk of selection bias.

The sponsor's response to this question has not resulted in any changes to the conclusions of the first round of evaluation.

Question 2

Please provide the baseline demographic and disease characteristics of the twenty four hour population in studies DB2113361, DB2113373.

The sponsor provided the baseline demographics, COPD history, smoking history, and screening lung function and ICS use of the TFH populations in studies DB2113361 and DB2113373. The baseline demographic and disease characteristics for the TFH populations in these studies were generally comparable across treatment groups.

The sponsor's response to this question has not resulted in any changes to the conclusions of the first round of evaluation.

Question 3

Please elaborate on the sample size calculations for studies DB2113360 and DB2113374, with regards to the increase in the planned number of evaluable subjects in each arm from the calculated 111 to 146 subjects.

The sponsor clarified that the increase in sample size was due to the need to maintain the conditional power for the comparisons in the meta-analysis at approximately 90%. For the comparison of each UMEC/VI dose with TIO for the endpoint of TDI in the meta-analysis, statistical inference was conditional on having achieved statistical significance on the comparison of that dose with TIO on the individual study primary endpoint of trough FEV1 on Day 169 in each individual study, as determined by the specific testing hierarchy within each study. The power for the meta-analysis comparisons was thus affected by the fact that prior comparisons were required to be performed in the individual studies. In order to maintain the conditional power for the comparisons in the meta-analysis at approximately 90%, it was necessary to increase the power for the comparisons in the individual studies and hence increase the sample size in each treatment arm.

Increasing the sample size to 146 subjects per arm provided 98% power to detect a 100 mL difference in trough FEV1 between treatment groups in each study and 96% power to detect a difference of 1 unit in TDI in the combined analysis. This gave conditional power for the comparison of UMEC/VI 125/25 µg with TIO for TDI of 92% and conditional power for the comparison of UMEC/VI 62.5/25 µg with TIO for TDI of 89%.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of UMEC/VI in the proposed usage are unchanged from those identified the first round assessment.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of UMEC/VI in the proposed usage are unchanged from those identified the first round assessment.

Second round assessment of benefit-risk balance

The benefit-risk balance of UMEC/VI, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

It is recommended that the application for the registration of UMEC/VI 62.5/25 µg and 125/25 µg[19] as a long term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD be approved.

[19] Note: the sponsor subsequently withdrew the part of the application to register the UMEC/VI 125/25 µg strength

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan, EU-RMP Version 1.0, dated 5 December 2012, with an Australian Specific Annex (ASA) Version: 1.0 (undated), which was reviewed by the TGA's Post-Market Surveillance Branch (PMSB).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 8.

Table 8. Summary of ongoing safety concerns.

Summary of safety concerns	
Important identified risks	None identified
Important potential risks	Cardiac Disorders
	Asthma related intubations and deaths
Important missing information	Safety in pregnancy and lactation
	Off label use in Asthma (including paediatric use)

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns.

Furthermore the sponsor proposes to further monitor and characterise the important potential risk: 'Cardiac Disorders' and the important missing information: 'Off label use in Asthma (including paediatric use)' in the following manner:

- Assessment of co-morbidities in COPD in European symptomatic subjects from primary care (ACCESS) which will provide information on the background risks for cardiovascular events in the COPD population and will address the safety concerns related to cardiac disorders.
- An interventional post authorisation safety observational cohort study to quantify the incidence of selected cardiovascular endpoints in COPD patients using inhaled UMEC/VI. This study will quantify the incidence of cardiovascular events of interest after the start of exposure to UMEC/VI in the licensed indication, in the post marketing setting to address safety concerns related to cardiac disorders.
- WEUSKOP6679: Drug utilisation study of new users of inhaled UMEC/VI in the primary care setting: United Kingdom (UK) Clinical Practice Research Datalink (CPRD) study. The study has the primary aim to describe the characteristics of new users of UMEC/VI compared to the total population of COPD patients in the CPRD. The secondary aim of the study is to quantify the disease burden of COPD and to estimate the incidence of outcomes of interest among new users of UMEC/VI and new users of TIO Handihaler). This is to address the safety issues of off label use and cardiac disorders.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient.

> ***PMSB reviewer comment:*** It is agreed the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities.

Routine risk minimisation activities will include precautionary statements and notification of undesirable effects in the Australian PI for all the specified ongoing safety concerns.

Reconciliation of issues outlined in the RMP report

Table 9 summarises the PMSB's first round evaluation of the RMP, the sponsor's responses to issues raised by the PMSB and the PMSB's evaluation of the sponsor's responses.

Table 9. Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
The important potential risk: 'Cardiac Disorders' is a broad term, although the EU-RMP states that only the MedDRA[20] term Cardiac arrhythmia SMQ[21] is used to monitor this ongoing safety concern. Consequently it is suggested that it be replaced by the important potential risks: 'Cardiac arrhythmias' (MedDRA term Cardiac arrhythmias SMQ); 'Myocardial infarction' (MedDRA term Myocardial infarction SMQ – narrow); and 'Cardiac failure' (MedDRA term Cardiac failure SMQ – narrow).	The following MedDRA terms have been included to assess the potential risk of cardio- and cerebrovascular disorders in the UMEC/VI EU RMP: 'Cardiac arrhythmias' (MedDRA term Cardiac arrhythmias SMQ), 'Cardiac failure' (MedDRA term Cardiac Failure SMQ), Cardiac Ischaemia (MedDRA terms Myocardial Infarction SMQ, Other Ischaemic Heart Disease SMQ), 'Stroke' (MedDRA terms CNS haemorrhages and cerebrovascular conditions SMQ).	This is acceptable.
The draft PI states: *"Consistent with its antimuscarinic activity, Anoro Ellipta should be used with caution in patients with narrow-angle glaucoma or urinary*	'Narrow-angle glaucoma' and 'Urinary retention/bladder outflow obstruction' have been included as important potential risks in the UMEC/VI	This is acceptable.

[20] Medical Dictionary for Regulatory Activities (MedDRA)
[21] Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest.

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
retention." In addition the safety specifications (SS) of the EU-RMP refers to 'Anti-cholinergic effects' as an important pharmacological class effect for LAMA. Consequently it is suggested that 'Narrow-angle glaucoma' and 'Urinary retention/bladder obstruction' should be included as important potential risks.	EU-RMP.	
The draft PI states: *"As with other inhalation therapies, administration of Anoro Ellipta may produce paradoxical bronchospasm that may be life threatening. Treatment with Anoro Ellipta should be discontinued if paradoxical bronchospasm occurs and alternative therapy instituted if necessary."* Consequently it is suggested that 'Paradoxical bronchospasm' should be included as an important potential risk.	'Paradoxical bronchospasm (which may be life threatening)' has been included as an important potential risk in the UMEC/VI EU-RMP.	This is acceptable.
The SS[22] of the EU-RMP refers to 'Hypokalaemia', 'Hyperglycaemia' & 'Tremor' as important pharmacological class effects for LABA and routine pharmacovigilance activities will monitor these effects. Consequently it is suggested that 'Hypokalaemia', 'Hyperglycaemia' & 'Tremor' should be included as important potential risks.	The sponsor has provided a justification based on clinical data to support the omission of 'Hypokalaemia', 'Hyperglycaemia' or 'Tremor' as important potential risks in the EU-RMP.	This is acceptable and it is noted that this appears to have been accepted by the EMA.

[22] Safety Specification (SS)

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
The SS of the EU-RMP refers to 'Gastrointestinal obstruction' as an important pharmacological class effect for LAMA and routine pharmacovigilance activities will monitor this effect. Consequently it is suggested that 'Gastrointestinal obstruction' should be included as important potential risk.	The sponsor has provided a justification based on clinical data to support the omission of 'Gastrointestinal obstruction' as an important potential risk in the EU-RMP.	This is acceptable and it is noted that this appears to have been accepted by the EMA.
The draft PI states: *"Anoro Ellipta has not been studied in patients with severe hepatic impairment (see PKs – Special Patient Populations)."* Consequently it is suggested that 'Use in patients with severe hepatic impairment' should be included as important missing information.	'Safety in subjects with severe hepatic impairment' has been included as missing information in the updated UMEC/VI EU-RMP.	This is acceptable.
The draft PI states: *"In a long-term safety study, 335 subjects were treated for up to 12 months with Anoro Ellipta 125/25 µg or placebo."* Consequently it is suggested that 'Long-term safety data' should be included as important missing information.	'Safety in long term use' has been included as missing information in the updated UMEC/VI EU-RMP.	This is acceptable.
If the sponsor decides to include these ongoing safety concerns in Australia for Anoro Ellipta then consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for them and the ASA should be revised accordingly.	The EU-RMP has been updated to reflect the inclusion of 'paradoxical bronchospasm', 'narrow angle glaucoma' and 'bladder outflow obstruction and urinary retention' as important potential risks. Additionally, missing information has been updated to include 'safety in long-	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
	term use' and 'safety in severe hepatic impairment'. The Summary of the Safety Concerns (Part II Module SVIII) has been updated accordingly. The proposed pharmacovigilance activities, including any risk minimisation measures have been updated in the pharmacovigilance plan to reflect the inclusion of these additional safety concerns. The ASA has been revised accordingly.	
It is suggested the important potential risk: 'Asthma related intubations and death' be revised to 'Asthma related intubations, hospitalisation and death' for completeness.	The sponsor will include the term 'hospitalisation' to the important potential risk of 'Asthma related intubations and death' at the next update of the EU-RMP.	This is acceptable.
The sponsor should definitively state whether the follow up pregnancy forms provided in Annex 7 of EU-RMP are to be used in Australia, and if so section 2.4: 'Other Pharmacovigilance Activities Referenced in the EU-RMP' of the ASA should be amended accordingly when this document is next updated.	The pregnancy follow-up forms in Annex 7 of the EU-RMP differ to those that will be used in Australia. The ASA has been revised to clarify this difference and to include the Pregnancy Notification Form and Pregnancy Outcome Form to be used in Australia.	This is acceptable.
The ongoing Study HZC115058 is not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocol has not been	The sponsor confirms that the progress/results/ analysis of Study HZC115058 will be presented in future Periodic Benefit-Risk	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
reviewed. Nevertheless an update on the progress/results/analysis of this study, as outlined in the EU-RMP, will be expected in future PSURs[23] and updated RMPs.	Evaluation Reports (PBRERs)[24]/PSURs and updated EU-RMPs.	
The studies referenced in the pharmacovigilance plan will generate safety data that will simply support the known safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. To this end it is suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	An overview of the forthcoming studies in the pharmacovigilance plan and the anticipated completion dates is provided in Table 1 of the ASA in the section 'Studies Referenced in the EU-RMP'. The results from these studies will be presented and discussed in PBRERs and the EU-RMP. GlaxoSmithKline (GSK) will submit PBRERs (including the EU-RMP and ASA when these have been updated) to the TGA in line with the PBRER reporting period. GSK proposes to provide additional information regarding these studies to the TGA upon request, following review of the PBRER/RMP. Any impact of these studies on the Australian Product Information (PI) will be provided to the TGA through the submission of an appropriate application.	This is acceptable.

[23] Periodic Safety Update Reports (PSURs)
[24] Periodic Benefit-Risk Evaluation Reports (PBRERs) (FDA)

Recommendation in RMP evaluation report	Sponsor's response	PSMB evaluator's comment
The submitted short study summaries do not lend themselves to detailed assessment. Nevertheless they will be considered by the ACSOM[25], as to whether the study design is adequate and if not, how could they be strengthened. In addition the committee will consider if Australian patient involvement is required. The sponsor should also provide an assurance that it will submit a draft protocol for these planned studies to the TGA for review once they become available.	The sponsor confirms that the protocols for the proposed post authorisation safety studies (PASS) will be submitted to the TGA upon endorsement by the EMA Pharmacovigilance Risk Assessment Committee. Once approved, the final PASS protocols will be provided in the updated UMEC/VI EU RMP.	This is acceptable. However, in the light of the ACSOM advice the sponsor should consider amending the draft protocol / synopsis of the drug utilisation study to include Australian patients and an updated version should be provided to the TGA for review once it is available (see above).
It is agreed the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities.	This is noted.	n/a

Key changes to the updated RMP

In their response to the TGA request for information the sponsor provided an updated EU-RMP (Version: 3.0, dated 14 October 2013) with an updated ASA (Version: 2.0, undated). Key changes from the version evaluated at Round 1 are summarised below:

Table 10. Key changes to the updated RMP

RMP Section	Changes introduced
Ongoing safety concerns	Modified to include the following updated or additional safety concerns: Potential risks: Cardio and Cerebrovascular disorders Paradoxical bronchospasm Narrow angle glaucoma Bladder outflow obstruction and urinary retention Missing information: Safety in long term use

[25] Advisory Committee on the Safety of Medicines (ACSOM).

RMP Section	Changes introduced
	Safety in subjects with severe hepatic impairment
Pharmacovigilance activities	The Pharmacovigilance Plan has been updated to include the safety concerns highlighted above. Inclusion of in period scientific and cumulative assessments of all-cause mortality and cardiac and cerebrovascular mortality in future PSURs for the safety concern of Cardio and Cerebrovascular Disorders. Timings for the proposed post authorisation safety observational cohort study have been updated to reflect the inclusion of mortality as a safety endpoint.
Risk minimisation activities	Risk minimisation measures have been updated to include the safety concerns highlighted above.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

Advice regarding Anoro Ellipta was requested from the 20th meeting of ACSOM. The following outstanding issues were raised:

- The ACSOM considered a 'Short Study Summary' (undated) for both the 'Post Authorisation Safety (PAS) Observational Cohort Study' and 'WEUSKOP6679: Drug utilisation study of new users of inhaled UMEC/VI in the primary care setting: UK Clinical Practice Research Datalink (CPRD) study' and stated: "ACSOM considered that it is reasonable not to involve Australian patients in post authorisation safety study, as populations being studied in the UK and Europe would be similar. Members also indicated that the classes of drugs used in this product were well understood and did not require a conservative Australian approach. However, members advised that the drug utilisation study should include Australian patients as it is necessary to obtain local data on off label and paediatric use. The committee advised that use in co-morbidities and accompanying ICS use would be of particular value and noted that data obtained regarding off label use in the UK would not be relevant in an Australian context." Consequently the sponsor should consider amending the draft protocol and synopsis of the drug utilisation study to include Australian patients and an updated version should be provided to the TGA for review once it is available.
- The ACSOM noted that the parents of paediatric patients may be concerned about steroid use in children and that off label use of UMEC/ VI would present an attractive alternative in this situation. Members advised that the TGA may wish to strengthen the paediatric statement in the product information. Consideration could be given to replacing the statement 'The use in children is not relevant in a COPD indication' with a more strongly worded statement text along the lines of 'This product should not be used in children.' This advice is raised with the Delegate for consideration.
- The ACSOM advised that given this is a new fixed dose combination product containing two new chemical entities, and the first LABA/LAMA FDC to be registered in Australia prescribers need to be made aware of what class the individual components are to prevent inadvertent off label prescribing. The committee added that the use of generic names that are long and unfamiliar compounds the risk of accidental off label use. The committee further advised that the product's labelling and associated education materials should ensure that health professionals and patients are aware of the

individual components and their associated risks. This advice is raised with the Delegate for consideration.

Comments on the safety specifications of the RMP

OMA clinical evaluation report

The clinical evaluator made the following comment in regard to safety specifications in the draft RMP;

"The Safety Specification in the draft Risk Management Plan is satisfactory."

OSE non-clinical evaluation report

The non clinical evaluator made the following summary comment in regard to SS in the draft RMP;

"Results and conclusions drawn from the nonclinical program for UMEC/VI detailed in the sponsor's draft Risk Management Plan (Part II, Module SII (version 2.0)) are in general concordance with those of the Nonclinical Evaluator."

Outstanding issues

Issues in relation to the RMP evaluation report

The sponsor was asked to provide a tabular 'Summary of the Risk Management Plan in Australia' in a revised ASA, including reference to specific routine risk minimisation in the Australian PI. The sponsor states that it does not believe it necessary to provide a separate 'Summary of the Risk Management Plan in Australia' in a revised ASA[26]. The sponsor has also provided an assurance that the draft Australian PI and Consumer Medicine Information (CMI) will be revised to reflect the risk minimisation activities described in the updated RMP upon receipt of the Delegate's overview. However, in regard to routine risk minimisation the EU-RMP makes reference to the Summary of Product Characteristics (SmPC), not the wording proposed in the draft Australian PI and CMI. Consequently this request remains outstanding.

Recommendations to the Delegate

The European Risk Management Plan Version 3.0 (dated 14 October 2013), with an Australian Specific Annex (ASA) Version: 2.0 (undated), to be revised as specified in the sponsor's correspondence dated 4 December 2013 and to the satisfaction of the TGA, must be implemented, as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

[26] The sponsor considered that all of the concerns identified in the EU-RMP are relevant for patients in Australia and therefore all of the planned pharmacovigilance actions proposed in the EU-RMP will be implemented in Australia.

Background

The product

Umeclidinium/vilanterol (UMEC/VI) inhalation powder is a fixed dose combination (FDC) product, Anoro Ellipta, administered by oral inhalation. The proposed dose is 62.5/25 µg once daily. (The 125/25µg product was withdrawn during the evaluation, see below). The proposed indication for Anoro Ellipta is:

> *... as a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)*

Umeclidinium, a LAMA (anti-cholinergic), is a new chemical entity. Vilanterol is a selective LABA. Vilanterol has been previously considered by the TGA as part of the Breo Ellipta fixed dose combination product. The mono product, Incruse Ellipta (UMEC), is also being considered by the TGA. Vilanterol is not marketed as a mono product.

UMEC/VI is administered by the same dry powder inhaler device approved for Breo Ellipta. The Ellipta inhaler is a plastic inhaler with dose counter. The device contains two separate, double foil, laminate blister strips that are activated in parallel and provide a total of 30 doses. One strip contains micronised UMEC and lactose. The second strip contains micronised VI, magnesium stearate, and lactose. The device is designed to deliver the contents from a single blister from each of the two blister strips simultaneously.

Safety of LAMAs

Common anticholinergic adverse effects include dry mouth, constipation, worsening of narrow angle glaucoma, and worsening of urinary retention. LAMAs have been associated with safety concerns regarding a possible increased risk of stroke, cardiovascular death, and myocardial infarction. Table 11, summarises some of the evidence, which involves tiotropium (TIO) (registered in Australia in 2002). (The 2008 Singh meta-analysis[27] also included the short acting muscarinc antagonist (SAMA) ipratropium.).

Table 11. Summary of evidence of safety concerns for LAMAs.

	29 pooled trials (2007)[1]	Singh meta-analysis (2008)[2]	UPLIFT (2009)[3]	Singh meta-analysis (2011)[4]
Type of LAMA	tiotropium Handihaler	tiotropium HandiHaler ipratropium	tiotropium HandiHaler	tiotropium Respimat
Relative risk (95% CI)				
Stroke	1.37 (0.73, 15.6)	1.46 (0.81, 2.62)	0.95 (0.70, 1.29)	
Myocardial infarction		1.53 (1.05, 2.23)	0.71 (0.51, 0.99)	

[27] Singh S, et al. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008;300:1439-50. (Erratum, *JAMA* 2009;301:1227-30.)

	29 pooled trials (2007)[1]	Singh meta-analysis (2008)[2]	UPLIFT (2009)[3]	Singh meta-analysis (2011)[4]
CV death	0.97 (0.54, 1.75)	1.80 (1.17, 2.77)	0.73 (0.56, 0.95)	2.05 (1.06, 3.99)
Any death		1.26 (0.99, 1.61)	0.85 (0.74, 0.98)	1.52 (1.06, 2.16)

1. Michele TM, et al. The safety of tiotropium – the FDA's conclusions. *N Engl J Med* 2010;363:1097-9.
2. Singh S, et al. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008;300:1439-50. (Erratum, *JAMA* 2009;301:1227-30.)
3. Tashkin DP, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:543-54.
4. Singh S, et al. Mortality associated with tiotropium mist inhaler in patients with COPD: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2011;342:d3215 doi:10.1136/bmj.d3215.

The UPLIFT trial (a 4 year trial of TIO in COPD) was large (approximately 6000 participants), had adequate follow up (4 years), and was specifically designed as a safety trial. Given the strength of these data over meta-analyses (problems of statistical multiplicity and heterogeneity), the FDA concluded in 2010 that: "current data do not support the conclusion that there is an increased risk of stroke, heart attack, or death associated with TIO HandiHaler". The signal for TIO Respimat remains unresolved (a large post marketing study is about to report)[28]. One hypothesis was that differences between HandiHaler and Respimat in terms of lung deposition and other factors may result in differential risk.

Withdrawal of 125µg strength of UMEC

The Phase III Anoro Ellipta program was designed to investigate two strengths of the combination product: 62.5/25 µg and 125/25 µg. The results for the intent to treat (ITT) population did not suggest a clear efficacy advantage for doses higher than UMEC/VI 62.5/25 µg. It is possible that there is a subgroup of patients who might benefit from the 125/25 µg strength. However, after discussion with the US, EU and Canadian regulatory agencies, the sponsor withdrew the application for registration of the 125/25 µg strength. The reason given by the sponsor was: "additional data are needed to further characterise the subpopulation which could derive most benefit from the higher strength (125/25 µg)".

Quality

Inhaled UMEC and VI have an approximate systemic bioavailability of 13% and 26%, respectively. Given low oral bioavailability, systemic exposure for both components is primarily due to absorption of the inhaled portion. The estimated half-life for both UMEC and VI after oral inhalation administration of UMEC/VI is 11 hours. UMEC C_{max} and $AUC_{0\text{-}24\,h}$ were < 50% lower in COPD patients compared to healthy subjects. No significant effects due to age, renal impairment, hepatic impairment, or ICS on PK parameters were observed.

No clinically meaningful differences were observed in normal and CYP2D6 poor metaboliser subjects following administration of UMEC 500 µg. VI is metabolised

[28] 5. Wise RA, et al. The tiotropium safety and performance in Respimat trial (TIOSPIR), design and rationale. *Resp Res* 2013 14:40.

principally via CYP3A4. Co administration with ketoconazole, a strong CYP3A4 and potent P-gp inhibitor, resulted in 65% and 22% increase in mean $AUC_{0\text{-}24\ h}$ and C_{max}, respectively. No dose adjustment is recommended for UMEC/VI when co-administered with ketoconazole.

A study to assess QTc effects did not indicate any clinically relevant prolongation of the QTc interval.

The pharmaceutical chemistry evaluator concluded that: "the chemistry, manufacturing and quality aspects of the submission are acceptable and approval is recommended."

Nonclinical

The nonclinical evaluator concluded that there are no nonclinical objections to the registration of Anoro Ellipta for the proposed indication.

UMEC and VI were not considered to pose a genotoxic or carcinogenic hazard to patients.

Although no adverse effects on embryofetal development were observed with UMEC alone, previously evaluated studies with VI showed fetal damage (including malformations). The sponsor therefore proposed "Pregnancy Category B3", which was supported by the nonclinical evaluator.

Clinical

Dose finding and frequency

The dose finding studies for vilanterol were previously considered by TGA, as part of the submission for Breo Ellipta (fluticasone furoate/vilanterol) in which the dose of 25 µg once daily was established. The data supporting the 25 µg dose of VI will not be re considered in this report.

For LAMAs, dose selection can be problematic, given relatively flat dose response curves and the relative lack of effect in asthmatic patients. However, the totality of data, from four Phase II studies (which assessed doses from 15.6 to 1000 µg), suggested that UMEC 62.5 µg and 125 µg once daily were doses on the steeper part of the dose response curve. Efficacy of once daily versus twice daily dosing regimens for UMEC was similar. Therefore, 62.5 µg and 125 µg once daily were carried forward into the Phase III trials.

Efficacy

Overview

One aim of the Phase III program was to show that use of two bronchodilators in combination provided added benefit over each alone. That is, one aim was to demonstrate the efficacy contribution of VI to UMEC/VI and of UMEC to UMEC/VI.

The Phase III program included two placebo controlled trials (3361, 3373) and two active controlled trials (3360, 3374). The placebo controlled trials were replicate in design and each compared UMEC/VI (either 62.5/25 µg or 125/25 µg) to placebo and to the mono products. The active controlled trials were also replicate in design and each compared UMEC/VI (62.5/25 µg and 125/25 µg) to TIO, and to the mono products. These four trials included patients with moderate to very severe COPD (Global Initiative for Chronic

Obstructive Lung Disease (GOLD) stages II to IV[29]), and the duration of the double blind treatment period was 24 weeks. They were multi-centre trials, conducted during 2011 and 2012, in more than 150 centres in USA, Western Europe, Eastern Europe, Asia, and Central and South America.

The two exercise endurance trials were replicate in design and each evaluated both doses of UMEC/VI, both doses of UMEC, VI, and placebo. In contrast to the parallel design of the primary efficacy trials, these trials were cross over in design and the duration of double blind treatment period was 12 weeks.

The primary efficacy endpoint was trough FEV1 on treatment Day 169 (Week 24) for the four primary efficacy trials; trough FEV1 on treatment Day 85 (Week 12) was pre-specified as a co-primary endpoint in the exercise endurance trials.

Phase III trial design

The trial design of the placebo controlled trials 3361 and 3373 is shown in Table 12.

Table 12. Trial design of placebo controlled trials (3361, 3373)

Category	Description
Participants	40+ years (mean = 63 years), approximately70% men, post bronchodilator FEV1/FVC[30] < 0.7, post-bronchodilator FEV1 < 0.7 predicted, 2+ on modified Medical Research Council Dyspnoea Scale, GOLD stage 2 (46%), GOLD stage 3 (43%), GOLD stage 4 (11%)[31]
Intervention	3361: UMEC/VI 125/25 3373: UMEC/VI 62.5/25
Comparator	placebo mono products (UMEC, VI)
Background therapy	Allowed: ICS (mono product), O_2 therapy < 12 hours/day, mucolytics, rescue SABA Prohibited: systemic CS, LABAs, ICS/LABA, SAMA, SAMA/SABA, TIO Phosphodiesterase type 4 inhibitors, leukotriene inhibitors, theophylline
Endpoints	Primary: trough FEV1 on day 169 (mean FEV1 23 and 24 hours after dosing on the previous day) "Key" secondary: weighted mean FEV1 (0 to 6 hours), Transitional Dyspnoea Index (this was at request of EMA) Other secondary: exacerbations, St Georges Respiratory Questionnaire, etcetera.
Duration	24 weeks

[29] GOLD classifies COPD into 4 grades of severity: Grade I (mild; FEV1 ≥ 80% predicted), Grade II (moderate; FEV1 ≥ 50% and < 80% predicted), Grade III (severe; FEV1 ≥ 30% and < 50% predicted), and Grade IV (very severe; FEV1 < 30% predicted). FEV1 is based on post bronchodilator FEV1.
[30] Forced Vital Capacity (FVC) is the maximum amount of air a person can forcibly expel from the lungs after a maximum inhalation.
[31] modified Medical Research Council Dyspnoea Scale: Grade 0 - I get breathless only with strenuous exercise; Grade 1 – I get short of breath if hurrying on level ground or walking up a slight hill; Grade 2 – On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath if walking at my own pace; Grade 3 – I stop for breath after walking about 100 yards or after a few minutes on level ground; Grade 4 – I am too breathless to leave the house or I am breathless when dressing.

Active-controlled trials (3360, 3374)

Design of these trials was similar to the placebo controlled trials, except that these trials allowed direct comparison of UMEC/VI 62.5/25 µg versus UMEC/VI 125/25 µg. The active comparator was TIO 18 µg.

Exercise trials (4417 and 4418)

The sponsor also submitted two, incomplete block, crossover (12 week treatment periods) exercise trials in support of UMEC/VI. The co primary efficacy endpoints were the EET (measured by the endurance shuttle walk test) and the trough FEV1 at Day 85 (pre bronchodilator and pre dose FEV1 obtained 24 hours after dosing on Treatment Day 84). The sponsor is not making an exercise claim; and the results are not reproduced in this overview. In short, these trials provide support for the bronchodilation claim.

Phase III trial results

Table 13. Results of placebo controlled trials (3361, 3373), trough FEV1, Day 169, ITT population.

Treatment	n	LS mean (L)	LS mean change (L)	Difference from UMEC (95% CI)	p	Difference from VI (95% CI)	p
Study 3361							
UMEC/VI 125 µg /25 µg	403	1.484	0.207	0.079 (0.046, 0.112)	<0.001	0.114 (0.081, 0.148)	<0.001
UMEC 125 µg	407	1.405	0.129				
VI 25 µg	404	1.379	0.093				
Placebo	275	1.245	-0.031	0.160 (0.122, 0.198)	<0.001	0.124 (0.086, 0.162)	<0.001
Study 3373							
UMEC/VI 62.5 µg /25 µg	413	1.406	0.171	0.052 (0.017, 0.087)	0.002	0.095 (0.060, 0.130)	<0.001
UMEC 62.5 µg	418	1.354	0.119				
VI 25 µg	421	1.311	0.076				
Placebo	280	1.239	0.004	0.115 (0.076, 0.155)	<0.001	0.072 (0.032, 0.112)	<0.001

Table 14. Active controlled trials (3360, 3374), trough FEV_1, Day 169, ITT population.

Treatment	n	LS mean (L)	LS mean change (L)	Difference from UMEC (95% CI)	p	Difference from VI (95% CI)	p
Study 3361							
UMEC/VI 125 µg /25 µg	207	1.521	0.211			0.088 (0.037, 0.139)	<0.001
UMEC/VI 62.5 µg /25 µg	208	1.519	0.209			0.093 (0.041, 0.144)	<0.001
VI 25 µg	205	1.431	0.121				
Tiotropium 18µg	203	1.431	0.121				
Study 3374							
UMEC/VI 125 µg /25 µg	217	1.355	0.208	0.022 (-0.027, 0.072)	0.377		
UMEC/VI 62.5 µg /25 µg	215	1.369	0.223	0.037 (-0.012, 0.087)	0.142		
UMEC 125 µg	222	1.332	0.186				
Tiotropium 18µg	215	1.295	0.149				

The active controlled trials allowed a direct comparison between UMEC/VI 125/25 µg and 62.5/25 µg. As shown in Table 14, there was no clear dose response.

Among these four trials, study completion rates ranged from 70 to 83%. Lack of efficacy was cited as a reason for discontinuation; most frequently in patients randomised to placebo. To assess the potential impact of missing data, the sponsor submitted several sensitivity analyses using different imputation strategies, including a more conservative approach requested by FDA. The results were statistically robust according to these various analyses.

Among the four trials, the results were robust to analyses conducted for various subgroups based on demographic factors (age, gender, race, geography) and on disease and other characteristics (COPD severity, concomitant ICS use, bronchodilator reversibility, and smoking status).

Results for secondary and other endpoints, including weighted mean FEV1 over 0 to 6 hours post dose at Week 24, transitional dyspnoea index, and reduction in exacerbations were supportive of the primary analysis. However, the sponsor is not seeking a claim in the indication for reduction of rescue medication use, reduction of exacerbations, or improvement in health related quality of life.

Safety

Overview

The sponsor submitted a 52 week safety study, comparing UMEC/VI 125/25 µg (n = 226) to placebo (n = 107) and UMEC 125 µg (n = 227). Endpoints included AEs, COPD exacerbations, ECG assessments, and Holter monitoring.

Exposure to UMEC/VI for patients in the safety database, who had COPD, is shown in Table 15 below.

Table 15. Exposure for the "All COPD clinical studies".

	Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	Tiotropium N=423
Exposure, days							
Median	110	166	167	165	166	168	167
min, max	1,372	1,177	1,371	1,179	1,375	1,384	1,176
Range n(%)							
>4 weeks	1366 (83)	1066 (95)	1262 (95)	548 (95)	954 (88)	2296 (92)	395 (93)
>8 weeks	1251 (76)	1034 (92)	1212 (91)	522 (91)	900 (83)	2153 (86)	382 (90)
>12 weeks	1103 (67)	932 (83)	1129 (85)	450 (78)	827 (76)	2045 (82)	374 (88)
>24 weeks	394 (24)	326 (29)	462 (35)	154 (27)	370 (34)	1147 (46)	116 (27)
>36 weeks	73 (4)	0	160 (12)	0	154 (14)	622 (25)	0
>48 weeks	66 (4)	0	146 (11)	0	133 (12)	590 (24)	0
>52 weeks	19 (1)	0	37 (3)	0	35 (3)	209 (8)	0

Evaluation for safety was unremarkable; the data were consistent with what is known about LAMAs and LABAs. An assessment of AE terms related to anticholinergic effects (for example, urinary retention, blurred vision, dry mouth, bowel obstruction, etcetera) and adrenergic effects (for example, electrolyte shifts, tachycardia, tremor, etcetera) did not indicate any specific safety signals. Also, the data do not suggest an increased risk of LTRI or pneumonia as has been observed with ICS/LABA combination products in COPD.

Most interest centred on cardiovascular safety; a summary of these results is given below.

Assessment of cardiovascular adverse events

Two analyses were conducted: major adverse cardiac events (MACE) and (cardiovascular) AESI. An imbalance was reported for cardiac ischaemia in the four pooled Phase III efficacy trials, but not from the 52 week safety trial (Tables 16 and 17).

Table 16. Cardiovascular AESI, Phase III efficacy trials.

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	Tiotro-pium
Numbers							
Acquired long QT	0	0	2	1	0	0	0
Arrhythmias	18	24	19	20	20	46	9
Cardiac failure	6	11	11	7	7	12	5
Cardiac ischaemia	5	11	12	7	5	12	4
Hypertension	11	25	17	12	21	29	11
Sudden death	0	0	0	0	0	1	0
Stroke	2	1	1	1	1	3	1
Incidence (per 1000 person-years)							
Acquired long QT	0	0	6	6	0	0	0
Arrhythmias	87	69	57	119	80	112	52
Cardiac failure	29	32	33	42	28	29	29
Cardiac ischaemia	24	32	36	42	20	29	23
Hypertension	53	72	51	72	84	71	64
Sudden death	0	0	0	0	0	2	0
Stroke	10	3	3	6	4	7	6

Table 17. Cardiovascular AESI, Safety trial.

	Placebo	UMEC/VI 125/25	UMEC 125
Numbers			
Acquired long QT	0	0	0
Arrhythmias	17	26	39
Cardiac failure	1	2	4
Cardiac ischaemia	4	4	4
Hypertension	7	8	6
Sudden death	0	0	0
Stroke	0	0	1
Incidence (per 1000 person-years)			
Acquired long QT	0	0	0
Arrhythmias	212	147	233
Cardiac failure	12	11	24
Cardiac ischaemia	50	23	24
Hypertension	87	45	36
Sudden death	0	0	0
Stroke	0	0	6

The lack of an imbalance in the long term safety trial is somewhat reassuring however, interpretation is complicated by the withdrawal of patients with ECG or Holter abnormalities.

Table 18. Subject disposition, long term safety trial.

	Placebo N=109	UMEC/VI 125/25 n=226	UMEC 125 N=227
Completion status n (%)			
Completed	66 (61)	143 (63)	133 (59)
Withdrew	43 (39)	83 (37)	94 (41)
Selected reasons for withdrawal n (%)			
Adverse event	13 (12)	17 (8)	21 (9)
Lack of efficacy	9 (8)	1 (<1)	3 (1)
Protocol defined stopping criteria n (%)			
ECG abnormality	0	13 (6)	12 (5)
Holter abnormality	8 (7)	26 (12)	26 (11)

In summary, cardiovascular safety analyses based on the integrated COPD study database and the long term safety trial were unremarkable. An imbalance for cardiac ischaemia was seen in the Phase III efficacy trials (24 weeks), but not in the 12 month safety trial or in the larger integrated, COPD safety database. However, differential withdrawal for protocol-specified ECG and Holter abnormalities in the long term safety trial, complicates the interpretation of these data.

Clinical evaluator's recommendation

The clinical evaluator recommended that the application for the registration of UMEC/VI 62.5/25 µg and 125/25 µg[32] as a long term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD be approved.

Risk management plan

The on-going safety concerns include the following:

Potential risks:

- Cardio and Cerebrovascular disorders
- Asthma related intubations, hospitalisation and death
- Paradoxical bronchospasm
- Narrow angle glaucoma
- Bladder outflow obstruction and urinary retention

Missing information:

- Safety in pregnancy and lactation
- Off label use in Asthma (including paediatric use)
- Safety in long term use
- Safety in subjects with severe hepatic impairment.

A post authorisation safety study for UMEC/VI is planned Europe (Poland, France, Germany, Spain, the Netherlands, Belgium and non-EU countries). The planned sample size is 4000 patients.

ACSOM advice

Members were concerned about the use of UMEC/VI in COPD patients with comorbid asthma. The use of a LAMA/LABA combination poses the risk of such patients receiving a LABA without an ICS which could increase the risk of asthma exacerbations, hospitalisations and intubations. The committee advised that such off label use would have to be managed by the prescribing doctor.

Members advised that the use of a LABA without an ICS carries significant increased risks when used in a paediatric population, including an increased mortality rate.

Members were also concerned that some parents or prescribers might view Anoro as an attractive product to use off-label in children with asthma (to avoid the adverse effects of ICS).

Risk-benefit analysis

Delegate's considerations

UMEC/VI 62.5/25 µg showed a placebo subtracted improvement in trough FEV1, at the end of 6 months, of about 170 mL; this is likely to translate into benefit for COPD patients. Also, the Phase III trials show that each of the components of the FDC product makes a

[32] Note: the sponsor subsequently withdrew the part of the application to register the UMEC/VI 125/25 µg strength.

contribution to the treatment effect of the combination. Secondary endpoints were supportive.

Therefore, at this point in time and pending ACPM advice, the Delegate's view is that the efficacy of Anoro Ellipta has been satisfactorily established.

Patients with COPD often have co existing cardiovascular problems. The Delegate's view, at this point in time and pending ACPM advice, is that the imbalance for cardiac ischaemic from the four Phase III efficacy trials (but not seen in the 52 week safety trial, with the caveat that patients with ECG or Holter abnormalities were discontinued), does not warrant rejection of registration. However, it does warrant further follow up via post marketing studies, as planned by the sponsor.

Proposed action

The Delegate had no reason to say, (at this time) that the application for Anoro Ellipta should not be approved for registration.

Proposed conditions of registration

- The European Risk Management Plan Version 3.0 (dated 14 October 2013), with an Australian Specific Annex (ASA) Version: 2.0 (undated), to be revised as specified in the sponsor's correspondence dated 4 December 2013 and to the satisfaction of the TGA, must be implemented.
- Any post marketing studies must be submitted to the TGA for evaluation as soon as results are available.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee provide advice on the following specific issues:

1. Is the ACPM satisfied that efficacy has been satisfactorily established?
2. Does the ACPM have any safety concerns about Anoro that would preclude registration?

Response from sponsor

Executive summary

The company welcomes the Delegate's recommendation to approve the registration of Anoro Ellipta for the following indication:

> *"Anoro Ellipta is indicated as a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)."*

This recommendation is supported by the clinical evaluator who has concluded that "the benefit-risk balance of UMEC/VI, given the proposed usage, is favourable" and recommended that the registration of Anoro Ellipta be approved.

The efficacy of Anoro Ellipta (also referred to as UMEC/VI 62.5/25 µg) was demonstrated across four Phase III clinical studies, two placebo controlled studies and two active controlled studies where Anoro Ellipta demonstrated clinically meaningful improvements in lung function (trough FEV1) compared to placebo, the individual monotherapies and the active comparator TIO. Anoro Ellipta has also demonstrated improved symptoms of dyspnoea (measured by TDI scores) and improved health outcomes (measured by SGRQ) compared to placebo providing additional evidence of beneficial effect.

The safety profile for Anoro Ellipta is based on 2,454 patients with COPD who received doses of UMEC/VI 62.5/25 µg or greater for up to one year during clinical studies. Anoro Ellipta was well tolerated with a similar incidence of AE across all treatment groups including placebo and there were no significant safety concerns. Overall, the Anoro Ellipta safety profile is unremarkable and as expected for a LAMA/LABA combination.

In totality, the data from the Anoro Ellipta development program supports a favourable benefit risk assessment for the registration of Anoro Ellipta for treatment of patients with COPD.

Anoro Ellipta received European Marketing Authorisation on 8 May 2014, and was approved by the USA FDA on 18 December 2013, by Health Canada on 23 December 2013 and by New Zealand Medsafe on 20 March 2014 for indications similar to the one proposed for Australia.

Background

Anoro Ellipta is a once daily fixed dose LAMA/LABA combination for oral inhalation. The rationale for development of a LAMA/LABA combination was based on the distinct and complementary mechanisms of action through which LAMA and LABA bronchodilators act to relax airway smooth muscle and improve airflow obstruction, thereby providing improved lung function with the combination over long acting bronchodilator monotherapy. Additional benefits of a once daily fixed dose LAMA/LABA combination are increased convenience and ease of use for patients, which will favour better adherence with treatments. Currently, there is only one other once daily LAMA/LABA combination registered in Australia for the treatment of COPD, glycopyrronium/indacaterol.

Anoro Ellipta complies with the European Guideline on Clinical Development of Fixed Combination Medicinal Products adopted by the TGA (CPMP/EWP/240/95 Rev1) and GSK's fixed combination product justification was accepted by the TGA prior to the submission for registration.

The registration application for Anoro Ellipta submitted to the TGA in April 2013 contained two strengths, UMEC/VI 62.5/25 µg and UMEC/VI 125/25 µg. Both strengths of Anoro Ellipta studied in Phase III were similar with regard to efficacy and safety, therefore after discussion with the USA, EU and Canadian regulatory agencies, GSK decided to pursue registration of UMEC/VI 62.5/25 µg only. GSK's aim throughout the development program has been to identify the lowest effective dose that produces a meaningful and important clinical benefit whilst minimising adverse effects and UMEC/VI 62.5/25 µg meets these requirements for the general population of COPD patients.

Specific questions raised by the Delegate for ACPM's advice

1. Is the ACPM satisfied that efficacy has been satisfactorily established?

Company response: The efficacy of Anoro Ellipta was demonstrated across four Phase III clinical studies, two placebo controlled studies (DB2113361, DB2113373) and two active controlled studies (DB2113374, DB2113360). It should be noted that one of the placebo controlled studies examined the efficacy of UMEC/VI 125/25 µg and therefore the efficacy findings for this study are not discussed in this response (DB2113361).

Overall, the UMEC/VI development program has demonstrated that Anoro Ellipta provides clinically relevant efficacy, as defined by measures of lung function over 24 weeks of treatment when compared with placebo, the individual monotherapies, and the active comparator TIO in a broad range of patients with COPD. In addition to lung function, Anoro Ellipta has demonstrated improved symptoms of dyspnoea as measured by TDI scores and health outcomes as measured by SGRQ scores compared with placebo, thereby providing additional evidence of beneficial effect.

Anoro Ellipta met the primary endpoint in the 24 week placebo controlled study (DB2113373) and the first 24 week active controlled (TIO 18 µg administered once daily) study (DB2113360) demonstrating a statistically significant improvement in lung function (defined by change from baseline trough FEV1 at Week 24) compared with placebo (improvement over placebo by 167 mL ($p < 0.001$)) and TIO (improvement over TIO by 90 mL ($p < 0.001$)). Whilst Anoro Ellipta did not demonstrate a statistically significant improvement in lung function in the second 24 week active controlled study (DB2113374) due to the pre-defined order of the testing hierarchy, the numerically greater improvement compared with TIO (improvement over TIO by 60 mL (95% CI=10 mL to 109 mL)) is supportive of clinically relevant efficacy. The increased benefit of Anoro Ellipta over the individual components was demonstrated in Study DB2113373 with statistically significant improvements in lung function compared with the monotherapies (UMEC 62.5 µg (52 mL, $p = 0.004$) and VI 25 µg (95 mL, $p < 0.001$)).

The Anoro Ellipta primary efficacy results are supported by the secondary endpoints of weighted mean FEV1 (over 0 to 6 hours post dose at Week 24) and TDI score. Anoro Ellipta demonstrated greater improvements from baseline in weighted mean FEV1 compared with placebo in Study DB2113373 (242 mL (95% CI = 202 mL to 282 mL)) and compared with TIO in Study DB2113360 (74 mL (95% CI = 22 mL to 125 mL; $p = 0.005$)) and Study DB2113374 (96 mL (95% CI = 50 mL to 142 mL)). Anoro Ellipta also demonstrated clinically meaningful improvements compared with placebo in dyspnoea (evaluated by TDI score), health outcomes (assessed by SGRQ total score) and rescue use throughout the study period providing further evidence of clinical benefit.

Overall, the data from the four Phase III clinical studies demonstrate that Anoro Ellipta provides clinically relevant efficacy in patients with COPD and supports the proposed indication. This is supported by the Delegate who has stated that *"at this point in time and pending ACPM advice, (the Delegate's) view is that the eff*icacy *of Anoro Ellipta has been satisfactory established"* and by the clinical evaluator who has concluded that "*efficacy results were supportive of the efficacy claim of both doses of UMEC/VI (125/25 µg and 62.5/25 µg) over placebo in terms of lung function as well as symptom relief*".

2. Does the ACPM have any safety concerns about Anoro that would preclude registration?

Company response: The safety profile for Anoro Ellipta is based on 2,454 patients with COPD who received doses of UMEC/VI 62.5/25 µg or greater for up to one year during clinical studies. Overall, the safety profile of Anoro Ellipta was similar to placebo, the individual components and TIO. Anoro Ellipta was well tolerated with a similar incidence of AEs across all treatment groups including placebo and no significant safety concerns were noted. This was acknowledged by the clinical evaluator who has stated that the Anoro Ellipta *"safety results did not raise any major safety concerns"* and supported by the Delegate who has stated that the *"evaluation for safety was unremarkable"*.

The clinical evaluator highlighted LAMA and LABA pharmacological class effects as potential risks of UMEC/VI for the proposed indication, in particular, cardiovascular effects. However, on review of the data concluded that *"analyses of cardiovascular safety and the adverse effects related to muscarinic antagonist and beta$_2$-agonist pharmacological class effects did not raise major safety concerns".* GSK agrees with this assessment.

The Delegate identified cardiovascular safety as the finding of most interest, specifically noting that in the Anoro Ellipta program there was an imbalance observed for cardiac ischemia in the 24 week Phase III efficacy trials that was not observed in the 52 week long term safety study (DB2113359) or the larger integrated COPD safety database. GSK acknowledges that there are concerns surrounding cardiovascular safety with LAMAs and for this reason the clinical program was designed to closely monitor cardiovascular safety in the Anoro Ellipta clinical development program through assessment of MACE, cardiovascular AESI groupings, extensive ECG and Holter monitoring and vital signs.

GSK's analyses of the Anoro Ellipta safety results have not identified any significant safety concern related to cardiovascular effects or class effects in general. Of note, the AE and SAE event rate with Anoro Ellipta and the individual components, specifically the absolute number of cardiovascular events, was very low. Additionally, the MACE score for UMEC/VI and the individual components, assessed through an integrated analysis of 8 studies, was similar to or lower than placebo and the percentage of patients with a myocardial infarction was < 1% across all treatment groups with 1 in the placebo group, 3 in each of the UMEC/VI groups, 1 in UMEC 62.5 µg group, 4 in the UMEC 125 µg group and 2 in the VI group. There was a small imbalance observed in the exposure adjusted events with 2.7 events per 1000 patient years of exposure in the placebo group, compared to 7.4 events in the UMEC/VI 62.5/25 µg group, 5.2 events in the UMEC/VI 125/25 µg group, 4.9 events in the UMEC 62.5 µg group, 8.9 events in the UMEC 125 µg group and 4.5 events in the VI 25 µg group (Table 19), however the data do not demonstrate a dose relationship between the doses of UMEC/VI or additive effect from the combination and are lower than reported in the general COPD population (Table 22), therefore these data are unlikely to represent a treatment related effect.

Table 19: Major adverse cardiac events: broad and narrow analyses. Integrated Studies (ITT population).

	PLA N=1053 [369SY]	UMEC/VI 62.5/25 N=1124 [408SY]	UMEC/VI 125/25 N=1330 [573SY]	UMEC 62.5 N=576 [202SY]	UMEC 125 N=1016 [449SY]	VI 25 N=1174 [441SY]	TIO N=423 [173SY]
Incidence	**Number (%) of Subjects**						
MACE composite (broad)	20 (2)	15 (1)	22 (2)	9 (2)	14 (1)	17 (1)	6 (1)
MACE composite (narrow)	7 (<1)	5 (<1)	6 (<1)	2 (<1)	7 (<1)	8 (<1)	1 (<1)
Cardiovascular death [a] (broad and narrow)	2 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)	0
Nonfatal stroke AESI [b] (broad and narrow)	4 (<1)	0	3 (<1)	1 (<1)	2 (<1)	4 (<1)	1 (<1)
Nonfatal cardiac ischaemia AESI [c] (broad)	14 (1)	13 (1)	19 (1)	8 (1)	11 (1)	12 (1)	5 (1)
Nonfatal myocardial infarction [d] (narrow)	1 (<1)	3 (<1)	3 (<1)	1 (<1)	4 (<1)	2 (<1)	0
Exposure-adjusted frequencies	**Number of Subjects with Events per 1000 Subject-Years**						
MACE composite (broad)	54.3	36.8	38.4	44.5	31.2	38.5	34.7
MACE composite (narrow)	19.0	12.3	10.5	9.9	15.6	18.1	5.8
Cardiovascular death [a] (broad and narrow)	5.4	4.9	0	0	2.2	4.5	0
Nonfatal stroke AESI [b] (broad and narrow)	10.9	0	5.2	4.9	4.5	9.1	5.8
Nonfatal cardiac ischaemia AESI [c] (broad)	38.0	31.9	33.2	39.5	24.5	27.2	28.9
Nonfatal myocardial infarction [d] (narrow)	2.7	7.4	5.2	4.9	8.9	4.5	0
Total MACE	**Total Number of Events**						
Total MACE, n (broad)	22	16	22	11	15	18	6
Total MACE, n (narrow)	8	5	6	2	7	8	1

Data Source: DB2_ISS Table 2.142

Abbreviations: AESI=adverse event of special interest; ECG=electrocardiogram; MACE=major adverse cardiac event; MedDRA= Medical Dictionary for Regulatory Activities; SMQ=standard MedDRA query; SY=subject-years; PLA=placebo; PT=preferred term; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Integrated studies: DB2113611, DB2113373, DB2113360, DB2113374, DB2114417, DB2114418, DB2113359 and AC4115408

Note: The broad analysis was *a priori* and the narrow analysis was post-hoc.

a. Cardiovascular deaths were independently adjudicated.

b. The following MedDRA SMQs contributed to the nonfatal stroke AESI category: Central nervous system haemorrhages and cerebrovascular conditions SMQ.

c. The following MedDRA SMQs contributed to the cardiac ischaemia AESI category: Myocardial Infarction SMQ; Other Ischaemic Heart Disease SMQ.

d. The following MedDRA PTs contributed to myocardial infarction: myocardial infarction and acute myocardial infarction.

Table 20. ECG Abnormality Findings Meeting the Withdrawal Criteria for Subjects with an ECG Protocol-Defined Stopping Criteria as the Primary Reason for Withdrawal (DB2113359, ITT Population).

	Number (%) of Subjects		
Abnormality Finding	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 mcg N=227
n	0	13 (6)	12 (5)
Any Finding	0	7 (54)	9 (75)
Multifocal premature ventricular complexes	0	3 (23)	1 (8)
Sinus tachycardia ≥110 bpm	0	2 (15)	2 (17)
Bigeminy	0	1 (8)	2 (17)
Left bundle branch block	0	0	2 (17)
Atrial fibrillation with rapid ventricular response (rate >100 bpm)	0	0	1 (8)
Bifascicular block	0	0	1 (8)
Increase in heart rate ≥40 bpm relative to baseline	0	0	1 (8)
Increase in QTcF >60 msec relative to baseline	0	0	1 (8)
Junctional tachycardia (heart rate >100 bpm)	0	1 (8)	0
Trigeminy	0	0	1 (8)

Data Source: Table 130.9
Abbreviations: bpm=beats per minute; ECG=electrocardiogram; ITT=intent-to-treat; QTcF=QT interval corrected for heart rate with Fridericia's formula; UMEC=umeclidinium bromide; VI=vilanterol
Note: Abnormalities are only displayed if they were experienced by at least one subject.
Note: Subjects may have had more than one abnormality.
Note: Denominators for abnormalities are the number of subjects with ECG protocol-defined stopping criteria as the primary reason for withdrawal.

Cardiac ischemia was further examined in the AESI analysis. There was a small numerical imbalance in the cardiac ischemia AESI grouping across some of the active treatment groups compared to placebo in the primary efficacy studies, which differed from the MACE analysis and the 52 week long term safety study (DB2113359). There was also an imbalance observed in the long term safety study where events in the cardiac ischemic AESI grouping were lower with UMEC 125 µg and UMEC/VI 125/25 µg than placebo. There was no evidence of a dose response for either UMEC/VI or UMEC nor an additive effect for the combination over components for cardiac ischemia. As imbalances were inconsistent across studies and the overall number of cardiac ischemia events and the incidence were low, cardiac ischaemia was not identified as a major safety concern.

Further to the initial MACE assessment, GSK has performed an analysis of its global safety database to identify any unexpected, serious adverse reactions not currently captured in the data provided to TGA. This analysis has only identified one case of acute myocardial infarction in the period between 23 August 2012 and 30 April 2014, providing reassurance that the incidence of cardiovascular events associated with UMEC/VI is low.

Overall, there were no dose or treatment related patterns identified in the incidence of AEs in the cardiovascular AESI categories acquired long QT, cardiac arrhythmias, cardiac failure, cardiac ischaemia, hypertension, sudden death, and stroke. The most commonly reported cardiovascular AESI category was cardiac arrhythmias followed by hypertension, with a low incidence of AEs in the cardiac arrhythmia AESI category. A higher number of subjects reported supraventricular tachyarrhythmias (for example, atrial fibrillation, atrial flutter, sinus tachycardia, and supraventricular extrasystoles) in the UMEC/VI and UMEC treatment groups compared with placebo, which is consistent with the ECG monitoring observations. These findings are consistent with evidence that suggests that atrial arrhythmias may be a class effect of anticholinergics[33].

The Delegate noted that differential withdrawal for protocol specified ECG and Holter abnormalities in the 52 week long term safety study (DB2113359) complicates the interpretation of the cardiovascular safety data. GSK recognises that although a higher number of patient withdrawals were observed in the long-term safety study due to Holter/ECG abnormalities in the active treatment groups compared with placebo, the majority of the ECG abnormalities leading to withdrawal were unlikely to have lead to

[33] Anthonisen NR et al. Lung Health Study Research Group (2002) Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med*. 2002:166; 333–339.

more severe cardiovascular events (Tables 20 and 21). None of these ECG or Holter withdrawals were associated with any concurrent clinically relevant symptoms. Overall, withdrawal rates were similar between the placebo group and active treatments.

Table 21. Holter Abnormality Findings Meeting the Withdrawal Criteria for Subjects with a Holter Protocol-Defined Stopping Criteria as the Primary Reason for Withdrawal (DB2113359, ITT Population).

	Number (%) of Subjects		
Abnormality Finding	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 mcg N=227
n	8 (7)	26 (12)	26 (11)
Any Finding	8 (100)	25 (96)	25 (96)
Non-sustained ventricular tachycardia (>100 bpm, 3-30 beats)	6 (75)	16 (62)	9 (35)
Sustained supraventricular tachycardia (>100 bpm, >30 beats)	0	4 (15)	6 (23)
Premature ventriculation complex >4000 in 24-hour period	0	5 (19)	4 (15)
Idioventricular rhythm (≤100 beats/min, defined by wide QRS complex)	1 (13)	2 (8)	5 (19)
Atrial fibrillation with rapid ventricular response (rate >100 bpm)	0	1 (4)	2 (8)
Second degree AV block (Mobitz type 2)	1 (13)	0	0
Sinus tachycardia >120 bpm/hour for 4 consecutive hours	0	0	1 (4)

Data Source: Table 130.11
Abbreviations: AV=atrioventricular; bpm=beats per minute; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol
Note: Abnormalities are only displayed if they were experienced by at least one subject.
Note: Subjects may have had more than one abnormality.
Note: Denominators for abnormalities are the number of subjects with Holter protocol-defined stopping criteria as the primary reason for withdrawal.

The exposure adjusted incidence of cardiovascular AEs, including serious cardiovascular AEs (that is, myocardial infarction) reported in UMEC/VI studies were similar to those reported in the general COPD population, including observational studies with LABAs and TIO, as well as a pooled analysis of TIO trials including UPLIFT[34] (Table 22). A similar pattern was also noted in the 52 week long term safety study (DB2113359). This suggests that any small imbalances noted in individual events in these categories are likely due to chance and are not a treatment related effect.

Table 22: Exposure adjusted incidence of CV adverse events in the COPD Population compared with UMEC/VI. Phase IIIa studies.

	Primary Efficacy Studies						Literature			
Preferred Term	PLA SY=208	UMEC/VI 62.5/25 SY=346	UMEC/VI 125/25 SY=336	UMEC 62.5 SY=168	UMEC 125 SY=249	VI 25 SY=411	Mapel 2005[1]	Jara 2007[4] LABA	Jara 2007[4] TIO	Celli 2005[5] TIO RCTs
SVT	4.8	0	3.0	6.0	0	2.4	1.8/2.0			2.6
Ventricular tachycardia	19.3	2.9	0	11.9	8.0	12.2	1.5/4.8[1]	0.4[3]	0.7[3]	1.6*
Tachycardia	9.6	5.8	11.9	29.8	8.0	12.2	20.5/22.9[1]	4.8-24.1	5.4-19.1	4.7
Atrial fibrillation	0	8.7	5.9	11.9	8.0	17.0	4.3 /7.4[1]	24.1-33.4	17.0-31.9	11.5
Atrial flutter	0	2.9	0	0	0	0	5.4/7.4[1]			
M.I.	0	8.7	3.0	0	4.0	0	10.2/14.3[1]	10-12.1	12.7-14.9	7.2
Angina pectoris	14.5	5.8	8.9	11.9	0	4.9	64.7/39.7[1]			11.9[6]
CAD	0	0	8.9	11.9	0	2.4	4.3[2]			
Stroke+	9.6	2.9	3.0	6.0	4.0	7.3	46.1/37.0[1]			8.6
Hypertension	48.2	37.6	44.6	59.6	72.3	58.4	20.5/22.9[1]			32.7

Data Source: DB_ISS 2.116
Abbreviations: UMEC – umeclidinium, VI – vilanterol, TIO – tiotropium, PLA – placebo; RCT – randomised controlled trial; SVT – supraventricular tachycardia, M.I. – myocardial infarction, CAD – coronary artery disease, VA – veterans association
*Includes ventricular fibrillation
+ Stroke AESI category
1. Mapel et al. COPD 2005;2:35-41; 2. Schneider et al. Eur J Epi 2010; 25(4):253-60; 3. Jara *et al.*, BMJ Open. 2012 May 22;2(3); 4. Jara *et al.*, Drug Saf. 2007;30(12):1151-60; 5. Celli et al. Chest 2010; 137: 20-30; 6. Kesten et al. Chest 2006; 130: 1695-1703

Whilst the Anoro Ellipta safety data are reassuring, cardio and cerebrovascular disorders have been included as an important potential risk in the Anoro Ellipta EU RMP and a comprehensive pharmacovigilance plan is proposed to further evaluate and characterise

[34] Kesten S et al. Pooled clinical trial analysis of tiotropium safety. *Chest* 2006: 130; 1695-703.

cardio and cerebrovascular disorders. As part of the EU RMP, GSK plans to undertake two PASS to collect data from a larger 'real world' dataset to determine the overall absolute and relative risks (Study 201038 and WWE117397). In addition, GSK has included text in the *Precautions* section of the PI advising of potential cardiovascular effects and that caution should therefore be used in treating patients with severe cardiovascular disease. Furthermore, GSK has included the adverse drug reactions (ADRs) tachycardia, supraventricular tachycardia and atrial fibrillation in the *Adverse Effects* section of the PI, as these events had an incidence of 1% for either UMEC/VI dose and greater than placebo, and were considered to be potentially related to UMEC/VI. Any further characterisation of the incidence, nature and outcome of the cardiovascular risk will be managed with updates to the PI as required.

Other issues raised by the delegate

Issues raised by the Advisory Committee on the Safety of Medicines

The Delegate noted that the ACSOM were concerned about the use of Anoro Ellipta in COPD patients with co morbid asthma and that a LAMA/LABA combination poses the risk of patients receiving a LABA without an ICS. GSK acknowledges this risk and agrees with ACSOM's advice that any off label use would have to be managed by the prescriber. To minimise this risk, GSK has included text in the *Precautions* section of the PI stating that *"Anoro Ellipta should not be used in patients with asthma"*. In addition, GSK will be examining any off label use in a post authorisation study (WWE117397) described in the most recent EU RMP (version 5.0, dated 28 January 2014), which will be submitted to the TGA.

The Delegate also noted ACSOM's concerns about the potential for off label use of Anoro Ellipta in children with asthma, as it may appear an attractive alternative to ICS use. GSK acknowledges these concerns and has strengthened the *Precautions* statement in the proposed PI to *"Anoro Ellipta should not be used in children."* as recommended by both ACSOM and the Delegate. GSK believes that this statement along with the statement that Anoro Ellipta should not be used for the treatment of asthma will minimise the risk of any potential off label use in children. The fact that the Anoro Ellipta device is a dry powder inhaler instead of an aerosol metered dose inhaler, which is the recommended inhaler for children, also minimises the risk of off label use in children. An analysis of Medicare prescribing data has found that over 99.9% of available LAMAs and LABAs have been prescribed to patients over 18 years in the past 12 months providing further reassurance that prescribers are using LAMAs and LABAs in appropriate populations.

To further minimise the risk of off label use, GSK will provide educational materials to prescribers on the appropriate use of Anoro Ellipta and will monitor off label use through PBRERs.

Any post-marketing studies must be submitted to the TGA for evaluation as soon as they are available.

Company response: GSK plans to undertake two post authorisation studies to assess the absolute and relative risks of cardio- and cerebrovascular disorders in patients with COPD using Anoro Ellipta and Incruse Ellipta (Study 201038), and to assess off-label use (WWE117397), as described in the EU RMP (version 5.0, dated 28 January 2014). GSK commits to submitting the final study reports for these studies to the TGA as soon as they are available.

Advisory committee considerations

The 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 Anoro Ellipta dry powder inhalation administered by the Ellipta inhaler device, containing 62.5 µg of umeclidinium bromide and 25 µg of vilanterol trifenatate to have an overall positive benefit-risk profile for the indication;

> *Anoro Ellipta is indicated as a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).*

In making this recommendation the ACPM;

- Noted the evaluations submitted in the concurrent monotherapy application for umeclidinium bromide also before the committee.

Proposed conditions of registration:

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

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice:

The ACPM advised the following in response to the specific delegate's questions on this submission:

1. Is the ACPM satisfied that efficacy has been satisfactorily established?

The ACPM advised the evidence submitted has demonstrated bronchodilation that is clinically meaningful and each component of the treatment makes a contribution to this effect.

2. Does the ACPM have any safety concerns about Anoro that would preclude registration?

The ACPM advised that while no major or significant concerns are apparent from the trial data the post registration data will be important, especially in regards to cardiac safety.

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 Anoro Ellipta 62.5/25 Umeclidinium (as bromide)/vilanterol (as trifenatate) 62.5 µg/ 25 µg powder for inhalation, indicated for:

> *Anoro Ellipta is indicated as a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).*

Specific conditions of registration applying to these goods

- The Anoro Ellipta (umeclidinium bromide/vilanterol trifenatate) EU Risk Management Plan IRMP), Version 30, dated 14 October 2013, with an Australian Specific Annex (AsA) Version 2.0 (undated), to be revised as specified in the sponsor's correspondence dated 4 December 2013, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

- Any post-marketing studies must be submitted to the TGA for evaluation as soon as results are available.

Details of additional specific conditions of registration applying to these goods including batch release conditions are beyond the scope of the AusPAR.

Attachment 1. Product Information

The Product Information approved for main Anoro Ellipta at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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