Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dianette 2mg/35 microgram coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.0 mg cyproterone acetate and 0.035 mg ethinylestradiol.

Excipients with known effect
Each tablet contains 31 mg lactose monohydrate and 19 mg sucrose.
Please see section 4.4 for further information.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet (tablet).
Beige, sugar-coated, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.
For the treatment of acne, Dianette should only be used after topical therapy or systemic antibiotic treatments have failed.
Since Dianette is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3).

4.2 Posology and method of administration

Posology

How to take Dianette

Dianette is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection. Combined oral contraceptives when taken correctly have a failure rate of approximately 1 % per year.

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

How to start Dianette

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

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2 - 5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

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

The woman should start with Dianette preferably on the day after the last hormone-containing tablet of her previous COC, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her previous COC.

If a vaginal ring or transdermal patch has been used, the woman should, preferably, start using Dianette on the day of removal of the last ring or patch of a cycle pack, but at the latest when the next application would have been due.

- *Changing from a progestogen-only-method (progestogen-only pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)*

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

- *Following first-trimester abortion*

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

- *Following delivery or second-trimester abortion*

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

For breastfeeding women see *section 4.6, Pregnancy and lactation*.

Management of missed tablets

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

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

1. Tablet-taking must never be discontinued for longer than 7 days
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian axis.

Accordingly the following advice can be given in daily practice:

- Week 1

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

- Week 2

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

- Week 3

The risk of reduced reliability is imminent because of the forthcoming tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first two options and to use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the current pack is finished, i.e. no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on the tablet-taking days.
2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

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

Advice in case of gastro-intestinal disturbances

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

Duration of use

Time to relieve of symptoms is at least three months. The need to continue treatment should be evaluated periodically by the treating physician.

The length of use depends on the severity of the clinical picture. Complete remission of acne is expected within a few months of commencing treatment, but in particularly severe cases treatment for longer may be necessary before the full benefit is seen.

It is recommended that treatment be withdrawn 3 to 4 cycles after the acne has satisfactorily resolved and that Dianette is not continued solely to provide oral contraception. Repeat courses of Dianette may be given if the androgen-dependent acne recurs. In this case, an early restart of Dianette should be considered. In case of a restart of Dianette (following a 4 week or greater pill free interval), the increased risk of VTE should be considered (see section 4.4 Special warnings and precautions for use).

Special populations

Elderly
Not applicable. Dianette is not indicated after menopause.

Hepatic impairment
Dianette is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See also section 'Contraindications'.

Renal impairment
Dianette has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

Method of administration
Oral use

4.3 Contraindications

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, Dianette should be stopped immediately.

- Concomitant use with another hormonal contraceptive (see section 4.1).
- Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism).

- Presence or history of arterial thrombosis (e.g. myocardial infarction) or prodromal conditions (e.g. transient ischaemic attack and angina pectoris).
- Presence or history of cerebrovascular accident
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see under section 4.4) such as:

    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia

- Hereditary or acquired predisposition for venous or arterial thrombosis, such as antithrombin III deficiency, protein C deficiency, protein S deficiency, Activated Protein C (APC) resistance, hyperhomocysteinaemia, and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- History of migraine with focal neurological symptoms.
- Severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumors (benign or malignant).
- Meningioma or history of meningioma.
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Lactation.
- Porphyria.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Dianette is not for use in men.

Dianette is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir or medicinal products containing glecaprevir/pibrentasvir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Dianette is composed of the progestogen cyproterone acetate and the oestrogen ethinylestradiol and is administered for 21 days of a monthly cycle. It has a similar composition to that of a combined oral contraceptive (COC).

The clinical and epidemiological experience with estrogen/progestogen combinations like Dianette is predominantly based on combined oral contraceptives (COC). Therefore the following warnings related to COC use apply also for Dianette.

Warnings

Duration of Use

Time to relief of symptoms is at least three months. The need to continue treatment should be evaluated periodically by the treating physician (see section 4.2).

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

Circulatory Disorders

The use of Dianette carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman starts Dianette or when restarting or switching after a pill-free interval of at least a month. Venous thromboembolism can be fatal in 1-2% of cases.

Epidemiological studies have shown that the incidence of VTE is 1.5 to 2 times higher in users of Dianette than in users of levonorgestrel-containing combined oral contraceptives (COCs) and may be similar to the risk for desogestrel / gestodene / drospirenone-containing COCs.

The user group of Dianette is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovarian syndrome.

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

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in hormonal contraceptive users.

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

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. Dianette should not be prescribed in case of a negative risk benefit assessment. (see section 4.3).

The risk of venous thromboembolic events increases with:

- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use Dianette);
- a positive family history (i.e. venous thromboembolism ever 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 hormonal contraceptive use;
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered if the use of Dianette has not been discontinued in advance.
- obesity (body mass index over 30 kg/m^2).

The risk of arterial thromboembolic complications or of a cerebrovascular accident increases with:

- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use Dianette);
- dyslipoproteinemia;
- obesity (body mass index over 30 kg/m^2);
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;
- a positive family history (arterial thrombosis ever 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 hormonal contraceptive use.

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

The increased risk of thromboembolism in the puerperium must be considered (for information on 'Pregnancy and lactation' see section 4.6).

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

Women using Dianette should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, Dianette use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

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

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 COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.
In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.
Malignancies may be life-threatening or may have a fatal outcome.

Meningioma
The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate, especially at high doses of 25 mg and above and for prolonged time (see section 5.1). If a patient is diagnosed with meningioma, any cyproterone containing treatment, including Dianette must be stopped, as a precautionary measure.

Other conditions
Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
Although small increases in blood pressure have been reported in many women taking COCs or Dianette, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

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

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

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

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence to alter the therapeutic regimen in diabetics using low dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis have been associated with COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

If in women suffering from hirsutism, symptoms have recently developed or increased substantially, the causes (androgen-producing tumor, adrenal enzyme defect) must be clarified by differential diagnosis.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption 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 or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see sections 4.3 and 4.5).

Depressed mood and depression
Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide.
Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Medical examination/consultation
A complete medical history and physical examination should be taken prior to the initiation or reinstitution of Dianette, guided by the contraindications and warnings (see sections 4.3 and 4.4), and should be repeated periodically. Pregnancy must be ruled out. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of Dianette. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

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

Reduced efficacy
The contraceptive effect of Dianette may be reduced in the event of e.g. missed tablets (see section 4.2**)**, gastro-intestinal disturbances (see section 4.2) during tablet taking or concomitant medication (see section 4.5).

Reduced cycle control
With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.
If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

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

4.5 Interaction with other medicinal products and other forms of interactions

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

Effects of other medicaments on Dianette
Interactions may occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure. Women on treatment with any of these drugs should temporarily use a barrier method in addition to Dianette or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.
If the period during which the barrier method is used runs beyond the end of the tablets in the Dianette pack, the next pack should be started without the usual tablet-free interval.

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

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Substances with variable effects on the clearance of Dianette, e.g.:
When co-administered with Dianette, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Pharmacodynamic interactions
Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, or glecaprevir/pibrentasvir may increase the risk of ALT elevations (see sections 4.3 and 4.4).

Therefore, Dianette-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Dianette can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Substances decreasing the clearance of CHC (enzyme inhibitors)
The clinical relevance of potential interactions with enzyme inhibitors remains unknown.
Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the estrogen or the progestin or both.
Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

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

Clinical data suggest that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Other forms of interactions
Laboratory tests
The use of preparations like Dianette 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

The administration of Dianette is contraindicated during pregnancy. If pregnancy occurs during medication with Dianette, the preparation must be withdrawn immediately (see *section 5.3 Preclinical safety data*).

Although low dose exposure to cyproterone acetate during pregnancy has not been associated with teratogenic effects or malformations, clinical data on fetal outcomes following exposure to cyproterone acetate is limited.

Animal studies have revealed that feminization of male fetuses may occur if cyproterone acetate is administered during the phase of embryogenesis at which differentiation of the external genitalia occurs. The possibility must be considered that administration of Dianette to women after the 45^{th} day of pregnancy could cause feminization of male fetuses. It follows from this that pregnancy is an absolute contra-indication for treatment with Dianette, and must be excluded before such treatment is begun (*see section 5.3 Preclinical safety data*).

The administration of Dianette is also contraindicated during lactation. Cyproterone acetate is transferred into the milk of lactating women. About 0.2 % of the maternal dose will reach the newborn via milk corresponding to a dose of about 1 mcg/kg. 0.02 % of the daily maternal dose of ethinylestradiol could be transferred to the newborn via milk during established lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
No effects on ability to drive and use machines have been observed in users of Dianette.

4.8 Undesirable effects

4.8.1 Summary of safety profile

The most commonly reported adverse reactions with Dianette are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in ≥ 1 % of users.
There is an increased risk of thromboembolism for all women who use Dianette (see section 4.4).

4.8.2 Tabulated list of adverse reactions

The most serious undesirable effects associated with the use of COCs are listed in s*ection 4.4, Special warnings and precautions for use.*

Other side effects that have been reported in users of Dianette are:

System Organ Class (MedDRA)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1000)	Not known (cannot be estimated from available data)
Vascular Disorders			Thromboembolism	Increase in blood pressure
Eye disorders			Contact lens intolerance	
Gastrointestinal disorders	Nausea, Abdominal pain	Vomiting, Diarrhea		
Immune system disorders			Hypersensitivity	
Investigations	Weight increased		Weight decreased	
Metabolism and nutrition disorders		Fluid retention		
Nervous system disorders	Headache	Migraine		
Psychiatric disorders	Depressed mood, Mood altered	Libido decreased	Libido increased	
Reproductive system and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge, Breast discharge	
Skin and subcutaneous tissue disorders		Rash, Uticaria	Erythema nodosum, Erythema multiforme	

*The most appropriate MedDRA term (version 12.0) to describe a certain adverse reaction is listed.
Synonyms or related conditions are not listed, but should be taken into account as well.

4.8.3 Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.
The following serious adverse events have been reported in women using CHCs, which are discussed in section 4.4 Special warnings and precautions for use:
- Venous thromboembolic disorders;
- Arterial thromboembolic disorders;
- Hypertension;
- Liver tumors;
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;
- Chloasma;
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.
The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections 4.3 and 4.4.

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

There have been no reports of serious deleterious effect from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding, withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche, if they accidentally take the medicinal product. There are no antidotes and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, antiandrogens and oestrogens.

ATC Code: G03HB01

The pilosebaceous unit – consisting of the sebaceous gland and the hair follicle – is an androgen-sensitive skin component. Acne and seborrhea are clinical conditions resulting from aberrations of this target organ which may be caused by increased sensitivity or higher plasma levels of androgen. Both substances contained in Dianette influence beneficially the hyperandrogenic state: Cyproterone acetate is a competitive antagonist on the androgen receptor, has inhibitory effects on the androgen-synthesis in target cells and produces a decrease of the androgen blood concentration through an antigonadotropic effect. This antigonadotropic effect is amplified by ethinylestradiol which up-regulates as well the synthesis of Sexual-Hormone-Binding-Globulin (SHBG) in plasma. It thereby reduces free, biologically available androgen in the circulation.

Treatment with Dianette leads – usually after 3 to 4 months of therapy – to the healing of existing acne efflorescences. The excessive greasiness of the hair and skin generally disappears earlier. The loss of hair which frequently accompanies seborrhea likewise diminishes. The contraceptive effect of Dianette is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

Meningioma

Based on results from a French epidemiological cohort study, a cumulative dose dependent association between cyproterone acetate and meningioma has been observed. This study was based on data from the French Health Insurance (CNAM) and included a population of 253,777 women using 50 - 100 mg cyproterone tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥3 g) and women who were slightly exposed to cyproterone acetate (cumulative dose <3 g). A cumulative dose-response relationship was demonstrated.

Cumulative dose of cyproterone acetate	Incidence rate (in patient-years)	HR_{adj} (95% CI) [a]
Slightly exposed (<3 g)	4.5/100,000	Ref.
Exposed to ≥3 g	23.8/100,000	6.6 [4.0-11.1]
12 to 36 g	26/100,000	6.4 [3.6-11.5]
36 to 60g	54.4/100,000	11.3 [5.8-22.2]
more than 60 g	129.1/100,000	21.7 [10.8-43.5]

[a] Adjusted based on age as a time-dependent variable and oestrogen at inclusion

A cumulative dose of 12g for example can correspond with one year of treatment with 50 mg/day for 20 days each month.

5.2 Pharmacokinetic properties

Cyproterone Acetate

Absorption
Orally administered cyproterone acetate is rapidly and completely absorbed. Peak serum concentrations of 15 ng/ml are reached at about 1.6 hours after single ingestion.
Bioavailability is about 88 %.

Distribution
Cyproterone acetate is almost exclusively bound to serum albumin. Only 3.5 – 4.0 % of the total serum drug concentrations are present as free steroid. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of cyproterone acetate. The apparent volume of distribution of cyproterone acetate is about 986 ± 437 l.

Biotransformation
Cyproterone acetate is almost completely metabolized. The main metabolite in plasma was identified as 15β-OH-CPA which is formed via the cytochrome P450 enzyme CYP3A4. The clearance rate from serum is about 3.6 ml/min/kg.

Elimination
Cyproterone acetate serum levels decrease in two phases which are characterized by half-lives of about 0.8 h and about 2.3 – 3.3 days. Cyproterone acetate is partly excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1 : 2. The half-life of metabolite excretion is about 1.8 days.

Steady-state conditions
Cyproterone acetate pharmacokinetics are not influenced by SHBG levels. Following daily ingestion drug serum levels increase about 2.5-fold reaching steady-state conditions during the second half of a treatment cycle.

Ethinylestradiol

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8 and CYP2J2.

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 71 pg/ml are reached at 1.6 hours. During absorption and first-liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45 % with a large interindividual variation of about 20 – 65 %.

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

Biotransformation
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The clearance rate was reported to be about 2.3 – 7 ml/min/kg.

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

Steady-state conditions
Steady-state conditions are reached during the second half of a treatment cycle when serum drug levels are higher by 60 % as compared to single dose.

5.3 Preclinical safety data

Ethinylestradiol

The toxicity profile of ethinylestradiol is well known. There are no preclinical data of relevance to the prescriber that provide additional safety information to those already included in other sections of the product information.

Cyproterone acetate

Systemic toxicity

Preclinical safety data reveal no specific risk for humans based on conventional studies of repeated dose toxicity.

Embryotoxicity/teratogenicity

Investigations into embryotoxicity using the combination of the two active ingredients showed no effects indicative of a teratogenic effect following treatment during organogenesis before development of the external genital organs. Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs led to signs of feminization in male fetuses following higher doses. Observation of male newborn children who had been exposed in utero to cyproterone acetate did not show any signs of feminization. However, pregnancy is a contraindication for the use of Dianette.

Genotoxicity and carcinogenicity

Recognized first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, further tests showed that cyproterone acetate was capable of producing adducts with DNA (and an increase in DNA repair activity) in

liver cells from rats and monkeys and also in freshly isolated human hepatocytes, the DNA-adduct level in dog liver cells was extremely low.

This DNA-adduct formation occurred at systemic exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. In vivo consequences of cyproterone acetate treatment were the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats, and an increase of mutation frequency in transgenic rats carrying a bacterial gene as target for mutations.

Clinical experience and well conducted epidemiological trials to date would not support an increased incidence of hepatic tumors in man. Nor did investigations into the tumorigenicity of cyproterone acetate in rodents reveal any indication of a specific tumorigenic potential.

However, it must be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumors.

On the whole, the available findings do not raise any objection to the use of Dianette in humans if used in accordance with the directions for the given indication and at the recommended dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose monohydrate
Maize starch
Povidone 25 000
Magnesium stearate
Talc

Tablet Coating
Sucrose
Povidone 700 000
Polyethylene glycol 6000
Calcium carbonate
Talc
Glycerol 85%
Titanium dioxide (E 171)
Ferric oxide pigment yellow (E 172)
Montanglycol wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Dianette tablets are contained in blister packs consisting of the following standard pharmaceutical packaging material:

Deep drawn strips made of polyvinyl chloride film with counter-sealing foil made of aluminium with heat sealable coating.

Presentation:
Calendar-pack containing 21 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1410/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 18 November 2008

10 DATE OF REVISION OF THE TEXT

December 2021