Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Erlidona 0.10mg/0.02mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.10 mg levonorgestrel and 0.02 mg ethinylestradiol
Excipients with known effect:
Each tablet contains 89.38 mg of lactose anhydrous.
Red aluminium lake (E129) and soya lecithin are present in the film-coating.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Tablets are pink and rounded with a diameter of 6 mm approx.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral contraception

4.2 Posology and method of administration

How to use Erlidona tablets

The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval, during which time a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to start Erlidona tablets

- *No preceding hormonal contraceptive use (in the past month)*

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding).

Starting on days 2-5 is allowed but in that case an additional barrier method is recommended for the first 7 days of the first cycle.

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

The woman should start with Erlidona preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Erlidonapreferably on the day of removal, but at the latest when the next application would have been due.

- *Changing from a progestogen-only-method (progestogen-only pill, injection, implant) or from a*

progestogenreleasing intrauterine system (IUS)

The woman may switch any day from the progestogen-only pill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due) but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- *Following first-trimester abortion*

The woman may start immediately. When doing so, she does not need to take additional contraceptive measures.

- *Following delivery or second-trimester abortion*

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

For breastfeeding women see section 4.6. Pregnancy and Lactation.

Management of missed tablets

Erlidona contains a very low dose of both hormones, and, as a consequence, the contraceptive efficacy margin is small, if a tablet is missed.

If the user is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days

2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitaryovarian-axis.

Accordingly the following advice can be given in daily practice:

Week 1

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the tablet-free interval phase, the higher is the risk of a pregnancy.

Week 2

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Week 3

The risk of reduced reliability is imminent because of the forthcoming 7-day tablet-free interval. However, by adjusting

the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next blister pack must be started as soon as the current blister pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue tablet-taking from the current blister pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next blister pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the first normal tablet-free interval, the possibility of a pregnancy should be considered.

Advice in case of gastrointestinal disturbances

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, the advice concerning missed tablets, as given in section 4.2 “Management of missed tablets”, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed

To delay a period the woman should continue with another blister pack of Erlidona without a tablet-free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of Erlidona is then resumed after the usual 7-day tablet-free interval. To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

Method of administration

Oral use.

4.3 Contraindications

Combined oral contraceptives (COCs) 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 COC use, the product should be stopped immediately.

- Venous thrombosis present or in history (deep venous thrombosis, pulmonary embolism)
- Arterial thrombosis present or in history (e.g. myocardial infarction)
- Presence or history of prodromal of a thrombosis (e.g. transient ischaemic attack, angina pectoris)
- Cerebrovascular accident present or in history
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4):
  - diabetes mellitus with vascular symptoms
  - severe hypertension
  - severe dyslipoproteinemia
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as APC-resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)

- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- History of migraine with focal neurological symptoms
- Amenorrhoea of unknown cause
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Erlidona is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, (see sections 4.4 and section 4.5).

4.4 Special warnings and precautions for use

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

Circulatory Disorders

Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low oestrogen content (<50 µg ethinylestradiol) ranges from about 20 to 40 cases per 100,000 women-years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 women-years for non-users. The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use.

The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.

The overall absolute risk (incidence) of VTE for levonorgestrel containing combined oral contraceptives with 30 µg ethinylestradiol is approximately 20 cases per 100,000 women-years of use.

Epidemiological studies have also associated the use of combined COCs with an increased risk for myocardial infarction, transient ischaemic attack and for stroke.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries, in contraceptive pill users. There is no consensus as to whether the occurrence of these events is associated with the use of hormonal contraceptives.

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include:
- unusual unilateral leg pain and/ or swelling
- sudden severe pain in the chest, whether or not it radiates to the left arm
- sudden breathlessness
- sudden onset of coughing
- any unusual, severe, prolonged headache
- first occurrence or worsening of migraine
- sudden partial or complete loss of vision
- diplopia
- slurred speech or aphasia
- vertigo
- collapse with or without focal seizure
- weakness or very marked numbness suddenly affecting one side or one part of the body
- motor disturbances
- ‘acute’ abdomen.

Occurrence of one or more of these symptoms may be a reason for immediate discontinuation of Erlidona

The risk for venous thromboembolic complications in COCs users increases with:
- increasing age
- a positive family history (venous thromboembolism ever in a sibling or parent at relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered if the pills have not been discontinued in advance.
- obesity (body mass index over 30 kg/m²)
- there is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases with:
- increasing age
- smoking (women over 35 years should be strongly advised not to smoke if they wish to use an COC)
- dyslipoproteinemia
- hypertension
- migraine, especially migraine with focal neurological symptoms
- valvular heart disease
- atrial fibrillation

The presence of one serious risk factor or multiple risk factors for venous or arterial disease, respectively, can also constitute a contra-indication. The possibility of anticoagulant therapy should also be taken into account. COC users should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, COC use should be discontinued. Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

The increased risk of thromboembolism in the puerperium must be considered (see section 4.6 Fertility, pregnancy and lactation).

Other medical conditions which have been associated with adverse vascular events include diabetes mellitus, systemic lupus erythematosus, haemolytic uremic syndrome and chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Tumours

An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behavior and other factors such as human papilloma virus (HPV).

A meta-analysis of 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. This excess risk gradually disappears during the course of 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation.

The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intraabdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Other conditions

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which previously occurred during pregnancy or during previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs 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 low-dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed, particularly in the early stage of COC use.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.
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 COCs.

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.5).

Medical examination/consultation

Prior to the initiation or reinstitution of Erlidona a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (see section 4.3) and warnings (see section 4.4). The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g. missed active tablets (see section 4.2), gastro-intestinal

disturbances during active tablet taking (see section 4.2) or concomitant medication (see section 4.5).

Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet free interval phase. If the COC has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Warnings about excipients

The tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The film-coated contains red aluminium lake (E129) and soya lecithin which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

Influence of other medicinal products on Erlidona

Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Women on treatment with any of these drugs should temporarily use a barrier method or another method of contraception in addition to the COC. With liver enzyme inducing drugs, the barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

Hepatic metabolism

Interactions can occur with drugs that induce hepatic enzymes which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, bosentan, nelfinavir and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing the herbal remedy St. John's Wort (hypericum perforatum)). Maximal enzyme induction is generally seen in about 10 days but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Also HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially increase hepatic metabolism.

Oral contraceptives may interfere with the metabolism of certain other drugs. Increased plasma concentrations of cyclosporin have been reported with concomitant administration of OCs. COCs have been shown to induce metabolism of lamotrigine resulting in sub-therapeutic plasma concentrations of lamotrigine.

Pharmacodynamic interactions
Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, Erlidona-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior

to starting therapy with this combination drug regimen. Erlidona can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy
Erlidona is not indicated during pregnancy.

If pregnancy occurs during use of Erlidona, the preparation should be withdrawn immediately. 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 at unintentional intake of contraceptive pills in early pregnancy

Breastfeeding

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the breast-feeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk during COC use. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most common adverse drug reaction is headache (in 17 – 24 % of the users of Erlidona).

The following adverse effects have been reported during use of ethinylestradiol/levonorgestrel:

Organ system	**Common** (>1/100 to <10)	**Uncommon** (>1/1,000 to <1/100)	**Rare** (>1/10,000 to < 1/1,000),
Immune system disorders			hypersensitivity
Metabolism and nutrition disorders		fluid retention	
Psychiatric disorders	depressed mood, mood altered	libido decreased	libido increased
Nervous system disorders	headache	migraine	
Eye disorders			contact lens intolerance
Gastrointestinal disorders	nausea, abdominal pain	vomiting, diarrhoea	
Skin and subcutaneous tissue disorders	**-**	rash ,urticaria	erythema nodosum, erythema multiforme
Reproductive system	breast tenderness,	breast enlargement	breast discharge,

and breast disorders	breast pain		vaginal discharge
Investigations	weight increased		weight decreased

The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4 Special warning and precautions for use:
- Venous thromboembolic disorders;
- Arterial thromboembolic disorders;
- Hypertension;
- Liver tumours;
- Crohn's disease, ulcerative colitis, epilepsy, migraine, endometriosis, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;

The frequency of diagnosis of breast cancer is slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections 4.3 Contraindications and 4.4 Special warning and precautions for use.
In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

There have been no reports of serious adverse effects from overdose. On the basis of general experience with combined oral contraceptives, symptoms that may possibly 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: Progestogens and estrogens, fixed combinations

ATC Code: G03AA07

The contraceptive effect of COCs is based on the interaction of various factors. The most important of these factors are the inhibition of ovulation and changes in the cervical mucus.

Clinical trials have been performed in 2498 women aged 18 to 40 years. The overall Pearl Index calculated from these trials was 0.69 (95% confidence interval 0.30-1.36) based on 15.026 treatment cycles.

5.2 Pharmacokinetic properties

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorved rapidly and completely. Peak serum concentrations of about 50 pg/mL are reached within 1-2 hours after taking a Erlidona tablet. During absorption and first-pass hepatic metabolism ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of about 45% (interindividual variation about 20-65%).

Distribution

Ethinylestradiol is highly (approximately 98%) but non specifically bound to serum albumin, and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of ethinylestradiol is 2.8–8.6 l/kg.

Biotransformation

Ethinylestradiol is subject to pre-systemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation, forming various hydroxylated and methylated metabolites that are present as free metabolites or as glucuronide or sulfate conjugates in serum. The metabolic clearance rate from serum is 2.3–7 ml/min/kg.

Elimination

Ethinylestradiol levels in serum decrease in two phases characterized by half-lives of about 1 hour and 10-20 hours, respectively.

Ethinylestradiol is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of 4:6, and the half-life is about 1 day.

Steady-State Conditions

Ethinylestradiol concentration in serum increases about twofold after continuous use of Erlidona tablets. Due to the variable half-life of the terminal phase in serum clearance and the daily administration, steady-state conditions are reached within about a week.

Levonorgestrel

Absorption

After oral administration, levonorgestrel is absorbed rapidly and completely. Peak serum concentrations of about 2.3 ng/ml are reached around 1.3 hours after taking a Erlidona tablet. The bioavailability is nearly 100%.

Distribution

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only 1.1% of the total serum drug concentrations are present as free steroid, approximately 65% are specifically bound to SHBG and approximately 35% are non-specifically bound to albumin. The ethinylestradiol-induced increase in the SHBG concentration influences the relative distribution of levonorgestrel into different protein fractions. Induction of the binding protein causes an increase in the SHBG-bound fraction and a decrease in the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is 129 1 after a single dose.

Biotransformation

Levonorgestrel is completely metabolised by the typical pathways of steroid metabolism. The metabolic clearance rate from serum is approximately 1.0 ml/min/kg.

Elimination

Levonorgestrel levels in serum decrease in two phases. The terminal phase is characterized by a half-life of approximately 25 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary (feces) ratio of about 1:1. The half-life of metabolite excretion is about 1 day.

Steady-state

During the continuous use of Erlidona tablets, serum levonorgestrel levels increase about threefold reaching steady-stat

conditions during the second half of the treatment cycle. Levonorgestrel pharmacokinetics are influenced by the SHBG levels in serum, which are increased 1.5–1.6-fold during the use of estradiol. Therefore, the clearance rate from serum and the volume of distribution are slightly reduced at steady state (0.7 ml/min/kg and about 100 1).

5.3 Preclinical safety data

Preclinical studies (general toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction) have not revealed other effects than those which can be explained based on the known hormone profile of ethinyl estradiol and levonorgestrel.

However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Povidone K-30 (E1201)
Magnesium stearate (E572)
Opadry II Pink:
- Polyvinyl alcohol
- Talc (E553b)
- Titanium dioxide (E171)
- Polyethylene glycol 3350
- Red aluminium lake (E129)
- Soya lecithin (E322)
- Iron oxide red (E172)
- Blue aluminium lake (E132)

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 storage conditions.

6.5 Nature and contents of container

Blisters of aluminium push-thru foil and PVC/PVDC film.

It is available in boxes of 1, 3 and 6 packs (calendar blisters), each one containing 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarjördur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/140/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th January 2014

10 DATE OF REVISION OF THE TEXT

August 2017