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DIENILLE film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2 mg dienogest and 0.03 mg ethinylestradiol.

PHARMACEUTICAL FORM

White or off-white, round, biconvex film-coated tablets.

CLINICAL PARTICULARS

Therapeutic indications

- Hormonal contraception.
- For the treatment of mild to moderate acne which is refractory to local treatment only in women who desire oral contraception for birth control and who have no contraindications to COCs.

POSOLOGY AND METHOD OF ADMINISTRATION

Application of Dienille

Film-coated tablets are taken daily at the same time (if necessary with some fluid), according to the sequence printed on the blister pack. One film-coated tablet a day is taken for 21 consequent days. Each subsequent pack is started after 7 tablet-free days; usually a break-through bleeding occurs in this period. Typically, it starts 2-3 days after the last pill and may still be present when the first film-coated tablet from the next blister pack is taken.

How to start Dienille

No previous application of hormonal contraception (in the last month)

One film-coated tablet should be taken starting on the first day of the menstrual cycle (the first day of menstruation counting as Day 1).

Changing from a combined contraceptive (combined oral contraceptive, vaginal ring, transdermal patch) to oral contraception

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

Changing from a monocomponent progestogen-only product (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

Women taking progestogen-only minipills can change at any time to combined oral contraceptives. Those using implants or IUS can start on the day when the implant or IUS is removed. Women receiving injections can start taking film-coated tablets when the next injection is due. But in all of these cases an additional contraceptive precautions must be taken for the first 7 days.

Application after an abortion in the first trimester

The product can be taken immediately; no additional contraceptive precautions are required.

Post-partum application and usage after an abortion in the second trimester:

The product can be started 21-28 days after delivery or an abortion in the second trimester. If the start of the product is delayed additional contraceptive precautions (e. g. barrier methods) will be required for the first 7 days of pill-taking. However, if sexual intercourse has already preceded, existence of a pregnancy should be excluded, or the start of the film-coated tablet should be delayed to the next menstrual cycle.

Advice in case of missed pills

If the forgotten film-coated tablet is taken **within 12 hours**, no further precautions are necessary; the product should be taken as soon as possible and further film-coated tablets should be taken at the usual time.

If the film-coated tablet is forgotten for **more than 12 hours**, contraceptive protection may be reduced. In this case the following rules have to be applied:

1. Taking the film-coated tablet should not be stopped for more than 7 days.
2. For the proper inhibition of the hypothalamus-hypophysis-ovary system film-coated tablets have to be taken for 7 days without interruption.

Based on these, the following advice can be given for the everyday practice:

First week

The patient should take the last forgotten film-coated tablet, even if this means taking two film-coated tablets in one day and then continue to take film-coated tablets at the normal time. Additional contraceptive precautions (e.g. condom) should be taken for the next 7 days. However, if sexual intercourse has already preceded in the previous 7 days, pregnancy cannot be excluded. Risk of getting pregnant is proportional to the number of film-coated tablets missed and is increasing as the "missed-period" gets closer to the tablet free period.

Second week

The patient should take the last forgotten film-coated tablet, even if this means taking two film-coated tablets in one day and then continue to take film-coated tablets at the normal time. If she has taken the film-coated tablets regularly on the preceding 7 days, there is no need to take additional contraceptive precautions. However, if there was more than one film-coated tablet missed or she has not taken the film-coated tablets regularly, additional contraceptive precautions must be taken for the next 7 days.

Third week

In this period the risk for incomplete contraception is extremely high because of the advancing tablet-free period. However, some sort of contraception can be ensured by modifying the schedule of the film-coated tablets. By using the next protocols, there is no need to take additional contraceptive precautions , given that the woman has taken the film-coated tablets regularly on the preceding 7 days. If not, the first protocol should be selected and additional contraceptive precautions must be taken for the next 7 days.

1. The patient should take the last forgotten film-coated tablet, even if this means taking two film-coated tablets in one day and then continue to take film-coated tablets at the normal time. The next pack must be started as soon as the current one is finished, i.e. no gap should be left between the packs. The patient is not likely to have a withdrawal bleeding until the end of the second pack and she might experience some spotting or break-through bleeding on film-coated tablet taking days

2. The second possibility is that she does not continue the pack already in use, but she observes a seven-day-long tablet free period (days when the film-coated tablet was missed should be counted), then she carries on with a new pack.

If several film-coated tablets were missed from the current package and there is no withdrawal bleeding in the tablet-free period the existence of a pregnancy cannot be excluded.

Gastro-intestinal upset

If vomiting or diarrhea occurs within 3-4 hours after film-coated tablet intake, a film-coated tablet may not be absorbed properly by the body. In this case a film-coated tablet should be taken as soon as possible.

After more than 12 hours, directions in section **Posology and method of administration** should be followed to take missed film-coated tablets. If the patient does not want to disturb the order of film-coated tablets in the current package, she has to take an extra film-coated tablet (or more) from a spare pack.

Delaying or modifying the time of menstrual bleeding

To delay bleeding after finishing the previous package, application of Dienille should be continued without a drug-free interval. During the application of the second pack the patient might experience some spotting or break-through bleeding on tablet taking days. After finishing the second pack 7 tablet-free days have to elapse, then application of Dienille can commence.

If she wants to have the start of the menstrual cycle on a different day of the week, length of the tablet-free interval can be decreased as necessary. However, the shorter is the tablet-free interval, the higher raises the probability of spotting or break- through bleeding during the application of the second pack. (It is similar to the case when the time of menstrual cycle is delayed).

CONTRAINDICATIONS

In the persistence of the following diseases and conditions usage of combined oral contraceptives is contraindicated. In case of first appearance of the diseases below while taking combined contraceptive film-coated tablets, its application should be stopped immediately.

Usage of Dienille is contraindicated:

- hypersensitivity to any of the active ingredients and excipients of the film-coated tablet;
- existing venous thrombosis (deep venous thrombosis, pulmonary embolism) or positive patient history;
- existing arterial thrombosis (cerebrovascular event, heart attack) or positive patient history or even in the presence of prodromal events (such as angina pectoris, and transient ischemic attack);
- in the presence of a severe risk factor or multiple risk factors of arterial thrombosis:
  - diabetes mellitus with vascular involvement;
  - severe hypertension;
  - severe dyslipidaemia;
  - biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis including activated protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant);
- active severe liver disease or positive patient history for it, if liver function tests have not been normalized yet;
- active liver tumor (benign or malignant) or a positive patient history for it;
- known or suspected steroid-dependent tumors, (tumors of genital organs or breasts);
- vaginal bleeding of unknown origin;
- migraine with focal neurological symptoms in the patient history;
- pancreatitis or a history thereof if associated with severe hypertriglyceridaemia;
- severe renal insufficiency or acute renal failure.

Dienille is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interactions with Other Medicaments).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

If any of the conditions listed below is present, the benefits of combined oral contraceptive use must be weighed against the possible risks for each individual woman and discussed with her before she decides to start using it. The patient should be warned that in case of appearance, aggravation, or exacerbation of any of these conditions medical advice should be sought without delay. The consulting physician should then decide whether Dienille's use must be discontinued.

Vascular diseases

Because of the possibility of severe health damage (see section **UNDESIRABLE EFFECTS**) persistence of risk factors (such as varicose veins, advanced stage phlebitis and thrombosis, existence of heart disease, obesity, blood clotting disorders) combined oral contraceptive use must be carefully weighed against the possible risks before the start of Dienille.

The use of any combined oral contraceptive (COC) carries an increased risk for venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a COC. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 per 100 000 pregnancies. VTE may be fatal in 1-2% of the cases. It is not known how Dienille influences the risk of VTE compared with other COCs.

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 woman-years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 woman-years for non-users.

Epidemiological studies have also associated the use of combined COCs with an increased risk for arterial (myocardial infarction, transient ischaemic attack) thromboembolism.

Incidence of VTE in users of oral contraceptives with 30 µg ethinylestradiol and levonorgestrel is up to 20 cases per 100 000 women-years. Studies show no data about different risks associated with the use of Dienogest/Ethinylestradiol compared to contraceptives containing levonorgestrel.

Thrombosis has very rarely been reported to occur in other veins or arteries, e.g. hepatic, mesenteric, renal, cerebral or retinal in combined oral contraceptive users. There is no consensus as to whether the occurrence of these events is associated with the use of combined oral contraceptives.

Symptoms of arterial or venous thrombosis are:

- unusual pains in or swelling of the leg(s);
- sudden severe pain in the chest, whether or not reaching to the left arm;
- sudden breathlessness;
- sudden coughing;
- any unusual severe, prolonged headache;
- sudden partial or complete loss of vision;
- diplopia;
- blurred speech or aphasia;
- vertigo;
- collapse with or without focal epilepsy;
- weakness or very marked numbness suddenly affecting one side or one part of the body;
- motor disturbances;
- 'acute' abdomen;

Women taking combined oral contraceptives have higher risk for **venous** thromboembolic complications in the presence of the following:

- increased age;
- a positive family history of venous thromboembolism (in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any combined oral contraceptive use;
- prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue combined oral contraceptive use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization. If stopping the combined oral contraceptive use was not possible in the right time, care should be taken to thrombosis prophylaxis;
- obesity (body mass index >30 kg/m^2).

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the development or course of deep venous thrombosis.

Women taking combined oral contraceptives have higher risk for **arterial** thromboembolic complications in the presence of the following:

- increased age;
- dyslipoproteinaemia;
- hypertension;
- valvular heart disease;
- atrial fibrillation;
- migraine;
- a positive family history (arterial 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;
- obesity (body mass index over 30 kg/m^2);
- smoking: cigarette smoking increases the risk of serious cardiovascular adverse reactions (such as heart attack, stroke) to oral contraceptive use. With heavier smoking and increasing age the risk further increases.

Women over 35 who use oral contraceptives should be strongly advised not to smoke. If she does not give up smoking, other contraceptive methods should be employed, especially, if other risk factors are also present.

Presence of severe risk factor/factors leading to the development of venous or arterial disorders might contraindicate application of Dienille. Introduction of anti-coagulatory treatment should also be considered. Women taking combined oral contraceptives should be warned that if they experience probable signs of thrombosis medical advice should sought without delay. In case of suspected or diagnosed thrombosis taking of the COC should be terminated and alternative methods of contraception should be employed because of the teratogenic effect of anti-coagulants (cumarin derivates).

It should also be noted that risk of thromboembolism is increased in the post-partum period (see section **PREGNANCY AND LACTATION**).

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

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

Cancer

An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects (such as sexual behavior, incidence of human papilloma-virus infection, etc).

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 combined oral contraceptives. The increased risk diminishes in 10 years after finishing combined oral contraceptives. For further information see section **UNDESIRABLE EFFECTS**.

Breast cancer belongs to the hormone-dependent tumors. Some conditions such as early menarche, late (after 52 years of age) menopause, being nullipara, anovulatoric cycles etc, have long been recognized as risk factors in the development of breast cancer. These risk factors raise the possibility of hormonal effects in the pathogenesis of breast cancer. Hormone receptors play a central role in the tumor biology of breast cancer. Some of them induce growth factors, such as transforming growth factor-alpha (TGF-alpha).

Estrogens and gestagens influence proliferation of breast cancer cells. Among others this is the tumor biological rationale for pharmaceutical treatment of receptor positive, postmenopausal breast cancer.

Several epidemiological studies investigating the connection between combined oral contraceptive use and breast cancer acknowledge that development of breast cancer in middle age women is related to the early start and extended application of combined oral contraceptives. However, this is only one factor among possible other factors.

Benignant or very rarely malignant hepatic tumors have been reported on rare occasions in long-term users of oral contraceptives. In isolated cases these tumors were sources of life-threatening abdominal bleedings. A hepatic tumor should be considered in the differential diagnosis when upper abdominal pain, enlarged liver or signs of intra-abdominal haemorrhage occurs.

Other conditions

If hypertriglyceridaemia is present in the patient's or family history, use of combined oral contraceptives can increase the risk of development of pancreatitis.

Although increase in the blood pressure is common in women taking combined oral contraceptives, clinical hypertension is a rare finding. However, if hypertension develops while taking combined oral contraceptives, treatment should be discontinued and blood pressure lowering measures initiated. After successful treatment of hypertension, application of combined oral contraceptives can be started again, if the consulting physician considers this safe.

If, during the use of a COC in pre-existing 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 hypertensive therapy.

Although no causative relationship has been proven, the following diseases / conditions worsen upon combined oral contraceptive use and pregnancy: cholestatic jaundice and/or pruritus, gallstones, porphyria, systemic lupus erythematosus, haemolytic uraemic syndrome, Sydenham chorea, gestational herpes, impaired hearing caused by otosclerosis in the middle ear.

If active or chronic liver disease is present, application of combined oral contraceptives should be suspended until liver function tests have been found to be normal.
If jaundice due to pregnancy or due to the use of steroids occurs or cholestatic pruritus develops, use of hormonal contraceptives should be stopped.

Combined oral contraceptives may diminish glucose tolerance and increase the need for insulin in peripheral tissues, however, usually it is not necessary to change anti-diabetic treatment regime in women taking combined oral contraceptives. Nevertheless, their status should be closely monitored, especially when starting the pill.

Development of Crohn's disease and ulcerative colitis has been described in women taking combined oral contraceptives.

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 this preparation.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.
Worsening of endogenous depression or epilepsy has been reported during COC use.

The use of oestrogens in girls may cause premature closure of the epiphyses resulting in decreased final adult height.

Progestin containing compounds may have aldosterone antagonist properties that can have an important impact on potassium level.

Medical examinations

Assessment of women prior to starting or re-starting Dienille should include a detailed personal (and family) medical history. Pregnancy should be excluded. Blood pressure should be measured and physical examination should be guided by this and by the sections **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**. Women taking Dienille should be encouraged to read the patient information leaflet carefully and to follow the suggestions in it. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman.

Women should be warned that taking the pill does not protect them against HIV-infection (AIDS) or other sexually transmitted diseases.

Regular medical assessment is also important because some contraindications or risk factors can appear at first during COC use.

Reduced reliability

Reliability of combined oral contraceptives may be reduced under the following circumstances: if the patient does not take the film- coated tablets on a regular basis, vomiting or severe diarrhea occurs (see section **POSOLOGY AND METHOD OF ADMINISTRATION**, or because of interaction with other medicinal products (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

Change in bleeding pattern

Combined oral contraceptives may cause irregular (spotting or break-through) bleeding, especially in the first few months of treatment. Thus, the investigation of irregular bleeding should be shifted until hormonal equilibrium develops; usually this takes three cycles.

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If irregular bleeding after regular cycles, or persistent bleeding is present, non-hormonal causes such as pregnancy and the presence of a malignant tumor should be excluded, this may indicate a diagnostic curettage as well.

Occasionally, withdrawal bleeding may not occur at all. If the film- coated tablets have been taken correctly (according to section **POSOLOGY AND METHOD OF ADMINISTRATION**), pregnancy is very unlikely. If withdrawal bleeding fails to occur at the end of a second pack or if she did not follow the suggestions above, pregnancy must be ruled out before resuming with the next pack.

Metabolic interactions leading to an increased clearance of sexual steroids might elicit break-through bleeding or lead to a decreased contraceptive potential (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

The herbal remedy St John's wort (Hypericum perforatum) should not be taken concomitantly with Dienille as this could potentially lead to a loss of contraceptive effect (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

Dienille
This medicinal product contains lactose, glucose and soy lecithin. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption, or are allergic to peanut and soya should not take this medicine.

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 / 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). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir / ritonavir and dasabuvir therapy (See Section Contraindications and Section Interactions with Other Medicaments).

INTERACTIONS WITH OTHERS MEDICINAL PRODUCTS AND OTHERS FORMS OF INTERACTION

Interactions

Several medicines leading to an increased clearance of sexual steroids might elicit break-through bleeding or lead to the loss of contraceptive potential. These effects have been shown in the case of hydantoine, barbiturates, primidon, carbamazepin and rifampicin. This applies possibly to rifabutin, efavirenz, nevirapin, oxcarbazepin, topiramat, felbamat, ritonavir, nelvinafir, griseofulvin and herbal remedies containing St John's wort (Hypericum perforatum). These medicines increase liver enzyme induction.

Some antibiotics (such as ampicillin or tetracycline) have been suspected to reduce efficacy of combined oral contraceptives. The reason for this side effect is not known yet.

Women receiving short courses (maximum one week) of the products above should take additional, contraceptive precautions (e. g. barrier method) during the time of concurrent medication and for 7 days afterwards.

With rifampicin additional contraceptive precautions (e. g. barrier method) should be taken during the time of concurrent medication and continued for 4 weeks after treatment stops. If the end of a pack overruns while taking other medicines, the next pack should be started without the usual tablet-free interval.

The dose of contraceptive steroids should be increased during long-term treatment with medicines inducing the enzyme system of the liver. If it leads to undesirable side effects (e. g. irregular bleeding), or if it seems ineffective, other non-hormonal contraceptive method should be applied.

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

The progestin compound may interact with ACE inhibitors, angiotensin II receptor antagonists, potassium-sparing diuretics, aldosterone antagonists, and nonsteroidal anti-inflammatory drugs.

In *in vitro* studies dienogest did not inhibit function of cytochrome P450 enzyme system in the dose applied, thus no interaction with other medicinal products can be expected from this site.

Laboratory tests

The use of steroids may influence the results of certain laboratory tests. Among these are: biochemical parameters of the liver, thyroid, adrenal and renal function, plasma levels of proteins (such as corticosteroid binding globulins) and lipid/lipoprotein fractions, carbohydrate metabolism, and parameters of coagulation and fibrinolysis. However, these changes remain within the normal range.

Note: The prescribing information of concomitant medications should be consulted to identify potential 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 Section Contraindications and Section Warnings and Precautions). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Dienille can be restarted 2 weeks following completion of treatment with this combination drug regimen.

PREGNANCY AND LACTATION

Dienille is not indicated during pregnancy.

If pregnancy occurs during medication with oral contraceptives, the preparation should be withdrawn immediately. Based on extensive epidemiological studies descendants of women taking combined oral contraceptives before their pregnancy are not threatened by higher risk for congenital malformations, nor exert combined oral contraceptives teratogenic effects on the offspring when taken in the early phase of pregnancy before pregnancy is realized. Such studies have not been carried out with Dienille.

Since there are only limited data about the use of Dienille during pregnancy, its negative effect on pregnancy or on the fetus and on the newborn cannot be established, no epidemiological data are available about this.

Animal studies have revealed reproduction toxicity during pregnancy and lactation (see section **Preclinical safety data**). Effects on humans are unknown. Based on the available studies taking combined oral contraceptives during pregnancy does not hint at teratogenic effects.

The use of combined oral contraceptives during lactation may lead to a reduction in the volume of milk produced and to a change in its composition. Minute amounts of the active substances and /or excipients are excreted with the milk, possibly affecting the newborn. Mothers who are breast-feeding are advised not to take Dienille.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on ability to drive and use machines have been observed.

UNDESIRABLE EFFECTS

There is an increased risk of venous and arterial thromboembolism (e.g. venous thrombosis, pulmonary embolism, stroke, heart attack) for women taking combined oral contraceptives. Certain factors such as smoking, hypertension, disorders of blood clotting and lipid metabolism, severe obesity, varicose veins, advanced phlebitis and thrombosis may increase the risk of venous and arterial thromboembolism. For the most severe side effects in women taking combined oral contraceptives see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

In the next table the undesirable effects of dienogest 2 mg / ethinylestradiol 0.03 mg tablets are listed in order of decreasing frequency. These are the frequencies of side effects observed during clinical tests with dienogest 2 mg / ethinylestradiol 0.03 mg tablets (a total of 3590 women participated in these studies); the appearance of these side effects can be linked to the use of Dienille. Since all the side effects were rarer than 1/10, none of the undesirable effects occurred "very common".

The following classification was used to specify the frequency of side effects:
Very common (≥ 1/10)
Common (≥1/100 and < 1/10)
Uncommon (≥ 1/1,000 and < 1/100)
Rare (≥ 1/10,000 and < 1/1.000)
Very rare (< 1/10,000), not known (cannot be estimated from the available data).

The following undesirable effects were reported during studies conducted with dienogest 2 mg / ethinylestradiol 0.03 mg Dienille:

Organ system	Frequency of undesirable effects		
	Common	Uncommon	Rare
Nervous system disorders	Headache	Migraine, Cramp in the legs	
Psychiatric disorders		Depressive mood, nervousness	Anorexia, decreased libido, aggressive reactions, indifference
Eye disorders		Ophthalmologic complaints	Disturbed visus, conjunctivitis, intolerability of contact lenses
Ear and labyrinth disorders			Hard of hearing
Cardiac disorders		High or low blood pressure	Tachycardia, cardiac troubles
Vascular disorders		Disorders of the veins	Thrombophlebitis, thrombosis / pulmonary embolism, haematoma, cerebrovascular disorders
Blood and lymphatic system disorders			Anemia
Respiratory, thoracic and mediastinal disorders			Sinusitis, asthma, upper airway infections
Gastrointestinal disorders	Abdominal pains	Nausea, vomiting	Diarrhea
Skin and subcutaneous tissue disorders		Acne/acne like dermatitis, exanthema, eczema, skin disturbances, chloasma, loss of hair	Erythema multiforme, itching
Endocrine disorders			Hypertrichosis, virilismus
Renal and urinary disorders		Urinary tract infections	
Reproductive system and breast disorders	Tenderness or pain in the breasts	Irregular bleedings, absence of the break-through bleeding, dysmenorrhoea, enlarged breasts, development of ovarian cysts, dyspareunia, vaginitis/ vulvovaginitis, changes in vaginal secrete	Hypomenorrhoea , mastitis, fibrocystic breast disorders, secretion of the breasts, leiomyoma, endometritis, salpingitis
Infections and infestations		Vaginal candidiasis or other fungal infections	
General disorders and administration site conditions		Hot flushes, fatigue / weakness, being indisposed, back pains, changes in the body weight, , increased appetite, oedema	Allergic reactions, flu-like symptoms

In women taking combined oral contraceptives the following undesirable effects have been reported:

- venous or arterial thromboembolism;
- hypertension;
- liver tumors;
- development or worsening of disorders upon application of combined oral contraceptives, such as Crohn's disease, ulcerative colitis, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham-chorea, haemolytic uraemic syndrome, cholestatic jaundice;
- chloasma.

The risk of breast cancer is slightly increased in women taking combined oral contraceptives. However, since the risk of development of breast cancer below the age of 40 is small, the risk of breast cancer is small compared to the total risk. For further information see sections **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

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

For further information see section **CONTRAINDICATIONS** and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

OVERDOSE

The acute oral toxicity of dienogest and ethinylestradiol is small. When a considerable amount of Dienille has been taken by a small child, the possibility of the development of toxic symptoms is small. Overdose may cause nausea, vomiting and, in young girls, withdrawal bleeding. There is no need for special treatment. If necessary, symptomatic treatment should be applied.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: progestogens and estrogens, fixed combination, ATC-code: G03AA.

Dienille is a combined oral contraceptive with anti-androgenic effect; its estrogen component is ethinylestradiol and its gestogenic component is dienogest.

The contraceptive property of Dienille is based on several factors. The primary mechanism of action is inhibition of ovulation and alterations to the cervical mucus.

Based on a large-scale surveillance study the unadjusted Pearl- index is 0.14 whereas the adjusted value is 0.09

The anti-androgenic effect of the combination of ethinylestradiol and dienogest is based among others on the reduction of serum androgen levels. In a multicenter study including 1040 female patients between 16 and 40 years, with mild to moderate acne papulopustulosa, dienogest 2 mg / ethinylestradiol 0.03 mg film- coated tablets was found to be no inferior to a reference triphasic COC containing ethinylestradiol and norgestimate concerning improvement of total lesions counts and of inflammatory lesions counts after 6 cycles of treatment.

Dienogest is a nortestosterone derivate. *In vitro* it binds to progesterone receptors with 10-30 times lower affinity compared to other synthetic gestogens. *In vivo* dienogest does not have any significant androgenic, mineralocorticoid or glucocorticoid effect.

Dienogest inhibits ovulation on its own in a daily dose of 1 mg.

Contraceptives with higher-dose of ethinylestradiol (e. g. 50 µg) offer substantial protection against the risk of developing certain other cancers (e.g. ovarian and endometrial cancer). It is not known whether lower-dose combined oral contraceptives have this advantage too.

Pharmacokinetic properties

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of Dienille maximum drug serum levels of about 67 pg/ml are reached at 1.5 – 4 hours. After absorption and the "first-pass-effect" ethinylestradiol is metabolized to a great extent, thus average oral bioavailability is about 44%.

Distribution
Ethinylestradiol is highly, but non-specifically bound to serum albumin (approximately 98%) and raises serum levels of steroid hormone binding globulin (SHBG). Ethinylestradiol has an apparent volume of distribution of about 2.8-8.6 l/kg.

Metabolism
Ethinylestradiol is conjugated both in the mucosa of the small intestine and in the liver. Ethinylestradiol is metabolized via aromatic hydroxylation, however a whole range of hydroxilated and methylated derivates is generated, which are present as free or glucuronide or sulfate metabolites. A metabolic clearance rate of about 2.3-7 ml/min/kg was determined.

Elimination
Ethinylestradiol serum levels decrease in two phases characterized by 1 hour and 10-20 hours half lives. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6 with a half-life of about 1 day.

Steady-state-status
Steady-state is reached at the second half of the treatment period when serum level is twice as much as the one after a single dose.

Dienogest

Absorption
Orally administered dienogest is rapidly and almost completely absorbed. Following ingestion of Dienille maximum drug serum levels of cca. 51 pg/ml are reached at 2.5 hours. In combination with ethinylestradiol its average bioavailability is about 96%.

Distribution
Dienogest binds to serum albumin, but it does not bind to SHBG or to corticosteroid-binding globulin (CBG). 10% of the drug levels are present unbound, while 90% is non-specifically bound to albumin. Dienogest has an apparent volume of distribution of about 37-45 l.

Metabolism
Dienogest is metabolized mainly via hydroxylation; however conjugation also plays an important role to create endocrinologically inactive metabolites. Those metabolites are eliminated from the plasma fast, thus besides the unchanged dienogest, no significant amount of its metabolites can be detected in the human plasma. After a single dose it has a total clearance (Cl/F) of 3.6 l/hour.

Elimination
Dienogest has a half-life of 8.5-10.8 hours. Only negligible amounts of dienogest are excreted via the kidneys in unchanged form. After 0.1 mg/kg dose, proportion of the renal and faecal excretion was 3:1. After oral application 86% of the dose is eliminated within 6 days; a big proportion of this is excreted in the first 24 hours, mainly with the urine.

Steady-state status
Pharmacokinetics of dienogest is not influenced by serum level of SHBG proteins. When applied daily, serum level of dienogest is increased to one and a half, and steady-state status is reached after 4 days.

Preclinical safety data

In animal studies effect of ethinylestradiol and dienogest is limited to pharmacological properties of the active ingredients.

Reproduction toxicology tests with dienogest have shown typical gestogenic effects: increase in abnormality of pre- and post-implantation, elongation of the gestational period, increase in the newborn mortality of pupils. If high dose dienogest is given to animals in the late phase of pregnancy and lactation, impaired fertility of the descendants could be observed.

Ethinylestradiol is the estrogen component in most of the combined oral contraceptive products. In high dose it was embriotoxic and it had detrimental effect on the differentiation of the urogenital organs.

There are no preclinical toxicity data obtained via conventional studies saying that repeated application of the product might be a special risk factor for genotoxicity and carcinogenity, besides the facts usually related to the use of combined oral contraceptives, mentioned above.
It should be retained though that sex hormones may favour the growth of the specific hormon-dependent tissues and tumours.

SHELF-LIFE

2 years.

STORAGE

Store below 30°C. Keep out of reach of children. Jauhi daripada kanak-kanak.

PRESENTATION

PVC/PVDC/Aluminum blister.
Pack sizes: 21 and 3 x 21 film-coated tablets. Not all pack sizes may be marketed.

MANUFACTURER

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PRODUCT REGISTRATION HOLDER

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