Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azalia 75 microgram film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 microgram desogestrel.

Excipient with known effect: 52.34 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White or almost white, round, biconvex film-coated tablets of about 5,5 mm in diameter, with a sign “D” on one side and “75” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Contraception

4.2 Posology and method of administration

Posology
To achieve contraceptive effectiveness, Azalia must be used as directed (see 'How to take Azalia' and 'How to start Azalia').

Special populations

Renal impairment
No clinical studies have been performed in patients with renal impairment.

Hepatic impairment
No clinical studies have been performed in patients with hepatic insufficiency. Since the metabolism of steroid hormones might be impaired in patients with severe hepatic disease, the use of Azalia in these women is not indicated as long as liver function values have not returned to normal (see section 4.3).

Paediatric population
The safety and efficacy of Azalia in adolescents below 18 years has not been established. No data are available.

Method of administration
Oral use.

How to take Azalia
Tablets must be taken every day at about the same time so that the interval between two tablets always is 24 hours. The first tablet should be taken on the first day of menstrual bleeding. Thereafter one tablet each day is to be taken continuously, without taking any notice on possible bleeding. A new blister is started directly the day after the previous one.

How to start Azalia
No preceding hormonal contraceptive use [in the past month]

Tablet-taking has to start on day 1 of the woman's natural cycle (day 1 is the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended for the first 7 days of tablet-taking.

Following first-trimester abortion
After first-trimester abortion it is recommended to start immediately. In that case there is no need to use an additional method of contraception.

Following delivery or second-trimester abortion
The woman should be advised to start any day between day 21 to 28 after delivery or second-trimester abortion. When starting later, she should be advised to additionally use a barrier method until completion of the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of Azalia use or the woman has to wait for her first menstrual period.

For additional information for breastfeeding women see section 4.6.

How to start Azalia when changing from other contraceptive methods
Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch)
The woman should start Azalia preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC or on the day of removal of her vaginal ring or transdermal patch. In these cases, the use of an additional contraceptive is not necessary. Not all contraceptive methods may be available in all EU countries.

The woman may also start at the latest on the day following the usual tablet-free, patch-free, ring-free or placebo tablet interval of her previous combined hormonal contraceptive, but during the first 7 days of tablet-taking an additional barrier method is recommended.

Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS))
The woman may switch any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due).

Management of missed tablets
Contraceptive protection may be reduced if more than 36 hours have elapsed between two tablets. If the user is less than 12 hours late in taking any tablet, the missed tablet should be taken as soon as it is remembered and the next tablet should be taken at the usual time. If she is more than 12 hours late, she should use an additional method of contraception for the next 7 days. If tablets were missed in the first week after initiation of Azalia and intercourse took place in the week before the tablets were missed, the possibility of a pregnancy should be considered.

Advice in case of gastrointestinal disturbances
In case of severe gastro-intestinal disturbance, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, absorption may not be complete. In such an event, the advice concerning missed tablets, as given in subsection "Management of missed tablets" is applicable.

Treatment surveillance
Before prescription, a thorough case history should be taken and a thorough gynaecological examination is recommended to exclude pregnancy. Bleeding disturbances, such as oligomenorrhoea and amenorrhoea should be investigated before prescription. The interval between check-ups depends on the circumstances in each individual case. If the prescribed product may conceivably influence latent or manifest disease (see section 4.4), the control examinations should be timed accordingly.

Despite the fact that Azalia is taken regularly, bleeding disturbances may occur. If bleeding is very frequent and irregular, another contraceptive method should be considered. If the symptoms persist, an organic cause should be ruled out.

Management of amenorrhoea during treatment depends on whether or not the tablets have been taken in accordance with the instructions and may include a pregnancy test.

The treatment should be stopped if a pregnancy occurs.

Women should be advised that Azalia does not protect against HIV (AIDS) and other sexually transmitted diseases.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active venous thromboembolic disorder.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Known or suspected sex-steroid sensitive malignancies.
- Undiagnosed vaginal bleeding.

4.4 Special warnings and precautions for use

If any of the conditions/risk factors mentioned below is present, the benefits of progestogen use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start with Azalia. In the event of aggravation, exacerbation, or first appearance of any of these conditions, the woman should contact her physician. The physician should then decide on whether the use of Azalia should be discontinued.

The risk for breast cancer increases in general with increasing age. During use of combined oral contraceptives (COCs) the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of COC use and is not related to the duration of use, but to the age of the woman when using the COC. The expected number of cases diagnosed per 10 000 women who use COCs (up to 10 years after stopping) relative to never users over the same period has been calculated for the respective age groups and is presented in the table below.

Age group	Expected cases COC-users	Expected cases non-users
16-19 years	4.5	4
20-24 years	17.5	16
25-29 years	48.7	44
30-34 years	110	100
35-39 years	180	160
40-44 years	260	230

The risk in users of progestogen-only contraceptives (POCs), such as Azalia is possibly of similar magnitude as that associated with COCs. However, for POCs the evidence is less conclusive. Compared to the risk of getting breast cancer ever in life, the increased risk associated with COCs is low. The cases of breast cancer diagnosed in COC users tend to be less advanced than in those who have not used COCs. The increased risk in COC users may be due to an earlier diagnosis, biological effects of the pill or a combination of both.

Since a biological effect of progestogens on liver cancer cannot be excluded an individual benefit/risk assessment should be made in women with liver cancer.

When acute or chronic disturbances of liver function occur the woman should be referred to a specialist for examination and advice.

Epidemiological investigations have associated the use of COCs with an increased incidence of venous thromboembolism (VTE, deep venous thrombosis and pulmonary embolism). Although the clinical relevance of this finding for desogestrel used as a contraceptive in the absence of an oestrogenic component is unknown, Azalia should be discontinued in the event of a thrombosis.
Discontinuation of Azalia should also be considered in case of long-term immobilisation due to surgery or illness. Women with a history of thrombo-embolic disorders should be made aware of the possibility of a recurrence.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Although progestogens may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using progestogen-only pills. However, diabetic patients should be carefully observed during the first months of use.

If a sustained hypertension develops during the use of Azalia, or if a significant increase in blood pressure does not adequately respond to antihypertensive therapy, the discontinuation of Azalia should be considered.

Treatment with Azalia leads to decreased oestradiol serum levels, to a level corresponding with the early follicular phase. It is as yet unknown whether the decrease has any clinically relevant effect on bone mineral density.

The protection with traditional progestogen-only pills against ectopic pregnancies is not as good as with combined oral contraceptives, which has been associated with the frequent occurrence of ovulations during the use of progestogen-only pills. Despite the fact that Azalia consistently inhibits ovulation, ectopic pregnancy should be taken into account in the differential diagnosis if the woman gets amenorrhoea or abdominal pain.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking Azalia.

The following conditions have been reported both during pregnancy and during sex steroid use, but an association with the use of progestogens has not been established: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss; (hereditary) angioedema.

The efficacy of Azalia may be reduced in the event of missed tablets (section 4.2), gastro-intestinal disturbances (section 4.2), or concomitant medications that decrease the plasma concentration of etonogestrel, the active metabolite of desogestrel (section 4.5).

Laboratory tests
Data obtained with COCs have shown that contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, serum levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. The changes generally remain within the normal range. To what extent this also applies to progestogen-only contraceptives is not known.

Excipient
Azalia film-coated tablets contain 52.34 mg lactose (as lactose monohydrate). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Interactions

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Effect of other medicinal products on Azalia
Interactions can occur with medicinal products that induce microsomal enzymes, which can result in increased clearance of sex hormones and may lead to breakthrough bleeding and/or contraceptive failure.

Management
Enzyme induction can occur after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 4 weeks.

Short-term treatment
Women on treatment with hepatic enzyme-inducing medicinal or herbal products should be advised that the efficacy of Azalia may be reduced. A barrier contraceptive method should be used in addition to Azalia. The barrier method must be used during the whole time of concomitant drug therapy and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product.

Long-term treatment
For women on long-term therapy with enzyme-inducing medicinal products, an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

Substances increasing the clearance of contraceptive hormones (diminished contraceptive efficacy by enzyme induction) e.g.:
Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate, rifabutin and products containing the herbal remedy St. John's Wort (*Hypericum perforatum*).

Substances with variable effects on the clearance of contraceptive hormones:
When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g. ritonavir, nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g. boceprevir, telaprevir), can increase or decrease plasma concentrations of progestins. The net effect of these changes may be clinically relevant in some cases.
Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Substances decreasing the clearance of contraceptive hormones (enzyme inhibitors):
Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of progestins, including etonogestrel, the active metabolite of desogestrel.

Effects of Azalia on other medicinal products:
Hormonal contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations of other active substances may either increase (e.g. ciclosporine) or decrease (e.g. lamotrigine).

4.6 Fertility, pregnancy and lactation

Pregnancy
Azalia is not indicated during pregnancy. If pregnancy occurs during treatment with Azalia, further intake should be stopped. Animal studies have shown that very high doses of progestogenic substances may cause masculinisation of female foetuses.

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy. Pharmacovigilance data collected with various desogestrel-containing COCs also do not indicate an increased risk.

Breast-feeding
Based on clinical study data Azalia does not appear to influence the production or the quality (protein, lactose, or fat concentrations) of breast milk. However, there have been infrequent postmarketing reports of a decrease in breast milk production while using Azalia. Small amounts of etonogestrel are excreted in the breast milk. As a result, 0.01-0.05 microgram etonogestrel per kg body weight per day may be ingested by the child (based on an estimated milk ingestion of 150 mL/kg/day). Like other progestogen-only pills, Azalia can be used during breast feeding.

Limited long-term follow-up data are available on children, whose mothers started using desogestrel 75 microgram tablets during the 4^{th} to 8^{th} week post-partum. They were breast-fed for 7 months and followed up to 1.5 years (n=32) or to 2.5 years (n=14) of age. Evaluation of growth and physical and psychomotor development did not indicate any differences in comparison to nursing infants, whose mother used a copper-IUD.

Based on the available data, Azalia may be used during lactation. The development and growth of a nursing infant, whose mother uses Azalia, should, however be carefully observed.

Fertility
Azalia is indicated for the prevention of pregnancy. For information on return to fertility (ovulation), see section 5.1.

4.7 Effects on ability to drive and use machines

Azalia has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported undesirable effect in the clinical trials is bleeding irregularity. Some kind of bleeding irregularity has been reported in up to 50% of women using desogestrel 75 microgram tablets. Since desogestrel causes ovulation inhibition close to 100%, in contrast to other progestogen-only pills, irregular bleeding is more common than with other progestogen-only pills. In 20-30% of the women, bleeding may become more frequent, whereas in another 20% bleeding may become less frequent or totally absent. Vaginal bleeding may also be of longer duration. After a couple of months of treatment, bleedings tend to become less frequent. Information, counselling and a bleeding diary can improve the woman's acceptance of the bleeding pattern.

The most commonly reported other undesirable effects in the clinical trials with desogestrel 75 microgram tablets (>2.5%) were acne, mood changes, breast pain, nausea and weight increase. The undesirable effects are mentioned in the table below.

All undesirable effects are listed by system organ class and frequency; common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and not known (cannot be estimated from the available data).

System Organ Class (MedDRA)	**Frequency of adverse reactions**			
	Common	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Vaginal infection		
Immune system disorders				Hypersensitivity reactions, including angioedema and anaphylaxis
Psychiatric disorders	Mood altered Depressed mood Libido decreased			
Nervous system disorders	Headache			
Eye disorders		Contact lens intolerance		
Gastrointestinal disorders	Nausea	Vomiting		
Skin and subcutaneous tissue disorders	Acne	Alopecia	Rash, Urticaria, Erythema nodosum	
Reproductive system and breast disorders	Breast pain, Menstruation irregular, Amenorrhoea	Dysmenorrhoea, Ovarian cyst		
General disorders and administration site condition		Fatigue		
Investigations	Weight increased			

Breast discharge may occur during use of Azalia. On rare occasions, ectopic pregnancies have been reported (see section 4.4). In addition, aggravation of hereditary angioedema may occur (See section 4.4).

In women using (combined) oral contraceptives a number of (serious) undesirable effects have been reported. These include venous thromboembolic disorders, arterial thromboembolic disorders, hormone-dependent tumours (e.g. liver tumours, breast cancer), and chloasma, some of which are discussed in more detail in section 4.4.

Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with hormonal contraceptives (see section 4.5).

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormonal contraceptives for systemic use, Progestogens, ATC code: G03AC09

Mechanism of action
Azalia is a progestogen-only pill, which contains the progestogen desogestrel. Like other progestogen-only pills, Azalia film-coated tablet can be used for women who may not or do not want to use oestrogens. In contrast to traditional progestogen-only pills, the contraceptive effect of Azalia film-coated tablet is achieved primarily by inhibition of ovulation. Other effects include increased viscosity of the cervical mucus.

Clinical efficacy and safety
When studied for 2 cycles, using a definition of ovulation as a progesterone level greater than 16 nmol/L for 5 consecutive days, the ovulation incidence was found to be 1% (1/103) with a 95% confidence interval of 0.02%-5.29% in the intention-to-treat (ITT) group (user and method failures). Ovulation inhibition was achieved from the first cycle of use. In this study, when desogestrel 75 microgram tablet was discontinued after 2 cycles (56 continuous days), ovulation occurred on average after 17 days (range 7-30 days).
In a comparative efficacy trial (which allowed a maximum time of 3 hours for missed pills) the overall intention-to-treat Pearl-Index found for desogestrel 75 microgram tablet was 0.4 (95% confidence interval 0.09-1.20), compared to 1.6 (95% confidence interval 0.42 - 3.96) for 30 microgram levonorgestrel.

The Pearl-Index for desogestrel 75 microgram tablet is comparable to the one historically found for COCs in the general COC-using population.

Treatment with desogestrel 75 microgram tablets leads to decreased oestradiol levels, to a level corresponding to the early follicular phase. No clinically relevant effects on carbohydrate metabolism, lipid metabolism and haemostasis have been observed.

Paediatric population
No clinical data on efficacy and safety are available in adolescents below 18 years.

5.2 Pharmacokinetic properties

Absorption
After oral dosing of Azalia desogestrel is rapidly absorbed and converted into etonogestrel. Under steady-state conditions, peak serum levels are reached 1.8 hours after tablet-intake and the absolute bioavailability of etonogestrel is approximately 70%.

Distribution
Etonogestrel is 95.5-99% bound to serum proteins, predominantly to albumin and to a lesser extent to sex hormone binding globuline (SHBG).

Biotransformation
Desogestrel is metabolised via hydroxylation and dehydrogenation to the active metabolite etonogestrel. Etonogestrel is primarily metabolised by the cytochrome P450 3A (CYP3A) isoenzyme and subsequently conjugated with sulphate and glucuronide.

Elimination
Etonogestrel is eliminated with a mean half-life of approximately 30 hours, with no difference between single and multiple dosing. Steady-state levels in plasma are reached after 4-5 days. The serum clearance after i.v. administration of etonogestrel is approximately 10 L per hour. Excretion of etonogestrel and its metabolites either as free steroid or as conjugates, is with urine and faeces (ratio 1.5:1). In lactating women, etonogestrel is excreted in breast milk with a milk/serum ratio of 0.37-0.55.

Based on these data and an estimated milk intake of 150 mL/kg/day, 0.01-0.05 microgram etonogestrel maybe ingested by the infant.

Special populations

Effect of renal impairment
No studies were performed to evaluate the effect of renal disease on the pharmacokinetics of desogestrel.

Effect of hepatic impairment
No studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of desogestrel. However, steroid hormones may be poorly metabolized in women with impaired liver function.

Ethnic groups
No studies were performed to assess pharmacokinetics in ethnic groups.

5.3 Preclinical safety data

Toxicological studies did not reveal any effects other than those, which can be explained from the hormonal properties of desogestrel.

Environmental Risk Assessment (ERA)
The active substance etonogestrel shows an environmental risk to fish.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Potato starch
Povidone K-30
Silica, colloidal anhydrous
Stearic acid
all-rac-α-Tocopherol

Tablet coat:
Poly[vinyl alcohol]
Titanium dioxide, E171
Macrogol 3000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions

6.5 Nature and contents of container

Azalia film-coated tablets are packaged in a blister made of transparent, hard PVC/PVDC- Aluminium foil. Each blister is placed in a laminated aluminium sachet. The blisters in the sachets are packed into a folded carton box with a patient leaflet and etui storing bag.
Pack sizes: 1x28, 3x28, 6x28, 13x28 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc
Gyömroi út 19-21
H-1103, Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER

PA1330/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th October 2010
Date of last renewal: 26th October 2014

10 DATE OF REVISION OF THE TEXT

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