1. **NAME OF THE MEDICINAL PRODUCT**

Exluton, tablets 0.5 mg.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 500 microgram of lynestrenol.

Excipient with known effect: lactose 43.37 mg.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Tablets.

The tablet is white, round and flat with a beveled-edge, coded TT above 2 on one side and ORGANON* on the reverse.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Contraception.

4.2 **Posology and method of administration**

**Dosage**

Tablets must be taken every day at about the same time with some liquid as needed. One tablet is to be taken daily for 28 consecutive days, as indicated on the strip. Each subsequent pack is started immediately after finishing the previous pack.

4.2.1 **How to start Exluton**

*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 (COC), vaginal ring, or transdermal patch)*

The woman should start with Exluton preferably on the day after the last active tablet (the last tablet containing the active substances), 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 (COC with only a progestogen, injection, implant or a progestogen-releasing intrauterine system [IUS])*

When the woman switches from a COC with only a progestagen she can start with Exluton any day, without a tablet free period.

In case the woman switches from an implant or an IUS she can start with Exluton on the day of its removal and in case she switches from an injection on the day the next injection would be due. In these cases, the use of 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 or second-trimester abortion
For breastfeeding women, see section 4.6.

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

4.2.2 Management of missed tablets
Contraceptive protection may be reduced if more than 27 hours have elapsed between two tablets. If the user is less than 3 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 3 hours late, she should follow the same advice but also additionally use a barrier method for the next 7 days of tablet-taking. If tablets were missed in the very first week of use and intercourse took place in the week before the tablets were missed, the possibility of a pregnancy should be considered.

4.2.3 Advice in case of gastro-intestinal 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 is applicable (see section 4.2.3).

4.3 Contraindications
Exluton should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during the use of Exluton, the product should be stopped immediately.

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

4.4 Special warnings and special precautions for use

4.4.1 Warnings
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 Exluton. 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 Exluton should be discontinued.

- The risk for breast cancer increases in general with increasing age. During the use of combined oral contraceptives (COCs) the risk of having breast cancer diagnosed is slightly increased. This increased risk gradually disappears 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 combined OCs (up to 10 years after stopping) relative to never users over the same period have been calculated for the respective age groups and are presented in the table below.
The risk in users of progestogen-only pills (POPs), as Exluton, is possible of similar magnitude as that associated with combined OCs. However, for POPs the evidence is less conclusive. Compared to the risk of getting breast cancer ever in life, the increased risk associated with OCs is low. The cases of breast cancer diagnosed in OC users tend to be less advanced than in those who have not used OCs. The increased risk may be due to an earlier diagnosis in OC users, biological effects of the COC, 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 combined OCs with an increased incidence of venous thromboembolism (VTE, deep venous thrombosis and pulmonary embolism). Although there is no evidence for the clinical relevance of this finding for lynestrenol used as a contraceptive in the absence of an estrogenic component, Exluton should be discontinued in the event of a thrombosis. Discontinuation of Exluton should also be considered in case of long-term immobilization due to surgery or illness. Women with a history of thrombo-embolic disorders should be made aware of the possibility of a recurrence.
- 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, during the first months diabetic women should be carefully observed while taking progestogen-only pills.
- If a sustained hypertension develops during the use of Exluton, or if a significant increase in blood pressure Exluton not adequately respond to antihypertensive therapy, the discontinuation of Exluton should be considered.
- The protection with Exluton 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 Exluton. Additional risk factors for ectopic pregnancy include a history of ectopic pregnancy and tubal damage from infection or surgery. Should pregnancy occur in spite of the use of Exluton, the physician should exclude extra-uterine pregnancy. In addition, in case of amenorrhea or abdominal pain the possibility of an ectopic pregnancy should be included in the differential diagnosis.
- 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 Exluton.
- The following conditions have been reported both during pregnancy and during COC 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.

- Exluton contains less than 50 mg lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.

### 4.4.2 Medical examination/consultation

Before prescription, a thorough case history should be taken and a thorough gynecological examination is recommended to exclude pregnancy. Bleeding disturbances, such as oligomenorrhea and amenorrhea should be investigated before prescription. The frequency and nature of additional periodical check-ups depend on the circumstances in each individual case. If the prescribed product possibly influences latent or manifest disease (see section 4.4.1), the control examinations should be timed accordingly.

Despite the fact that Exluton is taken regularly, bleeding disturbances may occur (see section 4.4.4). If bleeding is very frequent and irregular, another contraceptive method should be considered. If the symptoms persist, underlying pathology should be ruled out.

Management of amenorrhea 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.

It should be made clear to women that Exluton does not protect against HIV (AIDS) and other sexually transmitted diseases.

### 4.4.3 Reduced efficacy

The efficacy of Exluton may be reduced in the event of missed tablets (section 4.2.3), gastrointestinal disturbances (section 4.2.4) or concomitant medication (section 4.5).

Herbal medicines containing St. John’s Wort (Hypericum perforatum) should not be used during the use of Exluton, because this may lead to decreased serum concentrations and a reduced efficacy of Exluton (Section 4.5.1).

### 4.4.4 Changes in vaginal bleeding pattern

During the use of Exluton, 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 using Exluton or to be non-compliant.

Acceptance of bleeding pattern can be improved by offering women who have chosen to use Exluton careful counseling on this point. Evaluation of vaginal bleeding should be done on an ad hoc basis and may include examination to exclude malignancy or pregnancy (see section 4.4.2).

### 4.4.5 Follicular development

With all low-dose hormonal contraceptives, follicular development occurs and occasionally the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. Often, they are asymptomatic; in some cases they are associated with abdominal pain, but they rarely require surgical intervention.

### 4.5 Interaction with other medicinal products and other forms of interaction

#### 4.5.1 Interactions

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
Exluton. The following interactions have been reported in the literature (mainly with combined contraceptives but occasionally also with Exluton).

**Hepatic metabolism:** Interactions can occur with medicinal products that induce microsomal liver enzymes, which can result in increased clearance of sex hormones, such as hydantoins, (e.g., phenytoin), barbiturates (e.g., phenobarbital), primidone, carbamazepine, rifampicin; and possibly also oxcarbazepine, topiramate, rifabutine, felbamate, ritonavir and nelfinavir, griseofulvin,

In general it takes 2-3 weeks before the enzyme induction reaches its peak, but may then last up to 4 weeks after cessation of therapy.

Women on treatment with any of these drugs should temporarily use a barrier method in addition to Exluton. Women using drugs which lead to the induction of microsomal liver enzymes should use a barrier method in addition to Exluton during the time of concomitant drug administration and for 28 days after its discontinuation. In women on long-term treatment with hepatic enzyme-inducing drugs another, non-hormonal method of contraception is advised.

St. John’s Wort (Hypericum perforatum) must not be used simultaneously with Exluton, because it can impair efficacy of the COC. Breakthrough bleeding and unintended pregnancies due to induction of (liver) enzymes by St. John’s Wort have been reported. The inducing effect may last at least for two weeks after the treatment with St. John’s Wort has been stopped.

During treatment with medical charcoal, the absorption of the steroid in the tablet may be reduced 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 increased (e.g., cyclosporin) or decreased.

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

### 4.5.2 Laboratory tests

Data obtained with combined OCs 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.

### 4.6 Fertility, pregnancy and lactation

#### Pregnancy

Exluton should not be used during pregnancy. If a pregnancy occurs, Exluton treatment should be stopped immediately.

Animal studies have shown that very high doses of progestogenic substances may cause masculinization of female foetuses.

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

#### Lactation

Exluton does not influence the production or the quality of breast milk. However, a small amount of progestogen is excreted with the milk. The amount of lynestrenol and metabolites 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. Nevertheless development and growth of
the child should be closely monitored. Based on the data available, Exluton can be prescribed for lactating women.

4.7 Effects on ability to drive and use machines
Exluton has no or negligible influence on the ability to drive and use machines.

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

In about half of the women using Exluton the undesirable effects are reported during the first treatment cycle, and declining to approximately 30% in the 12th cycle. In lactating women, 28% experienced side effects during the first cycle, declining to 5% after the 12th cycle.

The following undesirable effects have been reported during the use of hormonal contraceptives, including Exluton:
### System Organ Class (MedDRA)*

<table>
<thead>
<tr>
<th>System Organ Class (MedDRA)*</th>
<th>Frequency of the undesirable effect.</th>
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<tbody>
<tr>
<td></td>
<td>The frequency of the adverse events is reported with the terms “common” (≥100, &lt;1/10), “uncommon” (≥1,000, &lt; 1/100) and “rare” (≥1/10,000 &lt;1/1,000).</td>
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</table>

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
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</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Fluid retention</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depressed mood</td>
<td>Libido increased</td>
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<tr>
<td></td>
<td>Mood altered</td>
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<tr>
<td></td>
<td>Libido decreased</td>
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<tr>
<td>Nervous System disorders</td>
<td>Headache</td>
<td>Contact lens intolerance</td>
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<td></td>
<td>Migraine</td>
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<tr>
<td>Eye disorders</td>
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<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Vomiting</td>
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<td></td>
<td>Abdominal pain</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Acne, Erythema multiforme, Photosensitivity, Chloasma, Erythema nodosum, Rash</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Breast tenderness or pain</td>
<td>Breast enlargement</td>
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<tr>
<td></td>
<td>Breast discharge</td>
<td>Persisting ovarian cysts, Dryness of the vagina</td>
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<tr>
<td></td>
<td>Menstruation irregular</td>
<td>Vaginal discharge</td>
</tr>
<tr>
<td></td>
<td>Amenorrhoea</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
<td>Weight decreased</td>
</tr>
</tbody>
</table>

* MedDRA version 10.1

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**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 Dutch Pharmacovigilance Center Lareb, website www.lareb.nl.
4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Since the toxicity of lynestrenol is very low, with Exluton toxic serious symptoms are unlikely to occur when several tablets are taken simultaneously. 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 category: hormonal contraceptives for systemic use, ATC code: G03AC02.

Total Pearl-Index (method failure + patient failure): 0.94 (upper, two-sided 95% confidence bound: 1.37).

Exluton is an oral contraceptive (OC) containing the progestogen lynestrenol. Exluton is best suited for use during breast-feeding and for women who may not or do not want to use estrogens.

In the body lynestrenol is converted into the biologically active metabolite norethisterone, which binds to the progesterone receptors in the target organs (e.g. the myometrium). The contraceptive effect of Exluton is achieved primarily by increasing the viscosity of the cervical mucus, thus reducing sperm penetration. Other effects include the decreased receptivity of the endometrium to the oocyte and the disturbed transport through the tubae. Furthermore, in about 70% of the women ovulation is inhibited, as can be concluded from the absence of the mid-cycle LH-peak and the absence of an increase of luteal progesterone. No clinically relevant effects on the carbohydrate metabolism, lipid metabolism and haemostasis have been observed.

The contraceptive efficacy of Exluton approaches that of the combined OC, provided the tablets are taken in accordance with the directions of use. In comparison with the combined pill, more irregular bleeding may occur with Exluton whereas incidentally a period may fail to occur. Generally, after a period of adaptation, the bleeding pattern with the product is acceptable.

5.2 Pharmacokinetic properties

Lynestrenol (LYN) is a pro-drug and is metabolized into the pharmacologically active metabolite norethisterone (NET).

Absorption
After oral dosing of Exluton, LYN is rapidly absorbed and converted into NET. Peak plasma levels (C_{max}) are reached 2 - 4 hours after tablet intake. Steady state is reached after 7 days. Absolute bioavailability of NET is 64%.

Distribution
NET is almost completely bound to plasma proteins, predominantly to albumin (60%) and to a lesser extent to SHBG (sex hormone binding globulin) (35%). The distribution volume is approximately 36 l.

Biotransformation
Phase I metabolism of LYN includes a 3-hydroxylation and subsequently a dehydrogenation. NET is further reduced; degradation products are 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 sulphates and to a lesser extent as unchanged LYN) and faeces. The ratio of urinary to faecal excretion is 1.5:1.

5.3 Preclinical safety data
Reproduction studies in rabbits have shown that exposure to higher 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
Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities
None

6.3 Shelf life
5 years.

6.4 Special precautions for storage
Store below 30°C, do not store in the freezer.
Store in the original package to protect against light and moisture.

6.5 Nature and contents of container
PVC/Aluminium foil push-through blister.
Each blister contains 28 tablets. The blisters are packed in printed cardboard boxes (1 or 3 blisters per box).
Not all pack sizes may be marketed.

6.6 Instructions for use and handling <and disposal>
No special requirements.

7. MARKETING AUTHORISATION HOLDER
N.V. Organon, Kloosterstraat 6, 5349 AB Oss, the Netherlands

8. MARKETING AUTHORISATION NUMBER(S)
RVG 06443
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 April 1972.

10. DATE OF REVISION OF THE TEXT

Last complete revision: 26 November 2009.

Last revision concerns the layout: 19 May 2015.