SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Primolut-Nor

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 milligrams of norethisterone acetate.

Excipient with known effect
Lactose monohydrate
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM.

Tablets.

White tablets with cross-score on one side and "AP" in regular hexagon on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dysfunctional bleeding, primary and secondary amenorrhea, premenstrual syndrome, timing of menstruation and endometriosis.

4.2 Posology and method of administration

Posology

The following dosage schemes are recommended:

- **Dysfunctional bleeding**

The administration of 1 tablet Primolut Nor 5 mg twice daily over 10 days leads to the arrest of uterine bleeding not associated with organic lesions within 1-4 days. In individual cases, bleeding diminishes during the first few days after the commencement of tablet-taking and does not stop until about 5-7 days later. For the treatment to be successful, Primolut Nor administration must be continued regularly even after arrest of bleeding (up to a total of 20 tablets Primolut Nor 5 mg).

About 2-4 days after discontinuation of treatment a withdrawal bleeding will occur resembling a normal menstruation in intensity and duration.

- **Slight bleeding during tablet-taking**

Occasionally slight bleeding may occur after initial arrest of bleeding. In these cases tablet-taking must not be interrupted.

- **Missing arrest of haemorrhage, heavy breakthrough bleeding**

If the bleeding does not stop in spite of regular tablet-taking, an organic cause or an extra-genital factor (e.g. polyps, high-situated carcinoma of the cervix uteri or endometrium, myoma, residua of abortion, extra-uterine pregnancy, thrombopenia, thrombasthenia) must be assumed, so that other measures are called for. This applies also in cases where, after

initial arrest of haemorrhage, fairly heavy bleeding recurs within a few days even during tablet-taking.

- **Prevention of recurrence**

To prevent recurrence of dysfunctional bleeding, it is recommended to administer Primolut Nor prophylactically during the next three cycles. This applies only to cases where the course of the basal body temperature, which must be measured regularly, points to a monophasic cycle and, hence to a danger of renewed follicular persistence with its sequelae.

1 tablet Primolut Nor 5 mg twice daily from the 19th to the 26th day of the cycle (1st day of the cycle = 1st day of the last bleeding). The withdrawal bleeding occurs some days after administration of the last tablet.

- **Primary and secondary amenorrhoea**

In the case of secondary amenorrhoea hormone treatment is to be given at the earliest 8 weeks after the last menstrual period.
In order to induce a menstruation-like bleeding, an estrogen (e.g. Progynon Depot 10 mg) is to be given before the administration of Primolut Nor.

However, before treatment is commenced the presence of a prolactin-producing pituitary tumour should be excluded because, according to the present state of knowledge, the possibility cannot be ruled out that macroadenomas increase in size when exposed to higher doses of estrogen for prolonged periods of time.

- **Commencement of treatment**

2 ampoules Progynon Depot 10 mg i.m. on the 1st day of treatment and 1 ampoule Progynon Depot 10 mg i.m. on the 14th day of treatment, followed by 1 tablet Primolut Nor 5 mg twice daily from the 19th to the 26th day of treatment. Withdrawal bleeding starts about the 28th day.

- **Continuation of treatment (over at least 2-3 cycles)**

1 ampoule Progynon Depot 10 mg i.m. on the 6th day and 16th day of the artificial cycle followed by 1 tablet Primolut Nor 5 mg daily from the 19th to the 26th day of the cycle (1st day of bleeding = 1st day of the cycle).

- An attempt can then be made to stop estrogen treatment and to induce a cyclical bleeding by the administration of 1 tablet primolut-Nor 5 mg daily from the 19th to the 26th of the cycle.

Exception: Patients of whom it can be safely assumed that endogenous estrogen production is insufficient (primary amenorrhoea in gonadal dysgenesia).

Please note: Contraception should be practiced with non-hormonal methods (with the exception of the rhythm and temperature methods). If withdrawal bleeding at regular intervals of about 28 days fails to occur under the therapeutic scheme (see above), pregnancy must be considered despite the protective measures. The treatment must then be interrupted until the situation has been clarified by differential diagnosis.

- **Premenstrual syndrome, mastopathy**

Premenstrual symptoms such as headaches, depressive moods, water retention, mastodynia may be relieved or palliated by 1 tablet Primolut Nor 5 mg once or twice daily from the 19th to the 26th day of the cycle.

The remarks under "Please note" for the indication "Primary and secondary amenorrhoea" apply also to this indication.

- **Timing of menstruation**

The monthly bleeding can be advanced or postponed if particular circumstances require this. However, advancement with progestogen-estrogen combinations is definitely to be preferred, because the occurrence of a pregnancy is virtually ruled out by the inhibition of ovulation. As opposed to this, the postponement of menstruation calls for the use of Primolut Nor at a time when the necessary exclusion of pregnancy can be problematical, since Primolut Nor must be given at a time when pregnancy cannot be excluded using the currently available examination methods. Therefore, this method remains restricted to those cases in which there is no possibility of early pregnancy in the cycle concerned.

Dosage: 1 tablet Primolut Nor 5 mg twice daily for not longer than 10-14 days, beginning about 3 days before the expected menstruation. Bleeding will occur 2-3 days after having stopped medication.

- **Endometriosis**

Treatment is commenced on the 5th day of the cycle with 1 tablet Primolut Nor 5 mg twice daily, increasing to two 5 mg tablets twice daily in the event of spotting. When the bleeding ceases, the initial dose can be resumed. Duration of treatment is at least 4-6 months. During treatment, ovulation and menstruation do not occur. After discontinuation of hormone treatment a withdrawal bleeding will occur.

Method of administration

The tablets are to be swallowed whole with some liquid.

4.3 Contraindications

Primolut-Nor should not be used in the presence of any of the conditions listed below. Should any of the conditions appear during the use of Primolut- Nor, the use of the product should be stopped immediately.

1. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
2. Known or suspected pregnancy.
3. Lactation.
4. Previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism).
5. Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).
6. Presence or a history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
7. A high risk of venous or arterial thrombosis (see section 4.4)
8. History of migraine with focal neurological symptoms.
9. Diabetes mellitus with vascular involvement.
10. Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
11. Previous or existing liver tumours (benign or malignant).
12. Known, past or suspected sex hormone-dependent malignancies, including of the genital organs or breast cancer.
13. History during pregnancy of idiopathic jaundice or severe pruritus.
14. Undiagnosed genital bleeding.
15. Untreated endometrial hyperplasia.

Primolut Nor is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Medical Examination

A complete personal and family medical history should be taken for each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines which should be adapted to the individual woman and should include measurement of blood pressure, and if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

Therapy should be discontinued immediately if the following occur:

- New onset of migraine-type headaches or more frequent occurrence of unusually severe headaches
- Sudden perceptual disorders (e.g. disturbances of vision or hearing)
- First signs of thrombophlebitis or thromboembolic symptoms, feeling of pain and tightness in the chest
- Pending operations (six weeks beforehand), immobilisation (e.g. after accidents)
- Onset of jaundice or deterioration in liver function, anicteric hepatitis, general pruritus
- Significant increase in blood pressure
- Pregnancy.

If any of the conditions/risk factors mentioned below is present or deteriorates while using Primolut-Nor, an individual risk-benefit analysis should be done before Primolut-Nor is started or continued.

- Circulatory disorders

It has been concluded from epidemiological surveys that the use of oral oestrogen/progestogen containing ovulation inhibitors is associated by an increased incidence of thromboembolic diseases. Therefore, one should keep the possibility of an increased thromboembolic risk in mind, particularly where there is a history of thromboembolic diseases.

A patient who develops symptoms suggestive of thromboembolic complications should stop treatment immediately. The need for treatment should be reassessed before continuing therapy.

Generally recognised risk factors for venous thromboembolism (VTE) include:

1. Positive personal or family history (VTE in a sibling or a parent at a relatively early age)
2. Age
3. Obesity
4. Systemic lupus erythematous (SLE)
5. Prolonged immobilisation
6. Major surgery
7. Major trauma.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. The treatment with steroid hormone may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thromboembolic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of progestogens in these patients should be viewed as contraindicated. Where a patient is already taking anticoagulants, the risk and benefits of progestogen therapy should be carefully considered.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE. Where prolonged immobilisation is likely to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to stopping progestogen therapy 4-6 weeks pre-operatively. Treatment should not be restarted until the patient is fully remobilised.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

- Known Hyperlipidaemias

Women with hypertriglyceridemia, or a family history thereof, may be at increased risk of pancreatitis when using COCs.

Women with hyperlipiaedmia are at increased risk of arterial disease (see section 4.4 “Circulatory disorders”). However, routine screening of women on COCs is not appropriate.

- Tumours

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in Primolut-Nor. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnosis and, if necessary, the preparation should be withdrawn.

- Other

Primolut-Nor can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should minimise exposure to the sun or ultraviolet radiation when taking Primolut-Nor.

Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Any patient who develops an acute impairment of vision, proptosis, diplopia or migraine headache should be carefully evaluated ophthalmologically to exclude papilloedema or retinal lesions before continuing medication.

Progestogens may cause fluid retention. Special care should be taken when prescribing norethisterone in patients with conditions which might be aggravated by this factor:

- Epilepsy
- Migraine
- Asthma
- Cardiac dysfunction
- Renal dysfunction.

If menstrual bleeding should fail to follow a course of Primolut-Nor, or if the patient wishes to postpone menstruation in special circumstances, the possibility of pregnancy must be excluded before a further course is given.

Additional warnings based on the partial metabolisation of norethisterone to ethinylestradiol

After oral administration, norethisterone is partly metabolised to ethinylestradiol resulting in an equivalent dose of about 4-6 micrograms ethinylestradiol per 1 milligram of orally administered norethisterone or norethisterone acetate (see section 5.2)

Due to the partial conversion of norethisterone to ethinylestradiol, administration of Primolut-Nor is expected to result in similar pharmacological effects as seen with COCs. Therefore, the following general warnings associated with the use of COCs should also be considered:

- Circulatory disorders (thromboembolic events)

Venous thromboembolic events (VTE)
Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in users of oral contraceptives with low oestrogen content (<50 µg 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 VTE compared with no use. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. The excess risk of VTE is highest during the first year a woman initially starts using a COC or when she restarts COC use after a pill-free interval of at least a month.

VTE may be life-threatening or may have a fatal outcome (in 1-2 % of the cases).

VTE manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs.

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

Common signs/symptoms of VTE include:
- Severe pain in the calf of one leg; swelling of the lower leg
- Sudden breathlessness, chest pain.

Arterial thromboembolic related conditions
The use of a combined oral contraceptive may also increase the risk of conditions such as stroke and myocardial infarction which are secondary to arterial thromboembolic events.

Common signs/symptoms associated with arterial thromboembolism include:
- sudden severe pain in the chest, whether or not reaching to the left arm;
- sudden coughing for no apparent reason
- any unusual severe, prolonged headache, especially if it occurs for the first time or gets progressively worse, or is associated with any of the following symptoms:
    - sudden partial or complete loss of vision or diplopia;
    - aphasia;
    - vertigo;
    - collapse with or without focal epilepsy;
    - weakness or very marked numbness suddenly affecting one side or one part of the body.

Risk Factors for Thromboembolic Events:
- Age
- Obesity (body mass index over 30 kg/m2)
- A positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation
- Smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- Dyslipoproteinaemia
- Hypertension
- Migraine (An increase in frequency or severity of migraine during COC use may be prodromal of a cerebrovascular event and therefore a reason for immediate discontinuation of the COC).
- Valvular heart disease
- Atrial fibrillation

Other factors affecting circulatory events

Other medical conditions which have been associated with adverse circulatory events include:

- Diabetes mellitus
- Systemic lupus erythematosus (SLE)
- Haemolytic uremic syndrome
- Chronic inflammatory bowel disease (Crohn's disease/Ulcerative colitis)
- 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
- Hyperhomocysteinaemia
- Antithrombin-III deficiency
- Protein C deficiency
- Protein S deficiency
- Antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COC use (<0.05 mg ethinylestradiol).

- Tumours

Cervical Cancer

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

Breast Cancer

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Malignancies may be life-threatening or may have a fatal outcome.

- Other

Blood pressure

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

Conditions which deteriorate in pregnancy or during previous COC use

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive:

- jaundice and/or pruritus related to cholestasis
- gallstone formation
- porphyria
- systemic lupus erythematosus (SLE)
- haemolytic uremic syndrome
- Sydenham's chorea
- herpes gestationis
- otosclerosis-related hearing loss.

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

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

Crohn's disease and ulcerative colitis have been associated with COC use.

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). As norethisterone is partly metabolized into ethinylestradiol, this warning applies to women using norethisterone (see sections 4.3 and 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on Primolut Nor

Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones which may lead to changes in the uterine bleeding profile and/or reduction of the therapeutic effect.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme-induction), e.g.:
Phenytoin, barbiturates, bosentan, primidone, carbamazepine, rifampicin and HIV medication ritonavir, nevirapine and efavirenz, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. Johns wort (Hypericum perforatum).

Substances with variable effects on the clearance of sex hormones, e.g.:
When co-administered with sex hormones, 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.

Substances decreasing the clearance of sex hormones (enzyme inhibitors):
The clinical relevance of potential interactions with enzyme inhibitors remains unknown. Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin),

diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestin or both.
Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal medicinal product containing 0.035 mg ethinylestradiol.

Effects of Primolut Nor on other medicinal products
Progestogens may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine). Clinical data suggest that ethinylestradiol inhibits the clearance of CYP1A2 substrates, leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in plasma concentration.

Pharmacodynamic interactions
Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 4.3 and 4.4). Primolut Nor can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Other forms of interaction
The use of progestogens may influence the results of certain laboratory tests (e.g. tests for hepatic function, thyroid function and coagulation).

4.6 Fertility, pregnancy and lactation

Pregnancy
The administration of Primolut-Nor during pregnancy is contraindicated.

Breast-feeding
Primolut-Nor can pass into breast milk and therefore should be avoided during lactation.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Undesirable effects are more common during the first months after start of intake of Primolut preparations, and subside with duration of treatment. The frequencies are based on reporting rates from postmarketing experience and literature.

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Very rare < 1/10,000	Frequency not known
Immune system disorders				Hyper-sensitivity reactions		
Nervous system disorders		Headache	Migraine			Dizziness
Psychiatric disorders						Depression aggravated
Eye disorders					Visual disturbances	
Respiratory, thoracic and mediastinal disorders					Dyspnoea	
Gastro-intestinal disorders		Nausea				Abdominal pain
Hepato-biliary disorders						Cholestasis Jaundice
Skin and subcutaneous tissue				Urticaria		

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Very rare < 1/10,000	Frequency not known
disorders				Rash		
Reproductive system and breast disorders	Uterine/ Vaginal bleeding including Spotting* Hypo-menorrhoea*	Amenorrhoea*				
General disorders and administration site conditions		Oedema				

* in the indication Endometriosis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

There have been no reports of ill-effects from overdosage and treatment is generally unnecessary. There are no special antidotes, and treatment should be symptomatic.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, progestogens, Estren derivatives ATC Code: G03DC02

Norethisterone has progestational actions similar to those of progesterone, but is a more potent inhibitor of ovulation and has weak oestrogenic and androgenic properties. It is used to treat a number of disorders of the menstrual cycle.

5.2 Pharmacokinetic properties

Norethisterone is absorbed from the gastro-intestinal tract and its effects last for at least 24 hours. It is excreted in the urine.

- Metabolism

Norethisterone is partly metabolised to ethinylestradiol after oral administration of

norethisterone or norethisterone acetate in humans. This conversion results in an equivalent dose of about 4-6
µg ethinylestradiol per 1 mg orally administered norethisterone / norethisterone acetate.

5.3 Preclinical safety data

Non-clinical data on norethisterone or its esters reveal no special risk for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential which is not already included in other relevant sections. However, it should be kept in mind that sexual steroids might stimulate the growth of hormone-dependent tissues and tumours.

Reproduction toxicity studies showed the risk of masculinisation in female fetuses when administered at high doses at the time of the development of the external genitalia. Since epidemiological studies show that this effect is relevant in humans after high doses, it must be stated that Primolut-Nor may provoke signs of virilisation in female fetuses if administered during the hormone-sensitive stage of somatic sexual differentiation (from day 45 of pregnancy onwards). Apart from this, no indications of teratogenic effects were obtained from the studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Polyvidone 25000
Talc
Magnesium stearate

6.2 Incompatibilities

Not known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

There are no special storage conditions. It is recommended to store at room temperature.

6.5 Nature and contents of container

Cardboard carton containing 2 blisters of 10 tablets.

6.6 Special precautions for disposal and other handling

Keep out of the reach of children.

7. MANUFACTURER

Bayer Weimar GmbH und Co. KG, Weimar, Germany

8. REGISTRATION HOLDER

Bayer Israel Ltd.,
36 Hacharash St., Hod Hasharon 45240.