1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TRIPHASIL 50 µg/30 µg ; 75 µg /40 µg ; 125 µg /30 µg sugar-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRIPHASIL contains six (6) brown active sugar-coated tablets, five (5) white active sugar-coated tablets, ten (10) yellow active sugar-coated tablets and seven (7) red placebo sugar-coated tablets.

Each brown active sugar-coated tablet of TRIPHASIL contains 50 µg of levonorgestrel and 30 µg of ethinyl estradiol.

Preservatives:

Methyl paraben 0,001 % *m/m*

Propyl paraben 0,001 % *m/m*

Contains sugar: Lactose monohydrate 33,070 mg and sucrose 22,526 mg.

Each white active sugar-coated tablet of TRIPHASIL contains 75 µg of levonorgestrel and 40 µg of ethinyl estradiol.

Contains sugar: Lactose monohydrate 33,035 mg, sucrose 19,660 mg

Each yellow active sugar-coated tablet of TRIPHASIL contains 125 µg of levonorgestrel and 30 µg of ethinyl estradiol.

Preservatives:

Methyl paraben 0,001 % *m/m*

Propyl paraben 0,001 % *m/m*

Contains sugar: Lactose monohydrate 32,995 mg and sucrose 22,481 mg.

Each red placebo sugar-coated tablet of TRIPHASIL contains sugar: Lactose monohydrate 38,006 mg, sucrose 24,599 mg.

Preservative:

Sodium benzoate 0,002 % *m/m*

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sugar-coated tablets

Brown active sugar-coated tablet: Pale brown, lustrous, round biconvex sugar-coated tablet.

White active sugar-coated tablet: White, lustrous, round biconvex sugar-coated tablet.

Yellow active sugar-coated tablet: Yellow, lustrous, round biconvex sugar-coated tablet.

Red placebo sugar-coated tablet: Red biconvex sugar-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TRIPHASIL is indicated for:

- Fertility control in women.
- Control of cases of dysfunctional uterine bleeding.
- Symptomatic treatment of primary dysmenorrhoea where contraception is also desired.

TRIPHASIL may benefit women on contraception with coincidental acne.

The decision to prescribe TRIPHASIL should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE) (see section 4.4).

4.2. Posology and method of administration

Posology

Adults

For contraception

To achieve maximum effectiveness, TRIPHASIL tablets must be taken exactly as directed and at intervals not exceeding 24 hours.

Patients should be instructed to take the tablets at the same time every day, preferably after the evening meal or at bedtime.

One tablet daily is taken 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 bleeding will usually begin on the 2nd or 3rd day after ingestion of the last tablet and it may not have ceased, before the next pack is started.

How to start TRIPHASIL

No preceding intake of hormonal contraceptives (within the last month)

First Cycle:

The patient is instructed to take the first TRIPHASIL tablet on the first day of the menstrual cycle (first day of bleeding).

Starting intake on day 2 to 5 is allowed, but during the first cycle the concurrent use of barrier contraceptive method during the first 7 days of tablet intake is advisable.

The first tablet should be selected from those in the red area of the pack marked with the appropriate day of the week. Thereafter, one tablet is taken daily, following the arrows marked

on the package until all the tablets have been taken.
Withdrawal bleeding should occur within 2 to 4 days after the patient has taken the last yellow tablet.

During the first cycle, where treatment with TRIPHASIL tablets is started after the first day of the menstrual cycle, contraceptive reliance should not be placed on TRIPHASIL tablets and a mechanical i.e. barrier, method of contraception should be supplemented for the first 14 consecutive days of administration. If the tablets are begun after Day 5 or postpartum, it must be considered that ovulation and conception may have occurred before the tablets were started.

New patients with a history of short menstrual cycles, (i.e. less than 25 days) should also use a supplementary, nonsteroidal method of contraception (e.g. mechanical) until they have taken a tablet daily for 14 consecutive days.

Subsequent Cycles:
A new pack should be started the day after completion of the previous pack by taking the tablet in the red area of the new pack indicated with the appropriate day of the week. There must be no interruption of treatment, i.e. the new pack is started immediately after completion of the previous pack and each new pack is started with the same tablet in the red area of the pack even if withdrawal bleeding has not occurred or is still in progress. This method should continue for as long as contraception is desired. Each cycle or pack will begin on the same day of the week.
The patient who is changing from another oral contraceptive product will begin TRIPHASIL tablets on the day she would usually start a new package of the other product. During the first TRIPHASIL tablet cycle, a mechanical, i.e. barrier, method of contraception should be used

until 14 consecutive daily tablets have been taken.

If:

- transient spotting or breakthrough bleeding occurs, the patient is instructed to continue the regimen since such bleeding is usually without significance.
- the bleeding is persistent or prolonged, the patient is advised to consult her doctor. In the non-lactating mother, use of TRIPHASIL tablets may be instituted immediately after delivery or at the first postpartum examination, whether or not menstruation has resumed.

MISSED TABLETS:

The patient should be instructed to take a missed tablet as soon as it is remembered.

If:

- two consecutive tablets are missed, they should both be taken as soon as remembered. The next tablet should be taken at the usual time.
- at any time the patient misses one or two tablets she should also use a supplementary, nonsteroidal method of contraception (e.g. mechanical) until she has taken a tablet daily for 14 consecutive days or until the package is finished if less than 14 tablets remain.
- the patient misses one or more inert tablets, she is still protected against pregnancy, provided she begins the active tablets on the proper day.
- three consecutive tablets are missed, all medication has to be discontinued and the remainder of the package discarded.

A new tablet cycle is started on the eighth day after the last tablet was taken and a supplementary nonsteroidal means of contraception (e.g. mechanical) should be used for the remaining days without tablets and until the patient has taken a tablet daily for 14 consecutive days.

If:

- withdrawal bleeding does not occur and TRIPHASIL tablets have been taken according to directions, it is unlikely that the patient has conceived. She should be instructed to begin a second course of TRIPHASIL tablets on the usual day.
- bleeding does not occur at the end of this second cycle, TRIPHASIL tablets should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been performed.
- the patient has not adhered to the prescribed regimen (missed one or more active tablets or started taking them on a day later than recommended), the probability of pregnancy should be considered at the time of the first missed period before TRIPHASIL is resumed.

Changing from another combined hormonal contraceptive (combined pill, vaginal ring, transdermal patch)

The woman should start with TRIPHASIL on the day after she took the last active tablet in her previous blister pack of contraceptive pills (or removed the transdermal patch or vaginal ring), or no later than on the day after the usual pill-free (or placebo, patch-free or ring-free) interval with her previous contraceptive.

Changing from a progestogen-only method (progestogen-only pills, injectable, implant)

The woman can change from progestogen-only pills on any day (changing from implant on the day of its removal; changing from injection when the next injection should have been given). In all these cases concurrent use of a barrier method during the first 7 days of tablet intake is advisable.

After abortion in 1st trimester

The woman may begin intake of tablets immediately. If she so does, it is not necessary to take

further contraceptive measures.

After delivery or abortion in 2nd trimester

The woman should be advised to start on day 21 to 28 after delivery or abortion in 2nd trimester, since there is an increased risk of thromboembolism during the post-partum period. She should be advised to use a barrier contraceptive method concurrently during the first 7 days of tablet intake if she starts later. If she has already had intercourse, pregnancy must be excluded before she starts tablet intake, or she must await her first menstrual bleeding.

FOR THE SYMPTOMATIC TREATMENT OF PRIMARY DYSMENORRHOEA AND CASES OF DYSFUNCTIONAL UTERINE BLEEDING - dosage as for contraception.

FOR THE TREATMENT OF ANDROGEN-DEPENDENT ACNE - dosage as for contraception.

Gastrointestinal upset

Vomiting or diarrhoea may reduce the efficacy of TRIPHASIL by preventing full absorption. If vomiting or diarrhoea occurs within 4 hours of taking TRIPHASIL tablet-taking from the current pack should be continued.

Additional non-hormonal methods of contraception (except the rhythm or temperature method) 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 starting the next pack. Other methods of contraception should be considered if the gastrointestinal disorder is likely to be prolonged.

Method of administration

For oral administration.

The tablets must be taken orally in the order directed on the blister package at about the same time every day, with some liquid if necessary.

4.3. Contraindications

TRIPHASIL is contraindicated in:

- Patients with hypersensitivity to ethinyl oestradiol or levonorgestrel or to any of the excipients in TRIPHASIL (see section 6.1).
- Patients with depression not well controlled with treatment.
- Patients with a history of depression with the use of hormonal contraceptives.
- Risk of venous thromboembolism (VTE).
- Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis (DVT) or pulmonary embolism (PE)).
- Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (a haemostatic disorder characterised by a poor anticoagulant response to activated protein C), (including Factor V Leiden), antithrombin – III – deficiency, protein C deficiency, protein S deficiency.
- Use of ritonavir.
- Major surgery with prolonged immobilisation.
- A high risk of venous thromboembolism due to the presence of multiple risk factors.
- Risk of arterial thromboembolism (ATE).
- Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris).

- Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA).
- Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- History of migraine with focal neurological symptoms.
- A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia.
- Presence or history of severe hepatic disease, e.g. active viral hepatitis and severe cirrhosis, as long as liver function values have not returned to normal.
- Patients with recurrent cholestatic jaundice.
- Undiagnosed vaginal bleeding.
- Medication should be discontinued immediately if migraine becomes focal or there is a loss of vision or if there is an onset of unexplained chest pain.
- Current or history of breast cancer.
- Benign or malignant liver tumours which developed during the use of oral contraceptives or oestrogen-containing medicines.
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Concomitant use with medicines containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.4 and 4.5).

- Ocular disorder of vascular origin.
- Dubin Johnson syndrome.
- Rotar syndrome.
- Porphyria.
- Pregnancy and lactation (see section 4.6).

Relative contraindications include a history of diabetes mellitus, epilepsy, asthma, hypertension, depression, or states in which fluid retention occur.

4.4. Special warnings and precautions for use

CIGARETTE SMOKING INCREASES THE RISK OF SERIOUS CARDIOVASCULAR SIDE EFFECTS FROM THE USE OF TRIPHASIL. THE RISK INCREASES WITH AGE AND WITH HEAVY SMOKING (15 OR MORE CIGARETTES PER DAY) AND IS MARKED IN WOMEN OVER 35 YEARS OF AGE. WOMEN WHO USE ORAL CONTRACEPTIVES SUCH AS TRIPHASIL SHOULD BE STRONGLY ADVISED NOT TO SMOKE.

If any of the conditions or risk factors mentioned below are present, the suitability of TRIPHASIL should be discussed with the woman. In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of TRIPHASIL should be discontinued.

Ocular Lesions

Discontinue TRIPHASIL and institute appropriate diagnostic and therapeutic measures if there is a gradual or sudden, partial or complete loss of vision, proptosis or diplopia, papilloedema, or any evidence of retinal vascular lesions or optic neuritis.

Carcinoma

Ovarian, endometrial, cervical and breast cancer have been reported in women using combined oral contraceptives such as TRIPHASIL. Data suggests that long-term continuous administration of either natural or synthetic oestrogen increases the frequency of carcinoma of the breast, cervix, vagina and liver. Under the influence of oestrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size. Close clinical surveillance is essential in all women taking TRIPHASIL.

In all cases of undiagnosed, persistent, or recurrent vaginal bleeding, appropriate diagnostic measures should be taken to eliminate the possibility of malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care.

Breast cancer

Epidemiological studies has shown that women using contraceptive pills such as TRIPHASIL have an increased risk of being diagnosed with breast cancer. This increased risk gradually declines for 10 years after cessation of contraceptive pills.

The most important risk factor for breast cancer in combined oral contraceptive (COC) users is the age at which women discontinue the COC; the older the age at stopping, the more breast cancers are diagnosed. The excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess. The possible increase in risk of breast cancer should be discussed with the user.

Cervical Cancer

The most important risk factor for cervical cancer is persistent HPV infection. Long-term use of

COCs may further contribute to this increased risk.

Tumours and cancer

A meta-analysis of 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed in women who are currently using COCs such as TRIPHASIL. 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, such as TRIPHASIL 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.

Benign liver tumours, and malignant liver tumours have been reported in users of COCs, such as TRIPHASIL. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Headache

The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of TRIPHASIL and evaluation of the cause.

Use during or immediately preceding pregnancy

Foetal abnormalities, including heart defects and limb defects, have been reported in offspring of women who have taken oral contraceptives in early pregnancy. Pregnancy should be ruled out before TRIPHASIL is begun and considered in women who have missed two consecutive menstrual periods. The possibility of pregnancy should be considered at the first missed menstrual period in a patient who has not adhered to the prescribed regimen. Further oral contraceptive use should be withheld until pregnancy has been ruled out.

TRIPHASIL have not been shown to have any deleterious effects on the foetus or to increase the incidence of miscarriage in women who discontinue their use PRIOR to conception. However, in women who discontinue TRIPHASIL with the intent of becoming pregnant, a non-hormonal method of contraception is recommended for a period of three months before attempting to conceive.

Female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that oestrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestins are effective for these uses. The administration of progestin-only or oestrogen-progestin combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

Use during lactation:

TRIPHASIL given in the postpartum period may interfere with lactation. There may be a decrease in the quantity of breast milk. Furthermore, the hormonal components of TRIPHASIL are secreted in the milk of mothers. The use of oestrogen containing oral contraceptives should be deferred until the infant has been weaned. Mothers taking TRIPHASIL should not breastfeed their infants (see section 4.6).

Bleeding irregularities

Breakthrough bleeding, spotting and amenorrhoea are frequent reasons for patients discontinuing TRIPHASIL. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent bleeding from the vagina, appropriate diagnostic measures are indicated to rule out pregnancy or malignancy.

If pathology has been excluded, time or a change to another formulation may solve the problem.

Changing to a regimen with a higher oestrogen content, while potentially useful in minimising menstrual irregularity, should be done only if necessary, since this may increase the risk of thromboembolic disease. Women with a history of oligomenorrhoea or secondary amenorrhoea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrhoeic after discontinuation of TRIPHASIL. Women with these pre-existing problemsshould be advised of this possibility and encouraged to use another method of contraception.

Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

Menstrual changes

- *Reduction of menstrual flow:* This is not abnormal and it is to be expected in some patients.
- *Missed menstruation:* Occasionally, withdrawal bleeding may not occur at all. If the tablets have been taken correctly, pregnancy is very unlikely. If withdrawal bleeding fails to occur at the end of a second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

Intermenstrual bleeding: 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. This may include curettage.

Ectopic pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

Circulatory/ thromboembolic disorders

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives such as TRIPHASIL is well established. The medical practitioner should be alert to the earliest manifestations of those disorders (e.g. thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, cerebral haemorrhage, cerebral thrombosis, coronary occlusion, retinal thrombosis, mesenteric thrombosis).

Should any of these occur or be suspected, TRIPHASIL should be discontinued immediately.

A four- to six-fold increased risk of thromboembolic complications following surgery has been reported in users of TRIPHASIL. If feasible, TRIPHASIL should be discontinued at least 4 weeks before surgery associated with an increased risk of thromboembolism or prolonged immobilisation.

Thrombosis has been reported to occur in COC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low oestrogen content (<50 microgram 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. The use of any combined oral contraceptive 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 combined oral contraceptive. 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 to 2 % of the cases. The overall absolute risk (incidence) of VTE for levonorgestrel containing combined oral contraceptives with 30 microgram ethinylestradiol,as in TRIPHASIL is approximately 20 cases per 100,000 women-years of use. Epidemiological studies have also associated the use of COCs with an increased risk for myocardial infarction, transient ischaemic attack and for stroke.
Thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, retinal veins and arteries, in contraceptive pill users. There is no consensus as to whether the occurrence of these events is associated with the use of hormonal contraceptives.

Table 1: Risk factors for VTE

Risk factor	Comment
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	In these situations, it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if TRIPHASIL has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age	Particularly above 35 years.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in the puerperium must be considered (see section 4.6).

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance (an increased tendency of the blood to clot), hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When weighing benefits/disadvantages the medical practitioner must take into consideration that adequate treatment of a given condition may lower the risk related to thrombosis and that the risk of developing thrombosis during pregnancy is higher compared to using contraceptive pills.

- *Symptoms of VTE (deep vein thrombosis and pulmonary embolism):*

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a TRIPHASIL.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg.
- pain or tenderness in the leg which may be felt only when standing or walking.
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing.
- sudden coughing which may be associated with haemoptysis.
- sharp chest pain.
- severe light headedness or dizziness.
- rapid or irregular heartbeat.

Some of these symptoms (e.g. shortness of breath, coughing) are non-specific and might be

misinterpreted as more common or less severe events (e.g. respiratory tract infections). Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE):

The use of COCs such as TRIPHASIL is associated with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE:

The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases in women with risk factors (see Table 2). TRIPHASIL is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative TRIPHASIL should not be prescribed (see section 4.3).

Table 2: Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use TRIPHASIL. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	

Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use
Migraine	An increase in frequency or severity of migraine during TRIPHASIL use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

- *Symptoms of ATE:*

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking TRIPHASIL.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body.
- sudden trouble walking, dizziness, loss of balance or coordination.
- sudden confusion, trouble speaking or understanding.
- sudden trouble seeing in one or both eyes.
- sudden, severe or prolonged headache with no known cause.
- loss of consciousness or fainting with or without seizure.
- 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.
- 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.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone.
- discomfort radiating to the back, jaw, throat, arm, stomach.
- feeling of being full, having indigestion or choking.
- sweating, nausea, vomiting or dizziness.
- extreme weakness, anxiety, or shortness of breath.
- rapid or irregular heartbeats.

Myocardial infarction and coronary artery disease

An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported. Studies found that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolaemia, obesity, diabetes, history of pre-eclampsia) the higher the risk of developing myocardial infarction. Oral contraceptives were found to be a clear additional risk factor.

Carbohydrate and lipid metabolic effects

A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives such as TRIPHASIL. For this reason, prediabetic and diabetic patients should be carefully observed while receiving TRIPHASIL. An increase intriglycerides and total phospholipids has been observed in patients receiving TRIPHASIL.

Diabetes (without vascular involvement)

Insulin-dependent diabetics without vascular disease can use TRIPHASIL. However it should be remembered that all diabetics are at an increased risk of arterial disease and this should be considered when prescribing TRIPHASIL. Diabetics with existing vascular disease are contraindicated from using TRIPHASIL (see section 4.3). Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs such as TRIPHASIL (containing < 0,05 mg ethinyloestradiol). However, diabetic women should be carefully observed while taking TRIPHASIL.

Known hyperlipidaemias

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs such as TRIPHASIL.

Women with hyperlipidaemias are at an increased risk of arterial disease (see Risk of arterial thromboembolism (ATE)).

Elevated blood pressure

An increase in blood pressure has been reported in patients receiving TRIPHASIL. In some women, hypertension may occur within a few months of beginning use. In the first year of use,

the prevalence of women with hypertension is low but the incidence increases with increasing exposure.

Age is also strongly correlated with the development of hypertension in oral contraceptive users.

Women who previously have had hypertension during pregnancy may be more likely to develop an elevation of blood pressure when given TRIPHASIL. If blood pressure rises markedly, the medicine should be discontinued. Hypertension that develops as a result of taking TRIPHASIL usually returns to normal after discontinuing TRIPHASIL.

If sustained hypertension develops during the use of TRIPHASIL, antihypertensive treatment should normally be instigated at a level of 140/90 mm Hg. . Decisions about the continued use of TRIPHASIL should be made and alternative contraception may be advised (see section 4.4).

Chloasma

Chloasma may 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.

Disturbances of liver function

Acute or chronic disturbances of liver function may necessitate the discontinuation of TRIPHASIL use until markers of liver function return to normal. Steroid hormones may be poorly metabolised in patients with impaired liver function and should be administered with caution to such patients.

Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of TRIPHASIL.

Gallbladder disease

Studies report an increased risk of surgically confirmed gallbladder disease in users of oestrogens and oral contraceptives.

Reduced efficacy

The effect of TRIPHASIL may be reduced in the case of missed tablets, vomiting or concomitant intake of other medicines (see section 4.2).

Other conditions

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 medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment. Women who get severely depressed during the use of contraceptive pills should stop taking he pills and be advised to use an alternative contraceptive method while trying to determine if the symptoms are due to the oral contraceptive preparation. Women who have previously suffered from depression should be closely monitored and stop the use of the oral contraceptive preparation if the symptoms of depression relapse.

Women with hypertriglyceridaemia or hereditary predisposition for this condition may have an increased risk of pancreatitis when taking contraceptive pills.

Hyperlipidaemic women should be closely monitored if they choose to use TRIPHASIL.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond

adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

It has been reported that the following conditions may arise or have been aggravated during the use of contraceptive pills: jaundice and/or itching in connection with cholestasis, formation of gallstones, porphyria, systemic lupus erythematosus, haemolytic uraemic syndrome, Sydenham's chorea, herpes gestationis, hearing loss due to otosclerosis.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and aquired angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until the liver function values return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs. Steroid hormones may be poorly metabolised in patients with impaired liver function.

TRIPHASIL may have an influence on peripherial insulin resistance and glucose tolerance Diabetics should be monitored during use of contraceptive pills.

Worsening of Crohn's disease and ulcerative colitis have been associated with the use of combined oral contraception such as TRIPHASIL.

Reduced cycle control

Irregular bleeding (spotting and break-through bleeding) may occur, during the first months in particular. It is therefore only relevant to evaluate the occurrence of irregular bleeding after a period of adaptation of approximately 3 cycles.

If the bleeding irregularities persist or occur after previous regular cycles non-hormonal causes should be considered and adequate, diagnostic precautions should be taken to exclude

malignancy or pregnancy. If non-hormonal causes are excluded, oral contraceptives containing a higher hormonal content may need to be considered.

Some women do not have a withdrawal bleed during the tablet-free interval. If the contraceptive pills have been taken according to the instructions, it is unlikely that the woman is pregnant. If, however, the contraceptive pills have not been taken according to the instructions prior to the first absent withdrawal bleed, or if two withdrawal bleeds have been missed, pregnancy must be excluded before continuing to take the contraceptive pills.

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicines 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). ALT elevations have also been observed with HCV anti-viral medicines containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

Depression

Mood changes and depression are side effects reported with the use of hormonal contraceptives including TRIPHASIL. There is some evidence that hormonal contraceptive use may be associated with severe depression and a higher risk of suicidal thoughts/behavior (e.g. talking about suicide, withdrawing from social contact, having mood swings, being pre-occupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with TRIPHASIL.

Women who get severely depressed during the use of contraceptive pills should stop taking the pills and be advised to use an alternative contraceptive method while trying to determine if the symptoms are due to TRIPHASIL. Women who have previously suffered from depression should be closely monitored and stop the use of TRIPHASIL if the symptoms of depression relapse.

Herbal preparations containing St John's wort (Hypericum perforatum) should not be used while taking TRIPHASIL due to the risk of decreased plasma concentrations and reduced clinical effects of TRIPHASIL (see section 4.5).

Medical examination / consultation

Prior to the initiation or reinstitution of TRIPHASIL a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (see section 4.3).

Laboratory tests and investigations should include but not be limited to Papanicolaou smears, blood glucose levels, liver- and kidney function tests, and monitoring of existing conditions. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and breast, abdominal and pelvic examination including cervical cytology.

Patient education should include recognition of VTE and ATE symptoms and associated risk factors, protection against contracting HIV and sexually transmitted diseases, informing a medical practitioner of TRIPHASIL use prior a major surgery and reporting of worsening of existing medical conditions or side effects.

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

Reasons for stopping TRIPHASIL immediately:

When stopping TRIPHASIL non-hormonal contraception should be used to ensure contraceptive protection is maintained.

- Occurrence for the first time, or exacerbation, of migrainous
- headaches or unusually frequent or unusually severe headaches
- Sudden disturbances of vision, of hearing or other perceptual disorders
- First signs of thrombosis or blood clots (e.g. unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason). Feeling of pain and tightness in the chest

Six weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin

- Onset of jaundice, hepatitis, itching of the whole body
- Significant rise in blood pressure
- Severe upper abdominal pain or liver enlargement

Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy (see Use during or immediately preceding pregnancy)

Lactose and sucrose warning

TRIPHASIL contains lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, or fructose intolerance the Lapp lactase deficiency, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not

take this medicine.

Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5. Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Concomitant use with medicines containing ombitasvir/paritaprevir/ritonavir, dasabuvir, with or without ribavirin, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, TRIPHASIL users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these medicines regimens. TRIPHASIL can be restarted 2 weeks following completion of treatment with these medicines.

Pharmacokinectic interactions

Interactions between COCs, such as TRIPHASIL and other medicines may impair the contraceptive efficacy and/or lead to breakthrough bleeding and/or contraceptive failure. Women on treatment with any of these medicines should temporarily use a barrier contraceptive method or another method of contraception in addition to the COC, such as TRIPHASIL. With liver enzyme inducing medicines, the barrier contraceptive method must be used during the whole time of the concomitant medicines therapy and for 28 days after its discontinuation.

If the medicine therapy runs beyond the end of the tablets in the TRIPHASIL pack, the next TRIPHASIL pack should be started without the usual tablet-free interval.

Hepatic metabolism: Interactions can occur with medicines that induce hepatic microsomal enzymes, resulting in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin).

The mechanism of this interaction seems to be based on the liver enzyme inducing properties of these active substance. Maximal enzyme induction is generally not seen until 2 to 3 weeks after start of treatment but may then persist for at least 4 weeks after discontinuation of treatment.

Herbal preparations containing St John's wort (Hypericum perforatum) should not be taken concomitantly with this medicine as this could potentially lead to a loss of contraceptive effect. Breakthrough bleeding and unintended pregnancies have been reported. This is due to induction of medicine metabolising enzymes by St John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort."

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

Enterohepatic circulation

Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic medicines (e.g. penicillins, tetracyclines) are given at the same time, which may reduce ethinylestradiol concentrations in serum.

The bioavailability of tricyclic antidepressants may increase when administered together with TRIPHASIL (increased risk of toxicity)

COCs , such as TRIPHASIL has been shown to induce metabolism of lamotrigine resulting in sub-therapeutic plasma concentrations of lamotrigine

Other forms of interactions COCs, such as TRIPHASIL

Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs, such as TRIPHASIL.

Medicines which induce hepatic enzymes (especially cytochrome P450 3A4) can increase the

metabolism of TRIPHASIL and hence may result in breakthrough bleeding and/or contraceptive failure (i.e. pregnancy). The following have been shown to have clinically important interactions with TRIPHASIL:

Anticonvulsants

- barbiturates (including phenobarbitone)
- primidone
- phenytoin
- carbamazepine
- oxcarbazepine
- topiramate
- felbamate

Antibiotics / antifungals

- griseofulvin
- rifampicin

Women on short term treatment with these antibiotics must temporarily use a barrier contraceptive method concomitantly with TRIPHASIL, i.e. during the period of other concomitant active substance intake and for 7 days after cessation of this active substance. Contraceptive failure has also been reported with antibiotics like ampicillin and tetracyclines. This mechanism of action has not been elucidated. Those on long-term antibiotic therapy need only take extra precautions for the first two weeks of antibiotic therapy. Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness.

Managing interactions with hepatic enzyme inducers:

Interactions can occur with medicine 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 short term treatment with any of these medicines should temporarily use a barrier contraception method in addition to the COC or choose another method of contraception. The barrier contraceptive method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation.

If the period during which the barrier contraceptive method is used runs beyond 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.

For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be used.

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

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and medicines containing St. John's wort.

Substances with variable effects on the clearance of COCs, e.g.:

When co-administered with TRIPHASIL, 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.

Effects on other medicines:

TRIPHASIL may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

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

The bioavailability of tricyclic antidepressants may increase when administered together with TRIPHASIL (increased risk of toxicity).

Laboratory tests

The use of TRIPHASIL 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 usually remain within the normal laboratory reference values. Laboratory staff should therefore be informed about .TRIPHASIL use when laboratory tests are requested.

4.6. Fertility, pregnancy and lactation

The use of TRIPHASIL is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

If pregnancy occurs during treatment with TRIPHASIL, further intake must be stopped immediately.

Foetal abnormalities, including heart defects have been reported in the infants of women who have taken oral contraceptives early in pregnancy. (see section 4.4).The increased risk of VTE during the postpartum period should be considered when re-starting TRIPHASIL

The increased risk of VTE during the postpartum period should be considered when restarting TRIPHASIL.

Breastfeeding

Mothers taking TRIPHASIL should not breastfeed their infants (see section 4.3). Lactation may be influenced by TRIPHASIL by reducing the amount and changing the composition of breast milk, thus, the use of TRIPHASIL should not be recommended until the nursing mother has weaned the child completely. Contraceptive steroids and/or their metabolites are excreted with the milk. Mothers who are breastfeeding their infants are advised to use another method of contraception.

Fertility

There is no fertility data.

4.7. Effects on ability to drive and use machines

TRIPHASIL has none or negligible influence on the ability to drive and use machines.
Since adverse reactions such as dizziness have been reported in patients receiving TRIPHASIL patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that TRIPHASIL does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

The most frequent adverse reactions include: nausea, vomiting, headache, breast tenderness, weight increased, depression, altered mood, acne, cholelithiasis, chloasma and metrorrhagia.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)

Infections and infestations		Vaginal candidiasis, acute attack of vaginitis	
Neoplasm benign, malignant and unspecified (including cysts and polyps)		Breast cancer, hepatic adenoma, hepatic neoplasm malignant, cervical cancer	
Immune system disorders		Hypersensitivity, exacerbation of hereditary angioedema	
Metabolism and nutrition disorders		Hyperlipidaemia , fluid retention, changes in appetite	Hypercholersterolaemia, hypertriglyceridaemia
Psychiatric disorders	Depression , altered mood	Decreased libido, increased libido, loss of libido, nervousness,	Irritability, severe depression with a higher risk of suicidal thoughts/behavior and suicide
Nervous system disorders	Headache	Cerebrovascular accident, Sydenham's chorea, migraine, dizziness	Cerebrovascular disorder, aggravated epilepsy
Eye disorders		Visual disturbance, corneal disorder due to contact lens (intolerance to contact lenses), changes in corneal curvature (steepening), intolerance to contact lenses, cataracts	
Ear and labyrinth disorders		Otosclerosis	

Cardiac disorders		Myocardial infarction	
Vascular disorders		Hypertension, venous embolism	Embolism arterial,pulmonary embolism, phlebitis
Gastrointestinal disorders	Nausea, abdominal; pain	Ulcerative colitis, Crohn's disease, pancreatitis, bloating, vomiting	
Hepato-biliary disorders	Cholelithiasis		Cholestatic jaundice
Skin and subcutaneous tissue disorders	Acne, chloasma	Erythema multiforme, erythema nodosum, rash, loss of scalp hair, haemorrhagic eruption, uticaria	Hypertrichosis, seborrhoea,
Musculoskeletal and connective tissue disorders		Systemic lupus erythematosus,	Sensation of heaviness
Renal and urinary disorders		Haemolytic uremic syndrome, porphyria	Cystitis like syndrome
Pregnancy, puerperium and perinatal conditions			
Reproductive system and breast disorders	Breast tenderness, breast pain,metrorrhagia	Breast enlargement, breast discharge,vaginal discharge	Amenorrhoea,anovulatory cycle,breast disorder,oligomenorrhoea, cervical erosion or cervical secretion.
General disorders and administrative site conditions	Fluid retention/ oedema		
Investigations	Changes in weight (increase or decrease)	Increase in blood pressure, changes in serum lipid levels, including hypertriglyceridemia.	

c) Description of selected adverse reactions

The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Hypertension
- Liver tumours
- Crohn's disease, ulcerative colitis, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice.

The frequency of diagnosis of breast cancer is 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.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and aquired angioedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ 011 239 6200

4.9 Overdose

Symptoms

Overdose may cause nausea, vomiting and withdrawal bleeding.

Treatment

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 18.8 Ovulation controlling agents.

Pharmacotherapeutic group: Progestogens and estrogens, sequential preparations; levonorgestrel and ethinylestradiol.

ATC: G03AB03

Mechanism of action

TRIPHASIL has a three-phase dosage regimen which conforms with physiological pattern of the normal cycle.

The oestrogen/progestogen ratio varies during the cycle, the dosage ratios being administered as a 6 - day / 5 - day / 10 - day regimen in order to ensure good cycle control and to bring about distinct cyclical changes at the level of the vaginal epithelium and the endometrium for less likelihood of implantation.

Ovulation is inhibited by suppression of gonadotropin release, particularly the mid-cycle peaks, and the viscosity of the cervical mucous increased, impairing sperm penetration and an endometrium less receptive for implantation is formed.

Sebaceous glands are androgen dependent, and excessive androgen activity of the skin may exacerbate acne. Oestrogens may exhibit androgen antagonism and suppress sebaceous gland activity.

5.2. Pharmacokinetic properties

Absorption

Ethinyl oestradiol and levonorgestrel are well absorbed from the gastrointestinal tract.

Distribution

Levonorgestrel is extensively plasma protein bound both to sex hormone binding globulin (SHBG) and albumin.

Ethinyl oestradiol is bound in plasma only to albumin and enhances the binding capacity of SHBG.

Following oral administration, peak plasma levels of each medicines occur within 1 to 4 hours.

Metabolism

The elimination half-life for levonorgestrel is approximately 24 hours. The medicine is primarily metabolised by reduction of the A ring followed by glucuronidation. Levonorgesterel does not undergo first-pass metabolism and is therefore completely bioavailable.

Ethinyl oestradiol is subject to considerable first-pass metabolism with a mean bioavailability of 40 to 45 %.

The elimination half-life for ethinyl oestradiol is approximately 25 hours. It is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present both free and as conjugates with glucuronide and sulphate.

Elimination

About 60 % of levonorgestrel is excreted in the urine and 40 % is eliminated in the faeces. The elimination half-life of levonorgestrel is approximately 24 hours.

TRIPHASIL is excreted in bile and subject to enterohepatic recirculation. About 40 % of the medicine is excreted in the urine and 60 % is eliminated in the faeces.

The elimination half-life of ethinyloestradiol is approximately 25 hours. The primary route of biotransformation is via 2-hydroxylation and subsequent formation of the corresponding 2- and 3-methyl ethers.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Brown active tablets: Calcium carbonate light, iron oxide red (C.I. 77492), iron oxide yellow (C.I. 77491), lactose monohydrate, magnesium stearate, methyl paraben, polyethylene glycol, povidone, propyl paraben, sucrose, starch maize, talc purified, titanium dioxide (C.I. No: 77891), Waradur XE.

White active tablets: Calcium carbonate light, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, sucrose, starch maize, talc purified, Waradur XE.

Yellow active tablets: Calcium carbonate light, iron oxide red (C.I. 77492), iron oxide yellow (C.I. 77491), lactose monohydrate, magnesium stearate, methyl paraben, polyethylene glycol, povidone, propyl paraben, sucrose, starch maize, talc purified, titanium dioxide (C.I. No: 77891), Waradur XE.

Red placebo tablets: Calcium carbonate light, FD&C Red No. 3 Lake (C. I. 45430), FD&C

Yellow 6 (C.I. 15985), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, Ponceau 4R Aluminium Lake (C. I. 16255), povidone, sodium benzoate, sucrose, talc purified, Quinoline Yellow Aluminium Lake (C.I. 47005), Waradur XE.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

60 Months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

6.5. Nature and contents of the container

28 sugar-coated tablets comprising of six (6) brown active, five (5) white active, ten (10) yellow active and seven (7) red placebo tablets are packed in a clear polyvinylchloride blister strip, sealed with an aluminium foil backing. The blister strip is packed in an outer cardboard carton together with a leaflet.

6.6. Secial precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

N/18.8/0040

9. DATE OF FIRST AUTHORISATION

13 February 1981

10. DATE OF REVISION OF TEXT

10 February 2023

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 11 008.

Botswana: B9320080 S2

Namibia: NS2 90/18.8/001250

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