Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ulipristal Acetate Rowex 30 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30 mg of ulipristal acetate.

Excipients with known effect
Each film-coated tablet contains 228 mg lactose.
Each film-coated tablet contains less than 1 mmol (23 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Round, white, biconvex, film-coated tablet, embossed with "U30" on one side, with a diameter of approximately 9 mm and thickness of 4.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Posology
The treatment consists of one tablet to be taken orally as soon as possible, but no later than 120 hours (5 days) after unprotected intercourse or contraceptive failure.
The tablet can be taken at any time during the menstrual cycle. If vomiting occurs within 3 hours of the tablet 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 the tablet is administered (see sections 4.4 and 4.6).

Special populations

Renal impairment
No dose adjustment is necessary.

Hepatic impairment
In the absence of specific studies, no alternate dose recommendations for Ulipristal Acetate Rowex can be made.

Severe hepatic impairment
In the absence of specific studies, Ulipristal Acetate Rowex is not recommended.

Paediatric population
There is no relevant use of Ulipristal Acetate Rowex for children of prepubertal age in the indication emergency contraception.

Adolescents:
Ulipristal Acetate Rowex for emergency contraception is suitable for any woman of child bearing age, including adolescents.
No differences in safety or efficacy have been shown compared to adult women aged 18 and older (see section 5.1).

Method of administration

Oral use.
The tablet can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Ulipristal Acetate Rowex is for occasional use only. It should in no instance replace a regular contraceptive method. In any case, women should be advised to adopt a regular method of contraception.

Ulipristal acetate is not intended for use during pregnancy and should not be taken by any woman suspected or known to be pregnant. However, it does not interrupt an existing pregnancy (see sections 4.2 and 4.6).

Ulipristal Acetate Rowex does not prevent pregnancy in every case

In case the next menstrual period is more than 7 days late, if the menstrual period is abnormal in character or if there are symptoms suggestive of pregnancy or in case of doubt, a pregnancy test should be performed. As with any pregnancy, the possibility of an ectopic pregnancy should be considered. It is important to know that the occurrence of uterine bleeding does not rule out ectopic pregnancy. Women who become pregnant after taking Ulipristal Acetate Rowex should contact their doctor (see section 4.6).

Ulipristal Acetate Rowex inhibits or postpones ovulation (see section 5.1). If ovulation has already occurred, it is no longer effective. The timing of ovulation cannot be predicted and therefore the tablet should be taken as soon as possible after unprotected intercourse.

No data are available on the efficacy of Ulipristal Acetate Rowex when taken more than 120 hours (5 days) after unprotected intercourse.

Limited and inconclusive data suggest that there may be reduced efficacy of Ulipristal Acetate Rowex with increasing body weight or body mass index (BMI) (see section 5.1). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI.

After the tablet intake menstrual periods can sometimes occur a few days earlier or later than expected. In approximately 7% of the women, menstrual periods occurred more than 7 days earlier than expected. In 18.5% of the women a delay of more than 7 days occurred, and in 4% the delay was greater than 20 days.

Concomitant use of Ulipristal Acetate Rowex and emergency contraception containing levonorgestrel is not recommended (see section 4.5).

Contraception after Ulipristal Acetate Rowex intake

Ulipristal Acetate Rowex is an emergency contraceptive that decreases pregnancy risk after unprotected intercourse but does not confer contraceptive protection for subsequent acts of intercourse. Therefore, after using emergency contraception, woman should be advised to use a reliable barrier method until her next menstrual period.

Although the use of Ulipristal Acetate Rowex for emergency contraception does not contraindicate the continued use of regular hormonal contraception, Ulipristal Acetate Rowex may reduce its contraceptive action (see section 4.5). Therefore, if a woman wishes to start or continue using hormonal contraception, she can do so after using Ulipristal Acetate Rowex, however, she should be advised to use a reliable barrier method until the next menstrual period.

Specific populations

Concomitant use of Ulipristal Acetate Rowex with CYP3A4 inducers is not recommended due to interaction (e.g. barbiturates (including primidone and phenobarbital), phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, herbal medicinal products

containing *Hypericum perforatum* (St. John's wort), rifampicin, rifabutin, griseofulvin, efavirenz, nevirapine and long term use of ritonavir).

Use in women with severe asthma treated by oral glucocorticoid is not recommended**.**

Ulipristal Acetate Rowex contains lactose and sodium

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Potential for other medicinal products to affect Ulipristal Acetate Rowex

Ulipristal Acetate Rowex is metabolised by CYP3A4 *in vitro*.

- *CYP3A4 inducers*

In vivo results show that the administration of Ulipristal Acetate Rowex with a strong CYP3A4 inducer such as rifampicin markedly decreases Cmax and AUC of Ulipristal Acetate Rowex by 90% or more and decreases Ulipristal Acetate Rowex half-life by 2.2-fold corresponding to an approximately 10-fold decrease of Ulipristal Acetate Rowex exposure. Concomitant use of Ulipristal Acetate Rowex with CYP3A4 inducers (e.g. barbiturates (including primidone and phenobarbital), phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, herbal medicinal products containing *Hypericum perforatum* (St. John's wort), rifampicin, rifabutin, griseofulvin, efavirenz and nevirapine) therefore reduces plasma concentrations of Ulipristal Acetate Rowex and may result in a decreased efficacy of {Nationally completed name}. For women who have used enzyme-inducing medicinal products in the past 4 weeks, Ulipristal Acetate Rowex is not recommended (see section 4.4) and non-hormonal emergency contraception (i.e. a copper intrauterine device (Cu-IUD)) should be considered.

- *CYP3A4 inhibitors*

In vivo results show that administration of Ulipristal Acetate Rowex with a potent and a moderate CYP3A4 inhibitor increased Cmax and AUC of Ulipristal Acetate Rowex with a maximum of 2- and 5.9-fold, respectively. The effects of CYP3A4 inhibitors are unlikely to have any clinical consequences.

The CYP3A4 inhibitor ritonavir can also have an inducing effect on CYP3A4 when ritonavir is used for a longer period. In such cases ritonavir might reduce plasma concentrations of Ulipristal Acetate Rowex. Concomitant use is therefore not recommended (see section 4.4). Enzyme induction wears off slowly and effects on the plasma concentrations of Ulipristal Acetate Rowex may occur even if a woman has stopped taking an enzyme inducer in the past 4 weeks.

Medicinal products affecting gastric pH

Administration of Ulipristal Acetate Rowex (10 mg tablet) together with the proton pump inhibitor esomeprazole (20 mg daily for 6 days) resulted in approximately 65% lower mean Cmax, a delayed Tmax (from a median of 0.75 hours to 1.0 hours) and 13% higher mean AUC. The clinical relevance of this interaction for single dose administration of Ulipristal Acetate Rowex as emergency contraception is not known.

Potential for Ulipristal Acetate Rowex to affect other medicinal products

Hormonal contraceptives

Because Ulipristal Acetate Rowexbinds to the progesterone receptor with high affinity, it may interfere with the action of progestogen-containing medicinal products:

- Contraceptive action of combined hormonal contraceptives and progestogen-only contraception may be reduced
- Concomitant use of Ulipristal Acetate Rowexand emergency contraception containing levonorgestrel is not recommended (see section 4.4).

In vitro data indicate that Ulipristal Acetate Rowexand its active metabolite do not significantly inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4, at clinically relevant concentrations. After single dose administration induction of CYP1A2 and CYP3A4 by Ulipristal Acetate Rowex or its active metabolite is not likely. Thus, administration of Ulipristal Acetate Rowexis unlikely to alter the clearance of medicinal products that are metabolised by these enzymes.

P-glycoprotein (P-gp) substrates
In vitro data indicate that Ulipristal Acetate Rowexmay be an inhibitor of P-gp at clinically relevant concentrations. Results *in vivo* with the P-gp substrate fexofenadine were inconclusive. The effects of the P-gp substrates are unlikely to have any clinical consequences.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ulipristal Acetate Rowex is not intended for use during pregnancy and should not be taken by any woman suspected or known to be pregnant (see sections 4.2 and 4.4).

Ulipristal Acetate Rowex does not interrupt an existing pregnancy.

Pregnancy may occasionally occur after Ulipristal Acetate Rowexintake. Although no teratogenic potential has been observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3). Limited human data regarding pregnancy exposure to Ulipristal Acetate Rowex do not suggest any safety concern.

Nevertheless, it is important that any pregnancy in a woman who has taken Ulipristal Acetate Rowex be reported to www.ulipristal-pregnancy-registry.com. The purpose of this web-based registry is to collect safety information from women who have taken Ulipristal Acetate Rowex during pregnancy or who become pregnant after Ulipristal Acetate Rowex intake. All patient data collected will remain anonymous.

Breast-feeding

Ulipristal Acetate Rowex is excreted in breast milk (see section 5.2). The effect on newborn/infants has not been studied. A risk to the breastfed child cannot be excluded. After intake of Ulipristal Acetate Rowex for emergency contraception, breast-feeding is not recommended for one week. During this time it is recommended to express and discard the breast milk in order to stimulate lactation.

Fertility

A rapid return of fertility is likely following treatment with Ulipristal Acetate Rowex for emergency contraception. Women should be advised to use a reliable barrier method for all subsequent acts of intercourse until the next menstrual period.

4.7 Effects on ability to drive and use machines

Ulipristal Acetate Rowex has minor or moderate influence on the ability to drive or use machines: mild to moderate dizziness is common after Ulipristal Acetate Rowex intake, somnolence and blurred vision are uncommon; disturbance in attention has been rarely reported. The patient should be informed not to drive or use machines if they are experiencing such symptoms (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were headache, nausea, abdominal pain and dysmenorrhea.

Safety of Ulipristal AcetateRowexhas been evaluated in 4,718 women during the clinical development program.

Tabulated list of adverse reactions

The adverse reactions reported in the phase III program of 2,637 women are provided in the table below.

Adverse reactions listed below are classified according to frequency and system organ class using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

MedDRA	**Adverse reactions (frequency)**		
System organ class	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)
Infections and infestations		Influenza	
Metabolism and nutrition disorders		Appetite disorders	
Psychiatric disorders	Mood disorders	Emotional disorder Anxiety Insomnia Hyperactivity disorder Libido changes	Disorientation
Nervous system disorders	Headache Dizziness	Somnolence Migraine	Tremor Disturbance in attention Dysgeusia Syncope
Eye disorders		Visual disturbance	Abnormal sensation in eye Ocular hyperaemia Photophobia
Ear and labyrinth disorders			Vertigo
Respiratory, thoracic and mediastinal disorders			Dry throat
Gastrointestinal disorders	Nausea* Abdominal pain* Abdominal discomfort Vomiting*	Diarrhoea Dry mouth Dyspepsia Flatulence	
Skin and subcutaneous tissue disorders		Acne Skin lesion Pruritus	
Musculoskeletal and connective tissue disorders	Myalgia Back pain		

Reproductive system and breast disorders	Dysmenorrhea Pelvic pain Breast tenderness	Menorrhagia Vaginal discharge Menstrual disorder Metrorrhagia Vaginitis Hot flush Premenstrual syndrome	Genital pruritus Dyspareunia Ruptured ovarian cyst Vulvovaginal pain Hypomenorrhea*
General disorders and administration site conditions	Fatigue	Chills Malaise Pyrexia	Thirst
Immune system disorders			Hypersensitivity reactions including Rash, Urticaria, Angioedema

*Symptom which could also be related to an undiagnosed pregnancy (or related complications)

Adolescents: the safety profile observed in women less than 18 years old in studies and post-marketing is similar to the safety profile in adults during the phase III program (see section 4.2).

Post-marketing experience: the adverse reactions spontaneously reported in post-marketing experience were similar in nature and frequency to the safety profile described during the phase III program.

Description of selected adverse reactions

The majority of women (74.6%) in the phase III studies had their next menstrual period at the expected time or within ± 7 days, while 6.8% experienced menses more than 7 days earlier than expected and 18.5% had a delay of more than 7 days beyond the anticipated onset of menses. The delay was greater than 20 days in 4 % of the women.

A minority (8.7%) of women reported intermenstrual bleeding lasting an average of 2.4 days. In a majority of cases (88.2%), this bleeding was reported as spotting. Among the women who received Ulipristal Acetate Rowex in the phase III studies, only 0.4% reported heavy intermenstrual bleeding.

In the phase III studies, 82 women entered a study more than once and therefore received more than one dose of Ulipristal Acetate Rowex (73 women enrolled twice and 9 enrolled three times). There were no safety differences in these subjects in terms of incidence and severity of adverse reactions, change in duration or volume of menses or incidence of intermenstrual bleeding.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Experience with Ulipristal Acetate Rowex overdose is limited. Single doses up to 200 mg have been used in women without safety concern. Such high doses were well-tolerated; however, these women had a shortened menstrual cycle (uterine bleeding occurring 2-3 days earlier than would be expected) and in some women, the duration of bleeding was prolonged, although not excessive in amount (spotting). There are no antidotes and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, emergency contraceptives. ATC code: G03AD02.

Ulipristal Acetate Rowex is an orally-active synthetic selective progesterone receptor modulator which acts via high-affinity binding to the human progesterone receptor. When used for emergency contraception the mechanism of action is inhibition or delay of ovulation via suppression of the luteinising hormone (LH) surge. Pharmacodynamic data show that even when

taken immediately before ovulation is scheduled to occur (when LH has already started to rise), Ulipristal Acetate Rowex is able to postpone follicular rupture for at least 5 days in 78.6% of cases (p<0.005 vs. levonorgestrel and vs. placebo) (see table).

Prevention of ovulation [1,§]			
	Placebo n=50	**Levonorgestrel** n=48	**Ulipristal Acetate Rowex** n=34
Treatment before LH surge	n=16 0.0%	n=12 25.0%	n=8 100% p<0.005*
Treatment after LH surge but before LH peak	n=10 10.0%	n=14 14.3% NS†	n=14 78.6% p<0.005*
Treatment after LH peak	n=24 4.2%	n=22 9.1% NS†	n=12 8.3% NS*

1: Brache et al, Contraception 2013
§: defined as presence of unruptured dominant follicle five days after late follicular-phase treatment
*: compared to levonorgestrel
NS: non statistically significant
†: compared to placebo

Ulipristal Acetate Rowex also has high affinity for the glucocorticoid receptor and *in vivo*, in animals, anti- glucocorticoid effects have been observed. However, in humans, no such effect has been observed even after repeat administration at the daily dose of 10 mg. It has minimal affinity to the androgen receptor and no affinity for the human estrogen or mineralocorticoid receptors.

Results from two independent randomised controlled studies (see table below) showed the efficacy of Ulipristal Acetate Rowex to be non-inferior to that of levonorgestrel in women who presented for emergency contraception between 0 and 72 hours after unprotected intercourse or contraceptive failure. When the data from the two studies were combined via meta-analysis, the risk of pregnancy with Ulipristal Acetate Rowex was significantly reduced compared to levonorgestrel (p=0.046).

Randomised controlled trial	Pregnancy rate (%) within 72h of unprotected intercourse or contraceptive failure[2]		Odds ratio [95% CI] of pregnancy risk, Ulipristal Acetate Rowex vs levonorgestrel[2]
	• Ulipristal Acetate Rowex	• 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]
Meta- analysis	1.36 (22/1617)	2.15 (35/1625)	0.58 [0.33-0.99]

2: Glasier et al, Lancet 2010

Two studies provide efficacy data on Ulipristal Acetate Rowex used up to 120 hours after unprotected intercourse. In an open-label clinical study, which enrolled women who presented for emergency contraception and were treated with Ulipristal Acetate Rowex between 48 and 120 hours after unprotected intercourse, a pregnancy rate of 2.1% (26/1241) was observed. In addition, the second comparative study described above also provides data on 100 women treated with Ulipristal Acetate Rowex from 72 to 120 hours after unprotected intercourse, in whom no pregnancies were observed.

Limited and inconclusive data from clinical studies suggest a possible trend for a reduced contraceptive efficacy of ulipristal acetate with high body weight or BMI (see section 4.4). The meta-analysis of the four clinical studies conducted with Ulipristal Acetate Rowex presented below excluded women who had further acts of unprotected intercourse.

BMI (kg/m^2)	**Underweight 0 - 18.5**	**Normal 18.5-25**	**Overweight 25-30**	**Obese 30-**
N total	128	1866	699	467
N pregnancies	0	23	9	12
Pregnancy rate	0.00%	1.23%	1.29%	2.57%

Confidence interval	0.00 – 2.84	0.78 – 1.84	0.59 – 2.43	1.34 - 4.45

A post-marketing observational study evaluating efficacy and safety of Ulipristal Acetate Rowex in adolescents aged 17 and younger showed no difference in the safety and efficacy profile compared to adult women aged 18 and older.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a single 30 mg dose, Ulipristal Acetate Rowex is rapidly absorbed, with a peak plasma concentration of 176 ± 89 ng/ml occurring approximately 1 hour (0.5-2.0 h) after ingestion, and with an AUC0-∞ of 556 ± 260 ng.h/ml.

Administration of Ulipristal Acetate Rowex together with a high-fat breakfast resulted in approximately 45% lower mean Cmax, a delayed Tmax (from a median of 0.75 hours to 3 hours) and 25% higher mean AUC0-∞ compared with administration in the fasted state. Similar results were obtained for the active mono-demethylated metabolite.

Distribution

Ulipristal Acetate Rowex is highly bound (>98%) to plasma proteins, including albumin, alpha-l-acid glycoprotein, and high density lipoprotein.

Ulipristal Acetate Rowex is a lipophilic compound and is distributed in breast milk, with a mean daily excretion of 13.35 µg [0-24 hours], 2.16 µg [24-48 hours], 1.06 µg [48-72 hours], 0.58 µg
[72-96 hours], and 0.31 µg [96-120 hours].

In vitro data indicate that Ulipristal Acetate Rowex may be an inhibitor of BCRP (Breast Cancer Resistance Protein) transporters at the intestinal level. The effects of Ulipristal Acetate Rowex on BCRP are unlikely to have any clinical consequences.

Ulipristal Acetate Rowex is not a substrate for either OATP1B1 or OATP1B3.

Biotransformation/elimination

Ulipristal Acetate Rowex is extensively metabolised to mono-demethylated, di-demethylated and hydroxylated metabolites. The mono-demethylated metabolite is pharmacologically active. *In vitro* data indicate that this is predominantly mediated by CYP3A4, and to a small extent by CYP1A2 and CYP2A6. The terminal half-life of Ulipristal Acetate Rowex in plasma following a single 30 mg dose is estimated to 32.4 ± 6.3 hours, with a mean oral clearance (CL/F) of 76.8 ± 64.0 L/h.

Special populations

No pharmacokinetic studies with Ulipristal Acetate Rowex have been performed in females with impaired renal or hepatic function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Most findings in general toxicity studies were related to its mechanism of action as a modulator of progesterone and glucocorticoid receptors, with antiprogesterone activity observed at exposures similar to therapeutic levels.

Information from reproductive toxicity studies is limited due to the absence of exposure measurement in these studies. Ulipristal Acetate Rowex has an embryo lethal effect in rats, rabbits (at repeated doses above 1 mg/kg) and in monkeys. At these repeated doses, the safety for a human embryo is unknown. At doses which were low enough to maintain gestation in the animal species, no teratogenic effects were observed.

Carcinogenicity studies (in rats and mice) showed that Ulipristal Acetate Rowex is not carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Pregelatinised starch (maize)
Sodium starch glycolate (Type A)
Magnesium stearate (E 470b)

Tablet coating
Hypromellose (E 464)
Hydroxypropylcellulose (E 463)
Stearic acid (E 570)
Talc (E 553b)
Titanium Dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

The tablets are packed in PVC/PVDC/Aluminium blister of 1 film-coated tablet and inserted in a carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/292/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st November 2019

10 DATE OF REVISION OF THE TEXT

July 2022