Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dianette 2mg/35micrograms coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:
Lactose monohydrate 31.115mg
Sucrose 19.371mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet (tablet).

Product imported from the UK:
Beige, sugar-coated, biconvex tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For use in the management of severe acne vulgaris, especially those forms which are accompanied by seborrhoea or by inflammation or formation of nodes (acne papulopustulosa, acne nodulocystica) in women.

Oral contraception for the woman suffering from the above.

Although Dianette also acts as an oral contraceptive, it should not be used in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent acne described.

4.2 Posology and method of administration

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.

- Switching 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 active tablet (the last tablet containing the active substances) of her COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her COC. If a vaginal ring or transdermal patch has been used, the woman should, preferably, start using Dianette on the day of removal, but at the latest when the next application would have been due.

- Switching from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)
  The woman may switch any day from the minipill (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 need not take 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.

If the woman forgets to take an active Dianette tablet then it must be taken within 12 hours of the usual time for taking it. If a missed tablet is not taken within 12 hours then it should be taken when remembered and the remaining tablets taken as usual with extra non-hormonal contraceptive measures (except rhythm or temperature method) used for the next 7 days. If these seven days extend beyond the end of the pack then the next pack of tablets should be commenced at once with no tablet-free interval. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be excluded before resuming with the next pack.

Advice in case of gastro-intestinal disturbances
In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets, as given in s*ection 4.2, Posology and method of administration* is applicable.

Tablet-taking from the current pack should be continued. Additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used during the gastro-intestinal upset and for 7 days following the upset. If these 7 days overrun the end of a pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack. In cases of persisting or recurrent gastrointestinal disturbances additional contraceptive measures should be taken and the physician should be informed.

Length of use

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.

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.

- Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism).
- Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g. transient ischaemic attack, angina pectoris).
- Known predisposition for venous or arterial thrombosis, such as antithrombin III deficiency, protein C deficiency, protein S deficiency, Activated Protein C (APC) resistance (e.g. Factor V Leiden), hyperhomocysteinaemia, and antiphospholipid antibodies.
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication *(see section 4.4, Special warnings and precautions for use).*
- Pancreatitis or a history of thereof if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Lactation.
- Hypersensitivity to the active substances or to any of the excipients.
- Porphyria.
- Uncontrolled hypertension.

4.4 Special warnings and precautions for use

Warnings
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 it. 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.

Dianette contains lactose monohydrate and sucrose. Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicine.

Conditions which need supervision
If any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous COC use, the woman should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Dianette, in particular:

- Risk factors for thrombo-embolic disorders (see above)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Cholelithiasis, jaundice and/or pruritus related to cholestasis
- Herpes gestationis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- Endogenous depression
- Asthma
- Otosclerosis related hearing loss.

Circulatory Disorders
The use of any COC 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 ever uses a COC. This increased risk is less than the risk of VTE associated with pregnancy which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases

Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low oestrogen content (less than 50 µg of ethinylestradiol) ranges from about 20 to 40 cases per 100,000 women years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 women years for non-users.

There is some epidemiological evidence that the incidence of VTE is higher in users of Dianette when compared to users of COCs with low oestrogen content (< 50µg). The user group of Dianette as a treatment for severe acne is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovarian syndrome.

The risk of venous embolism increases with:
- Increasing age;
- 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;
- Obesity (body mass index over 30 kg/m^2;
- Prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization
- The increased risk of venous thromboembolism in the puerperium must be considered *(see section 4.6, Pregnancy and lactation);*
- And possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.

The use of COCs in general has been associated with an increased risk of arterial thrombotic/thromboembolic events such as acute myocardial infarction (AMI) or cerebrovascular accident i.e. stroke, a risk that is strongly influenced by the presence of other risk factors (e.g. smoking, high blood pressure, and age) (see also below). These events occur rarely. It has not been studied how Dianette modifies the risk of AMI.

The risk of arterial thrombotic/thromboembolic events (cerebrovascular accident, myocardial infarction, peripheral artery disease) increases with:

- Increasing age;
- Smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age). Therefore, the COC user should be recommended to stop smoking. In women over 35 years of age, an alternative contraceptive method should be discussed;
- A positive family history (i.e. venous or arterial 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 COC use;

- Obesity (body mass index over 30 kg/m^2);
- Dyslipoproteinaemia;
- Hypertension;
- Migraine;
- Valvular heart disease;
- Atrial fibrillation.

Tumors
The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behavior including use of barrier contraceptives.

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 the 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.

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, 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: hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis.

In women with hereditary angioedema, exogenous oestrogens 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 which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

The use of COCs may have an effect on peripheral insulin resistance and glucose tolerance. Therefore, diabetic women should be carefully monitored during the first months of COC use.

Crohn's disease and 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.

Herbal preparations containing St. John's Wort (Hypericum perforatum) should not be used while taking Dianette due to the risk of decreased plasma concentrations and reduced clinical effects of Dianette *(see section 4.5, Interaction with other medicinal products and other forms of interaction).*

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 section 4.3, Containdications and section 4.4, Special warnings and precautions for use),* and should be repeated periodically. 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 local 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, Posology and method of administration),* gastro-intestinal disturbances *(see section 4.2, Posology and method of administration),* or concomitant medication *(see section 4.5, Interaction with other medicinal products and other forms of interaction).*

Reduced cycle control
With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use.
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 and 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 s*ection 4.2, Posology and method of administration* 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 interaction

Interactions
Interactions between estrogen-progestogen combinations like Dianette and other drugs may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism: Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort).

Also HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism.

Interference with Enterohepatic Circulation: Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Women on treatment with any of these drugs should temporarily use a barrier method in addition to Dianette or choose another method of contraception. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after 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.

Estrogen/progestogen combinations like Dianette may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

Note: The prescribing information of concomitant medications should be consulted to identify potential 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 functions, 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 is to 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. Although the results of these tests are not necessarily relevant to man, 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

Not applicable

4.8 Undesirable effects

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 but for which the association has been neither confirmed nor refuted are:

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and <1/100)	Rare (< 1/1000)
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, urticaria	erythema nodosum, erythema multiforme

*The most appropriate MedDRA term (version 7.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

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

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. There are no antidotes and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

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.

Metabolism
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

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.

Metabolism
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

Lactose monohydrate
Maize starch
Povidone
Talc
Magnesium stearate
Sucrose
Polyethylene glycol 6000
Calcium carbonate
Glycerol
Titanium dioxide (E171)
Yellow ferric oxide pigment (E172)
Montan glycol wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Outer carton contains aluminium foil and PVC blister calender pack containing 21 tablets. Each carton contains one blister calender pack.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Mc Dowell Pharmaceuticals
4 Altona Road
Lisburn
N. Ireland
BT27 5QB

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1473/32/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th of October 2010

10 DATE OF REVISION OF THE TEXT