PRODUCT INFORMATION

Marvelon® 28

NAME OF THE DRUG

Marvelon® 28

Each pack contains 21 active tablets each containing 150 micrograms desogestrel and 30 micrograms ethinyloestradiol and 7 inert (placebo) tablets.

Ethinyloestradiol

![Chemical structure of Ethinyloestradiol]

Molecular Formula $C_{20}H_{24}O$  Molecular mass 296.4
Chemical Name: 19-nor-17a-pregna-1,3,5,(10)-triene-20-yne-3,17b-diol
CAS No. 57-63-6

Desogestrel

![Chemical structure of Desogestrel]

Molecular Formula $C_{22}H_{30}O$  Molecular mass 310.5
Chemical name: 13β-Ethyl-11-methylene-18, 19-dinor-17α-pregn-4-en-20-yn-17β-ol.
CAS No. 54024-22-5

DESCRIPTION

Marvelon is a combined oral contraceptive (COC) preparation containing the oestrogen ethinyloestradiol and the progestagen desogestrel as the active substances.

Ethinyloestradiol: a white or slightly yellowish white crystalline powder. Melting Point: 181-185°C.
It is practically insoluble in water, freely soluble in ethanol (96%) and in ether, sparingly soluble in chloroform. It dissolves in dilute alkaline solutions.

Desogestrel: a crystalline powder, it is a progestagen, semi synthetically produced from naturally occurring plant steroids. It is optically pure, is practically insoluble in water, and slightly soluble in ethanol and ethylacetate.

**PHARMACOLOGY**

The contraceptive effect of COCs is based on the interaction of various factors. The primary mechanisms are inhibition of ovulation (by suppression of gonadotropins) and changes in the cervical secretion (blocking the entry of sperm into the uterus). Besides protection against pregnancy, COCs have several positive properties which, next to the negative properties (see PRECAUTIONS, ADVERSE REACTIONS), can be useful in deciding on the method of birth control. For the majority of users, the cycle is more regular, the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this, there is evidence of a reduced risk of endometrial cancer and ovarian cancer. Furthermore, the higher dosed (0.050 mg ethinyloestradiol) COCs have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to lower-dosed COCs remains to be confirmed.

Receptor binding studies as well as studies in animals and humans have shown that etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with low intrinsic androgenicity. As a result, desogestrel in Marvelon does not counteract the oestrogen-induced increase in SHBG, resulting in lower serum levels of free testosterone.

**Pharmacokinetic properties**

**DESOGESTREL**

**Absorption:** After oral dosing of Marvelon, desogestrel is rapidly absorbed and converted to 3-keto-desogestrel (etonogestrel). Peak serum concentrations of approximately 2ng/mL are reached after 1.5h after single ingestion, and absolute bioavailability is 62 - 81%.

**Distribution:** Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2 - 4 % of the total serum drug concentrations are present as free steroid, 40 - 70 % are specifically bound to SHBG. The ethinyloestradiol-induced increase in SHBG influences the distribution over the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of desogestrel is 1.5 l/kg.

**Metabolism:** Etonogestrel is completely metabolised by the known pathways of steroid metabolism. The metabolic clearance rate from serum is about 2mL/min/kg. No interaction was found when co-administered with ethinyloestradiol.

**Elimination:** Etonogestrel serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 30 hours. Desogestrel and its metabolites are excreted at a urinary to biliary ratio of about 6:4.

**Steady-state conditions:** Etonogestrel pharmacokinetics are influenced by SHBG levels, which are increased threefold by ethinyloestradiol. Following daily ingestion, drug serum levels increase about two- to threefold, reaching steady state conditions during the second half of the treatment cycle.

**ETHINYLOESTRADIOL**

**Absorption:** Orally administered ethinyloestradiol is rapidly and almost completely absorbed. Peak serum concentrations of about 80pg/mL are reached within 1-2 hours. Absolute bioavailability, as a result of presystemic conjugation and first pass metabolism, is approximately 60%.

**Distribution:** Ethinyloestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5L/kg was determined.
Metabolism: Ethinyloestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinyloestradiol 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 metabolic clearance rate is about 5 mL/min/kg.

Elimination: Ethinyloestradiol serum levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Unchanged drug is not excreted, ethinyloestradiol 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 concentrations are reached after 3-4 days when serum drug levels are higher by 30 - 40% as compared to single dose.

INDICATIONS
Oral contraception.

CONTRAINDICATIONS
COCs 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 COC use, the product should be stopped immediately.

- 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.
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see PRECAUTIONS).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected malignant conditions of the genital organs, the breasts, or other organs, if sex steroid-influenced.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients.

PRECAUTIONS
Special warnings and special precautions for use
If any of the conditions/risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether COC use should be discontinued.

1. 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, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely.
- The use of any COC is associated with an increased risk of venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism. The risk is highest during the first year a woman ever uses a COC. Some epidemiological studies have suggested that women using low-dose COCs with third generation progestogens, including desogestrel, have an increased risk of VTE compared with those using low-dose COCs with the progestogen levonorgestrel. These studies indicate an increase in risk, which would correspond to an additional 1-2 cases of VTE per 10,000 women-years of use. However, data from other studies have not shown this increase in risk.
Overall the approximate incidence of VTE in users of low oestrogen dose (< 50µg ethinyloestradiol) OCs is considered to be up to 4 per 10,000 women years compared to 0.5-3 per 10,000 women years in non-OC users. The incidence of VTE occurring during COC use is less than the incidence associated with pregnancy (i.e. 6 per 10,000 pregnant women years).

- 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 venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; ‘acute’ abdomen.

- The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:
  - age;
  - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
  - 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 suspected, the woman should be referred to a specialist for advice before deciding about any COC use;
  - obesity (body mass index over 30 kg/m²);
  - dyslipoproteinaemia;
  - hypertension;
  - migraine;
  - valvular heart disease;
  - atrial fibrillation;
  - 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.

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

- The increased risk of thromboembolism during the puerperium must be considered.

- Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic 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, 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 low-dose COCs (< 50µg ethinyloestradiol).

2. Neoplasms
Several epidemiological studies suggest that use of combined oral contraceptives, in particular if used for 5 years or longer, has been associated with an increase risk of cervical intra-epithelial neoplasia or invasive cervical cancer. After cessation of use of oral contraceptives the risk gradually decreases over time to that of non-users in about 8 years. Human papilloma virus is believed to be the most important cause of cervical cancer, but the independent association with the use of hormonal contraceptives suggests a contributing effect. These findings must be balanced against evidence of significant effects
attributable to sexual behaviour, smoking, parity and other factors. Refer to Medical Examination/consultation. (See also Carcinogenicity/Mutagenicity Section)

3. Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased 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 antihypertensive 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; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

- 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 < 50µg ethinyloestradiol). 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.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the Contraindications and Precautions, and should be repeated periodically during the use of COCs. In general, an annual examination is recommended. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be based on established guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology. Women who have ever been sexually active, including current and past users of hormonal contraceptives, should have scheduled Pap smear examinations in accordance with current public health guidelines.

Women should be advised that Marvelon does not protect against sexually transmitted diseases (STDs), including HIV infections (AIDS) and Human Papilloma Virus [HPV]. The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs, but that even barrier contraceptives may not protect against HPV.

Reduced efficacy

The efficacy of COCs may be reduced in the event of missed active tablets, gastrointestinal disturbances during active tablet taking or concomitant medication.

Reduced cycle control

With all COCs, 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. These may include curettage.

In some women withdrawal bleeding may not occur during the placebo tablet interval. If the COC has been taken according to the directions, 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.

Carcinogenicity/Mutagenicity

Carcinogenicity studies for human risk estimation were performed for both components of the preparation, ethinylestradiol and desogestrel, and the combination.

Long-term studies with ethinylestradiol/desogestrel in rats and mice at oral doses up to 0.2/0.5 mg/kg elicited an increased incidence of pituitary and mammary gland tumours. The tumours occurred at exposure levels (based on body surface area) 30 to 60 times human exposure at the maximum recommended dose. The mechanism involved oestrogen- and prolactin-sensitive pathways in rodents. These pathways have no direct counterpart in humans; therefore the clinical significance of these findings is uncertain.

Assays for gene mutations (S. typhimurium) and chromosomal damage (in vivo mouse micronucleus test) performed with desogestrel or the combination did not provide any evidence of a genotoxic potential.

An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

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 tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. 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.

Use in Pregnancy (Category B3)

Marvelon is contraindicated during pregnancy. If pregnancy occurs during treatment with Marvelon, further intake should be stopped. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

In animal studies, maternal administration of high doses of oestrogens has produced urogenital malformations in the offspring. The relevance of the animal findings for the clinical use of ethinylestradiol is not certain. However, there was no evidence for teratogenic activity when ethinylestradiol/desogestrel was given orally to pregnant rats (up to 0.2/0.5 mg/kg) or rabbits (0.04/0.1 mg/kg) during organogenesis. These doses correspond to exposure levels (based on body surface area) 15 to 60 times human exposure at the maximum recommended dose. The combination had no adverse peri/post natal effects in rats at similarly high exposure levels.

Use in Lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk but there is no evidence that this adversely affects infant health.

Interactions with other Drugs

Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or oral contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism: Interactions can occur with drugs that induce microsomal enzymes, which can result
in increased clearance of sex-hormones (e.g., hydantoins, barbiturates, primidone, carbamazepine, rifampicin, rifabutin and possibly also oxycarbazepine, topiramate, felbamate, ritonavir, griseofulvin and products containing St. John’s Wort).

*Interference with Enterohepatic Circulation:* Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic agents are given, which may reduce ethinylestradiol concentrations (e.g., penicillins, tetracyclines).

Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC 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 active tablets in the COC pack, the next COC pack should be started without the usual placebo tablet interval.

Oral contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected (e.g., cyclosporin).

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

**Effect on laboratory tests**
The use of contraceptive steroids 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 generally remain within the normal laboratory range.

**ADVERSE REACTIONS**
Various adverse reactions have been associated with oral contraceptive use. The most serious reactions associated with the use of oral contraceptives are dealt with under **PRECAUTIONS**.

In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether its use should be discontinued.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common (&gt; 1/100)</th>
<th>Uncommon (&gt; 1/1000 and &lt; 1/100)</th>
<th>Rare (&lt; 1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Fluid retention</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td>Depressed mood,</td>
<td>Libido decreased</td>
<td>Libido increased</td>
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<tr>
<td></td>
<td>mood altered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Migraine</td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>Contact lens intolerance, cataract</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, abdominal pain</td>
<td>Vomiting, diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, urticaria</td>
<td></td>
<td>Erythema nodosum, erythema multiforme, hirsutism, acne, alopecia</td>
</tr>
</tbody>
</table>
Reproductive system and breast disorders

Investigations

Breast pain, breast tenderness
Weight increased

Hypertrophy breast

Weight decreased

The most appropriate MedDRA term (version 9.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

**DOSAGE AND ADMINISTRATION**

**How to take Marvelon® 28**

One tablet is to be taken daily. The tablets must be taken in the order directed on the package at about the same time each day, with some liquid as needed. Daily tablet taking should be continuous, starting with the tablet marked with the corresponding day from the green zone. Each subsequent pack is to be started immediately following the last placebo (small) tablet. During the placebo days a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last active (large) tablet and may not have finished before the next pack is started.

**How to start taking Marvelon® 28**

The tablets are taken starting with the tablet marked with the corresponding day from the green zone of the pack. This way, the woman will virtually always have a menstruation-free weekend.

**No preceding hormonal contraceptive use [in the past month]**

Tablet-taking has to start on day 1 of the woman’s natural cycle (i.e. the first day of her menstrual bleeding). If the woman starts on a Thursday or Friday (although these tablets are in the green zone, they are inactive tablets) additional contraceptive precautions are necessary for the first 7 days of active tablet-taking.

**Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch)**

The woman should start with Marvelon 28 preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free interval or following the last placebo tablet of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Marvelon 28 preferably on the day of removal, but at the latest when the next application would have been due.

**Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system [IUS]**

The woman may switch any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but in all of these cases should be advised to additionally use a barrier method for the first 7 days of active tablet-taking.

**Following a first trimester abortion**

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

**After childbirth or a second or third trimester abortion**

For breastfeeding women see PRECAUTIONS. Women should be advised to start 21 to 28 days after delivery or second-trimester abortion (no later than day 26 if starting on a Thursday or day 27 if starting on a Friday). When starting later than day 28, the woman should be advised to additionally use a barrier method for the first 7 days of active tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

**Management of missed tablets**

When Marvelon is taken according to the directions for use, the occurrence of pregnancy is highly unlikely. However, the reliability of oral contraceptives may be reduced under the following circumstances:

If the user is **less than 12 hours late** in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours late** in taking any active tablet, contraceptive protection may be reduced.
The management of missed tablets can be guided by the following two basic rules:

1. ‘active tablet’-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted ‘active tablet’-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

If the user is more than 12 hours late in taking any large tablet (or several large tablets) from the pack, she should take the last forgotten tablet, even if this means taking two tablets in one day, and then continue to take tablets at the normal time. Additional contraceptive precautions should be taken for the next 7 days.

If these 7 days would usually include the taking of small (inert) tablets, the large (active) tablets of the next pack should be started as soon as the large tablets from the current pack are finished. This prevents an extended break in taking active tablets, which may increase the risk of the ovaries releasing an egg and thus reducing contraceptive protection. The woman will not have a period until the end of the second pack of tablets, but this is not harmful, nor does it matter if she experiences some bleeding on the days she is taking Marvelon.

Whenever large tablets are missed at the beginning of the pack (that is, missing one or more of the first 7 large tablets), and sexual intercourse has taken place, the possibility of pregnancy should be considered.

Advice in case of gastro-intestinal disturbances
In case of severe gastro-intestinal disturbance, 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, as given previously, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

Additional contraceptive precautions
When additional contraceptive precautions are required the woman should be advised either to abstain from sex, or to use a barrier method of contraception, such as a cap (or diaphragm) plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the Pill disrupts the cyclical changes associated with the natural menstrual cycle e.g. changes in temperature and cervical mucus.

How to shift periods or how to delay a period
To delay a period the woman should continue with another pack of Marvelon 28 without having a placebo tablet interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Marvelon 28 is then resumed after the usual 7-day placebo tablet interval.

To shift her period to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

OVERDOSAGE
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.

PRESENTATION
Nature and contents of container
Each pack of Marvelon (28 day pack), AUST R42894, consists of push-through strips with:

- 21 large, white, round, biconvex tablets coded TR5 on one side, and Organon and a star on the other, each containing 150 micrograms desogestrel (a progestagen) and 30 micrograms ethinyloestradiol (an oestrogen).
- 7 small, white, round, biconvex tablets coded KH2 on one side and a square on the other. These
tablets do not contain active ingredients.

Excipients

Active tablets: potato-starch, povidone, stearic acid, anhydrous colloidal silica, dl-alpha-tocopherol, lactose.

Inert tablets: potato-starch, magnesium stearate and lactose.

Shelf-life and Storage

The shelf-life of Marvelon 28\textsuperscript{®} is 3 years when stored below 30\textdegree C and protected from light.

NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell Street,
South Granville, NSW 2142
Australia

POISON SCHEDULE

Schedule 4

TGA Approval Date: 9 July 2007
Date of most recent amendment: 16-11-2011