1. NAME OF THE MEDICINAL PRODUCT

Exlutena 0,5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: Lynestrenol 0,5 mg.

For a complete list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round bevelled-edge tablet, coded TT2 on one side and ORGANON* on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

4.2 Posology and method of administration

How to take Exlutena

One tablet is to be taken daily without interruption, at about the same time every day with some liquid as needed. Each subsequent pack is started immediately after finishing the previous pack.

How to start Exlutena

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 in addition for the first 7 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive, vaginal ring or transdermal patch)

The woman can start with Exlutena on the day after the last active tablet, or on the day of removal of her vaginal ring, or patch. In these cases, the use of an additional contraceptive method is not necessary.

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, and from injection on the same day the injection was due. An additional contraceptive method is not necessary.

Following first-trimester abortion

The woman may start immediately, an additional contraceptive method is not necessary.

Following delivery and second-trimester abortion

For breast-feeding women, see Section 4.6.

The woman should start with Exlutena on day 21 to 28 after delivery or second-trimester abortion. When starting later, an additional contraceptive method for the first 7 days of tablet-taking should be used. If the woman has had intercourse, pregnancy should be excluded before she starts with Exlutena or wait until her first day of the menstrual cycle.

Management of missed tablets

The woman should take the missed tablet as soon as she has discovered it and thereafter she should take the next tablet at the usual time. If more than 27 hours have elapsed between two tablets, the contraceptive protection may be reduced and an additional contraceptive method should be used during the next week. If the woman has forgotten tablets in the very first week of use and if she has had intercourse during the 7 previous days, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal disturbances

In case the woman has had gastro-intestinal disturbance, absorption may not have been complete. In case the woman vomits within 3-4 hours after tablet-taking, the advice concerning missed tablets should be followed.

4.3 Contraindications

Progestogen methods should not be used at any of the following conditions. If any of the conditions occur for the first time during use of Exlutena, treatment should be interrupted.

- Known or suspected pregnancy
- Active venous thromboembolic disorder
- Present or history of liver disease as long as the liver function values have not returned to normal
- Known or suspected sex-steroid sensitive malignancies
- Undiagnosed vaginal bleeding

- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

If the woman has any of the conditions/risk factors mentioned below, the benefits of progestogen should be weighed against the possible risks and be discussed with the woman before she starts with Exlutena. If case of aggrevation, recurrence or first appearance of any of these conditions, the woman should contact her doctor/midwife. The doctor/midwife should then decide on whether she should discontinue using Exlutena.

- The risk of breast cancer generally increases with increasing age. During the use of combined oral contraceptives the risk of having breast cancer diagnosed is slightly increased. The increased risk gradually decreases within 10 years after discontinuation, and is not related to the duration of use, but to the age of the woman during the use. The expected number of breast cancer cases diagnosed per 10 000 women using combined oral contraceptives (up to 10 years after stopping) relative to non users over the same period, have been calculated for the respective age groups and are presented in the table below.

Age group	*Expected cases among users of combined oral contraceptives*	*Expected cases among non-users*
16-19 år	4,5	4
20-24 år	17,5	16
25-29 år	48,7	44
30-34 år	110	100
35-39 år	180	160
40-44 år	260	230

- The risk for users of progestogen methods, such as Exlutena, is possibly of similar magnitude as that associated with combined oral contraceptives, but the evidence is less conclusive. Compared to the risk of getting breast cancer ever in life, the increased risk associated with the use of combined oral contraceptives is low. The cases of of breast cancer diagnosed in those using combined oral contraceptives tend to be less advanced than in those who have not used combined oral contraceptives. The increased risk in those using combined oral contraceptives may be due to an earlier diagnosis, a biological effect or to a combination of both.
- Since a biological effect of progestogens on liver cancer can not be excluded, an individual risk/benefit 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.
- If the woman gets sustained hypertension during the use of Exlutena, or if she gets a significant increase in blood pressure, not responding to antihypertensive therapy, the discontinuation of Exlutena should be considered.
- Epidemiological investigations have shown an increased rik of venous thromboembolism (deep venous thrombosis and pulmonary embolism) in connection with the use of combined oral contraceptives. Although the clinical relevance of this finding when progestogen without estrogen is used as a contraceptive is unknown, Exlutena should be disconued in the event of a thrombosis. Discontination of Exlutena should also be considered in case of long-term immobilisation due to surgery or illness. Women with a history of thromboembolic disordes should be informed of the possibility of a recurrence.
- The protection with progestogen-only pills against ectopic pregnancies is not as good as with combined oral contraceptives. Additional risk factors for ectopic pregnancy include a history of ectopic pregnancy and tubal damage. Should pregnancy occur in spite of the use of Exlutena, ectopic pregnancy should be excluded, especially if the woman gets amenorrhea during the treatment or complains of abdominal pain.
- Chloasma may occasionally occur, especially in women with a history of chloasma during previous pregnancies. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking Exlutena.
- 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 while taking progestogen-only pills.
- 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 (SLE); haemolytic uraemic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosisrelated hearing loss, (hereditary) angioedema.
- 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.

- Exlutena contains less than 50 mg lactose and therefore should not be administered to patients with any of the following rare hereditary conditions: galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorbtion.

Medical examination/consultation

Before treatment, a thorough case history should be taken and a thorough gynaecological examination is recommended and pregnancy should be excluded. 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, the control examinations should be timed accordingly. Despite the fact that Exlutena is taken regularly by the woman, 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.

The woman should be advised that Exlutena does not protect against HIV (AIDS) or other sexually transmitted diseases.

Reduced efficacy

The efficacy of progestogen-only pills may be reduced in the event of missed tablets or gastro-intestinal disturbance (see Section 4.2) or interactions (see Section 4.5).

Changes in vaginal bleeding pattern

During the use of a progestogen-only contraceptive, vaginal bleeding may become more frequent or of longer duration in some women, whereas in others bleeding may become incidental or be totally absent. These changes are often a reason for the woman to stop use progestogen-only pills. Acceptance of the bleeding pattern can be improved by offering women careful counselling on this point.

Follicular development

With all low-dose hormonal contraceptives, follicular development and ovaluation can occur. Occasionally the follicle may continue to grow beyond the size it would attain in a normal cycle and form a follicular cyst. Generally, these enlarged follicular cysts disappear spontaneously. Often, they are asymptomatic; in some cases they are associated with abdominal pain. They rarely require surgical intervention.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. No specific interaction studies

have been performed with Exlutena. The following interactions have been reported in the literature (mainly with combined oral contraceptives but occasionally also with progestogen-only contraceptives).

Hepatic metabolism: Interactions can occur with medicinal products that induce microsomal enzymes, which can result in increased clearance of sex hormones (such as hydantoins (phenytoin), barbiturates (phenobarbital), primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, rifabutin, felbamate, ritonavir, nelfinavir, griseofulvin and herbal medicinal products containing St. John's wort *(Hypericum perforatum)*).

Women on treatment with any of these drugs should be informed that the contraceptive effect may be reduced. They should use a barrier method in addition to Exlutena or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

During treatment with medical charcoal, the absorption of the steroid may be affected and thereby the contraceptive efficacy. In such an event, the advice concerning missed tablets, as given in Section 4.2 is applicable.

Hormonal contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected (e.g., cyclosporine or lamotrigin).

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

Laboratory tests

Data obtained with combined oral contraceptives 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). These changes generally remain within the normal range. To what extent this also applies to progestogen-only contraceptives is not known.

4.6 Fertility, pregnancy and lactation

Pregnancy

Exlutena should not be used during pregnancy. If the woman becomes pregnant she should stop using Exlutena immediately.

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used oral contraceptives prior to pregnancy, nor a teratogenic effect when oral contraceptives were taken inadvertently during early pregnancy. Although this probably also applies to all oral contraceptives, it is not clear whether this is also the case for Exlutena.

Breastfeeding

Similar to other progestogen-only contraceptives, Exlutena does not influence the production or the quality of breast milk, but a small amount of lynestrenol is excreted in the breast milk. The amount of lynestrenol excreted in the milk is about 0.14% of the daily administered dose, but no adverse effects on infant growth and development have been reported.

4.7 Effects on ability to drive and use machines

Exlutena has no or negliable effect on the ability to drive and to use machines.

4.8 Undesirable effects

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. breast cancer), and chloasma. Some of the side effects are discussed in more detail in Section 4.4 Special warnings and precautions for use.

Classification of organ systems (MedDRA)*	Common (>1/100)	Uncommon (>1/1000, <1/100)	Rare (<1/1000)
Investigations	Weight gain		Weight loss
Central and periferal nervous system	Headache, migraine		
Eyes		Contact lance intolerance	
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Skin and subcutaneous tissue disorders	Rash, urticaria, erythema nodosum, erythema multiforme, chloasma		
Metabolism and nutrition disorders	Fluid retention		
Immune system disorders			Hypersensitivity
Reproductive system and breast disorders	Amenorrhoea, menstruation irregular, breast tenderness, breast pain, breast discharge	Vaginal discharge, breast enlargement	
Psychiatric disorders	Depressed mood, mood altered, decreased libido		Increased libido

* MedDRA version 10.1

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 listed in Appendix V*

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Since the toxicity of lynestrenol is very low, serious symptoms are not expected to occur when several tablets are taken simultaneously. Symptoms that may occur 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: Contraception – progestogen-only; ATC code: G03AC02

The active substance in Exlutena is the progestogenic substance lynestrenol. Lynestrenol is a synthetic progestogen belonging to the group 19-norsteroids. Lynestrenol is converted into the active metabolite norethisterone, which binds to the progesterone receptors in the target organs (e.g. the myometrium). The contraceptive effect of Exlutena is achieved primarily by increasing the viscosity of the cervical mucus, thus reducing sperm penetration. Exlutena also have effect on the endometrium which make the nidiation of an egg difficult. In about 70% of the women ovulation is inhibited, as can be concluded from both the absence of the midcycle LH-peak and the absence of an increase of luteal progesterone. Exlutena does not affect the carbohydrate metabolism, lipid metabolism or haemostasis.

Since Exlutena does not inhibit ovaluation for all users the contraceptive efficacy of Exlutena is not quite as high as for combined oral contraceptives, provided the tablets are taken in accordance with the directions of use. In comparison with the combined pill, more irregular bleeding may occur with Exlutena whereas incidentally a period may fail to occur. Generally, after a period of adaptation, bleeding pattern with the product is acceptable.

5.2 Pharmacokinetic properties

Lynestrenol (LYN) is metabolised in the body into the pharmacologically active metabolite norethisterone (NET).

Absorption

After oral dosing LYN is rapidly converted into NET. Peak plasma levels are reached 2 - 4 hours after tablet intake. Absolute bioavailability of NET is 64%.

Distribution

NET is approximately 96% bound to plasma proteins, predominantly to albumin (61%) and to a lesser extent to SHBG (sex hormone binding globulin, 35%).

Biotransformation

Phase I metabolism of LYN includes a 3-hydroxylation and a dehydrogenation. The active metabolite NET is conjugated to sulphates and glucuronides.

Elimination

NET is eliminated with a mean half-life of approximately 15 hours. The plasma clearance is approximately 0.6 l per hour. Excretion of LYN and its metabolites is with urine (predominantly as glucuronides and to a lesser extent as unchanged LYN) and faeces. The ratio of urinary: faecal excretion is 1.5:1.

5.3 Preclinical safety data

Reproduction studies in rabbits have shown that exposure to high doses of lynestrenol during organogenesis induces abnormalities of the central nervous system. Otherwise, toxicological studies did not reveal any effects other than those, which can be explained from the hormonal properties of lynestrenol. So far, the effects perceived in animal studies have not been confirmed in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch

Amylopectin

Lacose monohydrate (circa 43 mg)

Magnesium stearate

6.2 Incompatibilities

Not relevant

6.3 Shelf life

5 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Exlutena is provided in push-through blister of PVC/Aluminium foil. The blisters are packed in a cardboard box of paper.

Following pack sizes are available: 1 x 28 or 3 x 28 tablets.

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Box 581
2003 PC Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

8919

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 May 1974

Date of latest renewal: 01 July 2006

10. DATE OF SPC APPROVAL

2021-02-23