



Dianette (cyproterone acetate 2mg/ethinylestradiol 35 mcg): Strengthening of warnings, new contraindications, and updated indication

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and IMB, Bayer Limited would like to inform you of the outcome of a review of the known risk of thromboembolic events and benefits of medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms. The evaluation has been performed by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) following concerns about the risk of venous and arterial thromboembolism (VTE and ATE) associated with those products.

Summary

The PRAC recommendations include:

- Dianette is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age
- For the treatment of acne, Dianette should only be used after topical therapy or systemic antibiotic treatment have failed
- Since Dianette is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives
- To increase awareness of the risk and risk factors of thromboembolism in relation to the use of Dianette (e.g. increasing age, smoking, immobility), the warnings and precautions regarding this risk have been strengthened.

Further information on the safety concern and the recommendations

The PRAC assessed all available data on the risk of thromboembolism as well as the benefits of Dianette and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 mcg including the published literature.

The PRAC concludes that the risk of VTE and ATE is increased in users of Dianette. 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.

There is evidence from epidemiological studies 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 (COC) and may be similar to the risk for desogestrel / gestodene /drospirinone containing COCs.

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It is important that healthcare professionals and women using Dianette are aware of the risk of VTE in order to prevent complications and fatal outcomes and to facilitate a timely and correct diagnosis of VTE. Therefore educational material for prescribers and patients will be distributed.

For more details see relevant attached sections of SmPC (Annex).

Call for reporting

Bayer Limited encourages you to report any adverse reaction, including possible thromboembolic or cardiac events, which may be associated with the use of Dianette according to national procedures.

Adverse reactions can also be reported to the address given below.

Please report all adverse drug reactions (ADRs) concerning Dianette to:

Tel : + 353 (0)1 2999 313

Fax : + 353 (0)1 2061 456

Email: adr-ireland@bayerhealthcare.com

Suspected adverse reactions can also be reported to the IMB using a Yellow Card obtained either from the IMB, or electronically via the website at www.imb.ie. Adverse reactions can also be reported to the IMB by calling (01) 676 4971.

Company contact point

For further information, please contact

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Fax : + 353 (0)1 2061 456

Email: info.ireland@bayerhealthcare.com

Yours sincerely,

A handwritten signature in black ink, appearing to read "Tristan P. Cooper".

Dr. Tristan P. Cooper MB BCh BAO FFPM
Medical Director

Annex

PRAC recommendations for the summary of product characteristics (SmPC)

Note: The amendments to the summary of product characteristics may need to be subsequently updated by the national competent authorities, in liaison with the reference Member State if appropriate.

Section 4.1 Therapeutic indications

[The currently approved indications should be deleted and replaced by the following:]

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, <product name> should only be used after topical therapy or systemic antibiotic treatments have failed.

Since < product name> is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3).

Section 4.2 Posology and method of administration

[The wording below should be inserted in this section]

[...]

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.

[...]

Section 4.3 Contraindications

[The following contraindications related should be included in this section]

[...]

- Concomitant use with another hormonal contraceptive (see section 4.1)
- Venous thrombosis present or in history (deep venous thrombosis, pulmonary embolism)
- Arterial thrombosis present or in history (e.g. myocardial infarction) or prodromal conditions (e.g. angina pectoris and transient ischaemic attack).
- Presence or history of cerebrovascular accident
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see 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 activated protein C (APC) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)

[...]

Section 4.4 Special warnings and precautions

[The wording below should be inserted in this section]

<Product name> 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).

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 (see section 4.2).

[...]

If any of the conditions/risk factors mentioned below is present, the benefits of the use of <product name> should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using <product name>. 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 the use of <product name> should be discontinued.

[...]

Circulatory disorders

- The use of <product name> 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 <product name> 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 <product name> than in users of levonorgestrel-containing combined oral contraceptives (COCs) and may be similar to the risk for desogestrel / gestodene / drospirinone-containing COCs.
- The user group of <product name> 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
- 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 <product name>);
 - 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 <product name> has not been discontinued in advance.
- obesity (body mass index over 30 kg/m²).
- 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 <product name>);
 - dyslipoproteinemia;
 - obesity (body mass index over 30 kg/m²);
 - 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 <product name> (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of <product name>.

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

Section 4.8 - Undesirable effects

[The wording below should be inserted in this section]

[...]

- There is an increased risk of thromboembolism for all women who use <product name> (see section 4.4).

[The following to be included in the table of adverse reactions]

- Vascular Disorders Rare ($\geq 1/10,000$ to $< 1/1000$): Thromboembolism

[The following to be included below the table of adverse reactions]

The following serious adverse events have been reported in women using <product name>, which are discussed in section 4.4 Special warning and precautions for use:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders

[...]