



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for ulipristal acetate

Proprietary Product Name: EllaOne

Sponsor: ERA Consulting (Australia) Pty Ltd

September 2015

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
ASA	Australian Specific Annex
AUC	area under the plasma concentration-time curve
AUC _{t1-t2}	area under the plasma concentration-time curve from time t1 to t2
CBG	corticosteroid binding globulin
CL/F	apparent total body clearance of the drug from plasma
Cmax	maximum plasma drug concentration
CMI	Consumer Medicine Information
CNS	central nervous system
DAE	adverse event leading to discontinuation
ECG	electrocardiogram
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GI	gastrointestinal
HCG	human chorionic gonadotropin
HDL	high density lipoprotein
IC50	half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IUD	intrauterine device
LDL	lipoprotein
LH	lutenising hormone
MITT	modified Intention To Treat

Abbreviation	Meaning
P-gp	P-glycoprotein
PI	Product Information
PO	per os
PSUR	periodic safety update report
PR	progesterone receptor
RMP	Risk Management Plan
SAE	serious adverse event
SHBG	sex hormone binding globulin
SmPC	Summary of Product Characteristics
t½	elimination half life
Tmax	time to reach maximum plasma concentration following drug administration
UPI	unprotected intercourse

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	25 February 2015
<i>Active ingredient:</i>	Ulipristal acetate
<i>Product name:</i>	EllaOne
<i>Sponsor's name and address:</i>	ERA Consulting (Australia) Pty Ltd Level 3, 88 Jephson Street Toowong QLD 4066
<i>Dose form:</i>	Tablet
<i>Strength:</i>	30 mg
<i>Container:</i>	Blister pack
<i>Pack size:</i>	One tablet per pack
<i>Approved therapeutic use:</i>	EllaOne is indicated for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	One tablet to be taken orally as soon as possible, but no later than 120 hours (5 days), after unprotected intercourse or contraceptive failure
<i>ARTG number:</i>	219535

Product background

This AusPAR describes the application by ERA Consulting (Australia) Pty Ltd to register a new chemical entity, ulipristal acetate (trade name: EllaOne), for emergency contraception. The treatment consists of one tablet to be taken orally as soon as possible, but no later than 120 h (5 days) after unprotected intercourse (UPI) or contraceptive failure. The tablet can be taken with or without food.

Regulatory status

Ulipristal acetate (EllaOne, also known as Ella in some countries, amongst numerous trade names) was approved in the European Union (EU) using the Centralised Procedure on 15 May 2009 for emergency contraception within 120 h (5 days) of unprotected sexual intercourse or contraceptive failure.

It was also approved in the United States (US) on 13 August 2010 for the indication:

Prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure, ELLA is not intended for routine use as a contraceptive.

The status of worldwide approvals for EllaOne 30 mg ulipristal acetate tablet product is shown in Table 1.

Table 1: International regulatory status for ulipristal acetate 30 mg tablet.

Country	Tradename	Approval Date	Authorisation Nr	Launch Date
Armenia	Dvella 30 mg	06/06/2012	N11521	14/12/2012
Australia	EllaOne	06/03/2015	219535	Not yet launched
Austria	ellaOne	15/05/2009*	EU/1/09/522/001	02/01/2010
Azerbaijan	Dvella 30 mg	26/08/2013	13-00873	Not yet launched
Belarus	Dvella 30 mg	01/12/2011	9835/11	01/03/2013
Belgium	ellaOne	15/05/2009*	EU/1/09/522/001	01/10/2009
Benin	Ellaone	08/02/2013	G0063/12	15/03/2013
Bolivia	Upris	26/06/2012	II-46125/2012	Not yet launched
Bolivia	Upris	12/09/2012	II-47549/2012	29/07/2013
Bosnia and Herzegovina	ellaOne	17/06/2011	04-07.1-8261-1/10	18/04/2012
Bulgaria	ellaOne	15/05/2009*	EU/1/09/522/001	20/04/2010
Burkina Faso	Ellaone	14/05/2012	0624820122N000000	12/11/2012
Cameroon	Ellaone	14/02/2012	9111201	12/11/2012
Canada	Ella	23/01/2015	2436329	Not yet launched
Central African Republic	EllaOne	21/09/2011	N°200/011/017	05/11/2012
Chad	ellaOne	31/12/2012	1000001	15/02/2013
Colombia	PostDayPlus	15/11/2013	2013M-0014697	29/10/2014
Congo Brazzaville	EllaOne	07/10/2013	CV/13S - 02A/01	26/11/2013
Croatia	Ellaone	07/12/2011	EU/1/09/522/001	27/05/2011
Cyprus	ellaOne	15/05/2009*	EU/1/09/522/001	05/07/2010
Czech Republic	ellaOne	15/05/2009*	EU/1/09/522/001	30/11/2009
Denmark	ellaOne	15/05/2009*	EU/1/09/522/001	30/11/2009
Djibouti	Ellaone	15/05/2009	N/A	02/04/2012
Dominican Republic	Urge	27/06/2014	2014-0546	Not yet launched
Ecuador	Upris	29/08/2013	IEM-739-08-2012	Not yet launched

Table 1 (continued): International regulatory status for ulipristal acetate 30 mg tablet.

Country	Tradename	Approval Date	Authorisation Nr	Launch Date
El Salvador	Duprisal 30 mg	30/07/2012	F031505072012	Not yet launched
El Salvador	Erthia	03/04/2013	F017014032013	Not yet launched
Estonia	ellaOne	15/05/2009*	EU/1/09/522/001	Not yet launched
Finland	ellaOne	15/05/2009*	EU/1/09/522/001	03/11/2009
France + Dom-Tom*	ellaOne	15/05/2009*	EU/1/09/522/001	01/10/2009
Gabon	ellaOne	30/12/2010	3972/10	02/04/2012
Georgia	Dvella	23/05/2012	007899	Not yet launched
Germany	ellaOne	15/05/2009*	EU/1/09/522/001	01/10/2009
Greece	ellaOne	15/05/2009*	EU/1/09/522/001	14/01/2010
Guinea (Conakry)	ellaOne	23/03/2012	NA	12/11/2012
Hong-Kong	Ella	05/11/2012	HK-61541	31/07/2013
Hungary	ellaOne	15/05/2009*	EU/1/09/522/001	25/11/2009
Iceland	ellaOne	15/05/2009*	EU/1/09/522/001	05/2012
Ireland	ellaOne	15/05/2009*	EU/1/09/522/001	09/05/2012
Israel	Ella	23/06/2011	146-32-33299-00	21/05/2012
Israel	Ella	12/07/2011	146-39-33469-00	21/05/2012
Israel	Ella	08/03/2015	146-39-33469-01	21/05/2012
Italy	ellaOne	15/05/2009*	EU/1/09/522/001	02/04/2012
Ivory Coast (RCI)	ellaOne	14/08/2012	E-2012-048	05/11/2012
Kazakhstan	Dvella	22/12/2011	RK-LS-5-№018537	29/11/2012
Kyrgyzstan	Dvella	10/10/2012	Series R-2012-549 / KR n°9690	19/03/2013
Latvia	ellaOne	15/05/2009*	EU/1/09/522/001	04/02/2010
Lebanon	ellaOne	31/01/2012	96426/11	04/01/2013
Liechtenstein	ellaOne	15/05/2009*	EU/1/09/522/001	01/12/2013
Lithuania	ellaOne	15/05/2009*	EU/1/09/522/001	01/11/2009
Luxembourg	ellaOne	15/05/2009*	EU/1/09/522/001	01/10/2009

Table 1 (continued): International regulatory status for ulipristal acetate 30 mg tablet.

Country	Tradename	Approval Date	Authorisation Nr	Launch Date
Macau	Ella	24/04/2013	HK-61541	01/10/2013
Madagascar	ellaOne	07/10/2011	25.1.1.199	12/11/2012
Malaysia	ella	03/04/2012	MAL12035079AC	05/09/2012
Mali	ellaOne	18/11/2011	2011-1479/MS-SG	18/01/2013
Malta	ellaOne	15/05/2009*	EU/1/09/522/001	Not yet launched
Mauritius	ellaOne	23/12/2011	NA	04/06/2012
Mexico	Femelleone	21/02/2014	041M2014	15/07/2014
Moldavia	Dvella	21/06/2012	17854	11/02/2013
Morocco	ellaOne	02/04/2012	40/12/DMP/21/NNP	01/11/2013
Netherlands	ellaOne	15/05/2009*	EU/1/09/522/001	05/10/2009
Nicaragua	Erthia 30 mg	10/05/2012	01120470512	Not yet launched
Niger	ellaOne	12/12/2011	12-00443-11	12/11/2012
Norway	ellaOne	15/05/2009*	EU/1/09/522/001	15/12/2009
Panama	Duprisal 30 mg	11/04/2014	86857	Not yet launched
Panama	Erthia 30 mg	11/04/2014	86858	Not yet launched
Paraguay	ULIP	07/05/2013	1783801 EF	25/07/2013
Poland	ellaOne	15/05/2009*	EU/1/09/522/001	04/02/2010
Portugal	ellaOne	15/05/2009*	EU/1/09/522/001	01/04/2010
Romania	ellaOne	15/05/2009*	EU/1/09/522/001	01/04/2010
Senegal	Ellaone	04/07/2013		31/10/2013
Serbia	ellaOne	07/10/2010	4451/2010/12	15/09/2011
Singapore	ella	21/06/2011	SIN13979P	18/11/2011
Slovak Republic	ellaOne	15/05/2009*	EU/1/09/522/001	30/11/2009
Slovenia	ellaOne	15/05/2009*	EU/1/09/522/001	19/11/2010
South Korea	ellaone	14/07/2011	5006	27/07/2011
Spain	ellaOne	15/05/2009*	EU/1/09/522/001	17/12/2009
Sweden	ellaOne	15/05/2009*	EU/1/09/522/001	11/11/2009

Table 1 (continued): International regulatory status for ulipristal acetate 30 mg tablet.

Country	Tradename	Approval Date	Authorisation Nr	Launch Date
Switzerland	ellaOne	21/12/2012	62531	01/12/2013
Taiwan	ella	24/05/2012	025542	01/09/2012
Tajikistan	Dvella	13/12/2012	003818	Not yet launched
Togo	ellaOne	28/04/2014	SP.TG 4485	24/03/2015
Tunisia	ellaOne	26/03/2013	4983013	20/10/2014
Turkey	Ella	31/12/2013	137/35	15/05/2014
Turkmenistan	Dvella	11/04/2012	8197	08/03/2013
UK	ellaOne	15/05/2009*	EU/1/09/522/001	01/10/2009
Ukraine	Dvella	30/05/2012	UA/12179/01/01	02/04/2013
USA	ella	13/08/2010	NDA 022474	01/12/2010
Uzbekistan	Dvella	24/10/2012	B-250-95 No. 44112	Not yet launched
Venezuela	Evintualle	19/05/2014	E.F. 40,692/14	Not yet launched
Viet-Nam	ella	10/10/2012	VN1-751-12	17/06/2013

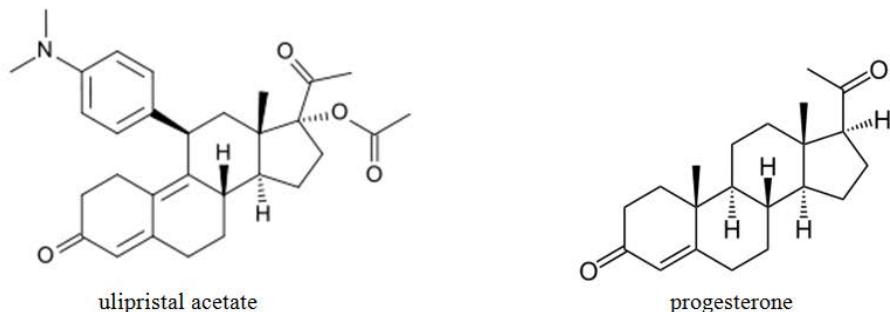
Product Information

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 www.tga.gov.au/product-information-PI.

II. Quality findings

Introduction (if applicable)

Ulipristal acetate is a synthetic derivative of progesterone (see comparison of structures in Figure 1). It is an orally active selective progesterone receptor (PR) modulator that acts via high affinity binding to the human PR. When used for emergency contraception, the mechanism of action is inhibition or delay of ovulation via suppression of the lutenising hormone (LH) surge.

Figure 1: Chemical structures of ulipristal acetate and progesterone.

There are no monographs for either the drug substance or the finished product.

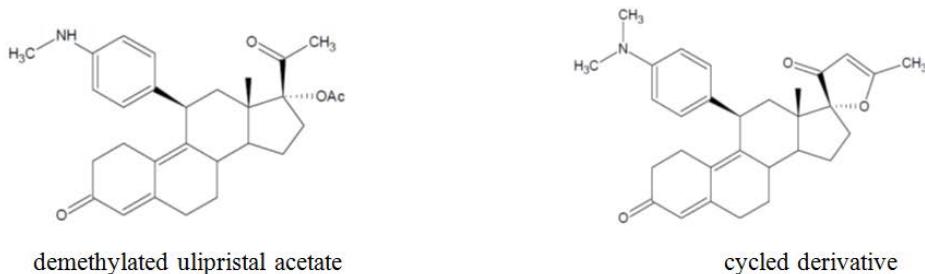
Drug substance (active ingredient)

The drug substance is manufactured by Crystal Pharma SA in Spain. The synthetic route has been adequately described and is adequately controlled. The process leads to a single crystalline form and the material is micronised prior to use in the product.

The specifications of the drug substance are acceptable and include tests, with appropriate limits, for:

- Assay;
- Related substances: demethylated ulipristal acetate (Figure 2, a degradant and metabolite) and a cycled derivative are controlled; individual unknown impurities, total unknown impurities, and total impurities are controlled;
- Residual solvents at levels at or below those required by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Figure 2: Chemical structures of demethylated ulipristal acetate and cycled derivative.



The particle size distribution after micronisation is controlled with appropriate limits.

The drug substance was found to be sensitive to both light and moisture and the storage of the drug substance (and the manufacture of the finished product) take these facts into account.

Drug product

The product contains no unusual excipients for this dosage form. The tablets are uncoated and unscored. Water is used as a granulating solvent in a typical process except that care is taken to omit light.

The finished product is manufactured at either Cenexi in Osny, France, or Delpharm Lille SAS in Lys Lez Lannoy, France.

The specifications are for the most part acceptable and where required the release limits are tighter than the expiry limits to allow for changes on storage. In particular:

- The assay limits at release comply with EU guidelines.
- The demethylated ulipristal acetate limits at release and expiry are set to also account for this impurity being a metabolite of ulipristal acetate.
- The cycled derivative limits at expiry and at release are in line with the *ICH qualification limit of 0.5% and this is acceptable*.

- Each unknown impurity limit at expiry and release is *in line with the ICH identification limit of 0.2% and this is acceptable.*
- Total impurities are limited at expiry and release. *Given the individual impurity limits these are acceptable.*
- The dissolution limits (both expiry and release) are appropriate.
- There is a test for disintegration with a limit.

The initially proposed assay limits at expiry were not acceptable. According to Therapeutic Goods Order No 78 (TGO78), the lower limit must be no less than 92.5%. The lower limit for assay was revised and this was acceptable.

In relation to the shelf life, data was included to support an unopened shelf life of 3 years when stored below 25°C with the additional storage conditions of "store in original container", "protect from light" and "protect from moisture" which will appear on the labels and in the PI as:

Store below 25°C. Store in the original packaging to protect from moisture. Keep the blister in the outer carton to protect from light.

The PI and labels have been finalised with respect to chemistry and quality control.

Biopharmaceutics

Four bioavailability/bioequivalence studies were provided:

- Study HRA2914-501 investigated how the particle size distribution of the drug substance affected the bioavailability. Micronisation led to an increase of ~40% in both the maximum plasma drug concentration (Cmax) and the area under the plasma concentration-time curve (AUC). It was also found that absorption was quicker and greater from a tablet containing micronised drug substance compared to a capsule containing micronised drug substance. It was decided to develop a 30 mg immediate release tablet using micronised drug substance.
- Study HRA2914-516 investigated the relative bioavailability of the commercial tablets from the proposed Cenexi site (at the time called Cardinal Health, France) and commercial tablets from the Leon Pharma site: not proposed to supply to Australia. This study indicated that the site of manufacture will not affect the bioavailability, for example, product from the Delpharm site can be taken as bioequivalent to product from the Cenexi site. The two tablets tested were bioequivalent.
- Study HRA2914-512 investigated the effect of food on the commercial tablet from the Cenexi site. Food increased the time to reach maximum plasma concentration following drug administration (Tmax) from 3/4 h to 3 h, reduced Cmax by ~40%, and increased AUC by ~25%. *This was brought to the attention of the Clinical Delegate to decide if these differences are clinically significant given that the draft PI states that the tablets can be taken with or without food.*
- Study HRA2914-668 determined the absolute bioavailability of the proposed tablet in the fasted state. This was 27%.

The test methods used in the studies were appropriate and were used to determine levels of ulipristal acetate and the active metabolite desmethyl ulipristal acetate in plasma.

The commercial formulation was used in the Phase III clinical efficacy studies and as such no relative bioavailability study comparing a clinical and commercial formulation is required.

Advisory committee considerations

Given that there were no complicated issues with the chemistry, manufacturing and control, and, bioavailability aspects of the submission, details relating to this submission were not presented to the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

Approval of this application cannot be recommended at this time on quality grounds or with respect to chemistry, manufacturing and control as:

The proposed lower limit for assay at expiry does not comply with that stipulated by Australian legislation; namely Therapeutic Goods Order No 78 (TGO 78) which requires the limit to be NLT 92.5%. The data in the dossier clearly show that this limit can be met.

If this limit was tightened to NLT 92.5%, approval could be recommended.

Evaluator comment update

The sponsor has now agreed to adopt this limit and the approval is now recommended with respect to all chemistry, manufacturing and control aspects. Ergo, approval is now recommended.

III. Nonclinical findings

Introduction

The general quality of the nonclinical dossier was mostly high. All pivotal safety-related studies were conducted according to Good Laboratory Practice (GLP).

Pharmacology

Primary pharmacology

Ulipristal acetate was shown to bind to human recombinant PR-A and -B (PR-A and PR-B) with nanomolar affinity (half maximal inhibitory concentration [IC50] values in radioligand binding assays, ~7-8 nM), comparable to that of the existing PR antagonist, mifepristone. Antagonism of PR mediated stimulation of transcription and alkaline phosphatase (ALP) activity was demonstrated for the drug in cell based functional assays; mifepristone produced similar inhibition.

In vivo, ulipristal acetate displayed significant anti progestogen activity, demonstrated by inhibition of ovulation (mice and rats), inhibition of endometrial proliferation (rabbits), and prevention of pregnancy (rats and rabbits; through inhibition of ovulation and/or inhibition of implantation). Ulipristal acetate was significantly more potent (~8 times) than mifepristone at inhibiting ovulation in the rat following oral administration. Anti ovulatory and anti fertility effects of the drug were dependent on the time of administration following coitus and up to implantation. With administration following establishment of pregnancy, ulipristal acetate caused abortion in guinea pigs when given in late gestation and pregnancy loss and stillbirths in some cynomolgus monkeys when given during the early period of organogenesis; surviving infants born to ulipristal acetate treated monkeys showed no teratogenicity.

The two major metabolites of ulipristal acetate, monodesmethyl ulipristal and didesmethyl ulipristal, also exhibited PR antagonist activity. Receptor affinity and *in vitro* functional activity of the monodemethylated metabolite were comparable to the parent molecule, while *in vivo* activity (inhibition of endometrial proliferation in rabbits) was weaker. The didemethylated metabolite was far less active than its parent (~13 fold lower receptor affinity; 100 fold lower potency against PR dependent transcription).

Secondary pharmacodynamics and safety pharmacology

Ulipristal acetate was found to also have significant affinity for the glucocorticoid receptor (comparable or several times less than for the PR across studies). However, this did not translate to significant anti glucocorticoid activity *in vitro*, with the drug's potency for inhibition of glucocorticoid receptor mediated transcription being 36 times lower than that against PR mediated transcription in cell based functional assays. *In vivo*, the drug was approximately half as potent as mifepristone at inhibiting thymic involution in rats. Monodesmethyl and didesmethyl ulipristal were 18 and 34 times less potent than ulipristal acetate at inhibiting glucocorticoid receptor mediated transcription *in vitro*, respectively.

Ulipristal had some affinity for the androgen receptor (8-10 times lower than for the PR) and negligible affinity for the oestrogen receptor and mineralocorticoid receptor. Receptor screening assays additionally revealed weak affinity for the GABA gated Cl- channel and PPAR γ (63% and 51% inhibition of reference ligand binding with ulipristal acetate at 10 μ M).

Specialised safety pharmacology studies covered the core battery of systems (central nervous system [CNS], cardiovascular and respiratory). Single oral administration of ulipristal acetate did not affect CNS or respiratory function in rats at \leq 125 mg/kg (yielding peak plasma levels of ulipristal acetate more than 50 times higher than in patients at the maximum recommended human dose). The drug did not inhibit the hERG K $+$ channel expressed in mammalian cells or affect action potential parameters in isolated dog Purkinje fibres at \leq 10 μ M (27 times higher than the clinical plasma Cmax for total ulipristal acetate, and \sim 1500 times the clinical plasma Cmax for unbound ulipristal acetate). In dogs, increased blood pressure was observed following dosing with ulipristal acetate at 25 and 125 mg/kg oral administration (per os, PO) (yielding 12-42 times the clinical plasma Cmax), although the magnitude and duration of the effect was not dose related. No effect on blood pressure was evident in dogs at 5 mg/kg PO (yielding \sim 0.7 times the clinical Cmax). Heart rate and electrocardiogram (ECG) were unaffected in dogs at \leq 125 mg/kg PO, and no treatment related effects on ECG were seen in the 6 and 9 month general repeat dose toxicity studies in monkeys (\leq 25 mg/kg/day PO).

Pharmacokinetics

Absorption of ulipristal acetate following oral administration was rapid in mice, rats, dogs and humans (Tmax, 0.5-1 h). Systemic exposure was dose proportional in the mouse, less than dose proportional in the rat and greater than dose proportional in the dog and Cynomolgus monkey. Oral bioavailability of ^{14}C ulipristal acetate derived radioactivity (representing unchanged drug plus radiolabelled metabolites) was high in rats and Cynomolgus monkeys. The plasma half life was typically \sim 2-4 h in mice, 3-6 h in rats, and 11-18 h in Rhesus monkeys compared with 32 h in humans. Repeated daily administration was not associated with significant plasma accumulation in animals.

Ulipristal acetate displayed very high plasma protein binding in all species studied (96.7-99.5% in mouse, rat, rabbit, dog and monkey plasma; 98.2% in human). Monodesmethyl ulipristal was also shown to be highly plasma protein bound (96.5-96.9% in human plasma). Albumin, α 1 acid glycoprotein, high density lipoprotein (HDL) and low density

lipoprotein (LDL) were shown to be the chief contributors to ulipristal acetate binding, with binding to sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) low. Tissue distribution of radioactivity occurred rapidly following oral administration of ^{14}C ulipristal acetate to rats. Outside of the gastrointestinal (GI) tract, highest levels of radioactivity were detected in liver, fat and the adrenal gland. The peak concentration in the ovary was almost 3 times the plasma Cmax. Distribution to the CNS was shown, but was modest (brain:plasma Cmax, ~ 0.2). Binding of drug related material to melanin was evident.

Sequential demethylation of ulipristal acetate, mediated by CYP3A4, generates monodesmethyl and didesmethyl ulipristal, the major human metabolites. These were also major metabolites in all laboratory animal species tested. *In vitro* experiments with liver microsomes showed a similar pattern of metabolism across species (mouse, rat, rabbit, dog, monkey and human). All human circulating metabolites were also identified *in vivo* in monkeys with the exception of a hydroxylated metabolite (M8). However, this was only a very minor metabolite, accounting for $\sim 3\%$ of drug related material in plasma at 1 h post dose. Excretion of ^{14}C ulipristal acetate derived radioactivity was primarily via the faecal route in rats, monkeys and humans. Biliary excretion was shown to be a major route of excretion in rats.

Sufficient similarities in the pharmacokinetic profiles of the nonclinical species and humans exist to allow them to serve as acceptable models for the assessment of ulipristal acetate toxicity in humans.

Pharmacokinetic drug interactions

Ulipristal acetate showed weak inhibitory activity against CYPs 2C8, 2B6, 2C9, 2D6 and 3A4 in experiments with human liver microsomes; IC50 values ranged from 22-100 μM (59-270 times higher than the clinical Cmax at the maximum recommended human dose). Monodesmethyl ulipristal was also shown to have some inhibitory activity against CYPs 2C8, 2B6, 2E1 and 2C19, with 14-40% inhibition observed at a concentration of 4 μM (27 times the clinical Cmax for the metabolite). Given the large margin between the inhibitory concentrations and peak plasma levels in patients, no clinical significance is attached to these findings. Neither ulipristal acetate nor its monodemethylated metabolite induced CYP1A2 or 3A4 activity in cultured human hepatocytes (each compound tested up to 13.5 times the clinical Cmax).

Ulipristal acetate and monodesmethyl ulipristal were shown to not be substrates of P-glycoprotein (P-gp). Both compounds were P-gp inhibitors: ulipristal acetate inhibited P-gp with an IC50 of 0.732 μM (2 times the clinical Cmax), and the IC50 for monodesmethyl ulipristal was slightly greater than 2 μM (>13.5 times the clinical Cmax). The P-gp inhibitory activity of the parent drug, but not the monodemethylated metabolite, is considered to be potentially clinically significant.

In experiments with expressed human transporters, ulipristal acetate inhibited the BCRP transporter with an IC50 value of 8.92 μM . This is 2.8 times lower than the maximum estimated concentration in the intestinal lumen on the apical side of the enterocytes after a 30 mg dose (that is, 25 μM [= 10% of 30 mg/250 mL]), and clinical relevance is predicted. Ulipristal acetate was shown to not be a substrate of OATP1B1 or OATP1B3. The drug did not produce significant inhibition of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3 or BSEP, but the maximum tested concentrations were around 2 times lower for the hepatic uptake transporters and 5 times lower for the renal transporters than those recommended in the relevant European Medicines Agency (EMA) guideline¹ (that is,

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

experiments with hepatic uptake transporters were conducted with ulipristal acetate at up to 13 times the predicted unbound hepatic inlet concentration rather than up to 25 times, and experiments with renal transporters and hepatic efflux transporters were conducted at up to 10.5 times the mean unbound Cmax rather than up to 50 times). Nevertheless, the extent of inhibition seen at the tested concentrations was such that inhibition of $\geq 50\%$ would not be expected to be reached if the higher recommended concentrations had been used; accordingly, no clinically relevant inhibition of these transporters is predicted.

Toxicology

Acute toxicity

Formal single dose toxicity studies were conducted with ulipristal acetate in female rats and rabbits. Administration was by the clinical route (PO). A single dose level was used, 1250 mg/kg, and is around 380 times (rat) and 760 times (rabbit) higher than the clinical dose on a body surface area basis. One treated rat (of 10) was sacrificed in moribund condition on day 2; there were no treatment related mortalities in rabbits. Body weight gain was unaffected in the rat and decreased in rabbits. Decreased food intake and faecal output were seen in both species; additional clinical signs (clear nasal or ocular discharge, piloerection and decreased motor activity) were observed in rats. The data support ulipristal acetate having a low order of acute toxicity.

Repeat dose toxicity

Three pivotal repeat dose toxicity studies were submitted: a 6 month study in rats and 6 and 9 month studies in Cynomolgus monkeys. Two non pivotal studies of 2 weeks duration were also submitted, conducted in rats and Rhesus monkeys. All involved daily oral administration. Only female animals were used, which is considered appropriate and acceptable given the indication. Species selection was appropriate (rodent and nonrodent, and based on pharmacokinetic and pharmacodynamic considerations), as well as group sizes. The duration of the pivotal studies exceeds the minimum 1 month duration recommended to support marketing of a product to be given as a single dose in the relevant ICH guideline.² The 9 month monkey study included a subsequent treatment free recovery period (2 months).

Relative exposure

Due to sparse toxicokinetic sampling and/or the use of assay methodology that does not distinguish between ulipristal acetate and metabolites in the studies, animal:human exposure ratios have been calculated based on single dose pharmacokinetic data (for the pivotal rat study) or doses adjusted for body surface area (all studies). Despite uncertainty over the exact exposure ratios achieved, it is clear that significant multiples of the clinical exposure level were obtained in all studies. Note that in addition to relative exposure, the assessment of human relevance of the findings in the repeat dose toxicity studies requires consideration of the duration of treatment/pattern of use (that is, subchronic or chronic dosing in animals compared with single clinical administration) (Table 2).

² International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonised Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals M3(R2)", 11 June 2009.

Table 2: Estimated relative exposure in repeat dose toxicity studies.

Species	Study duration	Dose		AUC _{0-24h} (μ g·h/mL)	Exposure ratio [#]	
		mg/kg/day	mg/m ² /day		AUC	BSA
Rat (SD)	2 weeks	4	24	–	–	1.2
		20	120	–	–	6.1
		100	600	–	–	30
	6 months	1	6	–	–	0.3
		5	30	3.65	6.6	1.5
		25	150	29.8	54	7.6
Monkey (Rhesus)	2 weeks	20	240	–	–	12
		100	1200	–	–	61
Monkey (Cynomolgus)	6 months; 9 months	1	12	–	–	0.6
		5	60	–	–	3.0
		25	300	–	–	15
Human (healthy volunteers) Single dose [Study HRA2914-504]		[30 mg]	19.8	0.556	–	–

= animal:human plasma AUC or doses adjusted for body surface area (BSA), based on mg/kg to mg/m² conversion factors of 6 (rat), 12 (monkey) and 33 (human; 50 kg body weight assumed); AUC_{0-24h} data shown for rats were obtained after a single dose in Study HRA2914-421.

Major findings

Effects on reproductive tissues were the most prominent finding in ulipristal acetate-treated animals. Such effects included:

- ovarian cysts (at all doses in rats; and in high dose monkeys treated for 2 weeks or 6 months);
- ovarian follicular atresia and reduced bodyweight relative ovary weight (at ≥ 5 mg/kg/day in the 6 month rat study);
- oviduct cysts (at all doses in the 9 month monkey study);
- squamous metaplasia of the oviducts (at 25 mg/kg/day in the 9 month monkey study);
- dilation of the lumen of the uterus (at all doses in the 2 week rat study);
- uterine glandular dilatation (at 25 mg/kg/day in the 6 month rat study, at 100 mg/kg/day in the 2-week monkey study, at ≥ 5 mg/kg/day in the 6 month monkey study);
- uterine cystic endometrial hyperplasia with squamous metaplasia, cystic dilatation and endometrial thickening (at all doses in the 9 month monkey study);
- interruption of menstrual cycling (sporadic menses in monkeys at 1 mg/kg/day in the 9 month study, and cessation of menses in monkeys at ≥ 5 mg/kg/day in the 6 and 9 month studies).

The histopathological changes in the uterus and oviducts of monkeys treated for 9 months were decreased in incidence and severity in recovery animals, and return of menses was observed (18 days after the end of treatment). Of particular note, findings of squamous metaplasia in monkeys are not considered indicative of a pre neoplastic change.

Changes to mammary tissues were noted in rats, comprising diffuse lobular hyperplasia (at ≥ 20 mg/kg/day) in the 2 week study, and galactoceles (all doses; ≥ 1 mg/kg/day) and mammary gland hyperplasia and chronic inflammation (at ≥ 5 mg/kg/day) in the 6 month study. No treatment related mammary gland changes were found with ulipristal acetate in monkeys. The effects in rats occurred in conjunction with increased serum prolactin.

The pituitary, liver and adrenal gland also showed notable changes with treatment. Pituitary gland hyperplasia was observed in rats at all doses in the 6 month study, and bodyweight relative pituitary weight was significantly increased in rats with treatment at ≥ 5 mg/kg/day for 6 months and at ≥ 20 mg/kg/day for 2 weeks. These effects were not observed in monkeys. Hepatocellular hypertrophy was observed in rats treated at the high dose levels in the 2 week and 6 month studies, together with increased bodyweight relative liver weight. Bodyweight relative liver weight was also increased at the high dose level in the 2 week monkey study, but there were no effects on liver weight or histology in the 6 and 9 month monkey studies (≤ 25 mg/kg/day). Adrenal cortical hypertrophy was commonly observed in high dose animals in the 2 week and 6 month rat studies and in the 6 month monkey study. Increased bodyweight relative adrenal weight was seen at the high dose levels in the 6 month rat study and the 2 week and 6 month monkey studies. Serum cortisol was found to be increased in monkeys at the high dose level in the 2 week study, at all doses in the 6 month study and at the high dose level in the 9 month study.

The effects observed with ulipristal acetate are similar to those seen previously with mifepristone, and are consistent with the drug's anti progesterone and anti glucocorticoid activities. No overt toxicity was seen in any of the repeat dose toxicity studies.

Genotoxicity

The potential genotoxicity of ulipristal acetate was investigated in a comprehensive set of *in vitro* and *in vivo* assays, comprising tests for bacterial mutagenicity, the *in vitro* mouse lymphoma tk assay, for chromosomal aberrations *in vitro* and for chromosomal damage *in vivo* (mouse micronucleus test; involving oral administration). The conduct of the studies was in accordance with the relevant ICH guideline,³ with concentrations/doses tested up to maximum recommended levels, or limited by solubility, cytotoxicity or mortality. All assays were appropriately validated and returned negative results for ulipristal acetate.

Carcinogenicity

Although not expected for a product to be given as a single dose, two rodent carcinogenicity studies with ulipristal acetate were submitted. The studies were conducted in rats (~ 2 years duration) and transgenic mice (TgRasH2; 6 months duration). Administration was by the clinical route (oral) and animals of both sexes were used. The design of the studies was consistent with relevant ICH/EU guidelines.⁴ Both studies included detailed toxicokinetic analyses, allowing the calculation of animal:human exposure ratios based on AUC. Appropriate doses were used, with the highest dose levels yielding exposure to ulipristal acetate surpassing the 25 fold AUC multiple recommended in ICH/EU guidance⁵ in both studies. Substantial exposure multiples were also obtained for the active metabolite (Table 3).

³ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonised Tripartite Guideline: Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use S2(R1)", 9 November 2011.

⁴ European Medicines Agency, "ICH Topic S 1 A The Need for Carcinogenicity Studies of Pharmaceuticals, Step 5: Note for Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals (CPMP/ICH/140/95)", July 1996; European Medicines Agency, "Committee for Proprietary Medicinal Products (CHMP): Note for Guidance on Carcinogenic Potential (CPMP/SWP/2877/00)", 25 July 2002.

⁵ European Medicines Agency, "ICH Topic S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals, Step 5: Note for Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals (EMEA/CHMP/ICH/383/1995)", October 2008.

Table 3: Relative exposure in carcinogenicity studies.

Species	Study duration	Dose (mg/kg/day)	AUC _{0-24h} (µg·h/mL)		Exposure ratio [#]	
			Ulipristal acetate	Mono-desmethyl ulipristal	Ulipristal acetate	Mono-desmethyl ulipristal
Mouse (TgRasH2)	26 weeks	15	15.0	8.1	27	33
		45	33.3	15.2	60	62
		130	67.8	31.0	122	126
Rat (SD)	♂: 100 weeks; ♀: 99 weeks	1	0.254	0.135	0.5	0.5
		3	2.83	0.923	5	3.8
		10	14.6	2.89	26	12
Human (healthy volunteers) Single dose [Study HRA2914-504]		[30 mg]	0.556	0.246	-	-

= animal:human plasma AUC

No treatment related increase in tumours was observed with ulipristal acetate in either species up to the highest doses tested (transgenic mice: ≤130 mg/kg/day [relative exposure, 122]; rat: ≤10 mg/kg/day [relative exposure, 26]).

Reproductive toxicity

Reproductive toxicity studies with ulipristal acetate covered all stages (fertility, early embryonic development, embryofoetal development, and pre and postnatal development). Numbers of animals were appropriate.

Doses of ulipristal acetate used in the reproductive toxicity studies were lower than in the general repeat dose toxicity studies in order to maintain pregnancy. Animal:human exposure ratios have been calculated based on doses adjusted for body surface area, with generally low multiples of the clinical exposure predicted to have been achieved in animals (Table 4). Limited toxicokinetic data from the main pre/postnatal development study in rats, obtained in late gestation, confirm low (subclinical) exposure: the exposure multiple based on AUC at the high dose level (0.3 mg/kg/day) was 0.4.

Table 4: Estimated relative exposure in reproductive toxicity studies.

Species	Study	Route	Dose		Exposure ratio [#]	
			mg/kg/day	mg/m ² /day		
Rat (SD)	Male fertility	PO	10	60	N/A	
	Embryofetal development		0.1	0.6	0.03	
			0.3	1.8	0.09	
			1	6	0.30	
	Pre-/postnatal development		0.03	0.18	0.01	
			0.1	0.6	0.03	
			0.3	1.8	0.09	
			1 (pilot)	6	0.30	
	Administration in the early post-coital period		1.9	11.4	0.58	
			3.8	22.8	1.2	
			5.9	35.4	1.8	
			11.7	70.2	3.5	
	Administration in late gestation		23	138	7	
Rabbit (NZW)	Embryofetal development	PO	0.1	1.2	0.06	
			0.3	3.6	0.18	
			1	12	0.61	
Guinea pig (unknown strain)	Effects on pregnancy maintenance ^a	SC	6 [†]	48	2.4	
			20 [†]	160	8	
			60 [†]	480	24	
Monkey (Cynomolgus)	Effects on pregnancy maintenance ^b	PO	0.5	6	0.3	
			5	60	3.0	
Human (healthy volunteers) Single dose [Study HRA2914-504]		PO	[30 mg]	19.8	-	

[#] = animal:human doses adjusted for body surface area (BSA), based on mg/kg to mg/m² conversion factors

of 6 (rat), 12 (rabbit), 8 (guinea pig), 12 (monkey) and 33 (human; 50 kg body weight assumed);

^a = Study HRA2914-407; ^b = Study HRA2914-409; [†] = converted from mg/animal doses assuming 500 g body weight

Effects on female fertility were chiefly investigated as part of the *in vivo* pharmacology studies, where inhibition of ovulation and prevention of pregnancy were shown in multiple laboratory animal species. Disruption of menstrual cycling was evident in monkeys with long-term treatment in the general repeat dose toxicity studies. Although not relevant to the proposed indication, a male fertility study was submitted. It showed no impairment of fertility or effects on sperm in male rats treated at 10 mg/kg/day PO for up to 70 days prior to mating (but noting that treatment in this study did not continue into the mating period as recommended in published guidelines).⁶

Placental transfer of ulipristal acetate was not investigated, but is expected based on structural considerations. Ulipristal and monodesmethyl ulipristal were detected in the milk of lactating rats (although levels were not quantified). Excretion of these compounds in human milk was also reported – milk:plasma ratios based on AUC were 0.74 for ulipristal acetate and 0.40 for monodesmethyl ulipristal, and milk:plasma ratios based on Cmax were 0.35 and 0.23 for the respective compounds, following administration of a 30 mg tablet.

⁶ European Medicines Agency, "ICH Topic S 5 (R2) Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility, Step 5: Note for Guidance on the Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (CPMP/ICH/386/95)", March 1994.

Conventional embryofoetal development studies (involving treatment from implantation and throughout organogenesis) were performed in rats and rabbits; subclinical exposure is predicted to have been achieved at all doses. Embryofoetal toxicity – as increased post implantation loss (due to increased early resorptions) and a corresponding decrease in live litter size – was evident at the high dose level (1 mg/kg/day PO) in both species, and occurred in the absence of maternotoxicity. Estimated relative exposure at this dose is 0.3 for rats and 0.6 for rabbits. Treatment with ulipristal acetate did not produce malformations or other foetal abnormalities in either the rat or rabbit, and mean foetal weight was unaffected. A study submitted under primary pharmacology showed loss of pregnancy and/or stillbirths in some monkeys when given at ≥ 0.5 mg/kg/day for 4 days during the early period of organogenesis (estimated relative exposure, ≥ 0.3); teratogenicity was not observed in surviving infants. Single subcutaneous administration of ulipristal acetate to guinea pigs in late gestation caused abortion at 20 and 60 mg/kg/day (estimated relative exposure, ≥ 8) but not at 6 mg/kg/day (estimated relative exposure, 2.4) (compared with mifepristone, which caused abortion at all of these doses).

In pre/postnatal development studies in rats (involving treatment from implantation and through the lactation period), ulipristal acetate caused complete litter loss (resorptions) at 1 mg/kg/day PO (estimated relative exposure, 0.3), and increased pre birth loss, decreased live litter size and increased stillbirths at 0.3 mg/kg/day (estimated relative exposure, 0.09), occurring in the absence of maternotoxicity. No adverse effects on birth weight, postnatal survival, bodyweight gain or other developmental parameters (including reproductive function) were observed in the liveborn offspring of rats treated at ≤ 0.3 mg/kg/day.

Additional studies in rats revealed decreases in the incidence of pregnancy and live litter size, but no effect on the development of liveborn pups, with administration at 3.8 mg/kg/day PO from day 0-3 post coitus (that is, prior to implantation; estimated relative exposure, 1.2). Treatment at ≥ 5.9 mg/kg/day for 3 days in late gestation (estimated relative exposure, 1.8) resulted in delivery of all dead pups, occurring in the absence of maternotoxicity.

Pregnancy classification

No pregnancy category was proposed for the product by the sponsor. Placement in Pregnancy Category D⁷ is warranted based on findings of embryofoetal lethality and abortion in animals. This matches the category for the existing emergency contraception products Levonelle-1, NorLevo, Postinor-1 and Postinor-2 (containing levonorgestrel as the active ingredient).

Paediatric use

No juvenile animal studies were performed.

Phototoxicity

No evidence of phototoxicity was found for ulipristal acetate in an adequately conducted *in vitro* study in 3T3 mouse fibroblast cells.

Impurities

The impurity specifications for the drug substance/product are toxicologically acceptable.

⁷ Pregnancy Category D: "Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details."

Comments on the nonclinical safety specification of the RMP

Results and conclusions drawn from the nonclinical program for ulipristal acetate detailed in the sponsor's draft Risk Management Plan (RMP) (Part II; Module SII) are in general concordance with those of the nonclinical evaluator except with regard to effects on pregnancy maintenance and embryofoetal development, carcinogenicity and drug interactions. Embryofoetal lethality (increased post implantation loss, resorptions, pregnancy loss, abortions and/or stillbirths) was observed with ulipristal acetate in rats at ≥ 0.3 mg/kg/day (estimated relative exposure based on body surface area adjusted doses, 0.09), in rabbits at 1 mg/kg/day (estimated relative exposure, 0.61), in guinea pigs at ≥ 20 mg/kg/day (estimated relative exposure, 8) and in monkeys at ≥ 0.5 mg/kg/day (estimated relative exposure, 0.3). The specification should be modified as outlined below in Table 5.

Table 5: Comments on the nonclinical safety specification of the RMP.⁸

Key safety findings (from nonclinical studies)	Relevance to human usage
...	...
<ul style="list-style-type: none"> • Reproductive toxicity Prevention of pregnancy maintenance: Repeated administration of ulipristal acetate prevented pregnancy maintenance in rats, rabbits, guinea pigs and monkeys as a consequence of its anti-progesterone activity. 	Based on the doses which have been shown in animals to impair the maintenance of pregnancy, it is very unlikely to be of consequence in women after a single 30 mg dose of ulipristal acetate. This is reinforced by the available clinical and post marketing evidence. Based on findings of embryofoetal lethality in multiple laboratory animal species at subclinical doses (based on body surface area), abortifacient activity at the clinical dose is considered possible.
<ul style="list-style-type: none"> • Developmental toxicity Embryofoetal development: In rats and rabbits, the NOEL for maternal toxicity was 1 mg/kg/day and that for developmental toxicology was 0.3 mg/kg/day; the 1 mg/kg/day dose caused some embryofoetal deaths but foetuses which survived developed normally. There was no indication of teratogenicity of ulipristal acetate in any of these studies. In the pharmacological study conducted in monkeys, administration of ulipristal acetate prevented pregnancy maintenance in some but not all animals. In the animals in which pregnancy continued, there were no structural or physiological anomalies in foetuses or infants. 	These findings suggest that in case a woman is exposed to a 30 mg dose of ulipristal acetate early during her pregnancy, no deleterious effects on the foetus development is <u>are expected should pregnancy continue</u> .
...	...
<ul style="list-style-type: none"> • Carcinogenicity No data available <u>Carcinogenicity studies in rats and transgenic mice showed no tumourigenic potential.</u> 	<u>Ulipristal acetate is not considered to pose a carcinogenic hazard to patients.</u>
...	...
<ul style="list-style-type: none"> • Mechanism for drug interactions Ulipristal acetate is predominantly metabolized by CYP3A. Co-administration with CYP3A4 inhibitors may therefore increase exposure to ulipristal acetate. Similarly co-administration with CYP3A4 inducers may decrease exposure to ulipristal acetate. Ulipristal acetate and CDB-3877 (<u>monodesmethyl ulipristal, the major metabolite</u>) did not demonstrate ability to induce CYP1A2 and CYP3A4 using fresh hepatocytes. Ulipristal acetate was not found to inhibit the activity of CYP1A2, CYP2C19 or CYP2E1 at the concentrations of (~5-50 µg/ml). Weak inhibition of CYP2B6 and CYP2C8 was observed for ulipristal acetate with IC50 values >30 µM and 22 µM respectively. Weak inhibition on these CYP enzymes was also demonstrated for CDB3877 (<u>ulipristal acetate main active metabolite</u>) at concentrations >20 µM and 4 µM respectively. Ulipristal acetate, but not CDB-3877, inhibits (>50%) CYP2C9, CYP2D6 and CYP3A4 activity, but only at the highest concentration tested (~50 µg/ml). Interaction effects of ulipristal acetate and its main metabolite CDB-3877 on P-gp transporters were investigated in Caco-2 cells. <i>In vitro</i> study showed that ulipristal acetate has an inhibitory activity on P-gp transporters, with an IC50 of 0.73 µM. <u>Ulipristal acetate inhibited BCRP with an IC50 of 8.92 µM.</u> 	Two DDI <i>in vivo</i> studies were performed to describe this interaction with a potent CYP3A4 inhibitor ketoconazole and a moderate CYP3A4 inhibitor erythromycin (Study HRA2914-547 and HRA2914-549). The <i>in vivo</i> concomitant use of the CYP3A4 inhibitors ketoconazole and erythromycin at therapeutic doses and ulipristal acetate led to increased exposure of ulipristal acetate and its main active metabolite which are unlikely to have any clinical consequences for a single dose administration. Concomitant use of ulipristal acetate with CYP3A4 inducers is a potential important risk for lack of efficacy. These effects on CYPs were observed at <u>doses concentrations</u> that are not clinically relevant. It is therefore concluded that ulipristal acetate is unlikely to participate in drug drug interaction with products that are metabolized by the CYP enzymes listed. A clinical DDI study (HRA2914-548) was performed to investigate interaction of ulipristal acetate with fexofenadine, a P-gp substrate. No changes in the PK parameters of fexofenadine were observed. It was therefore concluded co-administration of ulipristal acetate is not expected to affect the pharmacokinetics of P-gp substrates and should not be expected to result in a clinically relevant effect. <u>Ulipristal acetate is predicted to inhibit intestinal BCRP in patients at the clinical dose.</u>

⁸ During the second round nonclinical evaluation, the evaluator accepted that ulipristal acetate inhibition of BCRP activity is predicted to be restricted to the intestinal compartment. Taking into account the single dose administration, as indicated for emergency contraception, and the rapid absorption of ulipristal acetate, the observed *in vitro* inhibition of BCRP by ulipristal acetate is most likely not clinically relevant.

Nonclinical summary and conclusions

Summary

- The dossier was of satisfactory quality. All pivotal safety related studies were GLP compliant.
- Ulipristal acetate was shown to have nanomolar affinity for human PRs. *In vitro* functional assays showed antagonism of PR mediated activity comparable to that of mifepristone. *In vivo* anti progesterone activity by ulipristal acetate was demonstrated by inhibition of ovulation, inhibition of endometrial proliferation and prevention of pregnancy in various laboratory animal species. The drug's major metabolite, monodesmethyl ulipristal, retains significant anti progesterone activity.
- Ulipristal acetate also has significant affinity for the glucocorticoid receptor, but weak affinity for the androgen receptor and negligible affinity for the oestrogen receptor and mineralocorticoid receptor. Safety pharmacology studies revealed no significant or clinically relevant effects on the CNS, cardiovascular and respiratory systems.
- Rapid absorption of ulipristal acetate after oral administration was shown in mice, rats, dogs and humans. Tissue distribution was wide; CNS entry was limited. High plasma protein binding was found for both ulipristal acetate and monodesmethyl ulipristal. The major metabolites were formed by sequential demethylation, mediated by CYP3A4. Excretion is predominantly via the faecal route, with biliary excretion involved.
- *In vitro* assays examining inhibition of human CYPs and transporters indicated potential clinically significant inhibition of P-gp and intestinal BCRP by ulipristal acetate. Inhibition of CYPs by ulipristal acetate and monodesmethyl ulipristal was only seen at large multiples of the clinical Cmax.
- Ulipristal acetate exhibited a low order of acute toxicity in rats and rabbits.
- Repeat-dose toxicity studies in rats and monkeys (of up to 6 and 9 months duration, respectively) showed effects on reproductive tissues, mammary gland, pituitary, liver and adrenal gland – consistent with the drug's anti progesterone and anti glucocorticoid activity.
- Ulipristal acetate was not genotoxic in a comprehensive set of *in vitro* and *in vivo* assays, and was not carcinogenic in studies in rats and transgenic mice.
- Ulipristal acetate caused embryofoetal lethality at subclinical doses (based on body surface area) when administered at various time points following implantation in multiple animal species, including monkeys. Teratogenicity or other adverse effects were not seen in surviving foetuses/offspring of rats, rabbits and monkeys that had been treated during gestation, but the predictive values of these studies is limited by the low (subclinical) exposure margins.

Conclusions and recommendation

- No major deficiencies were identified.
- Primary pharmacology studies demonstrated potent anti progesterone activity for ulipristal acetate *in vitro* and *in vivo*, and support use for the proposed indication.
- Ulipristal acetate also has anti glucocorticoid activity.
- The drug's major metabolite (monodesmethyl ulipristal) is pharmacologically active.

- Pharmacokinetic studies established a significant role for CYP3A4 in the metabolism of ulipristal acetate, and predict potentially clinically significant inhibition of P-glycoprotein and intestinal BCRP by the drug.
- The effects observed with ulipristal acetate in the repeat dose toxicity studies are similar to those seen previously with mifepristone, and are consistent with the drug's anti progesterone and anti glucocorticoid activities. No overt toxicity was seen in any of the repeat dose toxicity studies.
- Ulipristal acetate was found not to be genotoxic or carcinogenic.
- Animal data indicate that embryofoetal lethality is possible at the clinical dose if used during gestation. The sponsor has proposed no pregnancy category; the drug should be placed in Pregnancy Category D.
- There are no nonclinical objections to the registration of EllaOne for the proposed indication.

IV. Clinical findings

Introduction

Ulipristal acetate is an orally active synthetic selective PR modulator that acts via high affinity binding to the human PR. When used for emergency contraception, the mechanism of action is inhibition or delay of ovulation via suppression of the LH surge.

The treatment consists of one tablet to be taken orally as soon as possible, but no later than 120 h (5 days) after UPI or contraceptive failure.

The tablet can be taken with or without food.

EllaOne can be taken at any time during the menstrual cycle. If vomiting occurs within 3 h of EllaOne intake, another tablet should be taken.

If a woman's menstrual period is late or in case of symptoms of pregnancy, pregnancy should be excluded before EllaOne is administered.

Special populations

Renal impairment: No dose adjustment is necessary.

Hepatic impairment: No alternate dose recommendations for EllaOne can be made.

Paediatric population (Adolescents): No differences in safety or efficacy have been shown compared to adult women aged 18 and older.

Clinical rationale

There is a clinical need for the availability of emergency contraception because of the health and social costs of unplanned pregnancy. Unplanned pregnancy may result from contraception failure or situations where intercourse is not anticipated or has been coerced. Abortion is a less acceptable alternative to emergency contraception. High dose oestrogen progestin regimens, and more recently levonorgestrel, have been previously used as emergency contraception. However, with levonorgestrel reported pregnancy rates rise from approximately 1.5 to 2.6%, respectively, for intake 0 to 24 h as compared to intake 48 to 72 h after intercourse. Hence, ulipristal offers the potential for emergency contraception that can be taken within 5 days of UPI.

Guidance

The sponsor undertook pre submission consultation with the TGA with regard to the suitability of the data presented in the application. The sponsor appears to have complied with the advice given by the TGA in these discussions.

Although there is a CHMP adopted guideline on clinical investigation of steroid contraceptives in women,⁹ this guideline relates to long term contraception rather than emergency contraception. The efficacy measure adopted is the Pearl index, which is the pregnancy rate per 100 women years of treatment. This measure would not be applicable to emergency contraception.

Contents of the clinical dossier

The submission contained the following clinical information:

- 19 clinical pharmacology studies, including 14 that provided pharmacokinetic data and 6 that provided pharmacodynamic data;
- No population pharmacokinetic analyses;
- One pivotal efficacy/safety study;
- Two dose finding studies;
- Two other efficacy/safety studies;
- Four pooled analyses, seven periodic safety update reports (PSURs), and one postmarketing study.

Paediatric data

The submission included data for females aged 13 years and over. The sponsor has an approved paediatric investigation plan (PIP) that includes adolescent girls aged 12 to 17 years. The sponsor has a waiver for children aged ≤12 years because pre menarchic girls are not considered to be at risk of pregnancy.

Good clinical practice

The clinical studies were stated, and appeared, to have been conducted according to Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 6 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

⁹ European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CPMP/EWP/519/98 Rev 1)", 27 July 2005.

Table 6: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Pasarro <i>et al</i> 2003 Study HRA2914-504 Study HRA2914-553 Study PGL09-023
	- Multi-dose	
	Bioequivalence - Single dose	Study 111014-001 Study 02-CH-0219 Study HRA2914-011
	Food effect	Study HRA2914-008
PK in special populations	Target population - Single dose	none
	Hepatic impairment	None
	Renal impairment	None
	Neonates/infants/children/adolescents	None
	Elderly	None
Genetic/gender-related PK	Lactating females	Study HRA2914-514
PK interactions	Esomeprazole	Study HRA2914-546
	Ketoconazole	Study HRA2914-547
	Fexofenadine	Study HRA2914-548
	Erythromycin	Study HRA2914-549
	Rifampicin	Study HRA2914-551

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

Evaluator's conclusions on pharmacokinetics

The pharmacokinetic data presented in the submission are consistent with the PK properties stated in the proposed PI document. The pharmacokinetics of ulipristal have been adequately described for the population intended in the proposed indication, that is, women of childbearing potential. However, should ulipristal be proposed for use in other populations, such as the elderly, patients with impaired renal function or patients with impaired hepatic function, then further pharmacokinetic data should be provided.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 7 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 7: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on luteolysis	Pasarro <i>et al</i> 2003
	Effect on foliculogenesis	Study HRA2914-505
	Follicle rupture	Study HRA2914-511
	Menstrual cycle	Study HRA2914-506
	Ovulation	Study HRA2914-510
		Study HRA2914-554

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

Evaluator's conclusions on pharmacodynamics

The pharmacodynamic studies examined the ulipristal dose range from 10 to 200 mg as a single dose. There were dose dependent effects on follicular growth, follicular rupture,

endometrial growth and cycle length. These effects were not significant at the 10 mg dose level. At the 30 mg dose level in Study HRA2914-511, following a single dose of ulipristal 30 mg, when lead follicle reached 18 mm, there were the following findings:

- Follicle rupture inhibited in 15 (44%) of ulipristal treated cycles and none (0%) of placebo treated, $p = 0.0001$;
- When administered after the LH surge, seven (36.8%) of ulipristal treated cycles had inhibition of follicle rupture, compared with none (0%) of the placebo, $p = 0.0082$;
- Mean (SD) time to follicular rupture was 6.03 (3.86) days in the ulipristal group and 2.41 (1.31) in the placebo, $p < 0.0001$;
- Continued growth of the follicle occurred for 18 (75%) of the ulipristal treated and 6 (25%) of the placebo, $p = 0.0013$;
- Mean (SD) cycle length was 32.68 (3.75) days in the ulipristal group and 30.18 (4.11) days in the placebo, $p = 0.0024$;
- LH surge was detected in 26 (76.5%) of ulipristal treated cycles and 33 (97.1%) of placebo.

Ulipristal did not alter cervical mucus.

The pharmacodynamic characteristics of ulipristal have been adequately characterised for the proposed indication.

Dosage selection for the pivotal studies

Study HRA2914-507

Study HRA2914-507 was a multicentre, randomised, double blind, active controlled study to assess the efficacy, safety and tolerance of ulipristal in comparison with levonorgestrel for emergency contraception. The study was conducted at seven sites in the US from September 1999 to September 2001.

The inclusion criteria included:

- Menstruating women >18 years age
- Requested emergency contraception within 72 h (3 days) after unprotected coitus, as defined by lack of contraceptive use, or condom breakage (including condoms lubricated with spermicide) or other barrier contraceptive method failure;
- Reported that all acts of unprotected coitus during the enrolment cycle were within 72 h prior to enrolment;
- Women who were willing to abstain from further acts of UPI during the treatment cycle;
- Had a history of regular menstrual cycles (mean length of 24-42 days with intra individual variation of ± 5 days);
- Had ≥ 1 normal menstrual cycle (2 menses) post delivery or abortion;
- If subject had recently discontinued hormonal contraception, one normal menstrual cycle (2 menses) must have been completed before entry in the study;
- For women who had a recent history of Depo-Provera use, the most recent injection must have been at least 3 months before study entry and the subject must have had at least one normal menstrual cycle (2 menses).

- Was available for follow-up \geq 4 weeks.

The exclusion criteria included:

- Pregnant at screening or enrolment (positive high-sensitivity urine pregnancy test);
- Had been pregnant or breast feeding within the 2 months prior to screening and enrolment;
- Had used hormonal methods of contraception during the enrolment cycle or previous two cycles;
- Was an intrauterine device (IUD) user at the time of screening or enrolment;
- Had a Tubal ligation;
- Had a partner with a history of vasectomy;
- Was unsure about the date of the last menstrual period (+3 days);
- Had irregular menstrual cycles, as defined in the inclusion criteria;
- Had experienced nausea and vomiting within the 2 weeks prior to screening and enrolment;
- Had impaired hypothalamic-pituitary-adrenal reserve or had received oral glucocorticoid replacement therapy in the year prior to screening and enrolment; and
- Was not concurrently enrolled in any other investigational trial and agreed not to re-enrol in this study.

The study treatments were:

1. Ulipristal 50 mg unmicroised in gelatin capsules
2. Levonorgestrel 0.75 mg, two doses taken up to 12 h apart

The treatments were self administered as a single dose up to 72 h after UPI.

The primary efficacy outcome measure was the rate of post treatment pregnancy. The secondary efficacy outcome measures were: the incidence of pregnancy in an efficacy evaluable population, the tolerability of ulipristal (as measured by the incidence of nausea and vomiting), and the effects of ulipristal on the menstrual cycle. The safety outcome measures were adverse events (AEs) and symptom diary.

A total of 1672 subjects were randomised: 832 to ulipristal and 840 to levonorgestrel. There were 792 subjects in the ulipristal group and 786 in the levonorgestrel that completed the study. The mean (SD) age was 24.4 (5.77) in the ulipristal group and 24.2 (5.59) in the levonorgestrel. The treatment groups were similar in demographic characteristics. The medical and gynaecological histories were similar for the two treatment groups.

There were 12 pregnancies in the ulipristal group and 14 in the levonorgestrel. The pregnancy rate (95% Confidence Interval [CI]) was 1.52 (0.785 to 2.632) % in the ulipristal group and 1.78 (0.977 to 2.970) % in the levonorgestrel. The mean (95% CI) difference in pregnancy rates, ulipristal – levonorgestrel was -0.27 (-1.992 to 1.420) %.

In the efficacy evaluable population, there were seven post treatment pregnancies in the ulipristal group and 13 in the levonorgestrel. The post treatment pregnancy rate (95% CI) was 0.91 (0.365 to 1.857) % in the ulipristal group and 1.68 (0.898 to 2.859) % in the levonorgestrel. The mean (95% CI) difference in pregnancy rates, ulipristal – levonorgestrel was -0.78 (-2.407 to 0.773) %.

Study HRA2914-508

Study HRA2914-508 was a multicentre, randomised, active controlled study to assess the efficacy, safety and tolerance of two different doses of ulipristal for emergency contraception. The study was conducted at nine sites in the US from August 2001 to November 2003.

The inclusion and exclusion criteria were the same as for Study HRA2914-507.

The study treatments were:

1. Ulipristal 50 mg, unmicronised in gelatin capsule
2. Ulipristal 10 mg, micronised in gelatin capsule
3. Ulipristal 10 mg, unmicronised in gelatin capsule (discontinued arm)

The treatments were administered as a single dose up to 72 h after UPI. There was no placebo or other active comparator.

The primary efficacy outcome measure was pregnancy. Suspected pregnancy was initially detected by a urine pregnancy test, and if this was positive quantitative serum β -hCG (human chorionic gonadotropin) and ultrasound to determine gestational age. Tolerance was measured by comparing the incidence of vomiting and nausea using a daily diary. The safety outcome measures were AEs and concomitant medications.

A total of 1026 subjects were randomised to treatment: 413 to unmicronised 50 mg, 399 to micronised 10 mg and 214 to unmicronised 10 mg. There were 952 evaluable subjects: 384 in the unmicronised 50 mg group, 365 in the micronised 10 mg and 203 in the unmicronised 10 mg. The mean (SD) age was 24.4 (5.6) years and the treatment groups were similar in demographic characteristics.

There were five pregnancies in the ulipristal unmicronised 50 mg group and ten in the micronised 10 mg group. The pregnancy rate (95% CI) was 1.30 (0.423 to 3.016) % in the unmicronised 50 mg group and 2.74 (1.320 to 4.985) % in the micronised 10 mg. The mean (95% CI) difference in pregnancy rates, 10-50 mg, was 1.44 (-0.660 to 3.820) %. The expected number of pregnancies in each of the treatment groups was 21: hence the contraceptive effectiveness was 76.19% for the unmicronised 50 mg and 52.38 for the micronised 10 mg. There were ten pregnancies in the 203 subjects in the unmicronised 10 mg arm (discontinued arm).

Conclusions with regard to the dose finding studies

Study HRA2914-507 and Study HRA2914-508 were both conducted using dose levels other than that proposed for marketing. Up to 72 h after UPI, ulipristal 50 mg, unmicronised in gelatin capsules, as a single dose had comparable efficacy to levonorgestrel 0.75 mg, two doses taken up to 12 h apart. However, although ulipristal 10 mg, micronised, appeared to have lower efficacy than an unmicronised 50 mg dose, both were considered to be at least 50% effective. Although there was more nausea with the 10 mg micronised dose, indicating this AE did not appear to be dose related, the sponsor opted for a dose lower than the 50 mg level in further development.

Efficacy

Evaluator's conclusions on efficacy

In the pivotal study (Study HRA2914-513), ulipristal 30 mg as a single dose was demonstrated to have efficacy in comparison with expected pregnancy rates, and non

inferiority in comparison with levonorgestrel when administered up to 120 h post UPI. There were the following efficacy findings:

- The observed pregnancy rate (95% CI) within 72 h of UPI for ulipristal was 1.51% (0.62% to 3.32%), whereas the expected pregnancy rate was 5.63%
- Up to 120 h post UPI the pregnancy rate (95% CI) was 1.60 (0.93 to 2.67) %, which was significantly lower than the expected pregnancy rate of 5.72%.
- The upper bounds of the 95% CI for pregnancy rates at 72 h and 120 h, for ulipristal in the modified Intention To Treat (mITT) population, were both below the clinical relevance threshold of 4%.
- Ulipristal was non inferior to levonorgestrel at 72 h and 120 h post UPI. The observed rate (OR) (95% CI) for pregnancy for ulipristal in comparison with levonorgestrel was:
 - For the interim mITT population at 72 h: 0.53 (0.20 to 1.44)
 - For the mITT population at 72 h: 0.68 (0.35 to 1.31)
 - For the interim mITT population at 120 h: 0.59 (0.31 to 1.14)
 - For the mITT population at 120 h: 0.69 (0.36 to 1.32)

In each case, the upper 95% CI was less than the predefined level of non inferiority of 1.6.

- The pregnancy rates over time for ulipristal were 1.60% for the 0 to 24 h time interval, 2.12% for the 24 to 48 h interval and 1.48% for the >48 to 72 h interval. No pregnancies were observed at the >72 to 96 and >96 to 120 h intervals.
- At 72 h after UPI, the prevention fraction (95% CI) was 68.1 (45.8 to 81.2) % for ulipristal and 52.2 (25.1 to 69.5) % for levonorgestrel.
- At 120 h after UPI, the prevention fraction (95% CI) was 72.2 (52.8 to 83.7) % for ulipristal and 52.8 (27.8 to 69.2) % for levonorgestrel.
- In the time interval >72 to 120 h after UPI, the prevention rate was significantly greater for ulipristal than for levonorgestrel: 0.07736 for ulipristal compared with 0.4514 for levonorgestrel, $p = 0.0374$.

The supportive efficacy studies demonstrated similar pregnancy rates and prevention fraction to the pivotal study. In Study HRA2914-509, the observed pregnancy rate (95% CI) was 2.10 (1.41 to 3.10) % compared to the expected pregnancy rate of 5.53%. The upper 95% CI for pregnancy rate was below the clinically relevant threshold of 4%. The estimated pregnancy rates were 1.61% at 48 to 60 h, 2.85% at 61 to 72 h, 2.90% at 73 to 84 h, 1.38% at 85 to 96 h, 1.21% at 97 to 108 h, and 1.31% at 109 to 120 h. The prevented fraction (95% CI) was 62.32 (41.89 to 75.56) %. In Study HRA2914-515, the pregnancy rate was 1.5%.

Efficacy was decreased by further UPI after treatment (OR 5.691). Although increasing BMI (body mass index) decreased efficacy, there was no identifiable weight threshold.

The clinical studies were conducted in a population similar to that intended in the proposed indication. The criterion for non inferiority was appropriate. The dose and indication for the active comparator (levonorgestrel) was appropriate.

Safety

Studies providing safety data

The following studies provided evaluable safety data.

Pivotal efficacy studies

In the pivotal efficacy study, the following safety data were collected:

- General AEs
- Menstrual symptoms
- Routine laboratory tests were not performed

Pivotal studies that assessed safety as a primary outcome

Study HRA2914-515 was a multicentre, open label, single arm, observational study to assess the safety and tolerability of ulipristal in routine conditions of use for EC in post menarcheal adolescents and adult women in particular menorrhagia, metrorrhagia, dysmenorrhoea and effect on menstrual cycles.

Dose response and non pivotal efficacy studies

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

- General AEs
- Nausea/vomiting
- Menstrual symptoms
- Routine laboratory tests were not performed

Clinical Pharmacology studies

- General AEs
- Routine laboratory tests

Patient exposure

In Study HRA2914-507, there were: 832 subjects treated with 50 mg ulipristal as a single dose.

In Study HRA2914-508, there were 399 subjects treated with a single dose of 10 mg micronised ulipristal and 413 treated with a single dose of 50 mg unmircronised ulipristal.

In Study HRA2914-513, a total of 1104 subjects were exposed to a single dose of 30 mg ulipristal.

In Study HRA2914-509, there were 1533 subjects exposed to ulipristal 30 mg on at least one occasion, with 66 subjects treated on two occasions and nine on three.

In Study HRA2914-515, there were 579 subjects treated with ulipristal 30 mg. There were 279 subjects aged <18 years and 76 aged <16 years.

Safety issues with the potential for major regulatory impact

Use in younger age groups

Study HRA-2914-555 was a pooled analysis that investigated the safety profile in subjects <18 years of age. In 44 subjects aged <18 years, the most frequent AEs were nausea in four (9.09%) subjects and headache in three (6.82%).

Effects on the foetus

There were insufficient completed pregnancies reported in the data to be able to make any conclusions with regard to safety for the foetus and newborn.

Postmarketing data

There were seven PSURs covering the time period 15 May 2009 to 14 May 2013. There was no regulatory action for safety reasons over this time period. The case reports were predominantly of unintended pregnancy. Other than pregnancy or drug exposure during pregnancy, the serious medically confirmed unlisted reactions were one case of syncope, one case of viral infection, one case of grand-mal seizure, and one case of haemorrhage (unknown site). Since the product's international birth date (IBD), the sponsor has received 282 reports of pregnancy. There were 149 reports of unintended pregnancy. The results for these 149 cases were: healthy newborn for four, spontaneous abortion for eight, elective abortion for 39, ectopic pregnancy for two, six were ongoing, and 90 were lost to follow-up.

Study HRA2914-648 was a retrospective, postmarketing analysis of pregnancies due to inadvertent exposure or treatment failure. The study used data from Planned Parenthood Columbia Willamette, a group of clinics in the US. There were 55 pregnancies identified from the clinic database. The age range was 18 to 42 years and mean (SD) BMI was 25.4 (4.5). The outcome of the pregnancies was: induced abortion for 33, spontaneous abortion 2, ectopic pregnancy 1, and continuation of pregnancy in 9. There were 10 subjects lost to follow-up.

Evaluator's conclusions on safety

Ulipristal appears to have a favourable safety profile. The most commonly reported AEs were headache, nausea and abdominal pain. There is some prolongation of the menstrual cycle consistent with the mechanism of action and pharmacodynamic data. There were few serious adverse events (SAEs) or AEs leading to discontinuation (DAEs).

The 'Adverse Effects' section of the PI document is supported by the data presented in the submission.

First round benefit-risk assessment

First round assessment of benefits

In the pivotal study (Study HRA2914-513), ulipristal 30 mg as a single dose was demonstrated to have efficacy in comparison with expected pregnancy rates, and non inferiority in comparison with levonorgestrel when administered up to 120 h post UPI. There were the following efficacy findings:

- The observed pregnancy rate (95% CI) within 72 h of UPI for ulipristal was 1.51% (0.62% to 3.32%), whereas the expected pregnancy rate was 5.63%.
- Up to 120 h post UPI, the pregnancy rate (95% CI) was 1.60 (0.93 to 2.67) %, which was significantly lower than the expected pregnancy rate of 5.72%.
- The upper bounds of the 95% CI for pregnancy rates at 72 h and 120 h, for ulipristal in the mITT population, were both below the clinical relevance threshold of 4%.
- Ulipristal was non-inferior to levonorgestrel at 72 h and 120 h post UPI. The OR (95% CI) for pregnancy for ulipristal in comparison with levonorgestrel was:
 - For the interim mITT population at 72 h: 0.53 (0.20 to 1.44)
 - For the mITT population at 72 h: 0.68 (0.35 to 1.31)
 - For the interim mITT population at 120 h: 0.59 (0.31 to 1.14)
 - For the mITT population at 120 h: 0.69 (0.36 to 1.32)

In each case, the upper 95% CI was less than the predefined level of non-inferiority of 1.6.

- The pregnancy rates over time for ulipristal were 1.60% for the 0 to 24 h time interval, 2.12% for the 24 to 48 h interval and 1.48% for the >48 to 72 h interval. No pregnancies were observed at the >72 to 96 and >96 to 120 h intervals.
- At 72 h after UPI, the prevention fraction (95% CI) was 68.1 (45.8 to 81.2) % for ulipristal and 52.2 (25.1 to 69.5) % for levonorgestrel.
- At 120 h after UPI, the prevention fraction (95% CI) was 72.2 (52.8 to 83.7) % for ulipristal and 52.8 (27.8 to 69.2) % for levonorgestrel.
- In the time interval >72 to 120 h after UPI, the prevention rate was significantly greater for ulipristal than for levonorgestrel: 0.07736 for ulipristal compared with 0.4514 for levonorgestrel, $p = 0.0374$.

The supportive efficacy studies demonstrated similar pregnancy rates and prevention fraction to the pivotal study. In Study HRA2914-509, the observed pregnancy rate (95% CI) was 2.10 (1.41 to 3.10) % compared to the expected pregnancy rate of 5.53%. The upper 95% CI for pregnancy rate was below the clinically relevant threshold of 4%. The estimated pregnancy rates were 1.61% at 48 to 60 h, 2.85% at 61 to 72 h, 2.90% at 73 to 84 h, 1.38% at 85 to 96 h, 1.21% at 97 to 108 h, and 1.31% at 109 to 120 h. The prevented fraction (95% CI) was 62.32 (41.89 to 75.56) %. In Study HRA2914-515, the pregnancy rate was 1.5%.

Efficacy was decreased by further UPI after treatment (OR 5.691). Although increasing BMI decreased efficacy, there was no identifiable weight threshold.

The clinical studies were conducted in a population similar to that intended in the proposed indication. The criterion for non inferiority was appropriate. The dose and indication for the active comparator (levonorgestrel) was appropriate.

First round assessment of risks

Ulipristal appears to have a favourable safety profile. The most commonly reported AEs were headache, nausea and abdominal pain. There is some prolongation of the menstrual cycle consistent with the mechanism of action and pharmacodynamic data. There were few SAEs or DAEs.

First round assessment of benefit-risk balance

The benefit-risk balance of EllaOne (ulipristal acetate) 30 mg tablets, given the proposed usage, is favourable.

First round recommendation regarding authorisation

The evaluator would have no objection to the approval of EllaOne (ulipristal acetate) 30 mg tablets for the indication of:

Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

Clinical questions

No questions.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU RMP Version 13.1 (dated 31 December 2013, Data Lock Point [DLP] 31 December 2013) and EU RMP Version 14 (dated 15 September 2014, DLP 14 May 2014) with Australian Specific Annex (ASA).

Safety specification

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

Table 8: Ongoing safety concerns.

Important identified risks	None
Important potential risks	<ul style="list-style-type: none"> Effects on pregnancy maintenance/off label use Risk of incomplete abortion and heavy bleeding Effects on foetus and newborns Risk of ectopic pregnancy Concomitant use of CYP3A4 inducers Liver effects Delayed menstrual period >60 days / amenorrhea Ovarian cysts
Missing information	<ul style="list-style-type: none"> Effect of concomitant use of progestin-only contraception Effect in patients with severe asthma treated by oral glucocorticoid Effects in women with impaired liver function

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities (as stated above). The additional pharmacovigilance activities are summarised in Table 9.

Table 9: Additional pharmacovigilance activities (planned or ongoing).

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
A Pregnancy Registry to Collect Clinical Follow-up Information and Outcomes of Pregnancies Resulting from ellaOne Failure or Pregnancies inadvertently exposed to ellaOne	<ul style="list-style-type: none"> Risk of ectopic pregnancy Effects on foetus and newborn 	To assess clinical follow-up and outcome of pregnancies resulting from ellaOne failure or pregnancies inadvertently exposed to ellaOne.	Reports of the aggregate data in the Registry will be compiled and submitted to health authorities via PSURs.

Risk minimisation activities

The sponsor is not proposing any additional risk minimisation activities.

Reconciliation of issues outlined in the RMP report

Reconciliation of issues outlined in the RMP report is as follows.

Recommendation #1 in RMP evaluation report

The sponsor does not seem to have submitted an ASA document. The sponsor should submit such a document incorporating the provided recommendations.

Sponsor response

The sponsor has included in the revised RMP the ASA. This document provides a summary of the Australian specific information in the RMP that supports assessment of the risk of the use of the product in Australia. This includes a comparison between the proposed PI in Australia and the currently approved European Summary of Product Characteristics (SmPC) in a tabular format, a summary of pharmacovigilance practice and the risk minimisation plan in Australia, with special reference to the annexes.

OPR evaluator's comment

This is considered acceptable.

Summary of recommendations

Outstanding issues

It is considered that the sponsor's response to the TGA Section 31 request has adequately addressed the issues identified in the RMP evaluation report. There are no outstanding issues, other than the changes to the safety specification recommended by the nonclinical evaluator.

Comments on the safety specification of the RMP

Clinical evaluation report

The clinical evaluator made the following first round summary comment in regard to safety specifications in the draft RMP:

The Safety Specification in the draft RMP is satisfactory.

There is no second round report.

Nonclinical evaluation report

Results and conclusions drawn from the nonclinical program for ulipristal acetate detailed in the sponsor's draft RMP (Part II; Module SII) are in general concordance with those of the nonclinical evaluator except with regard to effects on pregnancy maintenance and embryofoetal development, carcinogenicity and drug interactions. Embryofoetal lethality (increased post implantation loss, resorptions, pregnancy loss, abortions and/or stillbirths) was observed with ulipristal acetate in rats at ≥ 0.3 mg/kg/day (estimated relative exposure based on body surface area adjusted doses, 0.09), in rabbits at 1 mg/kg/day (estimated relative exposure, 0.61), in guinea pigs at ≥ 20 mg/kg/day (estimated relative exposure, 8) and in monkeys at ≥ 0.5 mg/kg/day (estimated relative exposure, 0.3). Based on findings in multiple species at predicted subclinical exposure levels, abortifacient activity at the clinical dose is predicted in humans from the animal data. The specification should be modified as outlined in Table 5.

OPR reviewer comment: The RMP evaluator supports the changes proposed by the nonclinical evaluator.

Key changes to the updated RMP

EU RMP Version 13.1 (dated 31 December 2013, DLP 31 December 2013) has been superseded by EU RMP Version 14 (dated 15 September 2014, DLP 14 May 2014) with ASA Version 14 (dated 15 September 2014, DLP 14 May 2014).

Table 10 shows a summary of key changes between EU-RMP Version 13.1 and EU-RMP Version 14.

Table 10: Summary of key changes between EU-RMP Version 13.1 and EU-RMP Version 14.

Safety specification	'Effects of interaction with progestin-containing contraception' was added as an Important Potential Risk.
Other	Australian Specific Annex added.

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:

Implement EU RMP Version 14 (dated 15 September 2014, DLP 14 May 2014) with ASA Version 14 (dated 15 September 2014, DLP 14 May 2014), and future updates, where approved by the TGA, as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The evaluator states that, "Ulipristal acetate is a synthetic derivative of progesterone... It is an orally active selective PR modulator that acts via high affinity binding to the human PR... There are no monographs for either the drug substance or the finished product."

The specifications for the drug substance and finished product are acceptable.

Data support an unopened shelf life of 3 years when stored below 25°C with the additional storage conditions of "store in original container", "protect from light" and "protect from moisture" which will appear on the labels and in the PI as "Store below 25°C. Store in the original packaging to protect from moisture. Keep the blister in the outer carton to protect from light".

The evaluator discussed 4 bioavailability studies.

- Study HRA2914-501 investigated whether the particle size distribution affected bioavailability. Micronisation increased Cmax and AUC by approximately 40%. It was decided to develop a 30 mg immediate release tablet using micronized drug substance.
- Study HRA2914-516 investigated whether site of manufacture (2 sites) affected bioavailability. No such effect was observed.
- Study HRA2914-512 investigated the effect of food on the commercial tablet from the Cenexi site. Food increased Tmax from $\frac{3}{4}$ h to 3 h, reduced Cmax by ~40%, and increased AUC by ~25%. Note: This does not warrant any statement in the PI regarding the administration with or without food.
- Study HRA2914-668 determined the absolute bioavailability of the proposed tablet in the fasted state. This was 27%.

Approval is recommended from a chemistry point of view.

Nonclinical

The evaluator mentions that the nonclinical data was of satisfactory quality. All pivotal safety related studies were Good Laboratory Practice compliant.

Ulipristal acetate had nanomolar affinity for human PRs. *In vitro* studies showed antagonism of PR mediated activity comparable to mifepristone.

The evaluator mentions that:

"ulipristal acetate also has significant affinity for the glucocorticoid receptor, but weak affinity for the androgen receptor and negligible affinity for the oestrogen receptor and mineralocorticoid receptor. Safety pharmacology studies revealed no significant or clinically relevant effects on the CNS, cardiovascular and respiratory systems".

Ulipristal acetate was rapidly and well absorbed after oral administration in mice, rats, dogs and humans. Bioavailability was approximately 80% in rats. T_{1/2} was 6 h in rats, 87 h in monkeys. It is highly protein bound (96.7% to 99.5%) in mouse, rat, rabbit, dog, monkey and human. It is widely distributed in rats and monkeys. There is rapid and extensive metabolism possibly via CYP 3A4. Inhibition of CYPs by ulipristal acetate and monodesmethyl ulipristal was only seen at large multiples of the clinical Cmax. A large number of metabolites are produced in rat and monkey. The main route of excretion is via faeces in rat and monkey. Biliary excretion was also involved.

Ulipristal acetate exhibited a low order of acute toxicity in rats and rabbits.

Repeat dose toxicity studies in rats and monkeys (of up to 6 and 9 months duration, respectively) showed exaggerated pharmacodynamic effect antiprogestrone and antiglucocorticoid effect.

There was no evidence of genotoxicity seen.

No long term carcinogenicity study was performed. This is acceptable as ulipristal acetate is proposed as a single dose.¹⁰

The evaluator mentions that

"ulipristal acetate caused embryofoetal lethality at subclinical doses (based on body surface area) when administered at various time points following implantation in multiple animal species, including monkeys. Teratogenicity or other adverse effects were not seen in surviving foetuses/offspring of rats, rabbits and monkeys that had been treated during gestation, but the predictive values of these studies is limited by the low (subclinical) exposure margins."

Overall, the evaluator recommends approval. Several PI amendments are recommended.

Clinical

Pharmacokinetics

14 studies are mentioned by the evaluator.

Absorption: In one study (111014-001) which was an open label single dose study on 6 healthy female volunteers, mean (CV%) Cmax after 30 mg was 223 (36.7%) ng/mL and

¹⁰ The sponsor states that long term carcinogenicity studies were performed and refers to wording in the EllaOne PI: "Oral carcinogenicity studies were performed with ulipristal acetate in rats (2 years duration) and transgenic mice (6 months). No carcinogenic effect was observed with treatment at up to 10 mg/kg/day in rats (yielding 26-times the plasma AUC in patients after a 30 mg dose) or up to 130 mg/kg/day in mice (122-times the clinical AUC)."

median Tmax was 0.5 h. The absolute bioavailability was also assessed in this study: mean (sd) was 27.46 (4.97) %.

The pharmacokinetics of 30 mg ulipristal was also assessed in HRA 2914-504 in 20 healthy females. Mean (SD) CL/F was 76.8 (64.0) L/h, Cmax was 176 (88.9) ng/mL, AUC_{0-∞} was 556 (260) h•ng/mL and t_{1/2} was 32.4 (6.33) h. Median (range) Tmax was 0.88 (0.50 to 2.00) h. The plasma concentration time profile was consistent with a two compartment model.

Bioequivalence of the clinical trial formulation versus the "to be marketed formulation" was seen in Study 2914-011.

Study 02-CH-0219 showed that the 10 mg micronised tablet formulation had an AUC that was increased by approximately 40% for both ulipristal and its major metabolite relative to the crystalline capsule formulation.

Food decreased the rate of absorption of ulipristal, but increased bioavailability. In Study 2914-008, following a high fat breakfast, compared to fasted, Cmax was decreased by 44% and Tmax was increased by 1.5 h for both ulipristal and its major metabolite (3877A). However, AUC increased by approximately 25%. No PI change (in relation to food) is recommended, based on these findings.

In Pasarro et al.,¹¹ the pharmacokinetics for ulipristal were not dose proportional in the dose range 1 mg to 200 mg, with a relative decrease in AUC and Cmax with increasing dose.

In Study 111014-001, mean (CV%) volume of distribution was 644.000 L (32.9%).

Ulipristal is extensively protein bound.

The evaluator states that ulipristal acetate is predominantly metabolised by CYP3A4. A radiolabelled study (HRA 2914-553) showed predominant non renal clearance. There was 72% of administered radioactivity recovered in faeces over 264 h. This study revealed that the principal metabolite, PGL4002, had a systemic exposure of 33%. There was a suggestion, in this study, that there were unidentified metabolites which were excreted more slowly. No further information on these metabolites is submitted.

The evaluator mentions that in Study 111014-001 mean (CV%) clearance of ulipristal was 10.300 L/h (26.1%). This study also showed that the mean (CV%) t_{1/2} was approximately 43.280 (30.4) h.

The pharmacokinetic interactions are discussed on page 13. Esomeprazole was studied in HRA2914-546. There was no significant effect on AUC. Co-administration with ketoconazole increased Cmax and AUC in HRA 2914-547. There was an increase in the pharmacokinetics of the principal metabolite also. In Study HRA2914-548, there was no significant effect of ulipristal on the pharmacokinetics of fexofenadine, a P-gp substrate. Erythromycin resulted in increased bioavailability of ulipristal and increased half life for PGL4002 (Study HRA2914-549). In Study HRA2914-551, co-administration of rifampicin decreased exposure to ulipristal by more than 90%.

These interactions are dealt with in the draft PI.

The evaluator concludes that the pharmacokinetics findings are adequately described in the target population. However, data are lacking in other populations, such as patients with impaired renal function or patients with impaired hepatic function.

Pharmacodynamics

There are 5 evaluable studies and one published paper.

¹¹ Passaro MD, et al. (2003) Luteal phase dose-response relationships of the antiprogestin CDB-2914 in normally cycling women. *Hum Reprod.* 18: 1820-1827.

The published study (Pasarro et al.)¹² examined the effect of mid luteal administration of a single dose: all 6 volunteers had early bleeding at doses of 200 mg; at lower doses, less number of subjects had bleeding.

Study HRA 2914-505 examined a single dose at the mid follicular phase. There was a dose dependent increase in the time to follicular collapse following ulipristal in the dose range 10 mg to 100 mg, compared to placebo. There was an arrest in follicular growth at the 100 mg dose level, with dose dependent decrease in follicular growth at the 10 mg and 50 mg dose levels. Plasma oestradiol concentrations were suppressed at the 50 mg and 100 mg dose levels ($p < 0.001$).

In Study HRA2914-506, there were no significant differences in length of follicular or luteal phase, or overall length of menstrual cycle. A significant delay in endometrial maturation occurred in 50 and 100 mg groups compared to placebo and 10 mg groups.

Study HRA 2914-510 examined the pharmacodynamics in 46 healthy females where 2.5 mg, 5 mg or 10 mg of the micronised formulation was administered daily for 12 weeks. There was a dose related incidence in anovulation. This was statistically significant for the 5 mg and 10 mg groups compared to placebo ($p < 0.001$). Amenorrhoea was also observed in a dose related manner.

In Study HRA2914-511, following a single dose of ulipristal 30 mg, when lead follicle reached 18 mm, follicle rupture inhibited was in 15 (44%) of ulipristal treated cycles and none (0%) of placebo treated, $p = 0.0001$. When administered after the LH surge, seven (36.8%) of ulipristal treated cycles had inhibition of follicle rupture, compared with none (0%) of the placebo, $p = 0.0082$. Mean (SD) time to follicular rupture was 6.03 (3.86) days in the ulipristal group and 2.41 (1.31) in the placebo, $p < 0.0001$. Continued growth of the follicle occurred for 18 (75%) of the ulipristal treated and 6 (25%) of the placebo, $p = 0.0013$.

Overall, the evaluator states that the 30 mg dose showed significant inhibition of follicle rupture (compared with placebo) at different stages of the menstrual cycle. It did not alter the cervical mucus. The evaluator states that, "the pharmacodynamics characteristics of ulipristal have been adequately characterised for the proposed indication".

Dose selection studies

Two studies (HRA2914-507 and 508) are discussed.

Study HRA2914-507 was a multicentre randomised double blind study conducted to assess the efficacy, safety and tolerance of ulipristal in comparison with levonorgestrel for emergency contraception. Those over the age of 18 requesting emergency contraception within 72 h (3 days) after unprotected coitus were eligible to enrol. Ulipristal 50 mg unmicroised in gelatin capsules or levonorgestrel 0.75 mg, two doses taken up to 12 h apart were administered. The primary efficacy outcome measure was the rate of post treatment pregnancy.

This study was designed as a non inferiority study with the delta being 2%. At the 2.5% level of significance (upper limit of the 95% CI), a sample size of 770 subjects in each treatment group was sufficient to reject with 80% power the null hypothesis.

A total of 1672 subjects were randomised, 832 to ulipristal and 840 to levonorgestrel. There were 792 subjects in the ulipristal group and 786 in the levonorgestrel that completed the study. The demographics were similar in the two groups.

¹² Passaro MD, et al. (2003) Luteal phase dose-response relationships of the antiprogestin CDB-2914 in normally cycling women. *Hum Reprod.* 18: 1820-1827.

There were 12 pregnancies in the ulipristal group and 14 in the levonorgestrel. The pregnancy rate (95% CI) was 1.52 (0.785 to 2.632) % in the ulipristal group and 1.78% (0.977 to 2.970) in the levonorgestrel. The mean (95% CI) difference in pregnancy rates, ulipristal – levonorgestrel was -0.27% (-1.992 to 1.420), demonstrating noninferiority.

Study HRA2914-508 was a multicentre randomised active controlled study which was similar in design to the previous study. However, ulipristal 50 mg, unmicroised in gelatin capsule and ulipristal 10 mg, micronised in gelatin capsule were used. (There was an additional arm using ulipristal 10 mg, unmicroised in gelatin capsule that was discontinued.) This was also a non inferiority study with the margin (delta) however, being 2.5%. The study showed that the 10 mg micronised ulipristal acetate was inferior to 50 mg unmicroised ulipristal acetate at preventing pregnancy (1.44, 95% CI -0.660, 3.820).

The evaluator states that both studies used **doses other than proposed for marketing** and also for a **different duration** in relation to the indication: 72 h post UPI. The report states that ... “although ulipristal 10 mg, micronised, appeared to have lesser efficacy than an unmicroised 50 mg dose, both were considered to be at least 50% effective... the sponsor opted for a dose lower than the 50 mg level in further development”.

Efficacy

There is one pivotal Phase III study, HRA 2914-513.

This study was a multicentre, single blind, randomised, two arm, comparator controlled study to evaluate the observed pregnancy rate following ulipristal 30 mg within 72 h of UPI. The study also investigated efficacy up to 120 h after UPI, as a secondary objective.

Women presenting for emergency contraception within 120 h after UPI were included. Those presenting more than 72 h after UPI were eligible for inclusion only if they declined or had contraindication to an IUD insertion.

Ulipristal acetate 30 mg tablet or levonorgestrel 1.5 mg tablet was administered as a single dose within 72 h of UPI.

The primary efficacy outcome measure was the pregnancy rate when ulipristal 30 mg is administered within 72 h of UPI; this needed to be statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception.

The primary efficacy analysis compared the upper bound of the 95% CI of the point estimate of the observed pregnancy rate in subjects who took ulipristal within 72 h after UPI to the estimated expected pregnancy rate in the absence of emergency contraception. (The estimated expected pregnancy rate was calculated using a pooled recognisable set of conception probabilities by cycle day relative to day of ovulation according to Trussell et al.).¹³

There were several secondary efficacy outcome measures. Those of note:

- the pregnancy rate when ulipristal 30 mg is administered within 120 h of UPI.
- the pregnancy rate when ulipristal 30 mg is administered within 72 h of UPI in comparison with the 4% rate considered as the clinical irrelevance threshold.
- test of non-inferiority for ulipristal 30 mg in comparison with levonorgestrel 1.5 mg as emergency contraception within 120 h of UPI.

Sample size calculations were based on the primary efficacy analysis and the main secondary analysis (inferiority to clinical threshold) and the non inferiority of ulipristal

¹³ Trussell J, et al. (1998) New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 57: 363-369.

acetate 30 mg versus levonorgestrel 1.5 mg as emergency contraception within 72 h of UPI. In order to reach at least 85% power with an equivalence margin of 1.6 in odds ratio, 1022 patients per group were randomised for a total of 2044 patients. Non inferiority of ulipristal 30 mg versus levonorgestrel 1.5 mg as emergency contraception was concluded if the upper bound of the 95% CI of the odds ratio of pregnancy in the ulipristal group and the levonorgestrel group is lower than the non inferiority margin of 1.6. Superiority was established if the upper bound of the 95% CI of the odds ratio is below 1.0.

Efficacy analysis was conducted on the mITT population. This was predefined in the protocol that an interim analysis would be performed once 1200 patients meeting the criteria for primary efficacy evaluation had completed the study. This was an interim analysis only. However, at the time of the interim analysis, the planned size was close to completion, so that the efficacy analyses of the entire mITT population were also completed and were presented as secondary analyses. The primary results, however, are the interim efficacy results.

There were 2321 subjects screened and 2221 were randomised to treatment: 1104 to ulipristal and 1117 to levonorgestrel. The age range of the study subjects was 16 to 55 years; mean age was 25 years; BMI was 25. The treatment groups were similar in demographic characteristics.

The evaluator mentions that:

"the primary efficacy analysis was based on the first 1200 subjects in the mITT population. The observed pregnancy rate (95% CI) within 72 h of UPI for ulipristal was 1.51% (0.62% to 3.32%), whereas the expected pregnancy rate was 5.63%. The observed pregnancy rate (95% CI) for levonorgestrel was 2.81% (1.54%, 4.97%), whereas the expected pregnancy rate was 5.88%".

It is noted that the estimated pregnancy rates were 1.61% at 48 to 60 h, 2.85% at 61 to 72 h, 2.90% at 73 to 84 h, 1.38% at 85 to 96 h, 1.21% at 97 to 108 h, and 1.31% at 109 to 120 h. Thus, the efficacy was sustained over 120 h.

The results satisfied the criteria for efficacy as defined in the protocol.

Delegate's comments: The evaluator does not discuss the completed mITT population where the treatment intake within 72 h was 1694 and within 120 h was 1893, with pregnancy rates of 1.78% (95%: 1.04%, 2.98%) and 1.60% (95%: 0.96%, 2.67%) respectively with statistically significant lower than the expected pregnancy rates of 5.54% and 5.72%.

Other efficacy studies

1. Study HRA2914-509

Study HRA2914-509 was a multicentre, open label, single arm study to assess the efficacy, safety and tolerance of a single dose of ulipristal 30 mg in emergency contraception. This study was to evaluate efficacy and safety of ulipristal as emergency contraceptive when taken between 48 and 120 h after UPI.

Women (over the age of 18) requesting emergency contraception between 48 and 120 h after UPI were included. Other inclusion and exclusion criteria are, in essence, similar to those of the previous study.

Eligible subjects received a single dose of 30 mg ulipristal acetate.

Primary efficacy endpoint

The pregnancy rate, calculated as the number of pregnancies after emergency contraception divided by the total number of women exposed to emergency contraception for whom pregnancy status was known. The primary efficacy analysis compared this pregnancy rate to the pregnancy rate that would be expected in the absence of emergency

contraception treatment which was calculated according to the method of Trussell et al.¹⁴ The protocol also stipulated that both the primary and main secondary endpoints needed to be positive for the study to be considered a success.

The secondary efficacy outcome measures were the pregnancy rate when ulipristal 30 mg is administered between 48 and 120 h of UPI in comparison with the 4% rate considered as the clinical irrelevance threshold; trend in pregnancy rates over time since intercourse; contraceptive effectiveness (prevented fraction) between treatment groups and the effect of ulipristal 30 mg on the menstrual cycle.

There were 1533 subjects in the ITT dataset, the mean age was 24.4 ± 6.1 ; most subjects were in the 18 to 25 years age group (69%); mean BMI was 25.3 kg/m^2 . A total of 1241 subjects were eligible for the mITT population on which the primary efficacy analysis was performed. The mITT population included women that received study drug and had at least one UPI reported at screening and from whom pregnancy status was known.

The observed pregnancy rate was to be concluded as statistically significantly lower than the calculated expected pregnancy rate if the upper bound of the 2 sided 95% CI of the observed pregnancy rate was below the calculated expected pregnancy rate. The latter calculated are described in the protocol; it should be noted that the 2 sided 95% CI of the observed pregnancy rate (as calculated for the primary efficacy analysis) was compared to a clinical irrelevance threshold of 4%.

Secondary efficacy endpoints

In comparison with the 4% rate considered as the clinical irrelevance threshold: the mITT and the ITT populations, the upper bound limit of the 95% CI did not exceed the 4% threshold.

The prevented fractions of pregnancies for the mITT and ITT were 62.35% (95% CI: 41.8-75.5) and 61.33 % (95% CI: 41.1-74.4) respectively. The European Public Assessment Report (EPAR) states that:

"these prevented fractions are comparable with prevented fractions that were reported for levonorgesterel in the time frame 73-120 h after UPI, 60% for 2X 0.75 mg levonorgestrel and 63% for 1.5 mg levonorgestrel (also calculated by Trussell et al.)¹⁵, but lower than is commonly reported for levonorgestrel within 72 h after UPI (approximately 80%)."

Trend in pregnancy rates was evaluated in three 24 h intervals. The rates for mITT populations were: 2.30% on Day 3, 2.04 % on Day 4 and 1.26% on Day 5. The primary efficacy evaluation was performed in 1241 women in the mITT population with 26 pregnancies. The observed pregnancy rate (95% CI) was 2.10 % (95%CI: 1.41 to 3.10) compared to the expected pregnancy rate of 5.53% (Table 7.1.2.1.4). The upper 95% CI for pregnancy rate was below the clinically relevant threshold of 4%.

Phase IV post approval observational study (HRA2914-515)

This was a multicentre, open label, single arm, observational study to assess the safety and tolerability of ulipristal in routine conditions of use for emergency contraception in post menarcheal adolescents and adult women. The study was conducted in Sweden, UK, France, US and Germany from December 2010 to January 2013. The study included subjects receiving ulipristal 30 mg as emergency contraception; post menarcheal adolescents or adult women in Sweden, France, the US and Germany and aged from 13 years in the United Kingdom. 579 included in the study and of these 464 (80%) were

¹⁴ Trussell J, et al. (1998) New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 57: 363-369.

¹⁵ Trussell J, et al. (1998) New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 57: 363-369.

included in the mITT. In this study, 7 subjects (1.5%) in the mITT were reported to have become pregnant and is consistent with that obtained in the previous studies.

Overall efficacy conclusion

Overall, the evaluator states that in the pivotal study (Study HRA2914-513) ulipristal 30 mg as a single dose demonstrated efficacy in comparison with levonorgestrel in relation to expected pregnancy rates, and non inferiority in comparison with levonorgestrel when administered up to 120 h post UPI.

Safety

Overall, 3560 subjects were evaluated for safety of ulipristal acetate. The number of patients exposed in the phase II and III studies was 3,391; of these 1,533 subjects used the "to be marketed dose". (EPAR)

The data on pregnancies is limited. All pregnancies that began during the clinical trials of ulipristal acetate were followed to term to determine outcome. This is extracted from the EPAR: of the 29 treated subjects in the Phase 3 study who became pregnant, 16 elected to have an induced abortion, 6 reported spontaneous abortion, 6 decided to carry the pregnancy to term and 1 was lost to follow up. The details of these 6 pregnancies should be submitted in the pre ACM response.

The AEs in the individual studies are discussed by the evaluator. The discussion overall, extracted from EPAR is as follows.

During the Phase III trial, 876 (61.4%) subjects experienced at least one AE. The majority (89%) of the AEs were mild or moderate intensity. The most common AE were headache (17.5%), nausea (12.2%) and abdominal pain (11.7%). The frequency was comparable to those reported with levonorgestrel.

Post treatment cycle length was 2.9 days longer from average length in the phase III trial. A shortened menstrual cycle was reported in 6.1% of women in HRA2914-509.

Table 11 was extracted from the safety review by the US Food and Drug Administration (FDA).

Table 11: Common drug related AEs ($\geq 1\%$ of subjects), ITT.

	HRA 2914-509	HRA 2914-513	Pooled Data (509 + 513)	HRA 2914-513
Drug	Ulipristal acetate (N=1,533) n (%)	Ulipristal acetate (N=1,104) n (%)	Ulipristal acetate (N=2,637) n (%)	Levonorgestrel (N=1,117) n (%)
Nausea	141 (9)	104 (9)	245 (9)	91 (8)
Headache	143 (9)	93 (8)	236 (9)	84 (8)
Dysmenorrhea	63 (4)	77 (7)	140 (5)	94 (8)
Abdominal pain (unspecified)	104 (6)	34 (3)	138 (5)	50 (5)
Fatigue	52 (3)	40 (3)	92 (4)	29 (3)
Dizziness	53 (3)	34 (3)	87 (3)	34 (3)
Upper abdominal pain	33 (2)	20 (2)	53 (2)	32 (3)
Pelvic pain	34 (2.2)	1 (0.1)	35 (1.3)	2 (0.2)
Back pain	15 (1.0)	14 (1.3)	29 (1.1)	7 (0.6)
Vomiting	15 (1.0)	11 (1.0)	26 (1.0)	4 (0.4)

A dose response relationship was observed in the pharmacodynamic studies between ulipristal acetate and the presence of ovarian cysts. In the Phase III study, HRA 2914-513, one AE of ovarian cyst rupture was reported in the ulipristal and levonorgestrel group.

Laboratory investigations were performed in HRA 2914-509 only. There were no clinically significant abnormalities observed.

There were no deaths reported. SAEs were reported in 9 subjects. None were stated to be related to the study drug.

The evaluator also states that, "there were insufficient completed pregnancies reported in the data to be able to make any conclusions with regard to safety for the foetus and newborn".¹⁶

Overall safety conclusions

Overall, the evaluator states that, "ulipristal appears to have a favourable safety profile. The most commonly reported AEs were headache, nausea and abdominal pain. There is some prolongation of the menstrual cycle consistent with the mechanism of action and pharmacodynamic data".

The draft PI addresses the safety aspects satisfactorily.

Risk management plan

Routine risk minimisation activities are proposed by the sponsor and considered acceptable by the evaluator.

The potential of off label use is discussed in the report and the evaluator is of the opinion that this is "sufficiently mitigated by the planned routine risk minimisation activities, if the recommendations made by the OPR evaluator are implemented in full, and assuming EllaOne remains a Schedule 4 medication".¹⁷

Several PI amendments have been recommended.

Risk-benefit analysis

Delegate's considerations

Overall benefits

In summary, the 2 Phase III studies met the protocol specified criteria for success: upper bound of the 2 sided 95% CI around the observed pregnancy was:

- less than the expected pregnancy rate and
- less than the clinical relevance threshold of 4%.

The submitted data also shows sustained evidence of efficacy at 0-72 h and 72-120 h (HRA 2914-513).

Overall risks

The evaluator states that this is acceptable.

Overall benefit-risk assessment

The evaluator opines that the benefit-risk balance of EllaOne (ulipristal acetate) 30 mg tablets, given the proposed usage, is favourable.

¹⁶ The sponsor points out the wording in the PI that states available human data regarding pregnancy exposure to EllaOne do not suggest any safety concern with use during early pregnancy.

¹⁷ Prescription Only Medicine.

Summary of issues

The two Phase III studies had some deficiencies. Study HRA2914-513, which was a well designed study, did not use emergency contraception within 120 h of UPI as a primary efficacy endpoint, which is the intended indication; rather, emergency contraception within 72 h was the primary efficacy endpoint (that is, pregnancy rate following emergency contraception); emergency contraception in 120 h only as a secondary efficacy endpoint. The second study was an open label single arm study.

Proposed action

There are 2 Phase III studies to support efficacy. The first study, HRA 2914-513 which was a double blind study has the primary efficacy endpoint as pregnancy rate when UA is administered within 72 h of UPI. The rate when administered within 120 h was a **secondary endpoint**. The second study, HRA 2914-509 was an open label study examined efficacy from 48 h to 120 h. Thus, both these studies have deficiencies in relation to the efficacy endpoint, that is, emergency contraception up to 120 h after UPI. Despite these deficiencies, there is evidence of sustained efficacy up to 120 h.

Regarding off label use, post market surveys conducted in EU reveals that this is not significant. The Delegate agrees with the evaluator that this is not likely to be a problem provided that ulipristal acetate is a Schedule 4 medication.¹⁸

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

The Committee's advice is sought.

Request for ACPM advice

Does the Committee agree that the risk-benefit profile is acceptable?

Response from sponsor

Quality

The Delegate notes that the storage conditions for the drug product will have to appear on the labels and in the PI as:

Store in the original packaging to protect from moisture. Keep the blister in the outer carton to protect from light.

The sponsor confirms the following storage conditions on the labels and in the PI, in compliance with the stability conclusions given:

Store below 25°C. Store in the original packaging to protect from moisture. Keep the blister in the outer carton to protect from light.

Nonclinical

The Delegate notes that the evaluator mentions:

Ulipristal acetate caused embryofoetal lethality at subclinical doses (body surface area) when administered at various time points following implantation in multiple animal species, including monkeys.

The sponsor wishes to clarify the wording to be included in the nonclinical Safety Specification in the RMP relating to reproductive toxicity. In the notification response to the second round nonclinical report, dated 13 November 2014, the sponsor proposed:

¹⁸ Prescription Only Medicine.

Embryofoetal lethality was observed in multiple laboratory animal species at subclinical doses (based on body surface area). The clinical relevance of these findings is uncertain.

This wording is in line with the proposed PI presented. However, the RMP second round advice endorsed the original nonclinical comments, and therefore the wording still remains pending.

The Delegate also notes:

No long term carcinogenicity study was performed.

The sponsor would like to clarify that two carcinogenicity studies (6 month study in transgenic mouse and 2 year study in rat) were provided in the original dossier. The studies did not reveal any safety concern in terms of carcinogenicity. These results are referred to in the PI.

Clinical

The Delegate notes:

The data on pregnancies is limited. All pregnancies that began during the clinical trials of ulipristal acetate were followed to term to determine outcome. This is extracted from EPAR: Of the 29 treated subjects in the Phase 3 study that became pregnant, 16 elected to have an induced abortion, 6 reported spontaneous abortion, 6 decided to carry the pregnancy to term and 1 was lost to follow-up. The details of these 6 pregnancies should be submitted in the pre ACM response.

The data on pregnancy cases from clinical trials have been updated since the completion of the EPAR, which is referred to by the assessor. The most updated data related to pregnancy cases from Study HRA2914-509 are presented in Table 12.

Table 12: Pregnancies and outcome in ulipristal acetate arms.

Study n subjects, in ulipristal acetate arms	Nº of pregnancies in ulipristal acetate group (Nº considered as <u>not</u> being a treatment failure in efficacy studies)	Pregnancy Outcome
HRA2914-509 (30 mg micronized ulipristal acetate) n=1,533	30 mg micronized ulipristal acetate: 29 (3)	30 mg micronized ulipristal acetate: - 16 induced abortions - 6 spontaneous abortions - 1 normal live birth - 1 live birth of a baby with subsequent diagnosis of optic nerve hypoplasia - 4 lost to follow-up

In total, among the 6 women who carried pregnancy to term, there are:

- 1 normal live birth
- 4 women lost to follow-up : these women who intended to carry pregnancy to term should have delivered between December 2007 and June 2009, however they were lost to follow-up despite extensive efforts by investigators
- 1 delivery of a baby with subsequent diagnosis of optic nerve hypoplasia

This last case has been thoroughly reviewed (EllaOne PSUR No. 1 and 2). The initial information available on this case was as follows:

One subject had UPI on 28 November 2007 and took ulipristal acetate 30 mg on 30 November 2007. Her last menstrual period before treatment intake was on 19 November 2007. On 9 January 2008, a pregnancy test revealed that she was pregnant and the estimated fertilisation date was 12 December 2007 +/- 5 days (12 days after ulipristal acetate exposure). The mother had taken thyroid medication (unspecified) from 1 January to 22 November 2007 for an underactive thyroid. On 8 December 2007, she took also 1

tablet of pseudoephedrine for headache. She reported further UPI after ulipristal acetate intake. Additional information received on 3 and 4 June 2009: the subject became pregnant and continued pregnancy to term. Her quantitative serum HCG level was <2 mIU/mL on 30 November 2007 at the time she took ulipristal acetate, and 1543 mIU/mL on 9 January 2008. She did not have an ultrasound until she was 17 weeks pregnant. She experienced an apparently normal pregnancy and delivery. There were subsequent concerns with the infant: blindness and possible developmental delays began at approximately 2 months of age on 31 October 2008. The baby (girl) appeared to be blind or at least severely limited in her vision. She was developmentally delayed about 4 months at the time of the report (9 months old). In the investigator's opinion, the relationship between the reported adverse events and ulipristal acetate is not suspected. An independent Data Safety Monitoring Board reviewed the case on 14 May 2010. The Board confirmed that optic nerve atrophy is a well known neonatal syndrome and a leading cause of infant blindness in many countries for which only two risk factors have been identified, the young age and primiparity of the mother. The Board members also stated that none of the drugs taken by the mother during pregnancy (pseudoephedrine, thyroid hormones, or the drug under study) are known to be associated with this syndrome. The Board concluded that the link between this neonatal outcome and study drug was unlikely.

Clinical trials

Two multicentre Phase III clinical studies evaluated the efficacy and safety of EllaOne up to 120 h after UPI. A single blind comparative study (HRA2914-513 study) provided the primary data to support the efficacy and safety of ulipristal acetate for emergency contraception when taken 0 to 72 h after UPI and provided supportive data for ulipristal acetate for emergency contraception when taken > 72 to 120 h after UPI. An open label study (Study HRA2914-509) provided the primary data to support the efficacy and safety of ulipristal acetate for emergency contraception when taken 48 to 120 h after UPI. Additionally, one Phase II study contributed to establishing efficacy of EllaOne compared to levonorgestrel within 72 h of UPI. The three studies are described below.

(i) Single Blind Comparative Study

This study was a multicentre, single blind, randomised comparison of the efficacy and safety of 30 mg ulipristal acetate (EllaOne) to levonorgestrel (another drug used for emergency contraception). Main inclusion criteria were women presenting for emergency contraception within 120 h of UPI, 16 years or more in UK (except Northern Ireland), 17 years or more in Northern Ireland (UK), and 18 years or more in Ireland and US, with regular cycle length (24 to 35 days).

In total, 2221 healthy women with a mean age of 25 years who requested emergency contraception within 120 h of UPI were enrolled and randomly allocated to receive EllaOne (n = 1104) or levonorgestrel 1.5 mg (n = 1117).

The primary efficacy measurement was the pregnancy rate, calculated as the number of pregnancies after administration of emergency contraception, divided by the number of subjects administered emergency contraception.

In the EllaOne group, 16 pregnancies occurred in 844 women aged 16 to 35 years when emergency contraception was taken 0 to 72 h after UPI. The number of pregnancies expected without emergency contraception was calculated based on the timing of intercourse with regard to each woman's menstrual cycle; EllaOne significantly reduced the pregnancy rate, from an expected 5.6% to an observed 1.9%, when taken within 72 h after UPI ($p = 0.001$). There were no pregnancies observed in the women who were administered EllaOne more than 72 h after UPI (10% of women who received EllaOne).

(ii) Open Label Study

This study was a multicentre open label trial designed to support the efficacy and safety of ulipristal acetate for emergency contraception when taken 48 to 120 h after UPI. Main inclusion criteria were women, 18 or greater years of age, with regular cycle length (24 to 35 days) presenting for emergency contraception between 48 h and 120 h of UPI. In total, 1533 healthy women with a mean age of 24 years received a dose of 30 mg ulipristal acetate (EllaOne).

The primary efficacy measurement was the pregnancy rate, calculated as the number of pregnancies after administration of emergency contraception, divided by the number of subjects administered emergency contraception. Twenty seven pregnancies occurred in 1242 women aged 18 to 35 years evaluated for efficacy for a pregnancy rate of 2.1%. The number of pregnancies expected without emergency contraception was calculated based on the timing of intercourse with regard to each woman's menstrual cycle. EllaOne significantly reduced the pregnancy rate, from an expected rate of 5.5% to an observed rate of 2.2%, when taken 48 to 120 h after UPI ($p < 0.001$).

(iii) Phase II Comparative Study

Study HRA2914-507 was a randomised double blind study conducted in healthy cycling women at least 18 years old and who requested emergency contraception at one of the participating clinical sites in the US within 72 h (3 days) of UPI. It was designed as a non inferiority trial to test the following hypothesis that 50 mg unmircronised ulipristal acetate had a pregnancy rate no worse than that of levonorgestrel with a non-inferiority margin of 2%. The efficacy evaluable (EE) population included 1546 women (773 in the ulipristal acetate group and 773 in the levonorgestrel group).

The pregnancy rate and prevented fraction for the EE population administered ulipristal acetate were, respectively, 0.91% (0.365-1.857) and 85% (68-93).

Pooled analysis

Results from the two independent randomized controlled trials (Studies HRA2914-507 and HRA2914-513 [Table 13]) showed the efficacy of ulipristal acetate to be non inferior to that of levonorgestrel in women who presented for emergency contraception between 0 and 72 h after UPI or contraceptive failure. When the data from the two trials were combined via pooled analysis, the risk of pregnancy with ulipristal acetate was significantly reduced compared to levonorgestrel, regardless of whether treatment occurred within 24 ($p = 0.035$), 72 ($p = 0.046$) or 120 h ($p = 0.025$) of intercourse (Glasier et al.).¹⁹

Table 13: Results of randomised controlled clinical trials.

Randomised controlled trial	Pregnancy rate (%) within 72h of unprotected intercourse or contraceptive failure ²		Odds ratio [95% CI] of pregnancy risk, ulipristal acetate vs levonorgestrel ²
	Ulipristal acetate	Levonorgestrel	
HRA2914-507	0.91 (7/773)	1.68 (13/773)	0.50 [0.18-1.24]
HRA2914-513	1.78 (15/844)	2.59 (22/852)	0.68 [0.35-1.31]
Pooled analysis	1.36 (22/1617)	2.15 (35/1625)	0.58 [0.33-0.99]

2: Glasier et al, Lancet 2010

¹⁹ Glasier AF, et al. (2010) Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *Lancet* 375: 555-562.

Data from the two Phase III studies were pooled to provide a total efficacy population of women treated with ulipristal acetate up to 120 h after UPI (Table 14). Time trend analysis for the five 24 h intervals from 0 to 120 h between UPI and treatment was conducted. There were no significant differences in the observed pregnancy rates across five time intervals.

Table 14: Summary of Clinical Trial Results for Women Who Received a Single Dose of EllaOne (30 mg Ulipristal Acetate).

	Open-Label Study 48 to 120 Hours *	Single-Blind Comparative Study 0 to 72 Hours *
	N = 1,242	N = 844
Expected Pregnancy Rate ***	5.5	5.6
Observed Pregnancy Rate *** (95% confidence interval)	2.2 (1.5, 3.2)	1.9 (1.1, 3.1)

* Time after unprotected intercourse when EllaOne was taken

*** Number of pregnancies per 100 women at risk for pregnancy

A postmarketing observational study evaluating efficacy and safety of EllaOne in 279 adolescents aged 17 and younger showed no difference in the safety and efficacy profile compared to adult women aged 18 and older.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered EllaOne tablet containing 30 mg of ulipristal acetate to have an overall positive benefit-risk profile for the proposed indication;

EllaOne is indicated for emergency contraception within 120 h (5 days) of unprotected sexual intercourse or contraceptive failure

Proposed conditions of registration

The ACPM proposed the following conditions of registration:

- Negotiation of PI and Consumer Medicine Information (CMI) to the satisfaction of the TGA.

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice

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

- Despite the deficiencies in the studies, does the Committee agree that the risk-benefit profile is acceptable?

There are 2 Phase III studies to support efficacy. The first study, HRA 2914-513 which was a double blind study has the primary efficacy endpoint as pregnancy rate when EllaOne is administered within 72 h of UPI. The rate when administered within 120 h was a secondary endpoint. The second study, HRA 2914-509 was an open label study examined efficacy from 48 h to 120 h. Thus, both these studies have deficiencies in relation to the efficacy endpoint, that is, emergency contraception up to 120 h after UPI. Despite Phase III studies having a predefined primary efficacy endpoint of that was suboptimal for proposed indication, the large population and, in other respects, well designed studies, and common use in other jurisdictions since 2010, the ACPM advised this represents sufficient evidence of sustained efficacy up to 120 h to support the indication as proposed.

- Is the risk-benefit profile acceptable to warrant registration?

The ACPM was of the view that the benefit-risk profile is positive for the indication as proposed.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of EllaOne ulipristal acetate 30 mg tablet blister pack indicated for:

EllaOne is indicated for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

Specific conditions of registration applying to these goods

- The EllaOne (ulipristal acetate) EU RMP Version 14, dated 15 September 2014 (DLP 14 May 2014) with Australian Specific Annex Version 14, dated 15 September 2014 (DLP 14 May 2014), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for EllaOne at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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