1. NAME OF THE MEDICINAL PRODUCT

DIMETRUM TABLET 2 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of dienogest.

Excipient with known effect: each tablet contains 62.81 mg lactose monohydrate. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to slightly yellowish round tablet marked with “D2” on one side and without marking on the other side, with a diameter of approximately 7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of endometriosis.

4.2 Dosage and method of administration

Method of administration For oral use.

Dosage Regimen

Tablet-taking can be started on any day of the menstrual cycle.

The dosage of Dimetrum is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed. Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption.

The efficacy of Dimetrum may be reduced in the event of missed tablets, vomiting and/or diarrhea (if occurring within 3-4 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 the next day to take the tablet at her usual time. A tablet not absorbed due to vomiting or diarrhea should likewise be

replaced by one tablet.

If a short acting, e.g. oral, hormonal treatment was prescribed before starting treatment with dienogest, treatment may be started on the first day of menstrual bleeding after cessation of treatment.

If a long-acting, i.e. injectable, hormonal treatment was administered before starting treatment with dienogest, then dienogest may be started once metabolism/excretion of the previously administered drug is expected to complete.

Additional information on special populations

Paediatric population
Dimetrum is not indicated in children prior to menarche period.

The efficacy of Dimetrum has been demonstrated in the treatment of endometriosis – associated pelvic pain in adolescent patients (12-18 years), with an overall favorable safety and tolerability profile.

The use of Dimetrum 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 physician should weigh the benefits of Dimetrum against the possible risks of use in each individual adolescent patient (see sections 'Special warnings and precautions for use', 'Pharmacodynamic properties'). If clinically warranted, BMD may be monitored and the results used in the risk-benefit assessment of use of Dimetrum.

Geriatric population
There is no relevant indication for use of Dimetrum in the Geriatric population.

Patients with hepatic impairment
Dimetrum is contraindicated in patients with present or past severe hepatic disease (see section 4.3).

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

4.3 Contraindications

Dimetrum should not be used in the presence of any of the conditions listed below, which are partially derived from information on other progesterone-only preparations. Should any of the conditions appear

during the use of Dimetrum, treatment must be discontinued immediately.

- active venous thromboembolic disorder
- arterial and cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischemic 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 tumors (benign or malignant)
- known or suspected sex hormone-dependent 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 Warnings

Before starting Dimetrum treatment, pregnancy must be excluded (see 'Pregnancy and Lactation'). During treatment, patients are advised to use non-hormonal methods of contraception (e.g. barrier method) if contraception is required.

Pregnancies that occur among users of progestogen-only preparations used for contraception (e.g. minipill) 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 Dimetrum should be decided on only after carefully weighing the benefits against the risks.

As Dimetrum is a progestogen-only preparation, it can be assumed that special warnings and special precautions for use of other progestogen-only preparations are also valid for the use of Dimetrum although not all of the warnings and precautions are based on respective findings in the clinical studies with Dimetrum.

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

- *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.

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 Dimetrum (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 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. 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 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 hormonal substances such as the one contained in Dimetrum. 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 Dimetrum.

Changes in Bone Mineral Density (BMD)

The use of Dimetrum in adolescents (12 to 18 years) 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. (see sections ‘Pediatric Population’ and ‘Pharmacodynamic Properties’)

Therefore, the treating physician should weigh the benefits of Dimetrum against the possible risks of use in each individual adolescent patient also taking into account the presence of significant risk factors for osteoporosis.

Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages.
No BMD decrease was observed in adults (see section ‘Pharmacodynamic properties’).

Changes in bleeding pattern

Dienogest treatment affects the menstrual bleeding pattern in the majority of women (see 'Undesirable effects'). Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of dienogest. If bleeding is heavy and continuous over time, this may lead to anemia (severe in some cases). Discontinuation of dienogest should be considered in such cases.

Medical examination
A complete medical history should be taken, and a physical and gynecological examination should be performed prior to the initiation or reinstitution of the use of dienogest, guided by the contraindications (see Contraindications) and warnings (see Special warnings and precautions for use), and these should be repeated regularly during the use of dienogest. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, and should also include cervical cytology.

- *Other conditions*

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

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

Dienogest may have a slight effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking Dimetrum.

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 Dimetrum.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

- *Effects of other medicinal products on Dimetrum*

Progestogens including dienogest are metabolized mainly by the cytochrome P450 3A4 system (CYP3A4)

located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the progestogen drug metabolism.

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

A reduced clearance of sex hormones due to enzyme inhibition may increase the exposure to dienogest 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 also 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 seen within a few weeks after cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

  The effect of the CYP 3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with estradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest and estradiol. The systemic exposure of dienogest and estradiol at steady state, measured by AUC(0-24h), were decreased by 83% and 44%, respectively.

- **Substances with variable effects on the clearance of sex hormones:**

  When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside 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 sex hormones (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 concentration of the progestin.

- In a study investigating the effect of CYP3A4 inhibitors (ketoconazole, erythromycin) on the combination of Estradiol valerate/dienogest, steady state dienogest plasma levels were increased. Co-administration with the strong inhibitor ketoconazole resulted in a 2.86-fold increase of AUC (0-24h) of dienogest at steady state was increased 1.62-fold. The clinical relevance of these interactions is unknown.

- ***Effects of Dimetrum on other medicinal products***

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

- *Drug-food Interactions*

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

- *Other forms of interactions*

The use of progestins 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. lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

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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/ fetal development, birth or development after birth for humans (see also section ‘ Preclinical safety data’). However, Dimetrum should not be administered to pregnant women because there is no need to treat endometriosis during pregnancy.

Lactation

Treatment with Dimetrum during lactation is not recommended. Physiochemical properties and animal data indicate excretion of dienogest in breast milk.
A decision must be made whether to discontinue breast-feeding or to abstain from Dimetrum therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Based on the available data, ovulation is inhibited in the majority of patients during treatment with Dimetrum. However, Dimetrum is not a contraceptive.

Dimetrum was not studied for contraceptive efficacy, but DNG 2 mg has been shown in a study involving 20 women to inhibit ovulation after 1 month of treatment. If contraception is required a non-hormonal method should be used (see section ‘ Special warnings and precautions for use’).

Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with Dimetrum.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

Undesirable effects are more common during the first months after start of intake of Dimetrum and subside with duration of treatment. The following undesirable effects have been reported in users of Dimetrum.

The most frequently reported undesirable effects during treatment that were considered at least possibly related to Dimetrum were headache (9.0 %), breast discomfort (5.4 %), depressed mood (5.1 %), and acne (5.1 %).

Table 1, the frequencies of adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs) reported with Dimetrum are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing frequency.
Frequencies are defined as common (≥1/100 to <1/10) and uncommon (≥1/1000 to <1/100).* The frequencies are based on pooled data of four clinical trials including 332 patients (100.0%).

Table 1: Categorized relative frequency of women with ADRs, by MedDRA SOC, 2 mg dienogest group – based on pooled data of four clinical trials including 332 patients.

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders		Anemia
Metabolism and nutrition disorders	Weight increased	Weight decreased Increased appetite
Psychiatric disorders	Depressed mood	Anxiety
	Sleep disorder	Depression
	Nervousness	Mood swings
	Loss of libido	
	Mood altered	
Nervous system disorders	Headache Migraine	Autonomic nervous system imbalance Disturbance in attention
Eye disorders		Dry eye
Ear and labyrinth disorders		Tinnitus
Cardiac disorders		Unspecified circulatory system disorder
		Palpitations
Vascular disorders		Hypotension
Respiratory, thoracic, and mediastinal disorders		Dyspnoea
Gastrointestinal disorders	Nausea Abdominal pain Flatulence Abdominal distension Vomiting	Diarrhoea Constipation Abdominal discomfort Gastrointestinal inflammation Gingivitis
Skin and subcutaneous tissue disorders	Acne Alopecia	Dry skin, Hyperhidrosis, Pruritus Hirsutism, Onychoclasis Dandruff Dermatitis, Hair growth abnormal Photosensitivity reaction, Pigmentation disorder

Musculoskeletal and connective tissue disorders	Back pain	Bone pain,Muscle spasms Pain in extremity Heaviness in extremities
Renal and urinary disorders		Urinary tract infection
Reproductive system and breast disorders	Breast discomfort Ovarian cyst Hot flush Uterine / Vaginal bleeding including Spotting	Vaginal candidiasis, Vulvovaginal dryness Genital discharge, Pelvic pain, Atrophic vulvovaginitis, Breast mass, Fibrocystic breast disease, Breast induration
General disorders and administration site conditions	Asthenic conditions Irritability	Oedema

*The most appropriate MedDRA term (version 11.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed but should be taken into account as well.

Uterine bleeding irregularities

Menstrual bleeding patterns were assessed systematically using patient diaries and were analysed using the WHO 90 days reference period method. During the first reference period (i.e. first 90 days of treatment with Dimetrum): The following bleeding patterns were observed (n=290; 100%): Amenorrhea (1.7 %), infrequent bleeding (27.2 %), frequent bleeding (13.4 %), irregular bleeding (35.2 %), prolonged bleeding (38.3 %), normal bleeding, i.e. none of the previous categories (19.7 %). [1] During the fourth reference period the following bleeding patterns were observed (n=149; 100%): Amenorrhea (28.2 %), infrequent bleeding (24.2 %), frequent bleeding (2.7 %), irregular bleeding (21.5 %), prolonged bleeding (4.0 %), normal bleeding, i.e. none of the previous categories (22.8 %).[13] Changes in menstrual bleeding patterns were only occasionally reported as adverse event by the patients (See Table 1).

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. There is no specific antidote. A daily intake of 20 - 30 mg dienogest (10 to 15 times higher dose than in 2 mg dienogest) over 24 weeks of use was very well tolerated.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: progestogens.

ATC code: G03DB08

Mechanism of action

Dienogest acts on endometriosis by reducing the endogenous production of oestradiol and thereby suppresses the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment causing initial decidualization of

endometrial tissue followed by atrophy of endometriotic lesions.

Pharmacodynamics effects

Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10% of the relative affinity of progesterone. 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*.

Data on efficacy:

Superiority of Dienogest over placebo with regard to reduction of endometriosis-associated pelvic pain (EAPP) and clinically meaningful reduction of pain compared to baseline were demonstrated in a 3-month study including 102 patients on Dienogest. EAPP was measured on a Visual Analog Scale (VAS) (0-100 mm). After 3 months of treatment with Dienogest, a statistically significant difference compared to placebo (Δ = 12.3 mm; 95% CI: 6.4-18.1; $p < 0.0001$) and a clinically meaningful reduction of pain compared to baseline (mean reduction = 27.4 mm ± 22.9) were demonstrated.

After 3 months of treatment, reduction of EAPP by 50% or more without relevant increase of concomitant pain medication was achieved in 37.3% of patients on Dienogest (placebo: 19.8%); a reduction of EAPP by 75% or more without relevant increase of concomitant pain medication was achieved in 18.6% of patients on Dienogest (placebo: 7.3%).

The open-label extension to this placebo-controlled study showed a continued improvement of endometriosis-associated pelvic pain for a treatment duration of up to 15 months (mean reduction at end of treatment = 43.2 ± 21.7 mm).

In addition, efficacy on endometriosis-associated pelvic pain was shown in a 6-month comparative trial of Dienogest versus the GnRH analogue leuprorelin acetate (LA) including 120 patients on Dienogest. EAPP was measured on a VAS (0-100 mm). A clinically meaningful reduction of pain compared to baseline was observed in both treatment groups (Dienogest: 47.5 ± 28.8 mm, LA: 46.0 ± 24.8 mm). Non-inferiority versus LA based on a pre-defined non-inferiority margin of 15 mm was demonstrated ($p<0.0001$).

Three studies including a total of 252 patients who received a daily dose of 2 mg dienogest demonstrated a substantial reduction of endometriotic lesions after 6 months of treatment.

A randomized, double-blind, parallel-group study (n=20 to 23 per dose group) investigated pharmacodynamics effects of four dienogest doses (0.5, 1.0, 2.0, or 3.0mg/day) for a maximum of 72 days. Ovulations were observed in 14% and 4% of women of the 0.5mg and 1mg groups, respectively. No ovulation occurred in the 2mg and 3mg groups. In the 2mg group, ovulation was confirmed in 80% of women within 5 weeks after cessation of therapy. Dienogest has not been tested for contraceptive efficacy in larger studies.

The efficacy of Dienogest was demonstrated in the treatment of endometriosis related symptoms (pelvic pain, dysmenorrhea, and dyspareunia) in a 12-month study with 111 female adolescents (after menarche between 12 and 18 years of age)

Data on safety:

Endogenous estrogen levels are only moderately suppressed during treatment with Dienogest.

Bone mineral density (BMD) was assessed in 21 adult patients before and after 6 months of treatment and there was no reduction in mean BMD. In a 12-months study involving 111 female adolescents, 103 had BMD measurements. The mean relative change in BMD of the lumbar spine (L2-L4) from baseline was -1.2 %. In a subset of the patients with decreased BMD a follow-up measurement was performed 6 months after end of treatment and showed an increase in BMD towards baseline levels.

No significant impact on standard laboratory parameters, including hematology, blood chemistry, liver enzymes, lipids, and HbA1C was observed during treatment with Dienogest for up to 15 months (n=168).

Long-term safety

A long-term post-approval observational active surveillance study was conducted to investigate the incidence of first-time occurrence or worsening of clinically relevant depression and occurrence of anemia. A total of 27,840 women with a newly prescribed hormonal therapy for endometriosis were enrolled in the study and followed up for up to 7 years.

A total of 3,023 women started with a prescription for dienogest 2 mg and 3,371 patients started with other approved endometriosis drugs. The overall adjusted hazard ratio for new occurrences of anemia comparing the dienogest patients with the patients on other approved endometriosis drugs was 1.1 (95% CI: 0.4 – 2.6). The adjusted hazard ratio for depression risk comparing dienogest and other approved endometriosis drugs was 1.8 (95% CI: 0.3-9.4). A slightly increased risk of depression in dienogest users compared with users of other approved endometriosis drugs could not be excluded."

The proportion of DNG users reporting "side effects" or "medication ineffective" as reasons for stopping the treatment was higher compared to other approved endometriosis drugs (e.g. Danazol, GnRH-a) and was more comparable to non-approved endometriosis drugs (e.g. CHCs, other progestins).
Overall, it is difficult to interpret the results owing to the heterogeneity of reasons for treatment discontinuation; the large inter-country variance in prescribed endometriosis treatment; the difference between (sub-)cohorts in the indicated duration of use; and in the methods of administration (e.g. injectable three-month Depo which does not allow for immediate discontinuation by the patient).

5.1 Pharmacokinetic properties

Absorption

Orally administered dienogest is rapidly and almost completely absorbed. Peak serum concentrations of 47 ng/ml are reached at about 1.5 hours after single ingestion. Bioavailability is about 91%. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1 – 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 drug concentration is present as free steroid, 90 % is non-specifically bound to albumin.
The apparent volume of distribution (V_d/F) of dienogest is 40l.

Biotransformation

Dienogest is completely metabolized by the known pathways of steroid metabolism, with the formation of endocrinologically mostly inactive metabolites. Based on in vitro and in vivo studies, CYP3A4 is the major enzyme involved in the metabolism of dienogest. The metabolites are excreted very quickly 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 characterized by a half-life of approximately 9-10 hours. Dienogest is excreted in 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 excreted within the first 24 h, mostly with the urine.

Steady-state conditions

Pharmacokinetics of dienogest are 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 of 2 mg dienogest can be predicted from single dose pharmacokinetics.

Pharmacokinetics in Special Population

2 mg dienogest has not been studied specifically in renally impaired subjects. 2 mg dienogest has not been studied in subjects with hepatic impairment.

5.2 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, Povidone K30, Pregelatinized maize starch, Microcrystalline cellulose, Crospovidone, Silica colloidal anhydrous, Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in the outer carton box packaging to protect from light.

6.5 Nature and contents of container

Dimetrum are packaged in blister packs consisting of green polyvinyl chloride (PVC) coated with polyvinylidene chloride (PVDC) and push-through heat-sealed aluminum (Alu) foil.

Pack sizes:
28, 84 and 168 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. PRODUCT OWNER

Laboratoires Besins International 3,
rue du Bourg L'Abbe
75003 Paris France

8. MANUFACTURER

Cyndea Pharma S.L.
Poligono Industrial Emiliano Revilla Sanz. Avda de Agreda 31,
Olvega, 42110-Soria, Spain

9. DATE OF REVISION OF THE TEXT

Oct 2022