28 June 2018
EMA/483416/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ulipristal Acetate Gedeon Richter

International non-proprietary name: ulipristal acetate

Procedure No. EMEA/H/C/005017/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gedeon Richter Plc. submitted on 06 April 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Ulipristal Acetate Gedeon Richter, through the centralised procedure.

As this application concerns active substance already authorised via the centralised procedure, 'automatic' access was granted by the CHMP on 22 March 2018.

The applicant applied for the following indications:

- Ulipristal acetate is indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH Gedeon Richter Plc. allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Esmya authorised on 23 February 2012 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Paula Boudewina van Hennik

The application was received by the EMA on	6 April 2018
The procedure started on	30 April 2018
The CHMP and PRAC Rapporteurs' joint Assessment Report was circulated to all CHMP members on	4 June 2018
During the PRAC meeting, the PRAC endorsed the relevant sections of the joint CHMP/PRAC Assessment Report on	14 June 2018
The CHMP and PRAC Rapporteurs' updated joint Assessment Report was circulated to all CHMP members on	14 June 2018
The CHMP and PRAC Rapporteurs' revised updated joint Assessment Report was circulated to all CHMP members on	20 June 2018
During the CHMP meeting, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ulipristal Acetate Gedeon Richter on	28 June 2018

2. Scientific discussion

2.1. Introduction

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.

The MAH for Esmya, has provided consent to make use of the pharmaceutical, preclinical and clinical documentation contained in the file of Esmya, assessed and approved. As a consequence, quality, safety and efficacy of Ulipristal Acetate Gedeon Richter are identical to the up to date quality, safety and efficacy profile of Esmya.

The application for Ulipristal Acetate Gedeon Richter concerns the strength 5 mg tablets and consists only of Module 1 information.

The benefit-risk of Ulipristal Acetate Gedeon Richter is considered to be positive, as it is a duplicate of Esmya, for which the B/R is positive in the following indications:

- Ulipristal acetate is indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

2.2. Quality aspects

Since this application is an informed consent of Esmya (EU/1/12/750/001-005), the quality data in support of the Ulipristal Acetate Gedeon Richter application are identical to the up-to-date quality data of the Esmya dossier, which have been assessed and approved (including all post-marketing procedures).

2.3. Non-clinical aspects

2.3.1. Introduction

Since Ulipristal Acetate Gedeon Richter is an informed consent of Esmya application, the non-clinical data in support of Ulipristal Acetate Gedeon Richter application is identical to the up-to-date non-clinical data of the Esmya dossier which has been assessed and approved (including all post-marketing procedures).

2.3.2. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Substance (INN / Invented Name): ulipristal acetate					
CAS-number (if available): 126784-99-4					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	4.21			Potential PBT Y
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	4.21			B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.025	µg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 930 to 5400 mL/g			List all values
Ready Biodegradability Test	OECD 301				not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =1.0 $DT_{50, sediment}$ =92.2 $DT_{50, whole\ system}$ =75.1 % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	>1.0	mg/L	Alga Pseudokirchneriella subcapitata
Daphnia sp. Reproduction	OECD 211	NOEC	>0.2	mg/	

Test			3	L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	$>10^6$	µg/L	Too high to be determined
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	<25		%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

2.3.3. Conclusion on the non-clinical aspects

The CHMP considered there were no non-clinical objections to the granting of the authorisation of this informed consent application for Ulipristal Acetate Gedeon Richter.

2.4. Clinical aspects

Since Ulipristal Acetate Gedeon Richter application is an informed consent of Esmya application, the clinical data in support of the Ulipristal Acetate Gedeon Richter application are identical to the up-to-date clinical data of Esmya dossier, which have been assessed and authorised (including all post-marketing procedures).

2.5. Risk Management Plan

Safety concerns

Table 2. Summary of the safety concerns

Summary of Safety Concerns	
Important identified risks	- Inappropriate management of endometrium thickening (unnecessary interventions or treatments) - Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)

Summary of Safety Concerns	
	- Drug Induced Liver Injury
Important potential risks	- Acute uterine bleeding requiring immediate intervention - Treatment course beyond three months
Missing information	- Long-term effects of prolonged treatment of the endometrium (including possible malignant changes) - Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma - Impact on surgery - Use in patients with moderate to severe hepatic impairment - Use in patients with severe renal impairment

Pharmacovigilance plan

Table 3. On-Going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
PREMIUM (PGL14-001) a prospective, non-interventional study to evaluate the long-term safety of Ulipristal Acetate Gedeon Richter, in particular the endometrial safety, and the current prescription and management patterns of Ulipristal Acetate Gedeon Richter in a long-term treatment setting. On-going	To investigate Ulipristal Acetate Gedeon Richter use in a 'real world' practice	-Inappropriate management of endometrium thickening (unnecessary interventions or treatments) - Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia) - Acute uterine bleeding requiring immediate intervention - Treatment course beyond three months - Long-term effects of prolonged treatment on the endometrium - Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma - Impact on surgery	Protocol version 1.2	March 2015
			Study start	Dec 2015
			Yearly reports	Q1 2017, 2018, 2019, 2020, 2021 and 2022
			Final report	Q1 2023 (8 years after variation approval)
Study 3083-N03-050, inhibition of MRP2 in vitro in membrane vesicles. Planned	To evaluate the potential for ulipristal acetate and its main metabolite (PGL4002) to be tested in vitro for their potential to inhibit MRP2 by measuring the uptake of a probe substrate into transporter-expressing and control vesicles in the	- Drug Induced Liver Injury	Study start	June 2018
			Study report	August 2018

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	presence of a range of ulipristal acetate and PGL4002 concentrations.			
Study 3083-N04-050, cell viability in 3D spheroid microtissues. Planned	To evaluate the effects of ulipristal acetate on cell viability in vitro in 3D spheroid microtissues made from primary human hepatocytes co cultured with non-parenchymal cells will be assessed for up to 14 days. The potential to form the glutathione conjugate metabolite of ulipristal acetate in hepatocytes will be assessed by using LC-MS/MS. If relevant effects of ulipristal acetate on cell viability are observed (IC50 < 100x plasma C_{max}), transcriptomics experiments will be performed to gain insight into the possible mechanisms.	- Drug Induced Liver Injury	Study start	June 2018
			Study report	September 2018
Study 3083-N05-050, cell viability in 'sandwich'. Planned	To evaluate the effect of ulipristal acetate on cell viability study in sandwich cultured primary human hepatocyte incubations for up to 24 hours, with and without a proprietary mix of bile acids added in the media. The potential for ulipristal acetate and its metabolites to cause cholestatic effects will be assessed by comparing the cell viability between incubations with and without added bile salts.	- Drug Induced Liver Injury	Study start	June 2018
			Study report	September 2018
Study 3083-S03-000, PBPK modelling under conditions of impaired bile secretion. Planned	To perform feasibility assessment of PBPK modelling of ulipristal acetate in bile secretion impaired conditions. If feasible, the concentrations of ulipristal acetate and PGL4002 in human blood and liver will be estimated in a PBPK model in which bile secretion is impaired.	- Drug Induced Liver Injury	Study start	June 2018
			Study report	September 2018
Study PGL18-002, retrospective, cohort study in multinational databases. Planned	To estimate the absolute and relative risk of liver injury with Ulipristal Acetate Gedeon Richter treatment and compare with patients with uterine fibroids not taking Ulipristal Acetate Gedeon Richter	- Drug Induced Liver Injury	Protocol submission	Within three months from EC decision on Article 20 procedure
Retrospective case control study utilising medical records of transplantation centres in at least five EU member	To estimate the overall population based absolute risk of acute liver failure leading to registration for transplantation in women exposed to Ulipristal Acetate Gedeon Richter	- Drug Induced Liver Injury	Feasibility report	Within two months from EC decision on Article 20 procedure

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
states. Planned				
Genetic analysis (HLA) study using data from EU registries with biomarker data in patients with severe DILI in registries such as, the International DILI Consortium (iDILIC), Spanish registry and the Pro-EURO DILI registry. Planned	To identify patients at risk for DILI	- Drug Induced Liver Injury	Feasibility report	Within two months from EC decision on Article 20 procedure
Observational study using EU registries with biomarker data e.g. THIN (United Kingdom), GePaRD (Germany), Pro-EURO DILI registry, Spanish registry and iDILIC registry. Planned	To identify patients at risk of DILI. Feasibility study to be performed prior to initiation of this study	- Drug Induced Liver Injury	Feasibility report	Within two months from EC decision on Article 20 procedure
Use of EU registries e.g. THIN, GePaRD, Pro-EURO DILI registry and the DILI registry databases to measure effectiveness of risk minimisation for risk of DILI. Planned	To measure effectiveness of monitoring of liver parameters in patients treated with Ulipristal Acetate Gedeon Richter in regular clinical practice	- Drug Induced Liver Injury	Feasibility report	Within two months from EC decision on Article 20 procedure
Study PGL18-001, retrospective drug utilisation study through a chart review across four major EU countries. Planned	To measure effectiveness of monitoring of liver parameters in patients treated with Ulipristal Acetate Gedeon Richter in regular clinical practice, also an effectiveness of adherence to modified indication and the new contraindication of underlying hepatic disorder.	- Drug Induced Liver Injury	Protocol submission	Within three months from EC decision on Article 20 procedure
			Study start	Q2 2019
			Study report	Q2 2020

Risk minimisation measures

Table 4. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Inappropriate management of endometrium thickening (unnecessary interventions or treatments)	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 5.1 Pharmacodynamic properties - PL section 1 Warnings and precautions Additional risk minimisation measures: - none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Targeted follow-up questionnaire Additional pharmacovigilance activities: - PREMIUM (PGL14-001) a prospective, non-interventional study
Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 5.1 Pharmacodynamic properties Additional risk minimisation measures: - none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Targeted follow-up questionnaire Additional pharmacovigilance activities: - PREMIUM (PGL14-001) a prospective, non-interventional study
Drug induced liver injury	Routine risk minimisation measures: - SmPC section 4.2 Posology and method of administration - SmPC section 4.3 Contraindications - SmPC section 4.4 Special warnings and precautions for use - Recommendation for liver function monitoring is included in SmPC sections 4.4 - SmPC section 5.2 Pharmacokinetic properties - PL section 2 Do not take Ulipristal Acetate Gedeon Richter and Warnings and precautions Additional risk minimisation measures: - Patient card (in package)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Targeted follow-up questionnaire Additional pharmacovigilance activities: - Study 3083-N03-050, inhibition of MRP2 in vitro in membrane vesicles - Study 3083-N04-050, cell viability in 3D spheroid microtissues - Study 3083-N05-050, cell viability in 'sandwich' - Study 3083-S03-000, PBPK modelling under conditions of impaired bile secretion - Study PGL18-002, retrospective, cohort study in multinational databases - Retrospective case control study utilising medical records of transplantation centres in at least five EU member states - Observational study using EU registries with biomarker data e.g. THIN (United Kingdom), GePaRD (Germany), Pro-EURO DILI registry, Spanish registry

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		and iDILIC registry - Genetic analysis (HLA) study using data from EU registries with biomarker data in patients with severe DILI in registries such as, the International DILI Consortium (iDILIC), Spanish registry and the Pro-EURO DILI registry. - Use of EU registries e.g. THIN, GePaRD, Pro-EURO DILI registry and the DILI registry databases to measure effectiveness of risk minimisation for risk of DILI - Study PGL18-001 retrospective drug utilisation study through a chart review across four major EU countries
Acute uterine bleeding requiring immediate intervention	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use Additional risk minimisation measures: - none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - none Additional pharmacovigilance activities: - PREMIUM (PGL14-001) a prospective, non-interventional study
Treatment course beyond three months	Routine risk minimisation measures: - SmPC section 4.2 Posology and method of administration - SmPC section 4.4 Special warnings and precautions for use - SmPC section 5.1 Pharmacodynamic properties - PL section 1 How to take Ulipristal Acetate Gedeon Richter Additional risk minimisation measures: - none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - none Additional pharmacovigilance activities: - PREMIUM (PGL14-001) a prospective, non-interventional study
Long-term effects of prolonged treatment of the endometrium (including possible malignant changes)	Routine risk minimisation measures: - SmPC section 4.2 Posology and method of administration - SmPC section 4.4 Special warnings and precautions for use Additional risk minimisation measures: - none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - none Additional pharmacovigilance activities: - PREMIUM (PGL14-001) a prospective, non-interventional study
Delayed diagnosis of atypical	Routine risk minimisation measures: - SmPC section 4.4 Special warnings	Routine pharmacovigilance activities beyond adverse reactions reporting and

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
endometrial hyperplasia or adenocarcinoma	and precautions for use Additional risk minimisation measures: - none	signal detection: - none Additional pharmacovigilance activities: - PREMIUM (PGL14-001) a prospective, non-interventional study
Impact on surgery	Impact of Ulipristal Acetate Gedeon Richter may be beneficial and/or adverse effect on the subsequent fibroid surgery. Routine risk minimisation measures: - none Additional risk minimisation measures: - none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - none Additional pharmacovigilance activities: - PREMIUM (PGL14-001) a prospective, non-interventional study
Use in patients with moderate to severe hepatic impairment	Routine risk minimisation measures: - SmPC section 4.2 Posology and method of administration - SmPC section 4.4 Special warnings and precautions for use - SmPC section 5.2 Pharmacokinetic properties - PL section 1 Warnings and precautions Additional risk minimisation measures: - none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - none Additional pharmacovigilance activities: - none
Use in patients with severe renal impairment	Routine risk minimisation measures: - SmPC section 4.2 Posology and method of administration - SmPC section 4.4 Special warnings and precautions for use - PL section 1 Warnings and precautions Additional risk minimisation measures: - none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - none Additional pharmacovigilance activities: - none

Conclusion

The CHMP and PRAC considered that the risk management plan version 16.0 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

Since Ulipristal Acetate Gedeon Richter application is an informed consent of Esmya application, the product information (PI) for Ulipristal Acetate Gedeon Richter 5 mg tablets is identical to the up-to-date PI of Esmya, with the only exception of the name of the medicinal product.

3. Benefit-Risk Balance

Ulipristal Acetate Gedeon Richter tablets are identical to Esmya tablets; the CHMP has previously reviewed data on quality, safety and efficacy of Esmya and considered the benefit/risk balance favourable.

Therefore recommended the granting of the marketing authorisation for the following indications:

- Ulipristal acetate is indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ulipristal Acetate Gedeon Richter is favourable in the following indication:

- Ulipristal acetate is indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.