PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Solvetta® 2 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg dienogest.

Contains sugar (lactose monohydrate 60.93 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

SOLVETTA tablets are white, round and plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of endometriosis.

SOLVETTA is indicated in the long-term treatment of endometriosis in adolescents after menarche from 12 years of age onward and adults.

4.2 Posology and method of administration

Posology

Tablet-taking from the very first pack should start on day 1 of the woman's natural cycle (i.e., the first day of her menstrual bleeding). The dosage of SOLVETTA is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed.

Tablets must be taken throughout 28 days without regard for bleeding. When a pack is finished, the next one should be started without interruption.

The efficacy of SOLVETTA may be reduced in the event of missed tablets, vomiting, and/ or diarrhoea (if occurring within 3 to 4 hours after tablet taking). In the event of missed tablet(s), the woman should take one tablet only, as soon as she remembers, and should then continue next day to take tablet at her usual time. A tablet not absorbed due to vomiting or diarrhoea should likewise be replaced by one tablet.

Special populations

Paediatric

SOLVETTA is not indicated in children prior to menarche. The efficacy of dienogest has been demonstrated in the treatment of endometriosis – associated pelvic pain in adolescent patients (12 – 18 years), with an overall favourable safety and tolerability profile.

The use of SOLVETTA in adolescents over a treatment period of 12 months was associated with a mean decrease in Bone Mineral Density (BMD) in the lumbar spine of 1,2 %. After cessation of treatment, BMD increased again in these patients.

Loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if BMD decrease in this population will reduce peak bone mass and increase the risk for fracture in later life.

Therefore, the treating medical doctor should weigh the benefits of SOLVETTA against the possible risks of use in each individual adolescent patient (see “section 4.4” and “section 5.1”).

Geriatric patients

There is no relevant indication for use of SOLVETTA in the geriatric population.

Patients with hepatic impairment

SOLVETTA is contraindicated in patients with present or past severe hepatic disease (see “section 4.3”).

Patients with renal impairment

There are no data to suggesting the need for a dosage adjustment in patients with renal impairment.

Method of administration

For oral use

4.3 Contraindications

SOLVETTA should not be used in the presence of any condition listed below. Should any of the conditions appear during the use of SOLVETTA, the use of SOLVETTA must be discontinued immediately.

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1
- History of or active venous thromboembolic disorder.
- Arterial and cardiovascular diseases, past or present (e.g., myocardial infarction, cerebrovascular events, ischaemic heart disease).
- Diabetes mellitus with vascular involvement.
- 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 hormone-dependent malignancies.
- Undiagnosed vaginal bleeding.

4.4 Special warnings and precautions for use

As SOLVETTA is a progestogen-only preparation it can be assumed that the special warnings and precautions for use of progestogen-only preparations are also valid for the use of SOLVETTA although

not all of the warnings and precautions are based on respective findings in the clinical studies with dienogest.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before treatment with SOLVETTA can be started or continued.

Serious uterine bleeding:

Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of SOLVETTA. If bleeding is heavy and continuous over time, this may lead to anaemia (severe in some cases). In the event of anaemia, discontinuation of SOLVETTA should be considered.

Changes in bleeding pattern:

The majority of patients treated with SOLVETTA experience changes in their menstrual bleeding pattern (see section 4.8).

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. In case of long-term immobilization, it is advisable to discontinue the use of SOLVETTA (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two weeks after complete remobilization.

The increased risk of thromboembolism in the puerperium must be considered.

Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof.

Tumours:

A meta-analysis from epidemiological studies reported that there is a slightly increased relative risk 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. 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. 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.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in SOLVETTA. 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 in women taking SOLVETTA.

Osteoporosis:

Changes in bone mineral density (BMD):

The use of dienogest in adolescents (12 to <18 years) over a treatment period of 12 months was associated with a decrease in bone mineral density (BMD) in the lumbar spine (L2 to L4).

Loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if BMD decrease in this population will reduce peak bone mass and increase the risk for fracture in later life. (See sections 4.2 and 5.1).

In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting SOLVETTA because endogenous estrogen levels are moderately decreased during treatment with SOLVETTA (see section 5.1).

Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.

Other conditions:

Patients who have a history of depression should be carefully observed and the medicine discontinued if the depression recurs to a serious degree.

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 medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Dienogest generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of SOLVETTA, it is advisable to withdraw SOLVETTA and treat the hypertension.

Recurrence of cholestatic jaundice and / or pruritus, which occurred first during pregnancy or previous use of sex steroids, necessitates the discontinuation of SOLVETTA.

SOLVETTA may have an effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed for uncontrolled glucose levels while taking SOLVETTA.

Pregnancies that occur among users of progestogen-only preparation are more likely to be ectopic than are pregnancies among users of combined oral contraceptives.

Therefore, in women with a history of extrauterine pregnancy or an impairment of tube function, the use of SOLVETTA should be decided on only after carefully weighing the benefits against the risks.

Patients are advised to use non-hormonal methods of contraceptives (barrier contraception e.g., condom) to prevent unwanted pregnancies.

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 SOLVETTA.

Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during the use of SOLVETTA. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.

Excipients:

SOLVETTA contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take SOLVETTA.

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on SOLVETTA:

Individual enzyme-inducers or inhibitors (CYP3A4):

Progestogens, including SOLVETTA, are metabolised mainly by the cytochrome P450 system (CYP3A4) located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the metabolism of SOLVETTA.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of SOLVETTA and may result in undesirable effects e.g., change in bleeding profile.

A reduced clearance of sex hormones due to enzyme inhibition may increase the therapeutic effects of SOLVETTA and may result in undesirable effects.

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

phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort (*Hypericum perforatum*).

Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally not seen within a few weeks but may then be sustained for at least 4 weeks after cessation of therapy.

Substances with variable effects on the clearance of sex hormones:

When co-administered with sex hormones, many combinations of HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of the progestin. The net effect of these changes may be clinically relevant in some cases.

Substances decreasing the clearance of progestins (enzyme inhibitors):

Dienogest is a substrate of cytochrome P450 (CYP) 3A4.

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g., itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestins.

Effects of SOLVETTA on other medicines:

Based on *in vitro* inhibition studies, a clinically relevant interaction of dienogest with the cytochrome P450 enzyme mediated metabolism of other medicines is unlikely.

Other forms of interactions:

Interaction with food:

A standardized high fat meal did not affect the bioavailability of dienogest.

Laboratory tests:

The use of progestogens 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:

There are limited data from the use of dienogest in pregnant women. Animal studies and data from women exposed to dienogest during pregnancy reveal no special risks on pregnancy, embryonic / foetal development, birth or development after birth for humans (see “section 5.3”). However, SOLVETTA should not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Breastfeeding:

Treatment with SOLVETTA during lactation is not recommended. Physiochemical properties and animal data indicate excretion of dienogest in breast milk.

Fertility:

Based on the available data, ovulation is inhibited in the majority of patients during treatment with SOLVETTA. However, SOLVETTA is not a contraceptive. If contraception is required, a non-hormonal method should be used (See section 4.2). Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with SOLVETTA.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or use machines have been observed in users of products containing dienogest.

4.8 Undesirable effects

Side effects are more frequent during the first month after start of intake of SOLVETTA. In addition to effects listed under "section 4.4", the following undesirable effects have been reported in individuals using dienogest.

Blood and lymphatic system disorders:

Less Frequent: Anaemia

Metabolism and nutrition disorders:

Frequent**:** Weight increased

Less Frequent: Weight decreased, increased appetite

Psychiatric disorders:

Frequent**:** Depressed mood (with a risk for suicidal behaviour and suicide), sleep disorder, nervousness, Loss of libido, mood altered

Less Frequent: Anxiety, depression, mood swings

Nervous system disorders:

***Frequent*:** Headache, migraine

Less Frequent: Autonomic nervous system imbalance, disturbance in attention

Eye disorders:

***Less Frequent*:** Dry eyes

Ear and labyrinth disorders:

***Less Frequent*:** Tinnitus

Cardiac disorders:

***Less Frequent*:** Unspecified circulatory system disorder, palpitations

Vascular disorders:

***Less Frequent*:** Hypotension

Respiratory, thoracic and mediastinal disorders:

***Less Frequent*:** Dyspnoea

Gastrointestinal disorders:

***Frequent*:** Nausea, abdominal pain, flatulence, abdominal distention, vomiting

***Less Frequent*:** Diarrhoea, constipation, abdominal discomfort, gastrointestinal inflammation, gingivitis

Skin and subcutaneous tissue disorders:

***Frequent*:** Acne, alopecia

***Less Frequent*:** Dry skin, hyperhidrosis, pruritus, hirsutism, onychoclasis, dandruff, dermatitis, abnormal hair growth, photosensitivity reaction, pigmentation disorder

Musculoskeletal and connective tissue disorders:

***Frequent*:** Back pain

***Less Frequency*:** Bone pain, muscle spasm, pain in extremity, heaviness in extremities

Renal and urinary disorders:

***Less Frequent*:** Urinary tract infection

Reproductive system and breast disorders:

***Frequent*:** Breast discomfort, ovarian cyst, hot flush, uterine/vaginal bleeding including spotting

Less Frequent: Vaginal candidiasis, vulvovaginal dryness, genital discharge, pelvic pain, atrophic vulvovaginitis, breast mass, fibrocystic breast diseases, breast induration

General disorders and administration site conditions:

***Less Frequent*:** Asthenic conditions, Irritability

***Less Frequent*:** Oedema

Uterine bleeding irregularities:

The following bleeding patterns were observed:

Menorrhagia (excessive menstrual bleeding), amenorrhea, infrequent bleeding, frequent bleeding, irregular bleeding, prolonged bleeding, and normal bleeding.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

Acute toxicity studies performed with dienogest did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. 20 to 30 mg dienogest per day (10 to 15 times higher dose than in SOLVETTA) over 24 weeks of use were well tolerated. However, overdosage may potentiate adverse effects (see section 4.8).

There is no specific antidote, treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.8.2 Progesterones with or without oestrogen

Pharmacotherapeutic group: progestogens

ATC code: G03D

Dienogest is a nortestosterone derivative with no androgenic activity. Dienogest binds to the progesterone receptor of the human uterus with only 10 % of the relative affinity of progesterones. Despite its low affinity to the progesterone receptor, dienogest has a strong progestogenic effect *in vivo*. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity *in vivo*.

Dienogest acts on endometriosis by abolishing the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment and decidualisation of endometrial tissue.

5.2 Pharmacokinetic properties

Absorption:

Orally administered dienogest is almost completely absorbed.

Peak serum concentrations of 47 ng/ml are reached at about 1,5 hours after ingestion of a 2 mg tablet.

A standardised high fat meal did not affect the bioavailability of dienogest.

Bioavailability is about 91 %. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1 to 8 mg.

Distribution:

Dienogest is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). 10 % of the total serum concentration of the active substance is present as free steroid, 90 % is non-specifically bound to albumin. The apparent volume of distribution (V_d/F) of dienogest is 40 litres.

Biotransformation:

Dienogest is completely metabolised by the known pathway of steroid metabolism, with the formation of inactive metabolites. Based on the *in vivo* and *in vitro* studies, CYP3A4 is the major enzyme involved in the metabolism of dienogest. The metabolites are rapidly excreted so that in plasma, unchanged dienogest is the dominating fraction. The metabolic clearance rate from serum Cl/F is 64 ml/min.

Elimination:

Dienogest serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 9 to 10 hours. Dienogest is excreted in the form of metabolites, which are excreted at a urinary to faecal ratio of about 3:1 after oral administration of 0,1 mg/kg. The half-life of urinary metabolites excretion is 14 hours. Following oral administration, approximately 86 % of the dose administered is eliminated within 6 days; the bulk of this amount is excreted within the first 24 hours, mostly with the urine.

Steady-state condition:

Pharmacokinetics of dienogest is not influenced by SHBG levels. Following daily ingestion drug serum levels increase about 1.24 fold reaching steady-state conditions after 4 days of treatment.
The pharmacokinetics of dienogest after repeated administration can be predicted from single dose pharmacokinetics.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. 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 monohydrate,

Maize starch,

Povidone K-30,

Vegetal Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

SOLVETTA tablets are packaged in PVC-PVDC/aluminium blisters. Aluminium foil is a foil of aluminium push-through with a dull side lacquered and a bright side heat sealable lacquered for sealing to PVC.

Outer packaging:

Blisters of SOLVETTA tablets are packaged in a carton box.

Pack sizes:

2 x 14 tablets, 6 x 14 tablets and 12 x 14 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBERS

52/21.8.2/0185

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10 August 2022

10 DATE OF REVISION OF THE TEXT

15 March 2023

[1]Company Reg. No.: 1990/001979/07