Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for conjugated estrogens / bazedoxifene acetate

Proprietary Product Name: Duavive

Sponsor: Pfizer Australia Pty Ltd

February 2018

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 Report (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; it provides 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

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ATE	Arterial thromboembolic event
BZA	Bazedoxifene acetate
CE	Conjugated estrogens
CMI	Consumer Medicines Information
FDC	Fixed dose combination
MHT	Menopause hormone therapy
MPA	Medroxyprogesterone
PI	Product Information
PO	Per os (oral)
RANZCOG	Royal Australian and New Zealand College of Obstetrics and Gynaecology
SERM	Selective estrogen receptor modulator
SmPC	Summary of product characteristics
TSEC	Tissue selective estrogen complex
VMS	Vasomotor symptoms
VTE	Venous thromboembolic event
VVA	Vulvar vaginal atrophy

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	12 December 2016
Date of entry onto ARTG	15 December 2016
Active ingredients:	Conjugated estrogens / bazedoxifene acetate
Product name:	Duavive
Sponsor's name and address:	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
Dose form:	Film coated modified release fixed dose combination tablet
Strength:	0.45 mg conjugated estrogens (CE) / 20 mg bazedoxifene acetate (BZA)
Container:	PVC/Aclar/PVC/Al blister pack sealed in a PET/Al/PE non-resealable laminated pouch
Pack size(s):	7 tablets (sample pack) or 28 tablets
Approved therapeutic use:	Duavive is indicated for treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus. · Duavive should be used for the shortest duration consistent with treatment goals and risks for the individual woman. · Experience in women older than 65 years is limited.
Route of administration:	Oral (tablet)
Dosage:	The recommended dose is 0.45 mg CE/20 mg BZA to be taken as a single oral tablet, once daily. The dose may be given at any time of the day, with or without food, and the tablets should be swallowed whole.
ARTG number:	262525

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd to register a new chemical entity bazedoxifene (BZA), which is to be used in a fixed dose combination (FDC) tablet with the existing drug substance conjugated estrogens (CE). The proposed product is a modified release oral film coated tablet containing CE 0.45 mg/BZA 20 mg in a FDC. The sponsor currently has registered CE monotherapy (slow release) tablet products (0.3 mg and 0.625 mg tablets) marketed under the trade name Premarin; however, bazedoxifene is a new chemical entity.

The proposed indication is:

> *Treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestogen-containing therapy is not appropriate.*
>
> *The experience treating women older than 65 years is limited.*

Compared to most other menopause hormone therapies (MHT), the progestogen component (for example, medroxyprogesterone [MPA], micronised progesterone) has been replaced by BZA. BZA is claimed to have both agonist and antagonist estrogen receptor activity: agonist activity on the skeletal system, and antagonist activity in breast and uterine tissues.

Single agent BZA (tradename: Conbriza) is registered in the EU for postmenopausal osteoporosis in women at increased risk of fractures. The approved EMA indication is:

> *Conbriza is indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. A significant reduction in the incidence of vertebral fractures has been demonstrated; efficacy on hip fractures has not been established. When determining the choice of Conbriza or other therapies, including estrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits*

Regulatory status

The international regulatory status at the time of this submission to TGA is listed in Table 1.

Table 1: International regulatory status at time of this submission to TGA.

Agency	Approval date	strength BZA/CE (mg)	Indication
EMA	Dec 2014	20/0.45	Treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate. The experience treating women older than 65 years is limited.
FDA (Duavee)	Oct 2013	20/0.45	Treatment of the following conditions in women with a uterus: · Treatment of moderate to severe vasomotor symptoms associated with menopause · Prevention of postmenopausal osteoporosis Limitation of Use: Duavee should be used for

Agency	Approval date	strength BZA/CE (mg)	Indication
			the shortest duration consistent with treatment goals and risks for the individual woman.
Health Canada	Oct 2014	20/0.45	Duavive (conjugated estrogens/bazedoxifene) is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause. Duavive should not be taken with a progestin, additional estrogens or selective estrogen receptor modulators (SERMs).
Swiss Medic	Apr 2015	20/0.45 20/0.625	Treatment of estrogen deficiency symptoms in postmenopausal women with confirmed menopause and intact uterus. The treatment duration is limited to a maximum of 24 months. In patients in whom only vulvovaginal symptoms are present, topical treatment should be used. When determining whether to use Duavive or other therapies for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks.

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 PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The regulatory timeline of this submission is detailed in Table 2.

Table 2: Regulatory timeline of this submission.

Description	
Submission dossier accepted and 1st round evaluation commenced	30 Nov 2015
1st round evaluation completed	19 May 2016
Sponsor provides responses on questions raised in 1st round evaluation	18 Jul 2016
2nd round evaluation completed	2 Sep 2016
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	6 Sep 2016
Sponsor's pre-Advisory Committee meeting response	16 Sep 2016
Advisory Committee meeting	7 Oct 2016
Registration decision	12 Dec 2016
Entry onto ARTG	15 Dec 2016
Number of TGA working days from submission dossier acceptance to registration decision *	218

* Target timeframe for standard applications: 220 working days

III. Quality findings

Introduction

Following advice from the TGA Clinical Section, the company changed the proposed trade name from the initially proposed "Duavive" to "Duavive 0.45/20". The trade name "Duavive 0.45/20" is acceptable from a clinical perspective and the labels are also acceptable.

The conjugated estrogens drug substance is subject to BP/Ph. Eur. and USP monographs. There is a USP monograph for conjugated estrogens monotherapy tablets, but no BP monograph. There are no BP/Ph., Eur., or USP monographs for bazedoxifene acetate drug substance and tablets. Bazedoxifene acetate used in this product is subject to a Drug Master File (DMF), which was evaluated in conjunction with this submission.

Drug substance (active ingredient)

Conjugated Estrogens (CE)

The drug substance CE contains blended equine estrogen compounds (primarily sodium estrone sulfate and sodium equilin sulfate and other estrogenic substances) isolated from the urine of pregnant mares.

CE is soluble in water (10-30 mL of water per gram of solute).

Control of the particle size of conjugated estrogen is not considered necessary, given its solubility.

The specification complies with the BP 2016 monograph for conjugated estrogens and aligns with the drug substance specification as currently registered for the CE monotherapy tablet, Premarin.

The quality control of the drug substance (including the drug substance specification) is acceptable.

Bazedoxifene (BZA)

The drug substance BZA is a white to tan crystalline powder.

The solubility of bazedoxifene is pH dependent i.e. increasing solubility with decreasing pH. The company indicated that bazedoxifene is likely to be a BCS Class II drug (low solubility/high permeability).

The quality control of the drug substance (including the drug substance specification) is acceptable.

Drug product

The CE 0.45 mg/BZA 20 mg modified release (MR) oval, biconvex, pink film coated tablets have "0.45/20" black branding on one side. The tablet consists of the "commercial" 0.45 mg CE Premarin tablet core[1] with an inert filler coat, but without the outer colour or clear film coating. The coated tablet is further coated with the BZA active layer is spray coated onto the tablet core.

The excipients used in the product are conventional pharmaceutical ingredients.

The product is to be packaged in PVC/Aclar/PVC/Al blister strips containing either 7 tablet (sample pack) or 28 tablets per blister card. The blister cards are then sealed in a PET/Al/PE laminated pouch under nitrogen purge.

Just one drug product manufacturer was nominated for the manufacture of the Duavive 0.45/20 tablet. GMP clearances for the active pharmaceutical ingredient (API) and drug product manufacturing sites are all acceptable, with the exception of the API manufacturer for CE. This matter is expected to be addressed in due course.[2]

The quality of the drug product is controlled by an acceptable specification.

The analytical methods used to analyse the product were adequately described and validated.

The stability data supplied supported a **shelf life of 36 months** for the unopened product (in PVC/Aclar/PVC/Al blisters) **when it is stored below 25°C in the original package in order to protect from moisture**.

The stability data supplied also supported an in-use **shelf life of 60 days** for the opened drug product (PVC/Aclar/PVC/Al blisters held in an open laminated pouch) **when stored below 25°C**.

Biopharmaceutics

Absolute bioavailability

No absolute bioavailability study was performed by the sponsor. Instead, the sponsor referred to an absolute bioavailability study (3068A1-111-EU) performed on a 10 mg BZA monotherapy tablet which gave a result of 6.2% and interaction studies (3115A1-1136-US) which showed CE did not affect the bioavailability of BZA at a dose of 20 mg. Given the pharmacokinetics of BZA are linear to 80 mg. The result of ~6% can be extrapolated to the proposed fixed dose BZA/CE tablets.

[1] In Australia, Premarin CE monotherapy tablets are only registered in 0.3 mg and 0.625 mg strengths. However, another registered product Premia Low 0.3/1.5 Continuous contains 0.45 mg CE/1.5 mg medoxyprogesterone acetate in a fixed combination MR tablet.
[2] GMP clearance of the drug substance and drug product manufacturers was addressed prior to decision.

Similarly for the CE, it was argued that BZA did not affect the bioavailability of the CE (interaction study 3115A1-1134-US) there was no interaction, so the absolute bioavailability of the CE is the same as for the monotherapy products. This is the same as an oral solution as determined in study 3117X3-102-US.

Effect of food

The effect of food was determined in two studies:

- Study 3115A1-102-US. This used Formulation A 0.625/40 tablets and a high fat meal. There was a 44% increase in C_{max} and a 17% increase in AUC for BZA, and, a 20% drop in C_{max} for total estrone, but no change in AUC for total estrone and no change in C_{max} or AUC for unconjugated estrone, total equilin or unconjugated equilin.
- Study 3115A1-116-US. This used Formulation C 0.625/20 tablets and a high fat meal. There was a no change in the in C_{max} of BZA, but the results were very variable. There was a 25% increase in the AUC for BZA. There was an 18% drop in C_{max} for total estrone, but no change in AUC for total estrone and no change in C_{max} or AUC for unconjugated estrone, total equilin or unconjugated equilin.

Given the linear pharmacokinetics between these strengths and the proposed strengths, these results are similar enough to extrapolate to the proposed 0.45/20 tablets.

Bioequivalence of market and clinical trial formulations

A number of different formulations of the CE/BZA 0.45/20 fixed dose combination tablets (and also 0.625/20 tablets) were used in clinical studies.

A very large number of comparative bioequivalence studies linking the different formulations used in the Phase III clinical studies and the formulation proposed for marketing were presented in the submission. The majority of these were on the 0.625/20 FDC strength or other strengths not proposed for marketing. Bioequivalence of the formulations administered in the clinical studies and the to-be-marketed formulation was adequately demonstrated.

IVIVC for the 0.45mg/20 mg CE/BZA tablets

A Level A IVIV correlation (IVIVC) was previously established by the sponsor in the submission to register a new formulation for Premarin 0.625 mg conjugated estrogens monotherapy tablets. The correlation between the dissolution profiles of sodium estrone sulphate (NES) and the concentration-time curves of the total estrone (free estrone + conjugated estrone) response was supported by data generated at the time.

In this submission, the sponsor provided a revised Level A IVIV correlation for the reformulated 0.625 mg Premarin Tablets and the conjugated estrogens component of the CE/BZA modified release tablets.

The IVIVC was deemed acceptable for the Premarin CE 0.625 mg tablets and CE/BZA 0.45/20 mg FDC tablet batches with dissolution profiles between those of the slow and medium dissolving tablet batches.

Quality summary and conclusions

The chemistry and quality aspects of the submission are considered acceptable and approval could be recommended except:

- There is one outstanding issue which relates to the acceptability of the GMP clearance for the conjugated estrogens API and CEDL intermediate manufacturing site located at

Pfizer Global. It is expected this issue will be addressed in due course, before the decision date.[3]

In relation to bioavailability it can be concluded the commercial formulation (CF) is bioequivalent to those used in the clinical studies.

However, there is concern that taking the tablets with ethanol will reduce the amount of conjugated estrogen released over time. Therefore, the issue should be considered by the Clinical Delegate as to whether the PI needs a statement stating that Duavive 0.45/20 tablets should not be taken with alcohol.

The application has not been considered by the Pharmaceutical Sub-Committee of the ACPM because no issues requiring their expertise were identified during the chemistry and quality evaluation.

IV. Nonclinical findings

Introduction

An application to register bazedoxifene as monotherapy for the prevention of postmenopausal osteoporosis was made previously (trade name: Viviant) but withdrawn by the sponsor. The nonclinical dossier included studies that had been submitted in that previous application, plus several new studies. The nonclinical dossier was generally of high quality. All pivotal safety related studies were conducted according to GLP except for those relating to in vivo cardiovascular safety pharmacology. These two non GLP studies were well documented nevertheless and conducted in an established laboratory, and the absence of GLP compliance is considered only a minor deficiency.

The dose of CE with this product (0.45 mg/day PO) is less than that already approved (up to 1.25 mg/day for the treatment of climacteric symptoms with Premarin). The nonclinical dossier included appropriate studies conducted with bazedoxifene and conjugated estrogens in combination.

Pharmacology

Primary pharmacology

Bazedoxifene acts as a SERM. In vitro, it was shown to bind to the human estrogen receptor with high affinity, with IC50 values of 17-25 nM and 15-72 nM at the α and β subtypes of the receptor, respectively, found in competition binding experiments. Functionally, bazedoxifene displayed both estrogen receptor antagonist and agonist activity depending on the assay system or tissue. In vitro, antagonist activity was most commonly seen; shown, for example, as inhibition of CE stimulated cell proliferation in a human breast cancer cell line, and inhibition of 17β-estradiol induced gene expression in rat hypothalamic cells and human osteoblast and hepatocarcinoma cell lines. In vivo, treatment with bazedoxifene provided significant protection against ovariectomy induced osteopenia in rats and monkeys (reflecting estrogen receptor agonist activity in bone). Bazedoxifene did not protect against ovariectomy-induced uterine atrophy in mice, rats and monkeys (denoting a lack of agonist activity in the uterus), and attenuated the uterotrophic effect of 17β-estradiol, ethinylestradiol and/or conjugated estrogens (indicating estrogen receptor antagonist activity in the uterus). Bazedoxifene reduced plasma cholesterol in rats and without affecting the reduction induced by conjugated estrogens (agonist activity in liver). It weakly supported mammary gland development in

[3] GMP clearance of the drug substance and drug product manufacturers was addressed prior to decision.

mice, and also antagonised the stimulation of mammary gland development induced by ethinylestradiol (predominant antagonist activity in breast). In postmenopausal monkeys, stimulatory effects on breast tissue by conjugated estrogens were shown to be attenuated by bazedoxifene co-treatment, with bazedoxifene alone having no stimulatory affect (antagonist activity). Progesterone receptor expression in the hypothalamus of the rat was unaffected by bazedoxifene alone, and the drug inhibited the increase induced by ethinylestradiol (antagonist activity). In a model of climacteric vasomotor symptoms (hot flushes; increased skin temperature during opiate withdrawal in rats), bazedoxifene had no significant effect alone and inhibited the suppressive effect of ethinylestradiol (indicating estrogen receptor antagonist activity). In a mouse venous thromboembolism model, bazedoxifene alone had no significant effect on the time to venous occlusion due to thrombus formation induced by an artificial stimulus, and ameliorated the acceleration produced by conjugated estrogens (estrogen receptor antagonist activity).

The major metabolites of bazedoxifene – bazedoxifene-5-glucuronide and bazedoxifene-4′-glucuronide – retain some pharmacological activity. The estrogen receptor binding affinity was not markedly different for these metabolites compared to their parent (IC50 values of 5.2-84 nM compared to 15-17 nM), but their functional activity was much weaker (antagonist potency 175 times lower for the 5-glucuronide and >900 times lower for the 4′-glucuronide compared with bazedoxifene in vitro in transcription assays).

Secondary pharmacodynamics and safety pharmacology

In vitro functional assays examining interactions with other steroid receptors revealed weak antagonist activity for bazedoxifene at the glucocorticoid receptor (acting with 75 times lower potency compared with at the estrogen receptor) and only very weak antagonism of androgen, progesterone and mineralocorticoid receptors (~650-840 times lower potency compared with the primary target). In vivo assays to examine glucocorticoid and anti-glucocorticoid activity, based on thymus weight in adrenalectomised rats, showed no effect of bazedoxifene (≤3 mg/kg/day PO).

An in vitro receptor binding screen identified binding by bazedoxifene to the sigma-1 receptor at 100 nM (but not at 1 nM), and various other interactions (testosterone receptor and L-type calcium channel binding and inhibition of dopamine, serotonin and noradrenaline transporters) at 10 μM. Considering the clinical Cmax (14.7 nM), no notable interaction at these off-target sites is anticipated in patients.

Specialised safety pharmacology studies covered the core battery: the CNS, cardiovascular and respiratory systems. Bazedoxifene did not affect CNS or respiratory function (tested in rats up to 1000 mg/kg PO). In vitro, bazedoxifene inhibited the hERG K+ channel with an IC50 of 1.2 μM (565 ng/mL). Being more than 80 times higher than the peak plasma concentration for total drug, and more than 8000 times the peak free concentration, no clinical relevance is seen. In isolated rabbit cardiac Purkinje fibres, bazedoxifene caused up to 55% reduction in the maximum rate of depolarisation (Vmax) at 10 μM (no effect at 1 μM); action potential duration and amplitude were unaffected. In vivo, blood pressure and heart rate (rats and cynomolgus monkeys) and ECG waveforms (monkeys) were unaffected by bazedoxifene at doses up to 5 mg/kg PO (rats) and 50 mg/kg PO (monkeys). Two instances of premature ventricular contractions were observed in a high-dose female monkey treated with 150 mg/kg/day bazedoxifene + 2 mg/kg/day conjugated estrogens in the final week of a 9 month repeat-dose toxicity study. This is seen to be a spontaneous finding.

Pharmacokinetics

Oral absorption of bazedoxifene was rapid to moderate in all laboratory animal species (typical Tmax, 2-4 h), as in humans. Oral bioavailability was low in all tested species (14%

in rat, 7% in dog and 11% in monkey compared to 6% in humans). The apparent elimination half-life was short in animals (~4-5.5 h in rats and monkeys), but was long for 14C-bazedoxifene derived radioactivity (~30 h). Exposure was generally dose proportional in mice, rats and cynomolgus monkeys, while less than dose proportional exposure was noted in rats at high doses (≥300 mg/kg/day). Co-administration of conjugated estrogens did not affect the pharmacokinetics of bazedoxifene in rats or monkeys.

Plasma protein binding by bazedoxifene was high to very high in all tested species (99.8–99.9% in mice, rats and monkeys at 500 ng/mL) including humans (99.3% in postmenopausal women at 100 ng/mL). Heat treatment of human plasma did not affect the extent of binding, taken to indicate a lack of binding to (the heat labile proteins) sex hormone binding globulin (SHBG) and cortisol binding globulin (CBG).

Tissue distribution of radioactivity was extensive following oral administration of 14C-bazedoxifene to rats, with highest exposure in liver, thyroid, pancreas, spleen and bone marrow. Overall exposure (AUC) in the uterus was 4.4 times higher than for plasma after a single dose and 1.5 times higher than plasma after repeated dosing (8 days). 14C-bazedoxifene derived radioactivity did not readily penetrate the blood-brain barrier (brain:plasma AUC, ≤0.3), although pharmacological activity of bazedoxifene in the rat brain following oral administration was demonstrated (antagonism of the ethinylestradiol-induced increase in progesterone receptor mRNA expression in the hypothalamus, as noted earlier). Binding to melanin was apparent, seen as significant and long-lasting radioactivity exposure in the skin and uveal tract of pigmented animals that accumulated with repeat dosing.

Metabolism of bazedoxifene involves oxidation and conjugation (glucuronidation) reactions, with extensive first-pass metabolism evident. The major circulating metabolite was bazedoxifene-5-glucuronide – formed by glucuronidation at the indole hydroxyl group – in all laboratory animal species tested (mouse, rat and cynomolgus monkey), as in humans (postmenopausal women). Plasma levels of bazedoxifene-5-glucuronide exceeded those of unchanged bazedoxifene in all species, and to a similar degree. Glucuronidation at the molecule's other hydroxyl group (phenyl) generated the other major human metabolite, bazedoxifene-4′-glucuronide. This compound was also a major metabolite in mice, but a relatively minor plasma metabolite in rats and cynomolgus monkeys. Other minor human metabolites were the di-glucuronide (found in plasma) and an N-oxide metabolite (detected in faeces); both of these were also formed in mice and the di-glucuronide was also formed in monkeys (detected in excreta). In vitro experiments with microsomal preparations showed predominant formation of bazedoxifene-4′-glucuronide in liver and bazedoxifene-5-glucuronide in kidney, with glucuronidation also occurring in the small intestine. Experiments with recombinant enzymes identified major roles for UGT1A1 and 1A10 in the glucuronidation of bazedoxifene, with an additional smaller role for UGT1A9.

Excretion of bazedoxifene was mostly via the faecal route in all species (mouse, rat, monkey and human). Biliary excretion was demonstrated in rats. Plateaus and occasional secondary peaks in the concentration-time profiles for bazedoxifene, seen across species, were suggestive of enterohepatic recycling.

The pharmacokinetic profiles of bazedoxifene in laboratory species and humans were sufficiently similar to allow these species to serve as appropriate models for assessing the toxicity profile of bazedoxifene.

Pharmacokinetic drug interactions[4]

Bazedoxifene was tested for inhibitory activity against CYPs 3A4, 2D6, 2C9, 1A2 and 2C19 in experiments with human liver microsomes, with respective IC50 values of 8, 7.5, 50, >100 and 25 μM observed. The IC50 values being massively greater (≥50,000 times) than the plasma Cmax for unbound drug (~0.15 nM), no systemic interaction is predicted. However, the IC50 for inhibition of CYP3A4 (8 μM) is around two times lower than the maximum expected concentration of bazedoxifene in the intestinal lumen on the apical side of the enterocytes (17 μM); as such, an in vivo interaction in patients due to inhibition of intestinal CYP3A4 is considered possible. The glucuronide metabolites of bazedoxifene displayed no or considerably weaker CYP inhibitory activity compared to the parent, and no CYP mediated interactions by them are predicted (either at the systemic or intestinal level).

No induction of CYPs (1A1/2, 2B, 2A1, 3A, 2B1 or 2C11) was observed in female rats treated with bazedoxifene at 100 mg/kg/day PO for 7 days, while hepatic UGT activity was modestly increased (by 42% cf. vehicle controls). Hepatic UGT activity was unaffected in animals treated at 25 mg/kg/day (estimated to yield more than 8 times the systemic exposure [plasma AUC] in patients).

UGT1A10 (which is expressed in intestines) was inhibited by bazedoxifene at concentrations greater than 20 μM; no clinically relevant interaction is predicted though. Bazedoxifene is a substrate of P-glycoprotein and a modest inhibitor of the transporter, with 60% inhibition observed at 100 μM; based on comparisons with the maximum intestinal and free plasma concentrations, no in vivo interaction due to P-glycoprotein inhibition by bazedoxifene is predicted in patients (at either the intestinal or systemic level).

With regard to the extent of human plasma protein binding, no significant interactions between bazedoxifene and warfarin, diazepam or digoxin were identified.

Finally, no significant metabolic interaction between bazedoxifene and conjugated estrogens was observed in vitro in experiments with female human hepatocytes, and hepatic microsomes and S9 fractions.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted with bazedoxifene in mice, rats and cynomolgus monkeys by various routes. Maximum non-lethal doses were 4000 mg/kg by the oral route (in mice and rats) [highest dose tested]; ≤2000 mg/kg (mice) and <500 mg/kg (rats) with IP administration, and 3 mg/kg IV (in rats and monkeys) [highest dose tested]. Decedent animals showed clinical signs (decreased activity, ptosis and dyspnoea) but no remarkable necropsy findings. Bazedoxifene exhibits a low order of acute toxicity by the clinical (PO) route.

[4] The following assumptions are made for bazedoxifene:
- molecular weight, 470.6 g/mol
- patient dose per administration, 20 mg
- plasma Cmax, 6.93 ng/mL [total drug] (Clinical Study 3115A1-1138-US)
- free fraction, 1%
- maximum expected concentration in the intestinal lumen on the apical side of the enterocytes, 17 μM (calculated as 0.1 × 20 mg ÷ 250 mL

as described in: European Medicines Agency, "Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**)", 21 June 2012.

Repeat dose toxicity

Repeat dose toxicity studies with bazedoxifene (single agent) of up to 3 months duration were conducted in mice, 6 months in rats and 9 months in cynomolgus monkeys. In addition, studies with bazedoxifene and conjugated estrogens in combination were performed in rats and monkeys (up to 6 and 9 months duration in the respective species). All studies used the clinical (PO) route, with administration by oral gavage in most studies and via the diet in some of the rodent studies. The duration of the pivotal studies, the species used (rats and cynomolgus monkeys), study design and conduct were consistent with the relevant TGA adopted guidelines.[5] Animals of both sexes were used in all of the mouse and most of the rat studies, while most of the monkey studies involved female animals only. The use of females only is not a deficiency given the indication.

Relative exposure

Exposure ratios have been calculated based on animal:human plasma AUC values for bazedoxifene. The human reference value is from Clinical Study 3115A1-1138-US, obtained in healthy postmenopausal women (50-64 years old) after 10 days dosing at the proposed clinical dose (20/0.45 mg/day bazedoxifene/conjugated estrogens). Multiples of the clinical exposures to bazedoxifene obtained at the highest doses in the pivotal studies were moderate to very high.

Table 3: Relative exposure to bazedoxifene in selected repeat dose toxicity and carcinogenicity studies.

Species		Study	Dose		AUC0–24 h^		ER#	
			♂	♀	♂	♀	♂	♀
Mouse	CD-1	3 months RPT-39802	40	50	469	558	7	8
			134	151	1922	2192	27	31
			392	454	8715	8729	123	123
	Tg.RasH2	6 months carcinogenicity RPT-57589	50		1816	1493	26	21
			150		3042	2880	43	41
			500		6400	7614	90	108
Rat (SD)		6 months pivotal GTR-34756	2		37.1	33.4	0.5	0.5
			10		145	189	2.0	2.7
			30		486	624	7	9
		6 months pivotal combination RPT-50335	–	3/0.33	–	97.8	–	1.4
			–	12/1	–	299	–	4.2
			–	60/3	–	966	–	14
		2 years carcinogenicity RPT-49489	1.3	1.8	4.1	21.5	0.06	0.3
			4.6	5.5	32.2	73.3	0.5	1.0
			13.6	16.9	131	215	1.9	3.0
			46.9	56.9	332	542	5	8
Monkey (Cynomolgus)		6 months GTR-34757	1		6.6	8.0	0.09	0.11
			5		135	156	1.9	2.2
			15		639	554	9	8
		9 months pivotal RPT-42079	–	10	–	318	–	4.5
			–	50	–	1136	–	16
			–	300	–	3180	–	45

[5] European Medicines Agency, "Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr*)", 18 March 2010; European Medicines Agency, "Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005)", 24 January 2008.

Species	Study duration [Study	Dose [BZ or BZ/CE] (mg/kg/day)		AUC0–24 h^ (ng·h/mL)		ER#	
	9 months pivotal combination RPT-50336	–	15/0.2	–	477	–	7
		–	50/0.66	–	1320	–	19
		–	150/2	–	4081	–	58
Human (postmenopausal women)	steady state 3115A1-1138-US	[20/0.45 mg BZ/CE]		70.8		–	

= animal:human plasma AUC_{0-24h}; ^ = data are from the last sampling occasion; BZ = bazedoxifene; CE= conjugated estrogens

With regard to conjugated estrogens, relative exposure was low in the pivotal rat combination study (≤2.4 fold), but substantial multiples were obtained in the pivotal monkey combination study (up to 17-30 fold) [based on animal:human plasma AUC values for the estrone and equilin components].

Major findings

Effects on reproductive tissues were the most prominent finding in treated animals, with additional effects on the mammary gland, pituitary and kidney seen. Effects on body weight and changes in serum chemistry were also observed.

Changes in the female reproductive tract of bazedoxifene-treated animals comprised:

- uterine, cervical and vaginal atrophy
  - at all doses and in almost all animals in the pivotal rat study (≥2 mg/kg/day for 6 months) [also in shorter studies in rats, including at doses as low as 1 mg/kg/day for 1 month]
  - at all doses and in all animals in the pivotal monkey study (≥10 mg/kg/day for 9 months) [also in shorter studies in monkeys, including at doses as low as 1 mg/kg/day for 6 months]
  - in mice, including in almost all animals treated at ≥50 mg/kg/day for 3 months
- vaginal mucification
  - at all doses and in almost all animals in the pivotal rat study (≥2 mg/kg/day for 6 months) [also in shorter studies in rats, including at doses as low as 0.5 mg/kg/day for 10 days]
  - in mice, including in most animals treated at ≥50 mg/kg/day for 3 months
  - not observed in monkeys (tested up to 300 mg/kg/day in the pivotal 9-month study)
- ovarian cystic follicles
  - at all doses and in almost all animals in the pivotal rat study (≥2 mg/kg/day for 6 months) [also in shorter studies in rats, including at doses as low as 3 mg/kg/day for 10 days]
  - at all doses and in all animals in the pivotal monkey study (≥10 mg/kg/day for 9 months, with cystic follicle haemorrhage seen in 1/5 monkeys at 50 mg/kg/day in the study) [also in shorter studies in monkeys, including at doses as low as 1 mg/kg/day for 6 months]
  - in mice, including in all animals treated at ≥50 mg/kg/day for 3 months

These findings are seen to represent exaggerated pharmacological (anti-estrogenic) effects of bazedoxifene. Reversibility following withdrawal of treatment was demonstrated in the animal species. The ovarian changes are due to follicular maturation arrest and persistent proliferative follicles, shown in monkeys to involve loss of the pre-ovulatory surge of luteinising hormone (LH) and a sustained increase in circulating LH levels. Similar effects are observed with other SERMs, such as raloxifene (Evista), and are not relevant to postmenopausal women with quiescent ovaries. For the most part, treatment with bazedoxifene in combination with conjugated estrogens produced similar changes in reproductive tissues to those seen with bazedoxifene alone. Squamous metaplasia of the uterine endometrial endothelium was observed in rats treated with 60/3 mg/kg/day bazedoxifene/conjugated estrogens for 6 months. This was not seen in monkeys treated with the combination (despite higher exposure), nor with bazedoxifene alone in rats. It is recognised to be a common (non-neoplastic) finding in rats with prolonged treatment with estrogenic compounds, as well as a spontaneous age related change in the species.[6]

Notable effects on the male reproductive tract comprised increased testes weight and tubular degeneration, seminal vesicle atrophy and decreased content, and prostatic atrophy (seen in rats).

Mammary gland changes were observed in bazedoxifene treated rats. In the pivotal rat study, mammary gland lobuloalveolar change (atrophy of glandular tissue; masculinisation) was seen at all dose levels tested (≥2 mg/kg/day for 6 months). This is consistent with anti-estrogenic activity by bazedoxifene. In the pivotal 6 month combination study, withdrawal of bazedoxifene and conjugated estrogen treatment resulted in an increased incidence of mammary gland lobular hyperplasia. This may be due to the removal of the prolactin attenuating influence of bazedoxifene (see below), and subsequent hyperplasia of estrogen primed mammary tissue. Mammary gland changes were not observed in monkeys (despite higher exposure compared with rats).

Pituitary weight was reduced in female rats at all dose levels tested in the pivotal study (≥2 mg/kg/day for 9 months) and in shorter studies at doses as low as 0.5 mg/kg/day (for 10 days), as well as in studies conducted with bazedoxifene and conjugated estrogens in combination but more mildly. Microscopically, decreased acidophil granules or acidophil depletion were seen (acidophils being lactotrophs or somatotrophs). Pituitary weight was also reduced in female mice (at ≥50 mg/kg/day in a 3 month study) and in a 1 month study in monkeys (≥10 mg/kg/day), but not in other monkey studies including the pivotal 9-month studies conducted with bazedoxifene alone and in combination with conjugated estrogens. The findings represent an anti-estrogenic effect of bazedoxifene. Such effects on the rat pituitary are expected to result in reduced prolactin secretion (prolactin levels were not monitored in any of the toxicity studies, however), with a consequent effect on mammary tissue.

Bazedoxifene caused renal toxicity in male rats, with haematuria, renal corticomedullary mineralisation and renal tubular basophilia seen at all dose levels in the pivotal 6 month study (≥2 mg/kg/day). Kidney mineralisation and haematuria were also seen in male rats at lower doses in shorter studies (that is, at ≥1 mg/kg/day for 1 month). Renal effects were not seen in female rats or in monkeys, and only in mice at very high, lethal doses (tubular degeneration in males at ≥460 mg/kg/day and females at ≥484 mg/kg/day for 2 weeks). The renal findings in male rats may be due a direct toxic effect of bazedoxifene on the kidney (with the male rat kidney recognised to be particularly susceptible to renal injury) or be pharmacologically mediated (with nephrocalcinosis known to be induced in

[6] Female genital tract. In: Greaves P, ed. Histopathology of Preclinical Toxicity Studies. 4th edition. New York, NY: Academic Press Inc. 2012, p. 681.

castrated male rats treated with estrogen); and are not considered to be relevant to patients.

Serum cholesterol and triglycerides were reduced, along with an increase in the LDL:HDL ratio (where monitored), in female rats at all doses in the pivotal 6 month studies conducted with bazedoxifene alone and in combination with conjugated estrogens. There were no notable effects on clinical chemistry in monkeys. Suppression of body weight gain was a common finding in rats. This occurred at all dose levels in the pivotal 6 month studies, accompanied by decreased food consumption. Treatment with bazedoxifene alone or in combination with conjugated estrogens had no effect on body weight gain in the pivotal 9 month studies in monkeys, though.

Additional histopathological changes were encountered at high/poorly tolerated doses in rodents (for example, lymphoid atrophy in spleen and thymus, adrenal cortical atrophy, accumulation of pigment in the jejunum and mesenteric lymph nodes [mice and rats], salivary gland eosinophilia [mice], bone marrow hypocellularity, hepatocellular atrophy, and stomach erosion [rats]). These were absent in the pivotal rat studies, and not observed in monkeys (at very high exposure multiples).

Genotoxicity

The genotoxic potential of bazedoxifene was investigated in a comprehensive set of assays, comprising tests for bacterial mutagenicity (Ames test), the in vitro mouse lymphoma tk assay, for chromosomal aberrations in vitro (in Chinese hamster ovary cells) and for chromosomal damage in vivo (mouse micronucleus test). The studies were conducted in accordance with the relevant TGA adopted guideline,[7] appropriately validated, and used appropriate concentrations/doses (up to maximum recommended levels or limited by cytotoxicity). The Ames test used an appropriate set of bacterial strains (*S. typhimurium* and *E. coli*). All studies returned negative results for bazedoxifene.

The genotoxicity of conjugated estrogens has not been fully investigated. Conjugated estrogens were reported to be not genotoxic in assays for bacterial mutagenicity or for clastogenicity in vitro (lymphoid cell lines) and in vivo (in Chinese hamster V79 cells cultured in diffusion chambers implanted into treated mice) in a published study,[8] but the assays did not use a sufficiently comprehensive set of bacterial strains (for example, none capable of detecting mutations at A-T sites), use recommended cell types or involve testing up to maximum recommended concentrations/doses. Weak genotoxic effects of estrogens are reported elsewhere in the literature.[9]

Carcinogenicity

The carcinogenic potential of bazedoxifene was investigated in a 6 month study in transgenic mice (Tg.rasH2) and a 2 year study in rats. Administration was by the oral route (gavage in mice; via diet in rats). Study conduct was consistent with relevant TGA adopted guidelines.[10] Dose selection was appropriate,[11] with the high dose levels producing significant suppression of body weight gain in both species.

[7] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (S2(R1))", 9 November 2011.
[8] Sirianni SR, et al. Study on the mutagenicity of conjugated estrogens in human, animal and bacterial systems. *J. Med.* 9: 423-432 (1978).
[9] Liehr JG. Genotoxicity of the steroidal estrogens oestrone and oestradiol: possible mechanism of uterine and mammary cancer development. *Hum. Reprod. Update* 7: 273-281 (2001); IARC Monographs of the Evaluation of Carcinogenic Risks to Humans. (2012) Estrogen-progestogen oral contraceptives (combined). Volume 100A.
[10] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Guideline on the need for carcinogenicity studies of pharmaceuticals (S1A)", 29

Benign ovarian granulosa cell tumours were observed in transgenic mice treated at 150 and 500 mg/kg/day (relative exposure, 41-108), and coincided with follicular cysts and interstitial cell hyperplasia. There were no treatment related neoplastic findings in female mice at 50 mg/kg/day (relative exposure, 21), nor in any of the male dose groups (≤500 mg/kg/day; relative exposure, ≤90).

Bazedoxifene also produced benign ovarian granulosa cell tumours in rats with treatment at 16.9 and 56.9 mg/kg/day (0.03% and 0.1% of diet; relative exposure, 3-8), again occurring in conjunction with hyperplasia and cystic follicles. No treatment related increase in tumour incidence was observed in female rats at 5.5 mg/kg/day (0.01% diet; relative exposure, 1.0). The incidence of pituitary and mammary gland tumours was decreased by bazedoxifene (consistent with anti-estrogenic activity, and associated with increased survival).

Ovarian neoplasia is attributed to the pharmacological activity of bazedoxifene – interfering with normal estrogen feedback at the level of the hypothalamus and/or pituitary, affecting LH levels, and giving rise to persistent proliferative follicles – and is not considered to be relevant to postmenopausal women with quiescent ovaries. Ovarian granulosa cell neoplasia has previously been seen in rats with the related compound raloxifene.[12]

Renal tubular adenoma and carcinoma were observed at all dose levels in male rats (≥1.3 mg/kg/day [≥0.003% diet]; relative exposure, 0.06-5), and were associated with findings of renal injury (tubular epithelial hyperplasia, chronic progressive nephropathy, kidney cysts and corticomedullary mineralisation). Bazedoxifene did not produce renal tumours in female rats though (≤56.9 mg/kg/day [≤0.1% diet]; relative exposure, 8], nor in transgenic mice of either sex despite higher exposure compared to rats (90-108 times the clinical AUC). While there were instances of renal tubular cell carcinoma in aged monkeys treated with bazedoxifene for 18 months in a long term pharmacology study, these displayed no dose relationship and they are considered to be a spontaneous, age related finding and not related to treatment. The finding of renal neoplasia in male rats is not considered to be relevant to patients.

Reproductive toxicity

Reproductive toxicity studies with bazedoxifene covered fertility (rats) and embryofetal development (rats and rabbits). No pre/postnatal development studies were conducted; this is acceptable given the indication and the patient population. The conduct of the studies (in terms of species used, group size, timing/duration of treatment, endpoints examined) was sound, and consistent with the relevant TGA adopted guideline.[13] The clinical route (PO) was used.

Relative exposure

Only a modest multiple of the clinical AUC was obtained in the rat embryofetal development study, while more substantial exposure ratios were attained at the upper dose levels in the other studies.

November 1995; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Testing for carcinogenicity of pharmaceuticals (S1B)", 16 July 1997.
[11] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Dose selection for carcinogenicity studies of pharmaceuticals (S1C(R2))", 11 March 2008.
[12] Long GG, et al. Proliferative lesions of ovarian granulosa cells and reversible hormonal changes induced in rats by a selective estrogen receptor modulator. *Toxicol. Pathol.* 29: 719-726 (2001).
[13] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Detection of toxicity to reproduction for medicinal products & toxicity to male fertility (S5(R2))", November 2005.

Table 4: Relative exposure in reproductive toxicity studies.

Species	Study type [Study no.]	Dose (mg/kg/day)	AUC0–24 h (ng·h/mL)	ER#
Rat (SD)	Male fertility RPT-56350	30	880	12
		100	1703	24
		300	2129	30
	Female fertility RPT-55685	0.3	2.14[a]	0.03
		1	22.7[a]	0.32
		10	257[a]	3.6
		30	692	10
	Embryofetal development RPT-55230	0.3	2.14	0.03
		1	22.7	0.32
		10	257	3.6
Rabbit (NZW)	Embryofetal development #1 RPT-48541	0.05	19.8	0.28
		0.5	123	1.7
		5	3231	46
	Embryofetal development #2 RPT-57563	0.05	11.5	0.16
		0.5	139	2.0
		5	1244	18
Human postmenopausal women	steady state 3115A1-1138-US	[20/0.45 mg BZ/CE]	70.8	–

# = animal:human plasma AUC_{0-24h}; [a] = based on data obtained in Study RPT-55230;
BZ = bazedoxifene; CE= conjugated estrogens

Bazedoxifene and/or its metabolites (monitored as 14C-bazedoxifene derived radioactivity) did not readily cross the placenta in rats. Excretion of bazedoxifene in milk was not examined.

Adverse effects on fertility were observed at all dose levels in female rats. At 0.3 mg/kg/day (relative exposure, 0.03), oestrus cycling was irregular, the number of corpora lutea was reduced and the incidence of pregnancy was halved; as well, there was a marked increase in pre-implantation loss (>7 fold) and resorptions (>4 fold), and a marked decrease in the number of live embryos per dam (>10 fold). At ≥1 mg/kg/day (relative exposure, ≥0.3), oestrus cycling ceased in almost all animals and none became pregnant. Oestrus cycling returned in most treated animals after a 4 week treatment free period, but remained irregular in many. Fertility was unaffected by bazedoxifene in male rats (≤300 mg/kg/day; relative exposure, 30).

Treatment with bazedoxifene during gestation produced embryofetal toxicity in pregnant rats at low or subclinical exposure levels. While no teratogenicity was observed, there was embryofetal lethality, evident as a marked increase in post-implantation loss (especially late resorptions) at 10 mg/kg/day (relative exposure, 3.6), with live litter size reduced at ≥1 mg/kg/day (relative exposure, >0.3). Mean fetal weight was reduced, fetal vascular variations were increased and ossification was impaired at 10 mg/kg/day; the incidence of absent innominate artery was increased at ≥1 mg/kg/day. These effects occurred in conjunction with maternotoxicity (seen as suppression of maternal body weight gain). The NOEL for effects on embryofetal development in the rat is 0.3 mg/kg/day, associated with systemic exposure (plasma AUC) 33 times lower than that of patients.

Two embryofetal development studies were conducted in rabbits, with the initial study repeated due to concerns that the findings were confounded by the suboptimal health of the animals used. While the same dose levels were used in the two studies, significantly lower exposure was obtained at the high dose level in the subsequent study cf. the first. Bazedoxifene was teratogenic in rabbits at 5 mg/kg/day in the first study (relative

exposure, 46), with ventricular septal defect seen. Foetal skeletal abnormalities were also increased in the first study (involving the vertebrae at ≥0.5 mg/kg/day and the skull at 5 mg/kg/day). No teratogenicity was observed in the second study (relative exposure, ≤18), and notable fetal findings were limited to an increase in the incidence of absent innominate artery at 5 mg/kg/day (variation; relative exposure, 18), however abortions occurred with treatment at ≥0.5 mg/kg/day (relative exposure, ≥2.0). All of the findings occurred in conjunction with maternotoxicity (seen as suppression of body weight gain). The second study establishes a NOEL for effects on embryofetal development in the rabbit of 0.5 mg/kg/day (relative exposure, 2.0) or 0.05 mg/kg/day (relative exposure, 0.16) if abortion is considered an effect on the foetuses rather than the dams.

Pregnancy classification

The sponsor has proposed Pregnancy Category D[14] for Duavive. This is considered appropriate. It matches the existing category for conjugated estrogens with Premarin, and is consistent with findings of embryofetal lethality in rats and abortion and teratogenicity in rabbits with bazedoxifene, taking into account the associated exposure margins and concordance across species, and that effects related to bazedoxifene's anti-estrogenic activity will be attenuated by estrogen co-therapy here.

Paediatric use

Duavive is not proposed for paediatric use and no juvenile animal studies were submitted.

Local tolerance and antigenicity

No studies on local tolerance were submitted; this is acceptable. Bazedoxifene was not antigenic in animals, with negative responses in the passive cutaneous anaphylaxis test (conducted in immunised mice and recipient rats, and guinea pigs) and in the active systemic anaphylaxis test (guinea pigs).

Immunotoxicity

Specialised studies on immunotoxicity were not conducted. This is consistent with the relevant TGA adopted guideline (ICH S8), with no cause for concern identified in general repeat dose toxicity studies nor predicted based on pharmacological activity.

Phototoxicity

No phototoxicity studies were conducted. Bazedoxifene absorbs light in the natural sunlight range (290-700 nm), with a 15648 $L \cdot mol^{-1} \cdot cm^{-1}$ molar extinction coefficient (MEC) observed at a peak occurring at 298 nm. This is well above the MEC threshold of 1000 $L \cdot mol^{-1} \cdot cm^{-1}$,[15] below which insufficient photoreactivity to result in direct phototoxicity is seen. Studies in rats indicated no special distribution to the skin or eye compared to other organs, although the Cmax for 14C-bazedoxifene derived radioactivity in non-pigmented skin was almost twice that in plasma and the $AUC_{0-\infty}$ was more than 5 times higher than for plasma. As well, melanin binding was found, but this does not necessarily present a photosafety concern. The available nonclinical data are not sufficient to allay concerns regarding phototoxicity potential, but this is assessable from clinical data.

[14] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[15] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Photosafety evaluation of pharmaceuticals (S10)", 13 November 2013.

Impurities

The proposed specifications for impurities/degradants in the drug substance/product are considered to be toxicologically acceptable.

Nonclinical summary and conclusions

- The dose of conjugated estrogens with this product does not exceed that already approved for the treatment of climacteric symptoms (as Premarin).
- The submitted nonclinical dossier was generally of high quality. Excluding in vivo studies on cardiovascular safety pharmacology, all pivotal safety related studies were GLP compliant. The nonclinical dossier included appropriate studies conducted with bazedoxifene, and with bazedoxifene and conjugated estrogens in combination.
- Bazedoxifene was shown to bind to the two human estrogen receptor subtypes with nanomolar affinity. Functionally, bazedoxifene acts a selective estrogen receptor modulator (SERM) – that is, it exhibits both estrogen receptor agonist and antagonist activity, depending on the tissue. Agonist activity was observed in bone and liver, and antagonist activity was seen in the uterus, breast and CNS. This was demonstrated in studies conducted in mice, rats and/or monkeys as significant protection against ovariectomy induced osteopenia, attenuation of the uterine and mammary gland stimulatory effects of estrogens, lowering of plasma cholesterol, and effects on hypothalamic receptor expression in the hypothalamus. In a rat model of climacteric hot flushes, bazedoxifene had no significant effect alone and inhibited the effect of ethinylestradiol (estrogen receptor antagonist activity).
- The nonclinical pharmacology studies offer support for bazedoxifene's efficacy in attenuating the uterine proliferative effects of conjugated estrogens.
- Secondary pharmacology studies with bazedoxifene identified no clinically relevant interactions at off-target sites. Safety pharmacology studies covered the core battery of systems, with no effects on CNS or respiratory function, and no clinically relevant effects on the cardiovascular system (including hERG K+ channel inhibition) seen with bazedoxifene.
- Oral absorption of bazedoxifene was rapid to moderate in laboratory animal species, with low bioavailability, as in humans. Co-administration of conjugated estrogens did not affect the pharmacokinetics of bazedoxifene in rats or monkeys. Plasma protein binding was high to very high in all tested species, including humans (with 99.3% binding observed in plasma from postmenopausal women at 100 ng/mL). Wide tissue distribution was demonstrated in rats, but without ready penetration of the blood-brain barrier. Binding to melanin was apparent. Bazedoxifene is extensively metabolised. The major metabolites are formed by glucuronidation (bazedoxifene-5-glucuronide and bazedoxifene-4′-glucuronide), and retain some pharmacological activity. Excretion of bazedoxifene is chiefly by the faecal route, with a role for biliary excretion.
- In vitro studies indicated potentially clinically relevant inhibition of CYP3A4 by bazedoxifene at the intestinal level, but not of CYPs systemically. Bazedoxifene is a substrate and inhibitor of P-glycoprotein; the potency of inhibition, though, is not so great as to suggest the potential for interactions mediated by P-gp inhibition in patients. No significant plasma protein binding interactions were seen between bazedoxifene and either warfarin, diazepam or digoxin.
- Bazedoxifene displayed a low order of acute toxicity by the oral route in mice and rats.
- Repeat-dose toxicity studies by the oral route were conducted with bazedoxifene in mice (up to 3 months), rats (up to 6 months) and cynomolgus monkeys (up to 9

months). Studies with bazedoxifene and conjugated estrogens in combination were also conducted in rats and monkeys (up to 6 and 9 months duration in the respective species). Major target organs were the ovary (cystic follicles), uterus, cervix and vagina (atrophy of each; vaginal mucification), mammary gland (atrophy; masculinisation), and pituitary (acidophil depletion). These represent exaggerated anti-estrogenic effects of bazedoxifene. The kidney was an additional target for toxicity by bazedoxifene in male rats, but this was seen to be a sex- and species-specific effect not considered relevant to patients.

- Bazedoxifene was not genotoxic in the standard battery of tests. Carcinogenicity studies with bazedoxifene were conducted in rats and transgenic mice. An increased incidence of benign ovarian granulosa cell tumours were observed in both species, attributed to the pharmacological activity of bazedoxifene (involving disruption of the hypothalamic-pituitary axis leading to persistent proliferative ovarian follicles); the finding is not considered to be relevant to postmenopausal women with quiescent ovaries. Renal tumours, occurring in conjunction with kidney injury, were observed in male rats. Renal neoplasia was not observed in mice or female rats treated with bazedoxifene, and the finding is not considered to be relevant to patients.
- Adverse effects on female fertility – associated with irregular or absent oestrus cycling and reduced number of corpora lutea – were observed with bazedoxifene in rats at all dose levels tested (including ones yielding subclinical exposure); pre-implantation loss and resorptions were markedly increased. In embryofetal development studies, bazedoxifene caused embryofetal lethality, increased fetal vascular variations and impaired ossification in rats, and caused abortions, teratogenicity (ventricular septal defect) and other adverse fetal effects in rabbits. These adverse effects on embryofetal development occurred in conjunction with maternotoxicity, but at low or subclinical exposure multiples (animal:human plasma AUC).
- The product is to be contraindicated in pregnancy and women who may become pregnant. Assignment to Pregnancy Category D, as proposed by the sponsor, is supported.
- The specified impurity profile is considered to be toxicologically acceptable.
- No critical deficiencies were identified. However, available nonclinical data are not sufficient to allay concerns regarding phototoxic potential.
- There are no nonclinical objections to the registration of Duavive provided that concerns regarding potential phototoxicity are satisfactorily addressed from the clinical data set.

V. 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

According to the Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG):[16]

[16] RANZCOG, Management of the menopause, Nov 2014.

> *the menopause refers to the final menstrual period. A woman is postmenopausal 12 months after her final menstrual period……The menopause transition commonly starts around 47 years and the average age of natural menopause is 51 years.*

Duavive is a FDC of BZA, a SERM, and CE (BZA/CE). BZA has both agonist and antagonist estrogen receptor activity - agonist activity on the skeletal system and antagonist activity in breast and uterine tissues. More specifically, compared to most MHT preparations with CE, in Duavive, the progestogen component has been replaced by BZA.

The first observational studies reporting an association between endometrial cancer (and hyperplasia) and un-opposed estrogen therapy were published in 1975.[17] As a result, clinicians started prescribing doses of CE at lower doses than the previous standard of 1.25 mg. However, rates of endometrial hyperplasia with CE administered at a lowered dose ranged from 7% with 12 months use to 15% with 24 months use at a CE dose of 0.45 mg CE and 10% with 12 months use to 27% with 24 months use at a CE dose of 0.625 mg.[18]

MPA was subsequently added to the CE for endometrium protection which proved successful[19] and the addition of a progestogen/progestin (natural or synthetic progesterone) has become the standard intervention to prevent estrogen induced endometrial stimulation in menopausal therapy. The Women's Health Initiative (WHI) study of 16,608 postmenopausal women reported that CE/MPA 0.625/2.5 mg carried no increased risk of endometrial cancer compared with placebo.[20]

Besides progestogens, an alternative approach for protecting the endometrium against estrogen stimulation in menopausal therapy is a TSEC. This involves combining a SERM with estrogen. Endometrial protection is achieved through modulation of the estrogen receptor. The clinical effect of a TSEC would be the blended tissue specific activities of the SERM and estrogens. An ideal SERM estrogen combination would have the positive attributes of estrogen and fewer of the adverse reactions (for example, stimulation of the endometrium or breast). Not all estrogen SERM combinations reduce endometrial stimulation. For example, oestradiol-raloxifene is associated with endometrial stimulation.[21]

Guidance

There are two relevant EMA guidelines (adopted by TGA) (Table 5).

Table 5: Relative exposure in reproductive toxicity studies.

[17] Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med.* 293: 1167-1170 (1975).
[18] Pickar JH, et al. Endometrial Effects of Lower Doses of Conjugated Equine Estrogens and Medroxyprogesterone Acetate: Two-Year Substudy Results. *Fertil Steril.* 80: 1234-1240 (2003).
[19] Woodruff JD, Pickar JH. *Am J Obstet Gynecol.* 170: 1213-1223 (1994).
[20] Anderson GL, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 290: 1739-1748 (2003).
[21] Stovall DW, et al. The Effects of Combined Raloxifene and Oral Estrogen on Vasomotor Symptoms and Endometrial Safety. *Menopause* 14 (3 Pt 1): 510-517 (2007).

Guideline	Key recommendations
Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1) October 2005[22]	Efficacy: · The most important estrogen deficiency symptom s are vasomotor symptoms (hot flushes) and only moderate to severe hot flushes are to be treated by HRT · Primary endpoint for efficacy trials is the frequency of moderate to severe hot flushes · Enrolled subjects should have a minimum of least 5 moderate to severe hot flushes per day at baseline · Placebo-controlled studies are sufficient · Duration of treatment for efficacy symptom evaluation – 3 months · Endometrial safety: · Biopsy is the gold standard method for assessing endometrial hypertrophy · Assessment should be done according to predefined and generally accepted criteria · Transvaginal uterine ultrasound should not replace biopsy · Studies of at least 12 month duration are required · The upper limit of the two-sided 95% confidence interval incidence of hyperplasia or more serious endometrial outcomes should not exceed 2% · Other safety: · Venous Thromboembolism – careful monitoring recommended • Bleeding o Minimum duration of 12 months o Monitor incidence of amenorrhoea during months 10-12 and % with bleeding and/or spotting in first 3 month and months 10-12. · Breast examination and monitoring required
Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev.1), February 2009[23] *Of note, currently this guideline is under revision*	· It should be clearly stated if the claimed indication is first line, second line therapy or a substitution, and the clinical development should be performed accordingly. · Exploration of interactions between the two substances should be explored · The benefit/risk assessment of the fixed combination should be equal or exceeds that of each substance taken alone · Where there are grounds to expect that a fixed combination product may be substantially more harmful or give rise to much more frequent adverse effects than any individual substances given alone, the applicant should provide evidence that this does not occur in therapeutic use, or that the advantages of the combination e.g. increased efficacy, outweigh such disadvantages.

The FDA offers draft guidance (January 2003) for industry entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation".[24] This is relevant to this submission as the sample sizes for Studies 303 and 3307 were calculated based on the FDA guidelines for endometrial safety which stipulate that the endometrial hyperplasia

[22] European Medicines Agency, "Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)", 13 October 2005.
[23] European Medicines Agency, "Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009.
[24] US Food and Drug Administration, "Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation", January 2003.

observed rate at year 1 should be ≤ 1% with the upper limit of the 1-sided 95% CI less than 4%.

Contents of the clinical dossier

See Attachment 1 for details of Phase II and III studies submitted by the sponsor.

Pharmacokinetics

BZA co-administered with CE as individual components does not appear to have an effect on PK of BZA and CE (and vice versa). An in vitro study in liver cell extracts showed the metabolism of BZA and the main components of CE (estrone and equilin) do not interfere with the other's metabolic pathways.

As CE has been marketed for decades and its PK is well established, its individual PK characteristics will not be discussed further in this report.

BZA alone – summary

Summary is shown in Table 6.

Table 6: BZA alone – summary.

	BZA alone
Cmax	6.2 +/- 2.2 (ng/ml) in multiple doses of 20 mg/day in healthy postmenopausal women (n = 23)
Tmax	~2 hours
$t_{1/2}$	30 hours
Absorption	Linear increase in plasma concentration following single (up to 120mg) and multiple (up to 80mg) daily doses
Distribution	Highly protein bound *in vitro* (98-99%) Volume of distribution is 14.7 ± 3.9 l/kg (after IV administration 3mg dose)
Metabolism	Major metabolic pathway: glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver Little or no cytochrome P450-mediated metabolism
Excretion	Mainly in faeces; < 1% is eliminated in urine

BZA/CE FDC – bioequivalence

Four main bioequivalence studies were performed. These studies compared to-be-marketed formulations of BZA 20 mg/CE 0.625 mg and the BZA 20 mg/CE 0.45 mg to formulations A and B which were used in a number of studies including phase III clinical studies.

EMA identified that the CE containing formulations contain about 160 components and there was:[25]

> *no regulatory experience within the EU regarding the investigation of bioequivalence of CE-containing formulations.*

The EMA's Pharmacokinetics Working Party determined that it was acceptable that bioequivalence should be proven with respect to the active substance "conjugated estrogens" based on two lead substances, that is, estrone and equilin as well as total (conjugated and unconjugated) estrogens.

[25] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

Regarding bioequivalence, the EPAR concludes:[26]

> *bioequivalence of the formulations administered in the clinical studies and the TBM (to be marketed) formulation was adequately demonstrated.*

PK interaction studies

Study B2311065 is a clinical drug-drug interaction study conducted as a post-approval commitment to FDA. This study was not submitted to the EMA prior to approval, however was submitted to TGA. The study was Phase I, open label, two period, fixed sequence, parallel group investigation, designed to estimate the effects of multiple dose administration of itraconazole on the single dose pharmacokinetics of CE/BZA in non-obese (BMI <30 kg/m^2) and obese (BMI ≥ 30 mg/m^2). The clinical study report was accepted by the FDA on 25 September 2015.

The European SmPC states the following with regards to what appears to be the drug interaction Study B23110685:

> *In vitro and in vivo studies have shown that estrogens are partially metabolised by cytochrome P450 enzymes, including CYP3A4. However, in a clinical drug-drug interaction study, repeat administration of 200 mg itraconazole, a strong CYP3A4 inhibitor, had minimal impact on the pharmacokinetics of CE (as measured by estrone and equilin) and bazedoxifene when administered with a single dose of CE 0.45 mg/bazedoxifene 20 mg… In a pharmacokinetic study (n = 24) BMI appeared to have little impact on systemic exposure to CE and bazedoxifene.*

Summary of other pharmacokinetic parameters

See Attachment 1 for summary of other pharmacokinetic parameters.

Pharmacodynamics

Descriptions of the PD properties of the BZA/CE combination have been derived from descriptions of both active substances alone.

Mechanism of Action

- CE active ingredients: primarily the sulphate esters of estrone, equilin sulphates and 17α/β-estradiol. CE relieves menopausal symptoms by replacing the loss of estrogen in menopausal women.
- Baxedoxifene reduces the risk of endometrial hyperplasia in non-hysterectomised women, induced by estrogens.

[26] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

Table 7: Summary of PD parameters.

Parameter	
Endometrial hyperplasia	**The effects of CE decrease appear to decrease when combined with increasing doses of BZA**
Hot flushes	**The effects of CE decrease appear to *decrease* when combined with increasing doses of BZA** 0.3 mg CE has been shown to be effective to preventing hot flushes as part of standard hormone therapy;[27] however, it was not effective in preventing hot flushes when given in combination with BZA.
QTc prolongation	No indication of QTc prolongation in single agent BZA or CE. There was also no evidence of QTc prolongation based on ECG findings at doses of BZA 20 mg / CE 0.45 mg or BZA 20 mg / CE 0.625 mg in the clinical trials.

Efficacy

Table 8 shows a summary of primary and secondary outcomes in trials accepted as pivotal for BZA 20 mg /CE 0.45 mg.

Table 8: Summary of primary and secondary outcomes in trials accepted as pivotal for BZA 20 mg /CE 0.45 mg.

Efficacy	Evidence
Vasomotor symptoms *According to European guidelines (adopted by the TGA), the most important estrogen deficiency symptom to be treated by MHT are vasomotor symptoms*	Study 305 primary endpoint - statistically significant decrease in mod-severe hot flushes vs placebo (change from baseline: -7.63 average daily number BZA/CE 20/0.45 compared to placebo -4.92; p value < 0.001) Study 305 - all secondary endpoints related to VMS show a statistically significant difference vs placebo
Other estrogen deficient symptoms (all secondary endpoints or substudies)	Bleeding 3307 - cumulative rate of amenorrhea was similar to placebo and sig lower than CE/MPA; bleeding and spotting BZA/CE sig better than CE/MPA
	Breast pain 305 - no difference compared with placebo 3307 - no difference compared with placebo; significantly higher in the CE/MPA group
	Sleep 305 - statistically significance difference vs placebo in most items 3307 - statistically significance difference vs placebo in 2/5 items
	QOL 305 - statistically significance difference vs placebo in 2/5 items 3307 - statistically significance difference vs placebo but not vs CE/MPA
	Breast density 3307 - no statistically significance difference vs placebo
	Osteoporosis 3307 - statistically significance increase in mean percent change from baseline in BMD of lumbar spine compared to placebo however failed non-inferiority test

[27] Utian WH, et al. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril.* 75: 1065-79 (2001).

Efficacy	Evidence
Safety endpoint – endometrial hyperplasia	3307 primary endpoint - incidence of endometrial hyperplasia below the reference limit stipulated by EMA guidelines however there are missing and non-specific biopsy results which may have impacted the final results.

Safety

Studies providing safety data

The safety analysis was mainly based on data of the five premarket, Phase III studies (303, 304, 305, 306, 3307). Data from Phase I and II studies, as well as data from the BZA monotherapy program provided additional data. PSURs for BZA/CE (3 October 2013 to 3 April 2015) and BZA monotherapy (1 April 2009 to 15 October 2014) were also available.

Summary of safety data

Most common adverse events (AEs)

- No unexpected results when comparing the most common AEs (≥ 10%) reported for BZA/CE 20mg/0.45mg, BZA/CE 20mg/0.625mg and placebo at the time points of 3m, 12 m and 24 m.
- The most common AEs included headache, nasopharyngitis, back pain, arthralgia, pain in extremity, influenza, and myalgia

Treatment emergent adverse events (TEAEs)

- The analysis of TEAEs starts at the active phase of the study from the first dose of double blind therapy until 30 days after the last dose of study medication all TEAEs:
  - No particular TEAEs noted
- Related TEAEs:
  - The most common severe drug-related TEAE was headache in all groups
  - See EPAR[28] for the incidence of severe, treatment related (as assessed by investigators) TEAEs reported for > 1 subject in any treatment group (cumulative data up to 2 years)
  - The EPAR notes that the original dossier showed that:[29]

    > *about 3-4% of women experienced treatment adverse events considered severe and related to therapy by the investigators; there was no clear pattern or significant differences between groups. However, GCP inspection findings clearly indicated that the relatedness of AEs has not been adequately assessed and there is considerable underreporting in this regard. Therefore, the Applicant [Sponsor] was asked [by the EMA] to provide updated overall numbers of adverse events considered to be related, using a most conservative approach in reassessing relatedness.*

  - According the EPAR, this updated data was deemed acceptable; however, the EPAR further notes that:[30]

[28] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).
[29] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

considerable doubts as relates to the quality of the safety data for BZA/CE remain.

Adverse Events of Special Interest (AESI)

Adverse events considered to be potential SERM and CE class effects have been analysed, including venous thromboembolic events (VTE), cardiovascular (CHD) events, cerebrovascular accidents (CVAs) and malignancies.

Analysis was carried out using a meta-analytic approach as follows:

- Incidence rates, rate differences, and relative risk versus placebo were first calculated for each study
- Incidence rates, differences in rate versus placebo, and relative rates were summarised across studies using an inverse variance approach
- Based on these calculations, each study and endpoint was weighted differently. Poisson variance was done due to large differences in study duration.
- For studies with no events, the number of such events was inflated by 0.5 events to allow inclusion.

The results were presented as incidence rates, risk differences, and relative risks and, of note, the 95% confidence intervals are considered to be 'nominal' as they have not been adjusted for multiple comparisons.

Table 9: Summary table of AESI.

AESI	
Venous Thromboembolism	· Absolute number of events was 3 events in the BZA/CD 20mg/0.45mg and no events in the 20 mg/0.625 mg group · Insufficient data to assess differences between groups · Identified as an important **identified** risk in the RMP
Cardiac Adverse Events	· Insufficient data to assess risk compared to placebo or CE/MPA · Identified as an important potential risk in the RMP
Cerebrovascular events	· Insufficient data to assess risk compared to placebo or CE/MPA · Identified as an important potential risk in the RMP
Cancer – specifically breast cancer, ovarian cancer, endometrial cancer, lung cancer, thyroid cancer and skin cancer	· Some cases of cancer were reported in the BZA/CE groups, including endometrial cancer and ovarian cancer. Thyroid and ovarian cancer events occurred in the Phase III trial of single agent BZA. · Insufficient data to assess risk compared to placebo or CE/MPA · Identified as an important potential risk in the RMP
Gynaecological safety	· Increased number of subjects experiencing AEs relating to endometrium on all BZA/CE arms compared to placebo · Statistically significant increase in difference in endometrial thickness vs placebo (measured on TVUS) · Ovarian volume not adversely affected in those treated with BZA/CE vs placebo · Bleeding pattern favourable for BZA/CE vs placebo, however relatively low dose of MPA was used · Endometrial hyperplasia identified as an important potential risk in the RMP

[30] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

AESI	
Fractures	· Incidence of traumatic (but not osteoporotic) fractures slightly higher in those treated with BZA/CE vs placebo. · Not identified as safety concern in the RMP
Ocular events	· Post marketing reports of ocular events associated with BZA monotherapy. The post marketing reports of ocular events listed in PSUR # 9 for BZA (the most recent supplied by the Sponsor) included visual acuity reduced, vision blurred, eyelid oedema, visual impairment, visual field defect, erythema of eyelid, eye inflammation, eye pruritus, retinal vein occlusion, and retinal vein thrombosis (29 ocular events in total during the one year period). · No increase in the incidence of ocular adverse events in those treated with BZA/CE vs placebo. · Identified as an important potential risk in the RMP

Regarding gynaecological safety, the following points regarding the dataset are noted:

- Safety data from Study 304 have been excluded from the assessment of endometrial safety due to reduced bioavailability of the formulation used in this study
- AEs relating to endometrium are drawn from Studies 303, 305, 306, 3307; however, as per EMA guidelines, safety data from Studies 305 and 306 was insufficient as the treatment duration was only 3 months.
- Endometrial thickness, ovarian volume and bleeding pattern conclusions based on single Study 3307.

Overall summary

- It appears that the efficacy of CE is decreased when given in combination with BZA; as compared to efficacy of CE when given in combination with MPA. However, no attempt was made to measure this possible decrease in efficacy because the pivotal study for VVS (Study 305) did not include a direct comparison to CE/MPA (or CE/micronised progesterone). This possible decrease in efficacy of CE with BZA is important because it runs counter to accepted clinical practice guidelines to prescribe CE in the lowest possible dose (and for the shortest period of time). This may mean that women, whose symptoms might be controlled on CE 0.3 mg, are exposed to CE 0.45 mg. This could lead to an increase in known adverse reactions with CE: Arterial Thromboembolism (stroke, acute coronary syndrome), VTE, breast cancer, ovarian cancer, etc.
- Endometrial safety assessment is made on the basis of one pivotal Study 3307. As Study 303 is considered GCP non-compliant, it has not been included for the purposes of endometrial evaluation. Further, although endometrial outcomes were the primary outcome in Phase II dosing Study 203, this was measured by transvaginal ultrasound, which is not recommended as replacement of biopsy in the evaluation of endometrial hypertrophy according to the EMA guidelines.[31]

  In Study 3307, although there were no identified cases of endometrial hyperplasia in the BZA/CE 20/0.45 mg group, a small number of missed cases could mean that the pre-specified acceptable incidence for endometrial hyperplasia according to EMA guidelines (an upper limit of the 2-sided 95% confidence interval of 2%) would not have been met. Specifically it is noted that in Study 3307, 12 of 445 subjects in the BZA/CE 20/0.45 mg group are missing follow up biopsy results.

[31] European Medicines Agency, "Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)", 13 October 2005.

The use of efficacy-evaluable population (EEP) to analyse endometrial hyperplasia is accepted. That is, EEP provides the appropriate denominator. However, some cases of endometrial hyperplasia might have been missed (numerator underestimated).

- The population of women for whom progestogen containing therapy is "not appropriate" is not a well characterised subset of women suitable for MHT. More specifically, this terminology is somewhat vague and vulnerable to differences in interpretation by both prescribers and women. Relevant issues include:
  - There are already other treatment options for "women for whom treatment with progestogen containing therapy is not appropriate". Existing options for management include using an alternative progestin, dose or administration route (intrauterine device or transdermal)[32] as well as non-progestin containing therapies such as tibolone.[33]
  - Different natural and synthetic progesterones have different effects in different women; intolerance to a specific natural or synthetic progesterone might not apply to all natural and synthetic progesterones, in general.
- The efficacy and safety for the subgroup of women specified in the proposed indication ("women for whom treatment with progestogen containing therapy is not appropriate") was not directly measured in the Phase III clinical development program. EMA guidelines[34] state that the claimed indication should be clearly identified – for example, first or second line therapy – and the clinical development performed accordingly. Further, the clinical development program does not contain direct data to support the use of Duavive for the proposed Indication. For example, there are no direct data on whether "women for whom treatment with progestogen containing therapy is not appropriate" will tolerate BZA/CE. More specifically, adverse effects which, according to the EPAR,[35] the sponsor considers to be "specific adverse effects of progestins" (for example, flatulence, depression, mood swings, peripheral edema, acne, hirsuitism, increased weight) might occur with the same frequency with BZA/CE. Further, there are no direct data on which co-existing conditions (for example, depression, diabetes) are exacerbated by natural or synthetic progesterones, but not by BZA/CE.

  The EPAR[36] refers to a post hoc subgroup analysis of women for whom progestin-containing therapy is not appropriate (including patients with a medical history of diabetes or depression). In other documents related to the EMA submission provided by the sponsor, the EMA refers to data regarding progestin intolerance in the proposed population. However these documents do not appear to have been provided to the TGA.
- Two of the sponsor designated pivotal trials – Studies 303 and 305 – were found to be GCP non-compliant by EMA. Although data from Study 305 was taken into account for the efficacy evaluation by EMA and TGA, data from Study 303 was not taken into account for the assessment of efficacy.

[32] Oestrogen/progestin hormone replacement [revised Feb 2014] In: eTG [Internet]. Melbourne: Therapeutic Guidelines Limited; November 2015.
[33] Stuenkel CA, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 100: 3975-4011 (2015).
[34] European Medicines Agency, "Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009.
[35] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).
[36] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

- Of the four studies (303, 305, 306, 3307) that the sponsor has indicated are pivotal in the letter to the Delegate dated 31 October 2015, it could be argued that only two should be accepted as pivotal: Studies 305 and 3307.
  - Study 303 was GCP non-compliant and due to this, data from study 303 was not taken into account for the assessment of efficacy and is not considered to be pivotal.
  - Study 306 primarily assessed the effect of BZA/CE on VVA. The European guideline states that:[37]

    > *the most important estrogen deficiency symptoms are vasomotor symptoms (hot flushes) … the proposed primary endpoint for efficacy trials is the frequency of moderate to severe hot flushes.*

  For women with vaginal symptoms only, local treatment is recommended.[38] As this trial primarily assessed the effect of BZA/CE on VVA, this trial is considered to be supportive and not pivotal.
- Long-term (>24 months) endometrial safety is unknown. The pivotal study for endometrial safety, Study 3307, measured the incidence of endometrial hyperplasia at month 12. Study 303 followed patients up for 24 months, however due to GCP non-compliance, this trial does not contribute to the efficacy data being evaluated. Nevertheless, it is noted that in study 303, the incidence of endometrial hyperplasia at 24 months for CE 0.45 mg/BZA 0.20 mg (n = 293; EE population) was 0.34 (n = 1) with 95% CI: 0.02-1.61.
- Safety data for the fixed dose combination are sparse beyond 2 years of exposure. This is relevant as the RANZCOG Menopausal Hormone Therapy Advice[39] notes that "most guidelines recommend using HRT for up to four to five years". It is also noted that in a study of 3302 women in the US, the median total duration of frequent VMS (≥6 days in the previous 2 weeks) is 7.4 years.[40]
- A total of 1585 women were exposed to the BZA 20 mg/CE 0.45 mg dose, 1241 to placebo and 1162 to active comparators. As stated by the EPAR:[41]

  > *due to this limitation in the number of women treated together with the limited treatment duration [as noted above] and missing data in elderly women [as noted below], the data set does not allow the safety assessment of rare AEs known to be relevant class effects for CE or BZA (e.g. VTE or cancer).*

  Therefore, assessment of the potential additive effects of the combination of BZA/CE on the individual components' safety profiles cannot be made.
- There is limited data in women over the age of 65 years of age. The North American Society Statement on Continuing Use of Systemic Hormone Therapy after age 65 notes that:[42]

[37] European Medicines Agency, "Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)", 13 October 2005.
[38] RANZCOG, Management of the menopause, Nov 2014.
[39] RANZCOG, Menopausal Hormone Therapy Advice, Jul 2015.
[40] Avis NE, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med.* 175: 531-539 (2015).
[41] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).
[42] North American Menopause Society. The North American Menopause Society Statement on Continuing Use of Systemic Hormone Therapy After Age 65. *Menopause* 22: 693 (2015).

> *vasomotor symptoms persist for an average of 7.4 years and for more than a decade in many women. Moderate to severe vasomotor symptoms have been documented in 42% of women aged 60 to 65 years. Thus, many women will continue to have vasomotor symptoms after age 65, and these symptoms can disrupt sleep and adversely affect health and quality of life.*

At the opposite end of the scale, it is noted that BZA/CE was not studied in patients with premature menopause.

Clinical questions

1. The evaluator seeks clarification regarding several key aspects of the proposed indication:

> *Treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestogen-containing therapy is not appropriate.*

Specifically:

- The approach for defining the targeted patient population.
- Subgroup analysis to justify the targeted patient population.
- The rationale for second line listing.
- Disparity in the indication across jurisdictions, in terms of the second line listing.

2. The EPAR report[43] states that Study 3307 showed that:

> *based on 314 and 333 evaluable biopsies in the BZA 20 mg/CE 0.45 mg group and the BZA 20 mg / CE 0.625 mg group, respectively, the incidence of endometrial hyperplasia / malignancy at month 12 was 0.32% (two-sided 95% CI 0.01%; 1.76%) and 0.30% (two-sided 95% CI 0.01; 01.66%), respectively. Thus, the upper limit of the 2-sided 95% confidence interval of the incidence of endometrial hyperplasia was below the reference limit of 2% stated in the CHMP HRT Guideline in each of the two groups.*

However, this specific data cannot be found in the Study 3307 final study report which indicates that for BZA 20 mg/CE 0.45 mg (n = 335) with one diagnosis of hyperplasia, the hyperplasia rate is 0.30% with an upper limit of 2-sided 95% CI is 1.65.

Similarly, the EPAR[44] indicates that in Study 303 the incidence for the purposes of assessing endometrial hyperplasia from a regulatory perspective contains a different denominator to that contained within the study report: the EPAR considers 294 biopsies to be evaluable with an incidence of endometrial hyperplasia/malignancy at month 12 of 0.00% (95% CI 0.00%; 1.25%).

Please indicate where the data in the EPAR report is located within the dossier and how it was derived.

3. Due to GCP non-compliance, the results from study 303 were not taken into account for the assessment of BZA/CE efficacy. However the Sponsor indicated that they considered it to be a pivotal study.

[43] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).
[44] European Medicines Agency, European Public Assessment Report: Duavive (oestrogens conjugated / bazedoxifene).

- Given that study 303 is GCP non-compliant and the EMA determined that the data should not be used to demonstrate the endometrial safety of Duavive, why is this listed as a pivotal trial in the Australian dossier?
- Please summarise why this study was found to be GCP non-compliant

4. Based on the data presented, BZA appears to reduce the efficacy of CE. This is potentially important for safety because it is possible that a higher dose of estrogen is required in a BZA/CE combination compared to CE/progestogen to achieve a similar level of efficacy. Please comment on this concern.
5. For Study 305, please provide the point estimates of the placebo - subtracted treatment effect for the co-primary endpoints with 95% confidence intervals. These were not found within the dossier.
6. It is noted that a number of recognised safety concerns for the individual components of BZA/CE such as arterial thrombotic events, breast cancer, and ovarian cancer for CE and ocular events for BZA have not been listed as an "important identified risk", only as potential risks. Why are these not listed as "identified" risks for the combination product?
7. Please provide the most recent SmPC for Duavive.

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU-RMP Version 2.7 (dated 22 December 2014, DLP 1 January 2013) and Australian Specific Annex (ASA) Version 1.1 (dated June 2016), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 10.

Table 10: Summary of safety concerns.

Safety concerns	Summary
Important identified risks	· Venous thromboembolism (VTE) · Increased triglycerides
Important potential risks	· Arterial thromboembolic events: Cerebrovascular events and myocardial infarction (MI) · Coronary heart disease (CHD) · Atrial fibrillation · New presentation or aggravation of pre-existing renal failure or insufficiency · Renal carcinoma or adenoma · Gallbladder disease · Cancers: breast, ovarian, endometrial, lung, thyroid, skin, gastrointestinal and other cancers. · Endometrial hyperplasia. · Depression · Ocular events

Safety concerns	Summary
	· Gastroesophageal reflux disease (GERD) · Drug-drug interactions · Off-label use
Missing information	· Use in elderly patients · Use in hepatic impaired patients · Use in renal impaired patients · Use in patients with malignancy · Use in patients with history of cardiovascular disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina), diabetes or obesity or long-term smoking · Long-term (>2 years) safety data on breast protection and gynaecological cancers (endometrial and ovarian in particular)

RMP reviewer comment

The US PI includes a boxed warning of increased risk of probable dementia in postmenopausal women aged ≥65 years. The draft Australian PI document and European SmPC also include Dementia in the Precautions section. On this basis, the RMP evaluator recommends that dementia should be added as an important potential risk.

The evaluation of the nonclinical and clinical aspects of the Safety Specification may also recommend the inclusion of other safety concerns.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor has proposed routine pharmacovigilance activities[45] to address all of the safety concerns. In addition, two post authorisation studies are proposed, as detailed below. These studies will not involve Australian participants. A drug-drug interaction study is listed in the EU-RMP and ASA. This study has been completed and the results were submitted.

Table 11: Proposed pharmacovigilance activities.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Post-authorisation safety study (US PASS)	VTE, CHD, MI, stroke, breast cancer, ovarian cancer, endometrial hyperplasia and endometrial malignancy	The objective of this study is to estimate the incidence of safety events of interest among postmenopausal women exposed to CE/BZA and compare to the incidence seen among postmenopausal women exposed to any estrogen/progestin (E+P) combination therapy.	March 2019; protocol currently under review
Drug utilisation study (EU)	Use in patients with history of cardiovascular	Collect data on: · the baseline and historical characteristics of patients	March 2019; protocol currently

[45] Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
	disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina), diabetes or obesity or long-term smoking; off-label use	(age, cardiovascular risk factors, history of a CVD event, history of breast, ovarian or endometrial cancers, other selected medical comorbidities, prior use of estrogen/progestin therapy, indication for use, and other current or recent drug therapies). · describe and compare the pattern of use during follow-up (average prescribed dose, prescribed days supply per prescription, number of prescriptions, and the duration of continuous treatment) · estimate off-label use (age of the patient, prescribed dose, or recorded indication)	under review

RMP reviewer comment

The planned 4 year duration of the US PASS study is considered inadequate for determining the effects of Duavive on breast, ovarian and endometrial cancer given the latency of tumour development and the knowledge that uterine effects may persist for 10 years. It is noted that the study protocols have not been finalised, and it is recommended that the duration of follow-up is reconsidered for the carcinogenic endpoints. Once finalised, the study protocols should be submitted to TGA. In addition, the sponsor should indicate in the ASA the anticipated dates for submission of the post market studies in Australia.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor has concluded that only routine risk minimisation activities[46] are required for all safety concerns.

RMP reviewer comment

The sponsor concluded that there is minimal risk for off-label use in adult and paediatric populations, overdose or transmission of infectious agents. Similarly, the potential for misuse for illegal purposes was considered to be low as bazedoxifene is not active in the CNS. The proposed routine risk minimisation activities are considered sufficient for these safety concerns.

[46] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

The sponsor has assessed the potential impact on the RMP which may result from their responses to clinical and nonclinical questions. The sponsor concludes that there is no new clinical or nonclinical safety considerations that warrant inclusion in the RMP.

In the clinical evaluation report received from TGA, reference to 'important identified risk' has been made. Refer to the sponsor's response to the clinical questions (excerpt reproduced below):

> *…Therefore, the sponsor believes that based on the totality of the data, and the consideration of the distinct pharmacology of the FDC from the monotherapy components, the classification of arterial thrombotic events, breast cancer, ovarian cancer, and ocular events as important potential risks for CE/BZA is appropriate. Moreover, the sponsor believes that these safety concerns are adequately monitored by its routine, and ongoing, pharmacovigilance activities. Through these activities, should evidence emerge that provides evidence of an association of CE/BZA with these recognized safety concerns for the individual components of the FDC, the Sponsor will re-evaluate the RMP with the potential to re-classify them to important identified risks, as appropriate.*

Evaluator's comment

The sponsor's justification for classifying "arterial thrombotic events", "breast cancer", "ovarian cancer" and "ocular events" as important potential risks is acceptable. These risks are identified risks for either one of the individual components, but it is possible that use in combination reduces the risk of these events as a function of the composite pharmacology of the combined tissue selective estrogen complex. The clinical trial data are supportive of this argument as they do not show an increased incidence, so until further data are available to confidently confirm or exclude these important potential risks, it is acceptable to retain the "important potential risk" classification.

Recommendation #2 in RMP evaluation report

Dementia should be included in the RMP as an important potential risk.

Sponsor response

Dementia was studied in Women's Health Initiative Memory Study (WHIMS) as a sub-study of the Women's Health Initiative (WHI) in women aged 65 and above. There are no data on the effect of either conjugated estrogens or conjugated estrogens combined with medroxyprogesterone acetate in younger, menopausal women regarding dementia/memory impairment.

The patient population (newly menopausal women) taking CE/BZA are symptomatic, not the population the WHIMS data describe (65 years and above). Observational data

suggests that both estrogens alone and SERMs may have a beneficial impact on memory and cognition.[47]

During the clinical development program of CE/BZA, in the 5 Phase III studies (all data up to 2 years), no TEAEs of memory impairment were reported in the treatment group "BZA 20 mg + CE any dose/BZA 20 mg" nor the placebo group. Additionally, a search of the post-marketing safety database has not revealed any reported cases of memory impairment. The guideline on good pharmacovigilance practices (GVP)[48] defines the "important identified and important potential risk" as an identified or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health. Therefore, the sponsor believes that there is currently insufficient evidence of a causal link of CE/BZA with dementia, and this event should not be included in the RMP as an important potential risk.

Evaluator's comment

The sponsor's response is noted, but the RMP evaluator disagrees with the sponsor's interpretation of the guidelines. In addition to sections referenced by the sponsor, the guidance also states that:

> *What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health (see also V.B.1). Normally, any risk which is clinically important and which is/is likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be included here.*

In addition, pharmacological class effects should also be included in the safety specification unless there is sufficient evidence to indicate that they do not apply to the product.

The sponsor has included probable dementia in the precautions section of the Australian PI (and EU SmPC), and it is also included as a boxed warning for Duavive in the US PI. It is acknowledged that there are no post-market reports of dementia, but adverse event reporting is known to have low sensitivity. The data from clinical trials has not led to the removal of the precautionary statement. On this basis, there is sufficient justification to include dementia as an important potential risk. Pharmacovigilance and risk minimisation measures should be proposed and documented in the ASA.

Recommendation #3 in RMP evaluation report

The ASA should be amended to include the anticipated dates for submission of the post-market studies in Australia.

Sponsor response

The final study report for the US Post Approval Safety Study (US-PASS) is expected to be available by 31 March 2019 and a supplement to the final study report, which will contain fatal outcomes, is expected to be available by 31 March 2021. The final study report for the European Union Drug Utilisation Study (EU-DUS) is expected to be available by 31 March 2020. The anticipated submission dates in the ASA have been amended accordingly. A copy of the amended ASA (version 1.1) is provided.

As previously discussed with TGA, copies the PASS and DUS protocols that were previously sent to TGA have also been provided.

[47] Maki PM. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. *Menopause* 20: 695-709 (2013); Fischer B, et al. Effects of hormone therapy on cognition and mood. *Fertility and Sterility* 101: 898-904 (2014).
[48] European Medicines Agency, "Guideline on good pharmacovigilance practices (GVP), Module V – Risk management systems (Rev 2) (EMA/838713/2011 Rev 2*)", 28 March 2017.

Evaluator's comment

The sponsor has updated the ASA as requested. It is noted that the anticipated submission of the PASS report is 2021, which is ~2 years after the final study report is expected. The sponsor should commit to submitting the final study report for the PASS when it becomes available in 2019, as well as the supplement to this report in 2021.

Recommendation #4 in RMP evaluation report

The sponsor should consider the adequacy of the duration of the proposed US-PASS study for its intended purpose of identifying effects on rates of reproductive malignancies.

Sponsor response

The sponsor provided justification regarding the adequacy of the study duration, including the following:

> *For the study protocol, the length of patient follow-up and the expected number of endometrial hyperplasia and endometrial cancer events was estimated based on pilot/feasibility analyses of the healthcare database that was used. This data, along with sample size calculations, showed that clinically meaningful hazard ratios (HRs) for endometrial hyperplasia and endometrial cancer should be detected by the end of the study.*
>
> *…Patients who enter the study in May 2014 will accrue 4 years of follow-up. Additionally, if not censored by an event, all users who enter the study/initiate drug as late as May 2017 will have a minimum of 12 months of follow-up.*

Evaluator's comment

The sponsor's response is noted, as has the submission of the study protocols. It is also noted that the study is currently ongoing and that the protocol has also been considered by PRAC/CHMP.

Recommendation #5 in RMP evaluation report

A boxed warning for the risk of endometrial cancer, cardiovascular and other risks, including dementia should be added to the PI.

Sponsor response

The sponsor does not agree with inclusion of a black box in the PI for Duavive as justified below.

The sponsor understands that there is rationale based on the WHI data for the inclusion of venous thromboembolism (VTE) and stroke in a boxed warning since both estrogens have a boxed warning in the Australian PI, and estrogens and SERMs have a USPI warning for VTEs. The age stratified data from the WHI should be included in the VTE warning for estrogens since the risk was definitively age related (as is known without any treatment). The stroke warning only applies to estrogens, and the age stratified data should be included. For BZA, there is no stroke risk based on Phase III clinical studies and nearly 10 years of real world safety data collection. Myocardial infarction should not be part of a boxed warning for Duavive, as there was no signal in Phase III studies, nor in all BZA clinical studies, and the WHI estrogen alone arm data revealed a reduced risk of myocardial infarction.

For the Duavive PI, we believe a contraindication for women with an active of a history of VTE as well as a precaution is sufficient. A comparison of an analysis of historical data from the WHI study of CE/MPA and the CE/BZA Phase III studies is provided. As enrolment in both studies was based on HT labelling, the WHI CE/MPA cohort aged 50 to 59 years provides a comparable population to the subjects enrolled in the CE/BZA Phase III studies. The comparison of the WHI 50 to 59 year age group cohort to the CE/BZA

Phase III studies showed that rates of VTEs in the placebo groups appear to be similar and the risk of VTEs in CE/BZA treated subjects does not appear to exceed the risk observed in CE/MPA treated subjects.

The sponsor disagrees with the inclusion of endometrial cancer in a boxed warning for Duavive. Duavive cannot be taken as two separate pills (CE and bazedoxifene) unlike other hormone therapies where the estrogen and progestin components can be prescribed separately. In that scenario, there is a possibility that the estrogen component can be taken unopposed, raising the risk of endometrial cancer. Bazedoxifene alone has been shown in the extension (7 years) of the Phase III Study 3068A1-301-GL (hereafter referred to as Study 301) osteoporosis treatment study to reduce the risk of endometrial cancer. In three different Phase III clinical studies, Duavive was shown to control endometrial hyperplasia to a level < 2% over a 1 year treatment period similar to what has been shown for estrogen plus progestin therapy.[49]

As documented in the response to point 2 (above), the sponsor has provided a justification for not including dementia as an important potential risk in the RMP. Therefore, the data currently available does not justify the inclusion of dementia as a warning in a black box.

Evaluator's comment

The sponsor's opposition to the inclusion of a boxed warning in the PI is noted. The differences in use of boxed warnings in different countries were also raised by the clinical evaluator. This issue is referred to the clinical Delegate for their final decision on the content of the PI. The RMP evaluator recommends that a boxed warning is used for consistency with other estrogen containing products.

It is also noted that in their response to the clinical evaluator, the sponsor stated that:

> *In considering the overall weight of evidence, the risks of breast cancer, VTEs, endometrial cancer and cardiovascular events are no greater for the CE/BZA fixed dose combination (FDC) in comparison to the individual components (BZA or CE) or CE/MPA.*

Recommendation #6 in RMP evaluation report

The contraindications of "severe uncontrolled hypertension" and "other undiagnosed breast pathology" should be added to be consistent with the contraindications for other conjugated estrogens.

Sponsor response

The sponsor has provided a justification that the safety profile of Duavive differs from that of unopposed estrogens. However, the sponsor's response also including the following:

> *…The conjugated estrogens component of Duavive cannot be taken independently and, as stated, the combination does not necessarily (and, in fact there is no evidence to date) result in any additive or synergistic response on either efficacy or safety endpoints. It is quite possible that with BZA degrading estrogens receptors in a selective manner that it may reduce certain "side effects" associated with estrogens, but this remains hypothetical at this time.*
>
> *Unlike the safety profile of unopposed estrogens, during the 10 years clinical development program of CE/BZA, there has been no adequate clinical evidence to suggest that 'severe uncontrolled hypertension' and/or 'other undiagnosed breast pathologies' should be declared as contraindications for this product. With regard to "severe uncontrolled hypertension" it is worthy to note that the clinical studies for CE/BZA were not powered to fully evaluate the risk of having this condition, and in*

[49] MacLennan AH, et al. Oral estrogen and combined estrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev.* 18: CD002978 (2004).

fact, the criteria of elevated blood pressure and/or uncontrolled hypertension, excluded the subject from study participation. Patients with certain risk factors including hypertension, should be closely supervised during treatment, and if a significant increase in blood pressure is reported, immediate evaluation should take place and CE/BZA withdrawn. Similarly, the CE/BZA studies also excluded subjects with a history of breast cancer and/or subjects having unresolved findings suggestive of malignant changes on a prestudy mammogram. Before initiating Duavive, a complete personal and family medical history should be taken. During treatment with CE/BZA, women should be advised to have periodic check-ups and report any changes in their breasts to their physician. Any necessary investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Evaluator's comment

- Hypertension – it is noted that the PI recommends close monitoring for patients with hypertension, and immediate withdrawal of treatment in the case of a significant increase in blood pressure. Consideration of whether this is sufficient, or whether a contraindication is more appropriate, is referred to the clinical Delegate.
- Undiagnosed breast pathology – advice is given regarding breast screening and risks with breast cancer, but not for undiagnosed breast pathologies (except by inference from "suspected" breast cancer in the contraindications). This matter is referred to the clinical Delegate for their consideration of the appropriate wording for the contraindication and precautions that may be appropriate for undiagnosed breast pathologies.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

- Dementia should be included in the safety specification as an important potential risk (see point 2)
- The nonclinical evaluator's comments should be addressed by the sponsor.

The delegate's attention is drawn to the following:

- A black boxed warning is recommended to be included in the PI, to inform prescribers of the risk associated with important safety concerns such as VTE, arterial thromboembolic events, coronary heart disease, malignancies and dementia: (see point 5)
- The PI should include appropriate contraindication or precaution statements for hypertension and undiagnosed breast pathology (see point 6)

Recommendations that should be addressed in the next update to the ASA

The sponsor should commit to submitting the final study report for the PASS when it becomes available in 2019, as well as the supplement to this report in 2021.

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

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

Clinical evaluation report

In the round 1 clinical evaluation report, the clinical evaluator asked the following question of the sponsor:

> *6. It is noted that a number of recognised safety concerns for the individual components of BZA/CE such as arterial thrombotic events, breast cancer, and ovarian cancer for CE and ocular events for BZA have not been listed as an "important identified risk", only as potential risks. Why are these not listed as "identified" risks for the combination product?*

The sponsor's response was considered in Reconciliation point 1.

Nonclinical evaluation report

The nonclinical evaluator provided the following advice on the nonclinical sections of the RMP:

> *Results and conclusions drawn from the nonclinical program for Duavive detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator except for the following:*
>
> § *Ovarian neoplasia with bazedoxifene in mice and rats is not reported.*

The addition of the following information is in order:

> *Treatment with bazedoxifene caused benign ovarian granulosa cell tumours in transgenic mice (at oral doses ≥150 mg/kg/day for up to 6 months) and in rats (≥16.9 mg/kg/day for up to 2 years). This is seen to occur via a pharmacological mechanism, with bazedoxifene interfering with normal estrogen feedback at the level of the hypothalamus and/or pituitary, causing hypersecretion of luteinising hormone, and giving rise to persistent proliferative follicles. It is not expected to be relevant to postmenopausal women with quiescent ovaries.*
>
> *It is further noted that sections titled "Carcinogenicity" and "General carcinogenicity findings" present duplicate information. The latter should be removed.*

The sponsor's PI does not fully reflect the nonclinical evaluator's recommendation. The sponsor should address the nonclinical evaluator's recommendations.

Key changes to the updated RMP

ASA Version 1.0 (dated September 2015) has been superseded by ASA Version 1.1 (dated June 2016). No substantive changes to the content of the ASA were made.

RMP Evaluator's comments

The evaluator has no objection to the above changes.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *The EU-RMP Version 2.7 (dated 22 December 2014, DLP 1 January 2013) with Australian Specific Annex Version 1.1 (dated June 2016) revised to the satisfaction of the TGA and any future updates must be implemented.*

VII. Overall conclusion and risk/benefit assessment

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

Quality

The pharmaceutical chemistry evaluator had no objections to registration.

Nonclinical

The nonclinical evaluator did not have any objections to the registration. No safety concerns were identified from the nonclinical data.

Clinical

Pharmacodynamics and pharmacokinetics

The submitted dossier included 20 clinical pharmacology studies; 15 were for the BZA mono product.

Efficacy

The clinical development programme started in 2001 and the last phase 3 trial (3307) was finalised in 2011. The pivotal trials were carried out in the US, Finland, Norway, Italy, Netherlands, Belgium, Poland, Spain, Denmark, Hungary, Brazil, Argentina, Chile, Columbia, Mexico, Australia, and New Zealand.

The pre-market clinical development program included four Phase III trials (303, 305, 306, 3307); however:

- There were concerns about whether 303 was GCP compliant.
- 306 used vulvular-vaginal atrophy as the primary endpoint, which is not an established endpoint for regulatory trials for menopausal symptoms: EMA guidelines[50] states that frequency of moderate to severe hot flushes (vasomotor symptoms) should be the primary regulatory endpoint.

These studies are not critical to satisfactorily establishing efficacy. Consequently, they are not discussed in this overview. They have been fully evaluated in the CER; as have all the submitted Phase II and Phase III trials. The two paragraphs below briefly provide some summary results for trials 305 and 3307, which were sufficient to satisfactorily establish efficacy.

Briefly, trial 305 was conducted at 43 sites in the US. It reported a statistically-significant, placebo-subtracted reduction from baseline to week 12 in number of moderate-to-severe hot flushes/day of 2.71, 95% CI (1.57, 3.84), for the 20/0.45 mg strength (proposed for registration in Australia). This endpoint was one of the co-primary endpoints. Results for the other co-primary endpoint of average daily severity score are given. The secondary endpoints were supportive.

Trial 3307 was conducted at 171 sites in various countries, including Australia. The results for the primary endpoint of endometrial hyperplasia by 12 months are summarised in the clinical evaluation report. There was one case of endometrial in 335 women in the 20/0.45

[50] European Medicines Agency, "Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1)", 13 October 2005.

mg group. The upper limit of the 2-sided CI was 1.65%, which is below the threshold of 2%, specified in EMA Guidelines, and adopted by TGA.

Safety

The safety analysis was mainly based on data from the five premarket, Phase III studies (303, 304, 305, 306, 3307). Data from Phase I and II studies, as well as data from the BZA monotherapy program provided additional data. PSURS for BZA/CE (3 October 2013 to 3 April 2015) and BZA monotherapy (1 April 2009 to 15 October 2014) were also available.

No unexpected safety concerns emerged from the pre-market studies; however, as is usually the case with pre-market studies, these were relatively small and follow-up was relatively short; mainly to 12 months, with extensions to 24 months; and sparse data beyond 24 months. Data from BZA mono-therapy were available out to 7 years.

No post-market regulatory action has been taken on CE/BZA by any OS regulator.

Post marketing ocular events have been reported with the BZA mono product (Conbriza) in the EU. The post marketing reports of ocular events listed in PSUR # 9 for BZA (the most recent PSUR supplied by the sponsor) included: visual acuity reduced, vision blurred, eyelid oedema, visual impairment, visual field defect, erythema of eyelid, eye inflammation, eye pruritus, retinal vein occlusion, and retinal vein thrombosis (29 ocular events in total during the one year period). This has been added to the Summary of safety concerns for Duavive.

The EMA approved SmPC for the BZA mono product (Conbriza) lists the following as contraindications: active or past history of venous thrombotic events (for example, deep vein thrombosis, pulmonary embolism, retinal vein thrombosis), unexplained uterine bleeding, endometrial cancer. Under “Special warnings and precautions for use” the following are listed: venous thromboembolism, lack of data on use in women with hypertriglyceridaemia, lack of data on use in women with breast cancer, lack of data on use in women with severe renal impairment.

Safety of CE/progestogen is well characterised. There is an increased risk of coronary heart disease, stroke, DVT, and breast cancer (and a reduction in the risk of fractures, colorectal cancer and diabetes.) On the other hand, at this point in time, safety of CE/BZA is subject to much more uncertainty than CE/progestogen. There are limited data on the safety (or efficacy) of CE/BZA versus CE/progestogen.

The EMA is requiring that all MHT update their SmPCs and PILs (patient information leaflets) with the latest information about ovarian cancer. The Australian PI for Duavive should align with these changes.

Risk management plan

Summary of safety concerns

The sponsor was asked why some of the important identified risks for CE/MPA (for example, ATE [stroke, MI], breast cancer, ovarian cancer) were not also listed as important identified risks for CE/BZA. Their response is provided.

The safety profile of CE/BZA is subject to much more uncertainty than CE/MPA. This is to be expected, given that there is less post-marketing experience with CE/BZA than CE/MPA. It is possible that CE/BZA does not increase the risk of ATE, breast cancer and ovarian cancer (in contrast to CE/MPA), although the sponsor does not currently have the necessary data to establish this.

At this point in time, pending further advice, and awaiting possible further explanation from the sponsor in their pre-ACPM response; ATE, breast cancer, and ovarian cancer should be listed as important identified risks in the ASA, similar to CE/MPA. As stated in the FDA's boxed warning for Duavee: In the absence of comparable data, these risks should be assumed to be similar for other doses of conjugated estrogens and other dosage forms of estrogens.

Also, the FDA has listed dementia in its boxed warning.

Pharmacovigilance plan

Two post-authorisation studies are planned – one to be carried out in the US and the other in the EU. Details as listed in the table below.

Table 12: Pharmacovigilance plan.

Title, Study/activity type, location	Objectives	Safety concerns addressed	Status
US PASS: Active surveillance of CE/BZA using US healthcare data	To estimate the incidence of VTE, CHD, MI, stroke, breast cancer, ovarian cancer, endometrial hyperplasia and endometrial cancer among postmenopausal women initiating CE/BZA or those initiating Oestrogen and Progesterone (E+P)	VTE, CHD, MI, Stroke, Breast cancer, Endometrial hyperplasia, Endometrial cancer, Ovarian cancer	Ongoing; began in May 2014. Final study report is due following accumulation of 4 years of post-US launch data. The first interim study report was finalised on 11 March 2016.
EU Drug Utilisation Study to be carried out in Belgium, Finland, France, Germany, Italy, Netherlands, Spain, Sweden and the United Kingdom	The study will provide information on the characteristics of users of CE/BZA or E+P therapy in real-world clinical care. Information to be collected includes baseline and historical characteristics and where possible, describe and compare the pattern of use during follow-up as well as estimate the proportion that may have been prescribed the product outside the specifications of the product label	Use in patients with history of cardiovascular disease or diabetes. Off-label use.	Planned. Final study report to be submitted following accumulation of 3 years of post-launch data.

Risk minimisation measures

The sponsor's plan is to mitigate the important safety concerns using routine risk minimisation measures (RMMs) (for example, statements in PI). No additional RMMs are proposed.

Risk-benefit analysis

Delegate's considerations

Benefits and associated uncertainties

Established benefits from pre-market trials include:

- reduction in the number and severity of vasomotor episodes.
- the BZA component protects the endometrium from hyperplasia due to the CE component.

The main areas of uncertainty in the benefits of Duavive are discussed. They are briefly paraphrased below.

1. There is no direct comparison of CE/BZA to CE/MPA (or CE/micronised progesterone) in trial 305, which is the pivotal study for the efficacy endpoint of vasomotor symptoms.

BZA could reduce the comparative efficacy of CE to reduce vasomotor symptoms versus progestogens. As stated in the clinical evaluation report, this is important because it runs counter to accepted clinical practice guidelines to prescribe CE in the lowest possible dose (and for the shortest period of time). This may mean that women, whose vasomotor symptoms might be controlled on CE 0.3 mg, are exposed to CE 0.45 mg. There is concern that this could lead to an increase in CE adverse reactions, including: ATE (stroke, acute coronary syndrome), VTE, breast cancer, ovarian cancer, etcetera; although there are no definitive data on this one way or the other (that is, uncertainty).

2. Endometrial biopsy results were missing for 12 women in the CE/BZA 0.45/20 mg group in trial 3307

A small number of missed cases could mean that the pre-specified acceptable incidence for endometrial hyperplasia specified in EMA guidelines (an upper limit of the 2-sided 95% confidence interval of 2%) might not have been met.

3. There are limited long-term data (beyond 12 months) on endometrial proliferation

(Endometrial proliferation is discussed under both efficacy and safety.)

Safety and associated uncertainties

CE/progestogen(s) are well established products, for which the safety is well-characterised. In contrast, CE/BZA is a newer product and, unsurprisingly, its safety is subject to more uncertainty. More specifically, there are currently limited data on:

- long-term endometrial safety (>12 months).
- long-term safety for uncommon adverse reactions (for example, VTE, ATE, breast cancer, ovarian cancer)

Summary of benefit-risk balance

The main weakness in the submitted evidence was the limited comparative data versus CE/progestogens, for both efficacy and safety.

The sponsor has satisfactorily established efficacy on the established regulatory endpoint of vasomotor symptoms versus placebo. And the sponsor has submitted evidence showing BZA controls endometrial hyperplasia due to CE, with some uncertainty due to missing data, and limited data beyond 12 months.

Based on the data submitted, the benefit-risk balance for Duavive is positive for the proposed Australian indications: women with estrogen deficiency symptoms in whom progestogen containing therapy is not appropriate. These are also the indications

approved by the EMA. The risk-benefit balance is also positive for the FDA approved indication: treatment of moderate to severe vasomotor symptoms associated with menopause. A discussion of the indications is given below.

In short, the benefit-risk balance for Duavive is subject to more uncertainty than the benefit-risk balance for CE/progestogens, but is positive. The relative increase in uncertainty associated with Duavive versus CE/progestogens is due to the limited post-marketing experience with Duavive versus the extensive post-marketing experience with CE/progestogens. The pre-market clinical development program for Duavive was acceptable.

Proposed action

Pending further advice, at this point in time, efficacy and safety have been satisfactorily established.

There are questions around the wording of the indications. EMA, FDA, Health Canada, and Swiss Medic have each approved different indications for Duavive/Duavee.

The Delegate has no reason to say, at this time, that Duavive should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Indication wording

The sponsor agrees with the proposed indication in the Delegate's Overview:

> *Treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.*
>
> *Notes:*
>
> *Duavive should be used for the shortest duration consistent with treatment goals and risks for the individual woman.*
>
> *Experience in women older than 65 years is limited.*

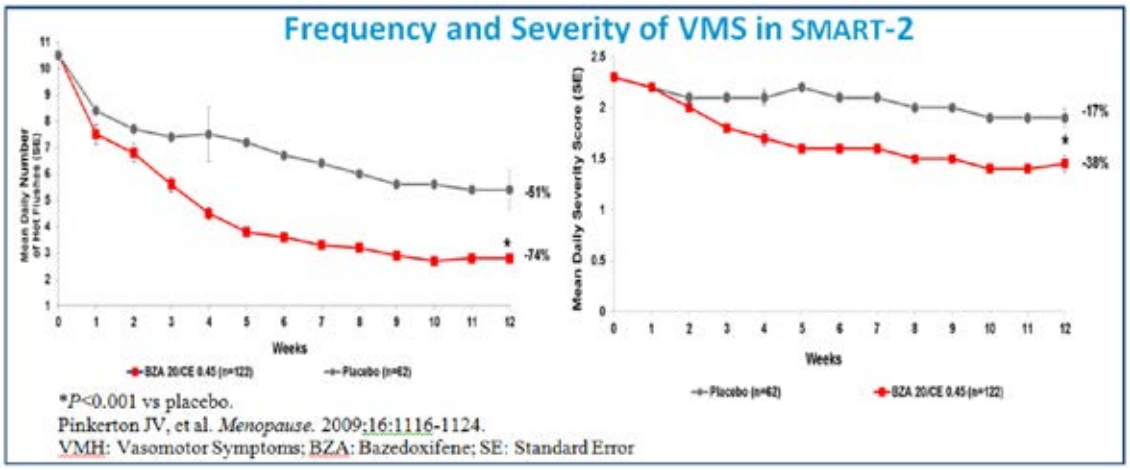
The proposed indication wording is in accordance with the rationale for the development of CE/BZA, and is in accordance with the patient population studied, providing an alternative to the available estrogen + progestin (E+P) therapies for efficacious management of the symptoms associated with estrogen deficiency in post-menopausal women with an intact uterus. By eliminating the progestin component and substituting with BZA, the stimulation of the endometrium by estrogen is abolished and therefore the most common side effects associated with progestin use including increased uterine bleeding, breast pain and increases in mammographic breast density are diminished or absent, thereby improving tolerability and compliance.

The sponsor is seeking registration approval for one dose of CE/BZA (CE 0.45 mg/BZA 20 mg). The following data support the proposed indication.

The safety and efficacy of CE/BZA as a treatment for moderate to severe vasomotor symptoms associated with menopause was established in the Phase III SMART 2 Study (3115A1-305). CE/BZA significantly reduced the number and severity of hot flushes compared with placebo (Figure 1). At week 12, CE 0.45 mg/BZA 20 mg reduced hot flushes from baseline by 74% (10.3 hot flushes [baseline] versus 2.8 [week 12]) compared

with 51% (10.5 versus 5.4) for placebo. More participants at week 12 had at least a 75% decrease in hot flushes with CE 0.45 mg/20 mg BZA (61%) versus placebo (27%; P < 0.001). Efficacy for CE 0.45 mg/BZA 20 mg for the treatment of estrogen deficiency symptoms demonstrated an onset of a clinically significant reduction in hot flushes as early as Week 3 and showed evidence of efficacy for up to 2 years of treatment (SMART- 1, Study 3115A1-303). Importantly, improvements in the estrogen deficiency symptoms of vasomotor symptoms (VMS) observed in the CE/BZA treated subjects also correlated with improvements in the time to fall asleep, improvement in sleep adequacy, a reduction in sleep disturbance, and a positive impact on the menopausal QoL.

Figure 1: Frequency and severity of VMS in SMART-2.



In addition to the efficacy shown for VMS, Duavive has also been shown to improve symptoms associated with other well established consequences associated with estrogen deficiency such as VVA as demonstrated in SMART 3 (Study 3115A1-306), and a positive impact on bone as shown in SMART 1 (Study 3115A1-303) and SMART 5 (Study 3115A1-3307) studies.

Duavive represents a new paradigm for treating menopausal symptoms due to estrogen deficiency in women with a uterus by utilizing bazedoxifene, a SERM paired with CE, instead of a progestin to protect the endometrium. The results from the SMART-1 and -5 studies demonstrated that CE/BZA met the pre-defined criteria for endometrial protection for products containing estrogens.[51]

Though not a conventional E+P hormone therapy, which has well established VMS efficacy, comparison with historical data from a recent Cochrane Systematic Database Review shows that CE 0.45 mg/BZA 20 mg has comparable efficacy to other progestin-containing hormonal therapies.[52]

Update the ASA to the EU-RMP to include ATE, breast cancer and ovarian cancer as important identified risk

Based on the totality of scientific data, and also as previously communicated by the sponsor, the inclusion of ATEs, breast cancer and ovarian cancer as 'important identified risks' rather than 'important potential risks' is not currently warranted.

Also, as acknowledged in the Round 2 RMP evaluation report:

> *The Sponsor's justification for classifying 'arterial thrombotic events', 'breast cancer', 'ovarian cancer' and 'ocular events' as important potential risks is acceptable. These*

[51] Pinkerton JV, et al. Relief of vasomotor symptoms with the tissueselective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. *Menopause* 16: 1116-1124 (2009).
[52] MacLennan AH, et al. Oral estrogen and combined estrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev.* 18: CD002978 (2004).

> *risks are identified risks for either one of the individual components, but it is possible that use in combination reduces the risk of these events as a function of the composite pharmacology of the combined tissue selective estrogen complex. The clinical trial data are supportive of this argument as they do not show an increased incidence, so until further data are available to confidently confirm or exclude these important potential risks, it is acceptable to retain the 'important potential risk' classification.*

CE/BZA is a FDC product that pairs CE with BZA, which is a SERM and acts as both an estrogen receptor agonist and antagonist. The pairing of a SERM with one or more estrogens (CE/BZA) is described as a TSEC. The pharmacology of a TSEC is a composite of its individual components. Therefore, the safety profile of CE/BZA is distinct from that of its individual components (CE and BZA) when administered as monotherapy.

The above referenced safety concerns have been included as potential risks in the CE/BZA RMP in order to be consistent with the risks identified for BZA monotherapy, the known class effects or experience with SERMs, and the known safety concerns reflected in the product labelling for CE and other estrogen products. Moreover, the reason for inclusion of these events is to maintain consistency between the CE/BZA and BZA RMPs and also to coincide with the feedback obtained from other health authorities.

The sponsor confirms that the data from the CE/BZA Phase III studies do not suggest an association between any of the above referenced safety concerns and treatment with CE/BZA.

With respect to ATEs, subjects with a history of arterial thromboembolic disease (stroke and myocardial infarction [MI]) were excluded from the Phase III studies. Active or past history of arterial thromboembolic disease are listed as contraindications in the proposed CE/BZA product labelling, consistent with class labelling for CE monotherapy.

With respect to breast cancers in Phase III studies, breast cancer was reported in 0.3% of subjects in the CE 0.45 mg/BZA 20 mg treatment group and 0.2% of subjects in the placebo group with a relative risk of 1.11 (95% confidence interval 0.33-3.78) compared with placebo.

In the estrogen plus progestin WHI study, after total mean follow-up of 11.0 years, CE 0.625 mg/medroxyprogesterone (MPA) 2.5 mg (note this utilises a higher dose of CE than that contained in Duavive) was associated with more invasive breast cancers compared with placebo (hazard ratio 1.25; 95% CI 1.07, 1.46). Breast cancers in the estrogen plus progestin group were similar in histology and grade to those in the placebo group, but were more likely to be node positive. There were more deaths directly attributed to breast cancer (hazard ratio 1.96; 95%CI 1.0, 4.04) in the CE 0.625 mg/MPA 2.5 mg treatment group compared with the placebo group.

No cases of ovarian cancer were reported for subjects treated with CE 0.45 mg/BZA 20 mg, or placebo in any of the CE/BZA Phase III studies.

The sponsor believes that the referenced safety concerns for ATEs, breast cancer, and ovarian cancer currently do not meet the criteria of an identified risk, and are more appropriately classified as important potential risks. The classification of these safety concerns as potential risks versus important identified risks in the CE/BZA RMP is in accordance with international standards on pharmacovigilance practices.[53]

Furthermore, ongoing evaluation of the post marketing safety surveillance data for CE/BZA to date has not revealed any new information concerning any of the important potential risks identified in the CE/BZA RMP that would warrant a re-classification to the

[53] European Medicines Agency, "Guideline on good pharmacovigilance practices (GVP), Module V – Risk management systems (Rev 2) (EMA/838713/2011 Rev 2*)", 28 March 2017.

category of 'important identified risks'. This includes three PSURs prepared and submitted to date and the first interim analysis of a post approval safety study currently being conducted in the US.

Therefore, the sponsor believes that based on the totality of the currently available data, and the consideration of the distinct pharmacology of the FDC from the monotherapy components, the classification of arterial thrombotic events, breast cancer and ovarian cancer as important potential risks for CE/BZA is appropriate. The sponsor believes that these safety concerns are adequately monitored by routine ongoing signal detection activities. Through these activities, should the evidence emerge that provides evidence of an association of CE/BZA with these recognised safety concerns for the individual components of the FDC, the sponsor will re-evaluate the RMP with the potential to re-classify the risks, as appropriate.

Inclusion of boxed warning in the Australian Duavive PI

The sponsor wishes to note that the class warnings (for example, in the US as referenced in the Delegate's Overview) which are represented by standard texts in the form of a boxed warning (for example, in the US, Canada, and Australia) were as a consequence of the results from the WHI which utilised CE (0.625 mg)/MPA (2.5 mg) or CE (0.625 mg) alone. Therefore, the relevance to Duavive which contains a lower dose of CE and no progestin component should be considered in this context.

For this reason, and based on the currently available scientific data, along with the reasons cited below, the Sponsor believes that a boxed warning as in the current Duavive US Prescribing Information does not accurately depict the risks attributable to or the potential risks attributable to Duavive. The sponsor believes that the information concerning endometrial cancer, cardiovascular disorders, and probable dementia is adequately conveyed to prescribers in the Precautions section of the proposed Australian Duavive PI. The justification is summarised below:

Venous Thromboembolism (VTE)

- For context, the sponsor acknowledges that the results of the WHI estrogen-alone (CE 0.625 mg) sub-study indicate an increased risk of VTE for women receiving estrogens alone therapy and that the increase in VTE risk was more likely to be in the first year of treatment. For women aged between 50-59 years, the VTE rate per 1,000 women-years through the 5-year study period was 7 in the placebo group with 1 additional case per 1000 estrogens only users. Note the likely age range of the potential Duavive patient is 50- 59 years.
- The proposed Duavive Australian PI includes active or previous history of VTE as contraindications. In addition, further details of this identified risk are provided in the Precautions section of the proposed Australian PI.

Stroke

- In the WHI estrogen-alone substudy, an increase risk of stroke was demonstrated in women between the ages of 50-79 taking estrogens-alone therapy. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) alone versus those receiving placebo (18 versus 21 per 10,000 women-years). For BZA, there is no risk of stroke based on the phase 3 clinical studies and nearly 10 years of collection of real world safety data.

In summary, for the proposed Duavive Australian PI, the sponsors believe that a contraindication for women with an active history of VTE located in the Precautions section and the Adverse Effects section of the proposed Duavive PI appropriately conveys the currently available information for risk of VTE and stroke associated with the use of

Duavive. This is based on the age stratified WHI data on estrogens-alone therapy and Phase III clinical trial data for BZA alone therapy.

Myocardial infarction (MI)

- MI should not be included in a boxed warning for Duavive, as there was no safety signal in the Phase III studies, or in any of the BZA clinical studies. Notably, the data from the WHI estrogen alone arm revealed a reduced risk of myocardial infarction. Current post-marketing safety data for Duavive and BZA also have not identified any safety signal concerning MI.

Endometrial cancer

- The sponsor disagrees with the inclusion of endometrial cancer in a boxed warning for Duavive but does believe that the appropriate place to locate the data is in the Precautions and Adverse Events section of the proposed Australian PI. Duavive cannot be taken as two separate pills (CE and BZA) unlike other hormone replacement therapies where the estrogen and progestin components can be prescribed separately. In this scenario, there is a possibility that the estrogen component can be taken unopposed, raising the risk of endometrial cancer. BZA alone has been shown in the extension (7 years) of the Phase III Study (Study 301): Osteoporosis Treatment Study to Reduce the Risk of Endometrial Cancer). In three different Phase III clinical studies, Duavive was shown to control endometrial hyperplasia to a level <2% over a 1 year treatment period similar to what has been shown for estrogen plus progestin therapy.[54] This is why endometrial cancer was not included as an 'identified risk' in the RMP.

Dementia

- The Sponsor disagrees with the inclusion of dementia in a boxed warning since dementia is not an 'identified risk' or 'potential risk' in the Duavive RMP. While the sponsor recognises that bazedoxifene is not registered in Australia, dementia is not an 'identified risk' or 'potential risk' in the EU approved bazedoxifene RMP.
- Dementia was studied in the WHIMS as a substudy of the WHI in women aged 65 and above. There are no data on the effect of either conjugated estrogens or conjugated estrogens combined with medroxyprogesterone acetate in younger, menopausal women regarding dementia/memory impairment. The patient populations are different, that is, the patients on Duavive will be newly diagnosed symptomatic postmenopausal women. The population of women in the WHIMS study was 65 years and above. Observational data suggests that both estrogens alone and SERMs may have a beneficial impact on memory and cognition.[55]

The sponsor believes that the safety profile of Duavive for a well-informed prescription decision is appropriately reflected in the Precautions section of the proposed Australian PI.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM) resolved to recommend to the TGA Delegate of the Secretary that:

[54] MacLennan AH, et al. Oral estrogen and combined estrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev.* 4: CD002978 (2004).
[55] Maki PM. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. *Menopause* 20: 695-709 (2013); Fischer B, et al. Effects of hormone therapy on cognition and mood. *Fertility and Sterility* 101: 898-904 (2014).

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Duavive modified release tablet containing 0.45 mg/20 mg of CE/BZA to have an overall positive benefit-risk profile for the Delegate's amended indication:

> *Duavive is indicated in the treatment of moderate to severe vasomotor symptoms associated with menopausal women with a uterus.*
>
> *Duavive should be used for the shortest duration consistent with treatment goals and risks for the woman.*
>
> *The experience treating women older than 65 years is limited.*

In making this recommendation, the ACPM:

- Noted that bazedoxifene (BZD) as a selective estrogen receptor modulator is approved for the treatment of postmenopausal osteoporosis in the EU.
- Noted that Duavive showed efficacy in the vasomotor symptoms of menopause in clinical trials.
- Noted that Duavive did not meet primary endpoint in reducing endometrial hyperplasia at 12 months in the clinical trials.
- Agreed that Duavive treatment should be initiated at least 12 months after last period and should be used for the shortest duration consistent with treatment goals and risks for the woman.
- Expressed concerns about the safety profile of Duavive especially the risk associated with extended use.
- Expressed concerns that the experience treating women older than 65 years is limited.

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) and specifically advised the following:

The committee noted that registered HRT products have a black-box warning included in the PI. There was a general agreement that the approval of this product should not be contingent upon the inclusion of a boxed warning in the PI but that this matter should be referred to the decision Delegate for resolution with the sponsor.

Specific advice

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

- *The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.*

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of 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 Duavive 0.45/20 conjugated estrogens/bazedoxifene acetate 0.45 mg/20 mg modified release tablet blister pack, indicated for:

> *Duavive is indicated for treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.*
>
> § *Duavive should be used for the shortest duration consistent with treatment goals and risks for the individual woman.*
>
> § *Experience in women older than 65 years is limited.*

Specific conditions of registration applying to these goods

· The Duavive (conjugated estrogens/bazedoxifene acetate) EU RMP, Version 2.7, dated 22 December 2014 (data lock point, 1 January 2013) with ASA Version 1.1, dated June 2016, and any subsequent revisions, as agreed with TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Duavive at the time this AusPAR was published is at Attachment 1. For the most recent PI, 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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