The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in August 2010.

1. NAME OF THE MEDICINAL PRODUCT

Diane-35  0.035 mg / 2.0 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 hormone-containing beige coated tablets:
Each coated tablet contains 0.035 mg ethinylestradiol, 2.0 mg cyproterone acetate
Excipient: lactose 30 mg
For a full list of excipients, see ‘Pharmaceutical Particulars’

3. PHARMACEUTICAL FORM

Coated tablet

4. CLINICAL PARTICULARS

4.1 Indication(s)

For the treatment of signs of androgenization in women such as pronounced forms of acne, androgenetic alopecia, and mild forms of hirsutism.

4.2 Dosage and method of administration

Method of administration

Oral use

Dosage regimen

How to take Diane-35
Diane-35 is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection. Previously used hormonal contraception should be discontinued. The dose regimen of Diane-35 is similar to the usual regimen of most of the combined oral contraceptives. Thus, the same administration rules must be considered. Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The irregular intake of Diane-35 can lead to intermenstrual bleedings and could deteriorate the therapeutic and contraceptive reliability.
Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval.

How to start Diane-35
Tablet-taking has to start on day 1 of the woman’s natural cycle (i.e. the first day of her menstrual bleeding).
Advice in case of gastro-intestinal disturbances
In case of severe gastro-intestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets, is applicable.

Length of use
The length of use depends on the severity of the symptoms of androgenization and their response to treatment. In general, treatment should be carried out over several months. Acne and seborrhea usually respond sooner than hirsutism or alopecia. 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 section 4.4 Special warnings and precautions for use).

Additional information on special populations

Children and adolescents
Diane-35 is only indicated after menarche.

Geriatric patients
Not applicable. Diane-35 is not indicated after menopause.

Patients with hepatic impairment
Diane-35 is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See also section ‘Contraindications’.

Patients with renal impairment
Diane-35 has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

4.3 Contraindications
Preparations containing estrogen/progestogen combinations should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during their use, the product should be stopped immediately.

- Personal or family history of confirmed, idiopathic venous thromboembolism (VTE) (where a family history refers to VTE in a sibling or parent at a relatively early age).
- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Sickle-cell anaemia
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see “Special Warnings and Precautions for Use”)
- History of migraine with focal neurological symptoms.
Diabetes mellitus with vascular involvement.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Severe hepatic disease as long as liver function values have not returned to normal, jaundice or persistent itching during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome.
- History of deterioration of otosclerosis during pregnancy.
- Presence or history of liver tumors (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Disorders of lipid metabolism.
- History of herpes gestationis.
- Lactation.
- Hypersensitivity to the active substances or to any of the excipients.

Diane-35 is not for use in men.

4.4 Special warnings and precautions for use

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

Warnings

Circulatory Disorders
Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 µg ethinylestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

VTE may be fatal (in 1-2 % of the cases).

Venous thromboembolism (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. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of deep venous thrombosis (DVT) can include: unilateral swelling of the leg 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 discolored 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 bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; 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).

An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). 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 confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen.

Symptoms of 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; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events may be fatal.

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- 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 immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization.
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- dyslipoproteinemia;
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;

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

The increased risk of thromboembolism in the puerperium must be considered (for information on pregnancy and lactation see section “Pregnancy and Lactation”).

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, polycystic ovary syndrome, systemic lupus erythematosus, hemolytic uremic
syndrome, chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis) and sickle cell disease.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardioplin 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 low-dose COCs (<0.05 mg ethinylestradiol).

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

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

In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

Other conditions
Women with hypertriglyceridemia, or a family history thereof, may be at an increase risk of pancreatitis when using COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with anihypertensive therapy.
The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic 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.

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 (containing <0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs.

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

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

Each coated tablet of this medicinal product contains 31.115 mg lactose monohydrate per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

Medical Examination/consultation

Women should be advised that preparations like Diane-35 do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The contraceptive effect of Diane-35 may be reduced in the event of e.g. missed tablets, gastro-intestinal disturbances (section ‘Advice in case of gastro-intestinal disturbances’) during tablet taking or concomitant medication (section ‘Interaction with other medicinal products and other forms of interaction’).

Reduced cycle control

With estrogen/progestogen combinations, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in Section "Dosage and method of
administration", it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicaments on Diane-35

Interactions of other drugs (enzyme inducers, some antibiotics) with estrogen/progestogen combinations like Diane-35 may lead to breakthrough bleeding and/or contraceptive failure. Women on treatment with any of these drugs should temporarily use a barrier method in addition to Diane-35 or choose another method of contraception. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the Diane-35 pack, the next pack should be started without the usual tablet-free interval.

Substances diminishing the efficacy of Diane-35 (enzyme-inducers and antibiotics)

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

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

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

Effects of estrogen/progestogen combinations on other medicaments

Estrogen/progestogen combinations like Diane-35 may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

Other forms of interactions

- Laboratory tests
The use of preparations like Diane-35 may influence the results of certain laboratory tests.
4.6 Pregnancy and lactation

**Pregnancy**

Diane-35 is not indicated during pregnancy. If pregnancy occurs during treatment with Diane-35, further intake must be stopped (see section ‘Preclinical safety data’).

**Lactation**

The administration of Diane-35 is contraindicated during lactation. Cyproterone acetate is transferred into the milk of lactating women. About 0.2% of the maternal dose will reach the newborn via milk corresponding to a dose of about 1 µg/kg. 0.02% of the daily maternal dose of ethinylestradiol could be transferred to the newborn via milk during established lactation.

4.7 Effects on ability to drive or use machines

4.8 Undesirable effects

Side effects that have been reported in users of COCs but for which the association has been neither confirmed nor refuted are:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common (≥ 1/100)</th>
<th>Uncommon (≥ 1/1000 and &lt; 1/100)</th>
<th>Rare (&lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>contact lens intolerance</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>nausea, abdominal pain</td>
<td>vomiting, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>Investigations</td>
<td>weight increased</td>
<td>fluid retention</td>
<td>weight decreased</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache</td>
<td>migraine</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>depressed mood, mood altered</td>
<td>libido decreased</td>
<td>libido increased</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>breast pain, breast tenderness</td>
<td>breast hypertrophy</td>
<td>vaginal discharge breast discharge</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, urticaria</td>
<td></td>
<td>Erythema nodosum, erythema multiforme</td>
</tr>
</tbody>
</table>

The following serious adverse events have been reported in women using COCs, which are discussed in section ‘Special warnings and precautions for use’:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Cerebrovascular accidents
- Hypertension
• Hypertriglyceridemia
• Changes in glucose tolerance or effect on peripheral insulin resistance
• Liver tumours (benign and malignant)
• Liver function disturbances
• Chloasma
• In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.
• Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis-related hearing loss, Crohn’s disease, ulcerative colitis, cervical cancer

The frequency of diagnosis of breast cancer is very slightly increased among OC 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 ‘Contraindications’ and ‘Special warnings and precautions for use’.

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. Pharmacologicl Properties

5.1 Pharmacodynamic properties

Cyproterone acetate is a competitive antagonist on the androgen receptor, has inhibitory effects on the androgen-synthesis in target cells and produces a decrease of the androgen blood concentration through an antigonadotropic effect. This antigonadotropic effect is amplified by ethinylestradiol which up-regulates as well the synthesis of Sexual-Hormone-Binding-Globulin (SHBG) in plasma. It thereby reduces free, biologically available androgen in the circulation.

5.2 Pharmacokinetic properties

Cyproterone acetate

Absorption
Orally administered cyproterone acetate is rapidly and completely absorbed. Peak serum concentrations of 15 ng/ml are reached at about 1.6 hours after single ingestion. Bioavailability is about 88%.

Distribution
Cyproterone acetate is almost exclusively bound to serum albumin. Only 3.5 - 4.0% of the total serum drug concentrations are present as free steroid. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of cyproterone acetate. The apparent volume of distribution of cyproterone acetate is about 986±437l.
**Metabolism**
Cyproterone acetate is almost completely metabolized. The main metabolite in plasma was identified as 15ß-OH-CPA which is formed via the cytochrome P450 enzyme CYP3A4. The clearance rate from serum is about 3.6 ml/min/kg.

**Elimination**
Cyproterone acetate serum levels decrease in two phases which are characterized by half-lives of about 0.8 h and about 2.3 – 3.3 days. Cyproterone acetate is partly excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:2. The half-life of metabolite excretion is about 1.8 days.

**Steady-state conditions**
Cyproterone acetate pharmacokinetics are not influenced by SHBG levels. Following daily ingestion drug serum levels increase about 2.5-fold reaching steady-state conditions during the second half of a treatment cycle.

**Ethinylestradiol**

**Absorption**
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 71 pg/ml are reached within 1.6 hours. During absorption and first-liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% with a large interindividual variation of about 20-65%.

**Distribution**
Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98%), and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2.8-8.6 l/kg was determined.

**Metabolism**
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The clearance rate was reported to be about 2.3- 7 ml/min/kg.

**Elimination**
Ethinylestradiol serum levels decrease in two disposition phases, characterized by half-lives of about 1 hour and 10-20 hours, respectively. Unchanged drug is not excreted, ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

**Steady-state conditions**
Steady-state conditions are reached during the second half of a treatment cycle when serum drug levels are higher by 60% as compared to single dose.
5.3 Preclinical safety data

*Ethinyl estradiol*

The toxicity profile of ethinyl estradiol is well known. There are no preclinical data of relevance to the prescriber that provide additional safety information to those already included in other sections of the product information.

*Cyproterone acetate*

**Systemic toxicity**

Preclinical data reveal no specific risk for humans based on conventional studies of repeated dose toxicity.

**Embryotoxicity/teratogenicity**

Investigations into embryotoxicity using the combination of the two active ingredients showed no effects indicative of a teratogenic effect following treatment during organogenesis before development of the external genital organs. Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs led to signs of feminization in male fetuses following higher doses. Observation of male newborn children who had been exposed in utero to cyproterone acetate did not show any signs of feminization. However, pregnancy is a contraindication for the use of Diane-35.

**Genotoxicity and carcinogenicity**

Recognized first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, further tests showed that cyproterone acetate was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes, the DNA-adduct level in dog liver cells was extremely low.

This DNA-adduct formulation occurred at systemic exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. In vivo consequences of cyproterone acetate treatment were the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats, and an increase of mutation frequency in transgenic rats carrying a bacterial gene as target for mutations.

Clinical experience and well conducted epidemiological trials to date would not support an increased incidence of hepatic tumors in man. Nor did investigations into the tumorigenicity of cyproterone acetate in rodents reveal any indication of a specific tumorigenic potential.

However, it must be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumors.

On the whole, the available findings do not raise any objection to the use of Diane-35 in humans if used in accordance with the directions for the given indication and at the recommended dose.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone 25000
Magnesium stearate
Sucrose
Povidone 700000
Macrogol 6000
Calcium carbonate precipitated
Talc
Glycerol 85%
Titanium dioxide
Ferric oxide pigment yellow
Wax E

6.2 Incompatibilities

None

6.3 Shelf life

60 months

6.3 Special precautions for storage

In a cool place

6.4 Nature and contents of container Package quantities

Diane-35 tablets are supplied in memo-packs of 21 tablets.

6.5 Instructions for use/handling

None

MANUFACTURER:
Bayer Schering Pharma AG, Berlin, Germany.

REGISTRATION HOLDER:
Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.