PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

DIANE®-35 0,035 mg/2 mg coated tablet
Ethinylestradiol/Cyproterone acetate
Contains sugar (sucrose and lactose)

Read all of this leaflet carefully before you start taking DIANE-35:

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- DIANE-35 has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1 What DIANE-35 is and what it is used for
2 What you need to know before you take DIANE-35
3 How to take DIANE-35
4 Possible side effects
5 How to store DIANE-35
6 Contents of the pack and other information

1. What DIANE-35 is and what it is used for

DIANE-35 is used to treat skin conditions such as acne, very oily skin and excessive hair growth in women of reproductive age.
These include patients with polycystic ovary syndrome, who require treatment for these symptoms.
DIANE-35 is a hormonal contraceptive (the "Pill"). Due to its contraceptive properties it should only be prescribed for you if your doctor considers that treatment with a hormonal contraceptive is appropriate as well.
You should only take DIANE-35, if your doctor considers that other anti-acne treatments, including topical treatments and antibiotics, are inappropriate.

Each of the 21 beige coated tablet contains the hormones ethinylestradiol and cyproterone acetate.

2. What you need to know before you take DIANE-35

General notes
Before you can begin taking DIANE-35, your doctor will ask you some questions about your personal health history and that of your close relatives. The doctor will also measure your blood pressure and, depending upon your personal situation, may also carry out some other tests.

In this leaflet, several situations are described where you should stop using DIANE-35, or where the reliability of DIANE-35 may be decreased. In such situations you should either not have sex or you should take extra non-hormonal contraceptive precautions, e.g. use a condom or another barrier method.

Do not use rhythm or temperature methods. These methods can be unreliable because DIANE-35 alters the monthly changes of body temperature and cervical mucus.

DIANE-35 does not protect against HIV infection (AIDS) or any other sexually transmitted disease.

Do not take DIANE-35

Do not use DIANE-35 if you have any of the conditions listed below. If any of these apply to you, tell your doctor before starting to use DIANE-35

- if you are allergic (hypersensitive) to ethinylestradiol, cyproterone acetate or any of the other ingredients in DIANE-35. This may cause, for example, itching, rash or swelling
- if you have (or have ever had) a blood clot in your leg (thrombosis), lung (pulmonary embolism) or other part of your body
- if you have (or have ever had) a heart attack or stroke
- if you have (or have ever had) a disease that may be an indicator of a heart attack in the future (e.g angina pectoris which cases severe pain in the chest) or 'mini-stroke' (transient ischaemic attack)
- if you have (or have ever had) a migraine, with visual disturbances, speech disability or weakness or numbness in part of your body.
- if you have a condition that may increase the risk of a blood clot in your arteries. This applies to the following conditions:
    - diabetes affecting your blood vessels.
    - very high blood pressure.
    - a very high level of fat in your blood (cholesterol or triglycerides)
- if you have problems with blood clotting (e.g. protein C deficiency)
- if you have (or have ever had) liver disease (symptoms of which may be yellowing of the skin or itching over the whole body) and your liver is still not working normally
- if you are taking any antiviral medicines which contain ombitasvir, paritaprevir, or dasabuvir, or any combinations of these. These antiviral medicines are used to treat chronic (long-term) hepatitis C (an infectious disease that affects the liver, caused by the hepatitis C virus).
- if you have (or have ever had) a cancer that may grow under the influence of sex hormones (e.g. of the breast or the genital organs)
- if you have (or have ever had) a benign or malignant tumour of the liver
- if you have any unexplained bleeding from the vagina
- if you are using another hormonal contraceptive
- if you are pregnant or think you might be pregnant
- if you are breast-feeding

If any of these conditions appear for the first time while using DIANE-35, stop taking it at once and consult your doctor. In the meantime, use non-hormonal contraceptive measures. See also 'General notes'.

DIANE-35 is not for use in men.

Warnings and precautions

In some situations you need to take special care while taking combined hormonal preparations like DIANE-35, and your doctor may need to examine you regularly. Consult your doctor before starting to use DIANE-35 if any of the following conditions apply to you or if any of them develop or worsen while you are taking DIANE-35:

- if you smoke
- if you have diabetes
- if you are overweight
- if you have high blood pressure
- if you have a heart valve disorder or a certain heart rhythm disorder
- if you have an inflammation of your veins (superficial phlebitis)
- if you have varicose veins
- if anyone in your immediate family has ever had a blood clot (thrombosis in the leg, lung 'pulmonary embolism', or elsewhere), a heart attack or a stroke at a young age
- if you suffer from migraine
- if you have epilepsy (see 'Other medicines and DIANE-35')
- if you or someone in your immediate family has ever had high blood levels of cholesterol or triglycerides (fatty substances)
- if a close relative has or has ever had breast cancer
- if you have a disease of the liver or gall bladder
- if you have Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease)
- if you have a polycystic ovary syndrome (a disorder of your ovaries that may cause infertility, sometimes combined with androgenetic symptoms and an increased risk of thrombosis)
- if you have systemic lupus erythematosus (or SLE, a disease of the immune system)
- if you have haemolytic uremic syndrome (or 'HUS', a disorder of blood coagulation causing failure of the kidneys)
- if you have sickle cell disease
- if you have a condition that occurred for the first time or worsened during pregnancy or previous use of sex hormones (e.g. hearing loss, a metabolic disease called porphyria, a skin disease called herpes gestationis, or a neurological disease called Sydenham's chorea)
- if you have (or have ever had) golden brown pigment patches so-called 'pregnancy patches' especially on the face (chloasma). If this is the case, avoid direct exposure to sunlight or ultraviolet light
- if you have hereditary angioedema. Consult your doctor immediately if you experience symptoms of angioedema such as swollen face, tongue or throat, and/or difficulty swallowing, or hives, together with difficulty breathing. Products containing estrogens may induce or worsen symptoms of angioedema

If any of the above conditions appear for the first time, recur or worsen while using DIANE-35, contact your doctor.

Stop taking tablets and contact your doctor immediately if you notice possible signs of a blood clot. The symptoms are described in section 'DIANE-35 and blood clots'.

If you suffer from hirsutism and it has only recently appeared or has lately intensified to a considerable extent the doctor must be expressly informed of this because of the necessity to clarify the cause.

DIANE-35 also works as an oral contraceptive. You and your doctor must consider all the factors that are important for the safe use of oral hormonal contraceptives.

The experience with estrogen/progestogen combinations like DIANE-35 is predominantly based on combined oral contraceptives ("the Pill"). Therefore, the following warnings related to the use of "the Pill" apply also for DIANE-35.

DIANE-35 and depression

Some women using hormonal contraceptives including DIANE-35 have reported depression or depressed mood. Depression can be serious and may sometimes lead to suicidal thoughts. If you experience mood changes and depressive symptoms contact your doctor for further medical advice as soon as possible.

DIANE-35 and blood clots

Blood clots (thrombosis)
When taking DIANE-35, the risk of a blood clot (also called a thrombosis) may be slightly increased. The likelihood of a blood clot is only slightly increased when taking DIANE-35 compared with women not taking DIANE-35 or any other birth control pill. A full recovery does not always happen and in 1-2 % of cases may be fatal.

Blood clots in a vein
A blood clot in a vein (also called a 'venous thrombosis') can block the vein. This may occur in the veins of the legs, lungs (pulmonary embolism), or any other organ.
When using a combined pill, a woman's risk of developing such clots is increased compared to a woman not taking a combined pill. The risk of developing a blood clot in a vein is highest in the first year of pill use. The risk is not as high as that of getting a blood clot during pregnancy.
The risk of blood clots in a vein among users of a combined pill rises further:

- with increasing age;
- if you smoke.
  If you take a hormonal contraceptive such as DIANE-35, you are strongly advised to stop smoking, especially if you are over 35 years of age;
- if a close relative has had a blood clot in the leg, lung or other organ at a an early age;
- if you are overweight;
- if you need to undergo surgery, or if you have been bedridden over a prolonged period due to an injury or illness, or you have your leg in a cast.

If this applies to you, it is important to tell your doctor you are using DIANE-35, as treatment may have to be discontinued in some cases. Your doctor may tell you to stop using DIANE-35 for several weeks before surgery or if you have only limited mobility. Your doctor will also tell you when you can start using DIANE-35 again, once you are back on your feet.

Blood clots in an artery
A blood clot in an artery can cause serious problems. For example, a blood clot in one of the arteries in the heart can cause a heart attack, or in one of the arteries in the brain, a stroke.
The use of a combined pill has been associated with an increased risk of clots in the arteries.
This risk increases further:

- with increasing age;
- if you smoke.
  If you take a hormonal contraceptive such as DIANE-35, you are strongly advised to stop smoking, especially if you are over 35 years of age;
- if you are overweight;
- if you have high blood pressure;
- if a close relative has had a heart attack or stroke at a young age;
- if you have high fat levels (cholesterol or triglycerides);

- if you get migraines;
- if you have a heart problem (heart valve defect, heart rhythm disorders).

Symptoms of blood clots

Stop taking the tablets at once and consult your doctor immediately if you notice possible signs of a blood clot, such as:

- sudden cough of unclear cause;
- severe chest pain, which may radiate into the left arm;
- shortness of breath and/or rapid or irregular heartbeats;
- unusual, severe, or prolonged headaches or worsening of migraine;
- partial or complete loss of vision, or double vision;
- slurred speech or problems in speaking;
- sudden changes in the sense of hearing, smell, or taste;
- dizziness or fainting fits;
- weakness or numbness in any part of the body;
- severe abdominal pain;
- severe pain or swelling in a leg.

A full recovery does not always happen after a blood clot. Rarely, serious permanent disabilities may occur or the blood clot may be fatal.

Immediately after childbirth, women are at increased risk of blood clots, which is why you should ask your doctor how soon after giving birth you can start taking DIANE-35.

Your doctor will check whether you have a higher risk of getting a thrombosis due to a combination of risk factors or perhaps one very strong risk factor. In the case of a combination of factors, the risk may be higher than simply adding two individual risks. If the risk is too high, your doctor will not prescribe the Pill. (see also 'Do not take DIANE-35').

DIANE-35 and cancer

Breast cancer has been observed slightly more often in women using combined pills, but it is not known whether this is caused by the treatment itself. For example, it may be that more tumours are detected in women on combined pills because they are examined by their doctor more often. The risk of breast tumours becomes gradually less after stopping the combined hormonal contraceptive. It is important to regularly check your breasts and you should contact your doctor if you feel any lump.

In rare cases, benign liver tumours, and in even fewer cases malignant liver tumours have been reported in contraceptive pill users. In isolated cases, these tumours have led to life-threatening internal bleeding. Contact your doctor if you have unusually severe abdominal pain.

The most important risk factor for cervical cancer is persistent Human Papilloma Virus (HPV) infection. Some studies suggest that long-term use of the pill increases a woman's risk of developing cervical cancer. However, it is not clear to what extent sexual behaviour or other factors such as HPV infection increases this risk.

The above-mentioned tumours may be life-threatening or may have a fatal outcome.

Bleeding between periods

For the first few months, you can have irregular vaginal bleeding (spotting or breakthrough bleeding) between your periods requiring the use of sanitary protection. Continue to take your tablets as normal. Irregular vaginal bleeding usually stops once your body has adjusted to DIANE-35 (usually after about 3 tablet-taking cycles). If it continues, becomes heavy or starts again, tell your doctor.

What to do if no bleeding occurs

If you have taken all the tablets correctly for one cycle, have not had any vomiting or severe diarrhoea and you have not taken any other medicines, it is unlikely that you are pregnant. Continue to take DIANE-35 as usual.

If you have taken the tablets incorrectly, or, if you have taken the tablets correctly but the expected bleeding does not happen twice in a row, you may be pregnant. Contact your doctor immediately. Do not start the next pack until you are sure that you are not pregnant. In the meantime, use non-hormonal contraceptive measures. See also ‘General notes’.

Other medicines and DIANE-35

Always tell your health care provider if you are taking any other medicine or herbal products. This includes all complementary or traditional medicines.
They can tell you if you need to take additional contraceptive precautions (for example condoms) and if so, for how long, or, whether the use of another medicine you need must be changed.

Some medicines
- can have an influence on the blood levels of DIANE-35 and
    - can make it less effective in preventing pregnancy, or
    - can cause unexpected bleeding.
- can be effected by DIANE-35.

These include:
- medicines used for the treatment of:
    - epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate)
    - tuberculosis (e.g. rifampicin)
    - HIV and Hepatitis C Virus infections (so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors)
    - fungal infections (griseofulvin, azole antifungals, e.g. itraconazole, voriconazole, fluconazole)
    - bacterial infections (macrolide antibiotics, e.g. clarithromycin, erythromycin)
    - certain heart diseases, high blood pressure (calcium channel blockers, e.g. verapamil, diltiazem)
    - arthritis, arthrosis (etoricoxib)
- the herbal remedy St. John's wort
- grapefruit juice

DIANE-35 may influence the effect of other medicines, e.g.
- lamotrigine
- cyclosporine

- melatonin
- midazolam
- theophylline
- tizianidine

Laboratory tests

If you need a blood test or other laboratory tests tell your doctor or the laboratory staff that you are taking DIANE-35 because oral contraceptives can affect the results of some tests.

Pregnancy and breastfeeding

Do not take DIANE-35 if you are pregnant, or, if you think you may be pregnant.
If you become pregnant while taking DIANE-35, stop taking it immediately and contact your doctor.
If you want to become pregnant, you can stop taking DIANE-35 at any time (see also 'If you stop taking DIANE-35').
DIANE-35 must not be used during breast-feeding.

Driving and using machines

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

DIANE-35 contains sucrose and lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take DIANE-35

DIANE-35 is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection. The dose regimen of DIANE-35 is similar to the regimen of most of the usual contraceptive Pills. Thus, the same administration rules must be considered. The irregular intake of DIANE-35 can lead to intermenstrual bleedings and could lessen the therapeutic and contraceptive reliability.

The DIANE-35 pack contains 28 tablets. Follow the direction of the arrows until all 28 tablets have been taken. Take your tablet at about the same time each day, with some liquid if necessary. Usually a period will start while you are taking tablets from the silver section (i.e. on day 2-3 after the last hormone-containing beige DIANE-35 tablet). Do not leave a gap between packs, i.e. start taking your next pack on the day after you have finished the current one, even if your period continues. This means that you will always start new packs on the same day of the week, and also that you have your withdrawal bleed on about the same days every month.

When can you start with the first pack?

<u>If you have not used a contraceptive with hormones during the previous month</u>

Wait for your next period to occur. Start with DIANE-35 on the first day of the cycle (= 1st day of bleeding) from the silver section of the pack and select the right tablet for that day of the week (e.g. "MO" for Monday). During the first cycle, you must use extra protective measures (for example, a condom) for the first 14 days of DIANE-35 use.

Changing from another combined hormonal contraceptive pill, or combined contraceptive vaginal ring or patch.

You can start taking DIANE-35 the day after you take the last tablet from your present Pill pack (this means no tablet-free break). If your present Pill pack also contains hormone-free tablets you can start DIANE-35 on the day after taking the last tablet containing hormones (if you are not sure which this is, ask your doctor or pharmacist). In case you have used a vaginal ring or transdermal patch, start using DIANE-35 on the day of removal of the last ring or patch of a cycle pack. If you follow these instructions, it is not necessary to use an additional contraceptive method.

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

You may switch from the progestogen-only pill any day (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due) but in all of these cases you must use extra protective measures (for example, a condom) during the first 14 days of DIANE-35 use.

After a miscarriage.

Follow the advice of your doctor, but remember to use extra protective measures (for example, a condom) during the first cycle for the first 14 days of tablet-taking.

After having a baby.

If you have just had a baby, your doctor may tell you to wait until after your first normal period before you start taking DIANE-35. Sometimes it is possible to start sooner. Your doctor will advise you, but remember to use extra protective measures (for example, a condom) during the first cycle for the first 14 days of tablet-taking. If, after having a baby, you have had sex before starting DIANE-35, be sure that you are not pregnant or wait until the next menstrual period.
If you want to start DIANE-35 after having a baby and are breastfeeding, discuss this first with your doctor.

Ask your doctor what to do if you are not sure when to start.

If you take more DIANE-35 than you should

There are no reports of serious harmful effects of taking too many DIANE-35 tablets. If you take several hormone-containing tablets at once, you may feel sick or vomit or may bleed from the vagina. Even girls who have not yet started to menstruate but have accidentally taken this medicine may experience such bleeding.

If you have taken too many DIANE-35 tablets, or you discover that a child has taken some, ask your doctor or pharmacist for advice.

If you forget to take DIANE-35

Depending on the day of the cycle on which one tablet has been missed, you may need to take additional contraceptive precautions, for example a barrier method such as a condom. In case of doubt, contact your doctor.

- If you forgot to take any of the 7 hormone-free larger white tablets, you should proceed with your next tablet at the normal time and discard the forgotten hormone-free larger white tablet(s) to avoid any confusion. If you forgot the last tablet of your current pack it is important that you still take the first tablet from the next pack at the correct time.

The following advice refers to the beige tablets (those containing hormones):
- If you are **less than 12 hours** late when taking a beige tablet, the protection against pregnancy is not reduced. Take the tablet as soon as you remember and then continue taking the tablets again at the usual time.
- If you are **more than 12 hours** late in taking any beige tablets your protection against pregnancy may be reduced. The more beige tablets you have forgotten, the greater the risk that the protection from pregnancy is reduced. There is a particularly high risk of becoming pregnant if you miss beige tablets at the beginning, right after the larger white tablets, or at the end (the last of the 21 beige tablets). If a beige tablet has been missed for more than 12 hours, use extra contraceptive precautions (barrier method) for the next 7 days.
- **More than one tablet forgotten in a pack**: Contact your doctor. Do not take more than 2 beige tablets on a given day, to make up for missed pills.

If you have forgotten beige tablets in a pack, and you do not have the expected bleeding that should start while taking tablets from the silver section of your pack, you may be pregnant. Contact your doctor before you start the next pack.

What to do if you vomit or have severe diarrhoea

If you vomit or have severe diarrhoea after taking any of the beige tablets, the active ingredients in that tablet may not have been completely absorbed. If you vomit within 3 to 4 hours after taking your tablet, this is like missing a tablet. Therefore, follow the advice under 'If you forget to take DIANE-35'. If you have severe diarrhoea, please contact your doctor. Vomiting or diarrhoea while taking the 7 hormone-free larger white tablets at the end of your blister does not have an influence on the contraceptive reliability.

For how long DIANE-35 should be used?

The length of use depends on the severity of your symptoms and their response to treatment. In general, treatment should be carried out over several months. Acne and seborrhoea usually respond sooner than hirsutism. It is recommended to take DIANE-35 for at least another 3 to 4 cycles after the signs have subsided. Should there be a recurrence, weeks or months after discontinuation of tablet-taking, treatment with DIANE-35 may be resumed. In case of a restart of DIANE-35 (following a 4 week or greater pill free interval), the increased risk of VTE should be considered (see also section 'DIANE-35 and blood clots').

If you stop taking DIANE-35

You can stop taking DIANE-35 at any time. If you do not want to become pregnant, ask your doctor for advice about other reliable methods of birth control. If you want to become pregnant, stop taking DIANE-

35 and wait for a menstrual period before starting to try to become pregnant. You will be able to calculate the expected delivery date more easily.

4. Possible side effects

DIANE-35 can have side effects.

Not all side effects reported for DIANE-35 are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking DIANE-35, please consult your health care provider for advice.

Frequent side effects:
- nausea
- abdominal pain
- weight gain
- headache
- depressed or altered mood
- breast pain including breast tenderness

Less frequent side effects:
- vomiting
- diarrhoea
- fluid retention
- migraine
- reduced interest in sex or increased interest in sex
- breast enlargement
- vaginal discharge
- breast discharge
- rash
- urticaria (hives)
- erythema nodosum or multiforme (skin disorders)
- venous blood clot
- contact lens intolerance
- allergic reactions (hypersensitivity)
- weight loss

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of DIANE-35.

5. How to store DIANE-35

Keep this medicine out of the sight and reach of children.
Store at or below 30 °C.
Return all unused medicine to your pharmacist. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What DIANE-35 contains

21 beige coated tablets containing ethinylestradiol (0,035 mg), cyproterone acetate (2 mg).
7 larger white hormone-free coated tablets.

The other ingredients are calcium carbonate precipitated, ferric oxide pigment yellow, lactose monohydrate, macrogol 6000, magnesium stearate, maize starch, montanglycol wax, povidone 25, povidone 700 000, sucrose, talc, glycerol 85%, titanium dioxide.

What DIANE-35 looks like and contents of the pack

DIANE-35 is presented as a blister pack containing 21 coated tablets containing hormones, and 7 hormone-free coated tablets.

DIANE-35 tablets are contained in blister packs consisting of transparent films made of PVC/PE.EVOH.PE/PCTFE and metallic foils made of aluminium.

Holder of Certificate of Registration

Bayer (Pty) Ltd
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1609

This leaflet was last revised in

21 July 2022

Registration number

V/21.8.2/300