SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Slinda 4 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

White active film-coated tablets:
Each tablet contains 4 mg of drospirenone.

Green placebo film-coated tablets:
The tablet does not contain active substances.

Excipient with known effect:
Each white active film-coated tablet contains 17.5 mg of lactose.
Each green placebo film-coated tablet contains 52.7 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

The active tablet is a round, white tablet with the letters “E” and “D” debossed on opposite sides, with a diameter of 5 mm.

The placebo tablet is a round, green tablet with the letter “E” and the number “4” debossed on opposite sides, with a diameter of 5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception

4.2 Posology and method of administration

Posology

How to take <Invented name>

One tablet is to be taken daily for 28 consecutive days, one white active tablet daily during the first 24 days and one green inactive tablet daily during the 4 following days. Tablets must be taken every day at about the same time of the day so that the interval between two tablets is always 24 hours. Tablets should be taken in the order shown on the blister. Stickers marked with the 7 days of the week are provided. The woman should choose the sticker that starts with the day she begins taking the tablets and stick it on the blister.

The first tablet of the treatment should be taken on the first day of menstrual bleeding. Thereafter tablet taking is continuous. A subsequent pack is started immediately after finishing the previous pack, without a break in daily tablet intake.

How to start <Invented name>

No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the woman's natural cycle (first day of her menstrual bleeding). When doing so, no additional contraceptive measures are necessary.

Following first-trimester abortion

After first-trimester abortion it is recommended to start <Invented name> immediately after abortion took place. In that case there is no need to use an additional contraceptive method.

Following delivery or second-trimester abortion

Contraceptive treatment with <Invented name> is recommended to start between 21 and 28 days after delivery or second trimester abortion. If contraceptive treatment with <Invented name> is initiated later but before the menstruations have returned, pregnancy must be ruled out and an additional method of contraception should be used for the first week.

For breast-feeding women, see section 4.6.

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

The woman should start <Invented name> 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.

The woman may also start <Invented name> at the latest on the day following the usual tablet-free, ring-free, patch-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 (progestogen-only pill (POP), injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from another POP and should start <Invented name> the day after, within 24 hours of discontinuing the previous POP. A woman may switch from an implant or following IUS removal on the same day that the implant or IUS is removed. A woman may switch from using an injectable contraceptive and should start <Invented name> on the day the next injection was due to occur. In all of these cases, the use of an additional contraceptive is not necessary.

Management of missed tablets

Tablets should be taken every 24 hours. If the woman is less than 24 hours late in taking any single 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 the user is more than 24 hours late in taking any white active tablet, contraceptive protection may be reduced and use of a barrier method such as a condom should be considered for the next 7 days. The missed tablet should be taken as soon as it is remembered, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time.

If tablets were missed in the first week after initiation of <Invented name> and intercourse took place in the week before the tablets were missed, the possibility of a pregnancy should be considered.

If tablets were missed in the third week of pill taking, the risk of reduced reliability is imminent because of the forthcoming 4-day hormone-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. 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 the active tablets at her usual time. The user is advised not to take the placebo pills and continue straight on to the next active blister pack.

Missed (green) placebo tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the interval between active tablet taking.

Advice in case of gastrointestinal disturbances
In case of severe gastrointestinal disturbances (e.g., vomiting or diarrhea), absorption may not be complete and additional contraceptive measures should be taken.

If vomiting or diarrhea 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 24 hours of the usual time of tablet-taking if possible. If more than 24 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.

Paediatric population

Safety and efficacy of <INVENTED NAME> have been established in women of reproductive age. Safety and efficacy are expected to be the same for post pubertal adolescents under the age of 18 and users 18 years and older. Use of this product before menarche is not indicated.

Method of administration

Oral use.

4.3 Contraindications

Progestogen-only contraceptives (POCs) like <Invented name> 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 <Invented name> use, the medicinal product should be discontinued immediately.

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

4.4 Special warnings and precautions for use

If any of the conditions/risk factors mentioned below is present, the benefits of <Invented name> should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using <Invented name>. 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 whether <Invented name> use should be discontinued.

Hyperkalemia
Drospirenone is an aldosterone antagonist with potassium sparing properties. In most cases, no increase of potassium levels is to be expected. However, it is recommended to check serum potassium levels during the first treatment cycle in women presenting with renal insufficiency and pre-treatment serum potassium in the upper reference range and during concomitant use of potassium sparing medicinal products (see section 4.5).

Circulatory disorders
From epidemiological studies there is little evidence for an association between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. Rather, the risk of

cardiovascular and cerebral events is related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only preparations.

Although not statistically significant, some studies indicate that there may be a slightly increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations. Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilization, major surgery or major trauma.

Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof and discontinuation of <Invented name> should be considered in case of prolonged immobilization due to surgery or illness.

Bone metabolism
Treatment with <Invented name> leads to decreased estradiol serum levels, to a level corresponding with the early follicular phase. It is currently unknown whether the decrease in estradiol serum levels may have a clinically relevant effect on bone mineral density. Loss of bone mineral density is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if bone mineral density decrease in this population will reduce peak bone mass and increase the risk for fracture in later life.

Breast Cancer
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs), mainly using estrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of combined OC (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 OC users, the biological effects of OCs or a combination of both. The breast cancers diagnosed in users of OCs tend to be less advanced clinically than the cancers diagnosed in those who have never used OCs.

The risk of having breast cancer diagnosed in users of progestogen-only preparations is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs.

Other tumours
In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of combined hormonal contraceptives. In isolated cases, these tumours have led to life-threatening intra-abdominal 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

Ectopic pregnancy
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 <Invented name> consistently inhibits ovulation ectopic pregnancy should be taken into account in the differential diagnosis if the woman presents amenorrhoea or abdominal pain.

Liver function
Discontinue <Invented name> if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may require the discontinuation of <Invented name> use until markers of liver function return to normal and <Invented name> causation has been excluded.

Diabetes

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 POPs such as <Invented name>. However, diabetic patients should be carefully observed during the first months of use. Special attention should be paid to diabetic patients with vascular involvement.

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

Like with any other hormonal contraceptive, 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 <Invented name>.

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, appearing shortly after initiation of the treatment.

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.

Each white active tablet contains 17.50 mg of lactose and each green placebo tablet contains 52.7 mg of lactose (as monohydrate). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Medical examination/consultation
Prior to the initiation or reinstitution of <Invented name> 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.

Changes in the menstrual bleeding pattern
Disruption of the menstrual bleeding pattern may occur during use of hormonal contraceptives that inhibit ovulation, including <Invented name> (see section 5.1).

If the 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.

Reduced efficacy
The efficacy of POPs may be reduced in the event of e.g. missed tablets (see section 4.2), gastro-intestinal disturbances (see section 4.2) or concomitant medication (see section 4.5).

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, serum levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis.

4.5 Interaction with other medicinal products and other forms of interaction

Influence of other medicinal products on <invented name>

Interactions can occur between <Invented name> and other medicinal products that induce microsomal enzymes. This can result in increased clearance of sex hormones and may lead to breakthrough bleeding and/or contraceptive failure.

Management
Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally seen within a few weeks. After drug therapy is discontinued, enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme inducing drugs should temporarily use a barrier method or another method of contraception in addition to the POP. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

If the drug therapy runs beyond the end of the active tablets in the POP pack, the placebo tablets must be discarded, and the next POP pack should be started right away.

Long-term treatment
In women on long-term treatment with enzyme-inducing active substances, another reliable, nonhormonal, method of contraception is recommended.

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

Substances increasing the clearance of contraceptive hormones (diminished contraceptive efficacy by enzyme induction) e.g.:

Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate 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 sex hormones, many combinations of HIV protease inhibitors (e.g. ritonavir, nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine, efavirenz) 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):

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Concomitant administration of strong or moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestogen.

In a multiple dose study evaluating the daily (10 days) co-administration of the strong CYP3A4 inhibitor ketoconazole with two drospirenone-containing hormone preparations (drospirenone 3 mg + estradiol 1.5 mg and drospirenone 3 mg + ethinylestradiol 0.02 mg) the AUC (0-24h) of drospirenone was increased 2.3-fold and 2.7-fold, respectively.

Influence of <Invented name> on other medicinal products

Hormonal contraceptives may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporine) or decrease (e.g. lamotrigine).

Based on in vitro studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, a clinically relevant interaction of drospirenone with the cytochrome P450 mediated metabolism of other active substances is unlikely.

Pharmacodynamic interactions

Published data did not show a significant effect on serum potassium following the concomitant use of drospirenone and ACE-inhibitors or NSAIDs in patients without renal insufficiency. The concomitant use of <Invented name> with aldosterone antagonists or potassium-sparing diuretics has not been studied. In this case, serum potassium should be tested during the first treatment cycle (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
<Invented name> should not be used during pregnancy.
If pregnancy occurs during treatment with <Invented name>, further intake should be stopped.
Epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used drospirenone prior to pregnancy, nor a teratogenic effect when drospirenone was taken inadvertently during pregnancy.

Animal studies have shown reproductive toxicity (see section 5.3) Based on these animal data, undesirable effects due to hormonal action of the active compound cannot be excluded.

Breastfeeding
Negligible amounts of drospirenone are excreted in the breast milk. The daily dose of drospirenone in the baby is <1% of the maternal dose. Thus, at therapeutic doses of <Invented name>, no effects on the breastfed newborns/infants are anticipated. Based on the available data <Invented name>may be used during lactation.

Fertility
<Invented name> is indicated for the prevention of pregnancy.

4.7 Effects on ability to drive and use machines

No studies on the influence on the ability to drive and use machines have been performed with <Invented name>.
No effects on ability to drive and use machines have been observed in users of oral hormonal contraceptives.

4.8 Undesirable effects

Changes in the bleeding pattern was an adverse reaction frequently reported in the clinical trials (see section 5.1).

The most commonly reported adverse reactions in long-term clinical trials of more than 9 cycles of treatment with <drospirenone> (2,700 women) were acne (3.8%), metrorrhagia (2.9%), headache (2.7%) and breast pain (2.2%).

Tabulated list of adverse reactions

Adverse reactions that have been reported in short- and long- term clinical trials with <Invented name> are listed in the table below.

All adverse reactions are listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000).

System Organ Class (MedDRA version 17.1)	**Common**	**Uncommon**	Rare
Infections and infestations		Vaginal infection	
Neoplasms benign. malignant and unspecified		Uterine leiomyoma	
Blood and lymphatic system disorders		Anaemia	
Immune system disorders		Hypersensitivity	
Metabolism and nutrition disorders		Appetite disorder Hyperkalaemia	
Psychiatric disorders	Libido disorder Mood disturbances	Anxiety symptoms Depression Depressed mood	
Nervous system disorders	Headache	Dizziness	
Eye disorders			Contact lens intolerance
Vascular disorders		Hot flush Hypertension	
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhoea Constipation	
Skin and subcutaneous tissue disorders	Acne	Alopecia Hyperhidrosis Rash Seborrhoea Pruritus Dermatitis	
Renal and urinary disorders			Polyuria
Reproductive system and breast disorders	Breast discomfort Metrorrhagia Vaginal haemorrhage Dysmenorrhea	Amenorrhoea Menstrual disorders Pelvic pain Ovarian cyst Vulvovaginal dryness Vaginal discharge	Breast cyst Cervical dysplasia Galactorrohoea Vulvovaginal pruritus

	Menstruation irregular		
General disorders and administration site conditions		Fatigue Oedema peripheral	
Investigations	Weight increased	Transaminases increased Blood bilirubin increased Blood creatine phosphokinase increased Gamma-Glutamyltransferase increased Blood triglycerides increased	Weight decreased

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. Symptoms that may occur in this case are nausea, vomiting and slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

Drospirenone however is a spironolactone analogue which has antimineralocorticoid properties. Serum potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormonal contraceptives for systemic use, progestogens

ATC code: G03AC10

Mechanism of action

<Invented name> is a progestogen-only-pill which contains the progestogen drospirenone, derived from spironolactone.

In a therapeutic dosage, drospirenone also possesses antiandrogenic and mild antimineralocorticoid properties. It has no estrogenic, glucocorticoid and antiglucocorticoid activity. This gives drospirenone a pharmacological profile closely resembling the natural hormone progesterone.

There are indications from clinical studies that for combined hormonal contraceptives containing 3 mg drospirenone and 0.02 mg ethinylestradiol, the mild antimineralocorticoid properties result in a mild antimineralocorticoid effect.

Pharmacodynamic effects

The contraceptive effect of <Invented name> is achieved primarily by inhibition of ovulation. Drospirenone exhibits a strong anti-gonadotropic activity inhibiting follicular stimulation and ovulation by suppression of the luteinising hormone (LH). In addition, drospirenone has an effect on the cervix increasing the viscosity of the cervical mucus. Drospirenone also exerts progestational effects on the endometrium, which becomes thinner.

Clinical efficacy and safety

The ovulation inhibition potential of <Invented name> (drospirenone 4 mg non-micronized administered daily for 24 days) as reflected by the ovarian activity [follicular growth, endogenous estradiol and progesterone serum concentrations (Hoogland score)] in comparison to 0.075 mg of desogestrel administered daily for 28 days over two treatment cycles was assessed in a randomized, open-label Phase II study conducted in 60 healthy young women. In cycle 1, no ovulation was observed in either treatment, whereas one ovulation was observed for <invented name> and one for 0.075 mg of desogestrel group in cycle 2.

In a Phase II study performed in 130 women, <Invented name> maintained the inhibition of ovulation in spite of four fixed scheduled delayed intakes of 24 hours each on day 3, 6, 11 and 22.

In two multicenter Phase III European clinical trials, one single-arm study and one controlled study *vs*. desogestrel 0.075 mg, 1596 women have been treated for 9 up to 13 consecutive cycles with <Invented name> and 341 with desogestrel for 9 months. In the pooled analysis of these two studies the following Pearl Indexes were calculated:

Pearl Index (18-45 years of age), user + method failure: 0.73 (upper limit 95% confidence interval 1.43)
Pearl Index (18-35 years of age), user + method failure: 0.93 (upper limit 95% confidence interval 1.84)

In a single arm multicenter Phase III clinical trial performed in 39 US sites, the efficacy population consisted of 953 females ≤ 35 years of age with 5,547 evaluable cycles. During these cycles, 17 (1.8 %) pregnancies were reported (irrespectively of confirmation by urine and serum pregnancy tests at the study site) leading to a Pearl Index (95% CI) of 4.0 (2.3, 6.4).

Bleeding pattern

The bleeding pattern during use of <Invented name> was assessed in a 9-month comparative, double blind trial vs desogestrel 0.075 mg, used continuously.

The occurrence of a withdrawal bleeding (defined as a bleeding starting during the 4 hormone-free days of <Invented name> lasting for up to 8 consecutive days), was highest – occurring in less than 40% - during the first cycles and decreased with time. After 9 months of use, a withdrawal bleeding was recorded in less than 20% of users.

The mean number of bleeding/spotting days in the <Invented name> group vs the desogestrel group during the cycles 2-4 was 13.1 ± 13.0 vs 16.9 ± 16.9, respectively. The mean number of bleeding/spotting days during cycles 7-9, was 9.7 ± 10.4 vs 10.8 ± 13.3, respectively.

In the same study, the proportion of subjects without any bleeding/spotting (amenorrhea) during cycles 2-4 was 20,1% for <Invented name> and 13,5% for desogestrel. The proportion of subjects with amenorrhea increased in cycles 7-9 to 26,7% for <Invented name> and to 32,1% in the desogestrel group.

The number of subjects with prolonged bleeding (>10 consecutive days) for <Invented name> vs desogestrel was 18,1% and 26,1 %, respectively, during cycles 2-4 and 9,1% and 16,7%, respectively, during cycles 7-9.

The rate of subjects who withdrew from the study due to bleeding related adverse events was 3.3 % in the <Invented name> group and 6.6 % in the desogestrel group.

Paediatric population

A phase III study was conducted in Europe to evaluate tolerability, safety and acceptability of <Invented name>. 103 adolescents were included in a 6-cycle core part and 7 additional cycles (extension phase) for a total of 13 cycles, <Invented name> was well tolerated and accepted by the subjects.

Bleeding pattern with <Invented name> was assessed and data were generally consistent with those from the Phase 3 studies in adults. <Invented name> was associated with a decrease in the percentage of subjects experiencing bleeding or spotting over time.

5.2 Pharmacokinetic properties

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of <Invented name> active substance in plasma of about 28 ng/ml are reached at about 3-4 h after single ingestion. Concomitant ingestion of food has no influence on the extent of absorption of drospirenone.

The pharmacokinetics of <Invented name> after single and repeated dose has been studied in comparison with the marketed product containing 3 mg of micronized drospirenone in combination with ethinyl estradiol. After multiple dose administration, the relative bioavailability of <Invented name> was 76.51 % for $AUC_{t,ss}$. The accumulation ratio expressed by Rac (AUC) was 1.9256 while it was 2.7684 for the combined product. These findings indicate that the total exposure to drospirenone is lower for <Invented name> than for the combined product on the market in a cycle of 28 days.

Distribution

Drospirenone is 95 % to 97 % bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG). The mean apparent volume of distribution of drospirenone is approximately 4 l/kg.

Biotransformation

Drospirenone is extensively metabolized after oral administration. Two major non-pharmacologically active metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, both of which are formed without involvement of the P450 system. Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4.
In vitro, drospirenone is capable to inhibit weakly to moderately the cytochrome P450 enzymes CYP1A1, CYP2C9, CYP2C19 and CYP3A4.

Elimination

After oral administration, plasma drospirenone levels decrease with a terminal half-life of 32 h.

The metabolic clearance rate of drospirenone in serum is 1.5 ± 0.2 ml/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of about 1.2 to 1.4.

Linearity/non-linearity

The pharmacokinetics of oral drospirenone is dose proportional following single doses ranging from 1-10mg.

Steady-state conditions

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 40 ng/ml are reached after about 7 days of treatment. Plasma drospirenone levels accumulate by a factor of about 2 as a consequence of the ratio of terminal half-life and dosing interval.

Special populations

Effect of renal impairment
No studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of <Invented name>. However, steady-state serum drospirenone levels in women under treatment with a COC containing drospirenone with mild renal impairment (creatinine clearance CLcr, 50-80 mL/min) were comparable to those of women with normal renal function. The serum drospirenone levels were on average 37% higher in women with moderate renal impairment (CLcr, 30 - 50 mL/min) compared to those in women with normal renal function. Drospirenone treatment was also well tolerated by women with mild and moderate renal impairment. Drospirenone treatment did not show any clinically significant effect on serum potassium concentration.

Effect of hepatic impairment
No studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of <Invented name>. However, steroid hormones may be poorly metabolized in women with impaired liver function.

In a single dose study in women taking a COC containing drospirenone, oral clearance (CL/F) was decreased approximately 50 % in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in drospirenone clearance in volunteers with moderate hepatic impairment did not translate into any apparent difference in terms of serum potassium concentrations. Even in the presence of diabetes and concomitant treatment with spironolactone (two factors that can predispose a patient to hyperkalemia) an increase in serum potassium concentrations above the upper limit of the normal range was not observed. It can be concluded that drospirenone is well tolerated in patients with mild or moderate hepatic impairment (Child-Pugh B).

Ethnic groups

No clinically relevant differences in the pharmacokinetics of drospirenone between Japanese and Caucasian women have been observed.

5.3 Preclinical safety data

In laboratory animals, the effects of drospirenone were confined to those associated with the recognised pharmacological action. In particular, reproduction toxicity studies revealed embryotoxic and fetotoxic effects in animals which are considered as species specific. At exposures exceeding those in users of drospirenone, effects on sexual differentiation were observed in rat fetuses but not in monkeys. Environmental risk assessment studies have shown that drospirenone may pose a risk for the aquatic environment as reproductive effects in fish were evident at 0.087 ug/L (the LOEC). (See section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White active film-coated tablets:

Tablet core:
Microcrystalline cellulose
Lactose
Silica, colloidal (E551)
Magnesium stearate (E470b)

Tablet coat:
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol
Talc (E553b)

Green placebo film-coated tablets:

Tablet core:
Lactose monohydrate
Maize starch
Povidone
Silica, colloidal (E551)
Magnesium stearate (E470b)

Tablet coat:
Hypromellose (E464)
Triacetin
Polysorbate 80 (E433)
Titanium dioxide (E171)
Indigo carmine aluminium lake (E132)
Yellow Iron Oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25ºC

6.5 Nature and contents of container

Transparent PVC-PVDC/Aluminium or PVC-PE-PVDC/Aluminium blister containing 28 film-coated tablets (24 white active film-coated tablets and 4 green placebo film-coated tablets).

Pack sizes: calendar-packs containing 1x28, 3x28, 6x28 and 13x28 film-coated tablets.

In addition to the carton box, a carton case for the blister is enclosed.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment. (See section 5.3).

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

7. MARKETING AUTHORISATION HOLDER

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2023-05-30

<Detailed information on this medicinal product is available on the website of {name of MS/Agency}>