Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NORDETTE Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 micrograms levonorgestrel and 30 micrograms Ethinylestradiol.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Coated tablets
Round, yellow sugar-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral Contraception.
Treatment of endometriosis.

4.2 Posology and method of administration

HOW TO TAKE NORDETTE
Regular daily intake of tablets for 21 consecutive days is important for the preservation of contraceptive efficacy. 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 during which time a withdrawal bleed occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

HOW TO START NORDETTE
No preceding hormonal contraceptive use in the past month.
Tablet-taking should start on day 1 of the woman’s natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2-7 is allowed, but during the first cycle a back-up method of birth control [such as, condoms and spermicide] is recommended in addition for the first 7 days of tablet taking.

CHANGING FROM ANOTHER COMBINED ORAL CONTRACEPTIVE (COC)
The woman should start NORDETTE preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or inactive tablet interval of her previous COC.

CHANGING FROM A PROGESTIN ONLY METHOD (PROGESTIN ONLY PILL, INJECTION, IMPLANT)
The woman may switch any day from the progestin only pill and should begin NORDETTE the next day. She should start NORDETTE on the day after an implant removal or, if using an injectable, the day after the next injection would be due. In all of these situations, the woman should be advised to additionally use a back-up method for the first 7 days of tablet taking.

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

FOLLOWING DELIVERY OR SECOND-TRIMESTER ABORTION
Since the immediate post-partum period is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than day 28 after delivery or second-trimester abortion. The woman should be advised to additionally use a back-up method for the first 7 days of 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. (see WARNINGS: Thromboembolism and 4.6 Pregnancy and lactation).

MANAGEMENT OF MISSED TABLETS
Contraceptive reliability may be reduced if tablets are missed and particularly if the missed tablets extend the tablet-free interval. If tablets were missed in the first week of the cycle and intercourse took place in the week before the tablets were missed, the possibility of a pregnancy should be considered.
Provided that the user is less than 12 hours late in taking any tablet, she should take it as soon as she remembers and further tablets should be taken at the usual time.

If she is more than 12 hours late in taking any tablet, contraceptive protection may be reduced.
The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets in one day. She then continues to take tablets at her usual time. In addition, a back-up method such as the condom should be used for the next 7 days.

If these 7 days run beyond the last tablet in the current pack, the next pack must be started as soon as the current pack is finished; no gap should be left between packs. This prevents an extended break in tablet taking which may increase the risk of escape ovulation. The user is unlikely to have a withdrawal bleed until the end of the second pack but she may experience spotting or breakthrough bleeding on tablet taking days.

If the user does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming tablet taking from the next pack.

IN CASE OF GASTROINTESTINAL UPSET
The onset of intercurrent digestive disorders within four hours after taking the tablet, such as vomiting or severe diarrhoea, may cause transient inefficacy of the method by reducing COC hormone absorption and such events should be dealt with in the same way as the case where a tablet has been forgotten for less than 12 hours. The extra tablet should be taken from a back-up pack. If these episodes recur over several days, a non-hormonal back-up contraceptive method should then be used, (condom, spermicide, etc.) until the beginning of the next blister pack.

HOW TO DELAY A PERIOD
To delay a period the woman should continue with another pack of NORDETTE without a tablet-free 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 NORDETTE is then resumed after the usual 7 day tablet-free interval.

ENDOMETRIOSIS
Treatment should be continuous with 2 Nordette tablets a day. If spotting or breakthrough bleeding occurs it may be necessary to give 4 tablets daily or rarely 5 tablets daily in divided doses.

4.3 Contraindications

Oral contraceptives should not be used in women with any of the following conditions:
- Thrombophlebitis or thromboembolic (arterial or venous) disorders or other diseases associated with an increased thromboembolic risk such as thrombogenic valvulopathies and thrombogenic rhythm disorders (current or history).
- Hereditary or acquired predisposition for venous or arterial thrombosis.
- Cerebrovascular or coronary artery disease.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal vaginal bleeding.

- Hepatic adenomas or carcinomas, or acute or chronic liver disease, as long as liver function has not returned to normal.
- Uncontrolled hypertension.
- Diabetes mellitus associated with vascular abnormalities.
- History of migraine with focal neurological symptoms, such as aura.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients of NORDETTE.

4.4 Special warnings and precautions for use

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with the extent of smoking and is marked in women over 35 years of age. All women who use oral contraceptives should be strongly advised not to smoke. Other methods of contraception should be considered for those women over 35 years old who smoke.

The use of COC's is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and hypertension. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and particularly diabetes with vascular involvement.

1. Thromboembolic Disorders and Other Vascular Problems

Oral contraception must be used with caution in women with risk factors for thrombotic and thromboembolic events or cardiovascular disease. Any of the following risk factors for venous or arterial disease may constitute an unacceptable level of risk.

a. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral-contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes.

Smoking in combination with oral-contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors. The risk of arterial thromboembolic complications in COC users increases with:

- Increasing age.
- Smoking.
- Dyslipoproteinemia.
- Hypertension.
- Valvular heart disease.
- Atrial fibrillation.
- Obesity (body mass index over 30kg/m^2).

b. Venous Thrombosis and Thromboembolism

The use of any COC carries an increased risk of VTE compared with no use. The excess risk 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 woman-years. VTE is fatal in 1-2% of cases.

The overall absolute risk (incidence) of Venous Thrombo Embolism (VTE) for levonorgestrel containing combined oral contraceptives with 30 micrograms ethinylestradiol is approximately 20 cases per 100,000 woman years of use.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the

use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.
The risk for venous thromboembolic complications in COC's users increases with:

- Increasing age.
- A positive family history (venous thromboembolism ever in a sibling or parent at relatively early age).
- Prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilization. Antithrombotic treatment should be considered if the pills have not been discontinued in advance.
- Obesity (body mass index over 30 kg/m^2).

The presence of one serious or multiple risk factors, depending on type and severity, for venous or arterial disease, may constitute an unacceptable level of risk.

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

c. Cerebrovascular Disease
Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension has been found to be a risk factor for both users and nonusers, for both types of strokes, while smoking appears to increase the risk for hemorrhagic stroke. Transient ischaemic attacks have also been associated with oral contraceptive use.

COC users with migraine (particularly migraine with aura) may be at increased risk of stroke.

2. Carcinoma of the Reproductive Organs
Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behaviour and other factors.

A meta-analysis from 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 COC's. The increased 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 lifetime 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 COC's or a combination of both. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

3. Hepatic Neoplasia/Liver Disease
Benign hepatic adenomas are associated with oral contraceptives use, although the incidence of these benign tumors is rare. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term oral contraceptive users however, these cancers are extremely rare.

Women with a history of COC-related cholestasis or women with cholestasis during pregnancy are more likely to have this condition with COC use. If these patients receive a COC they should be carefully monitored and, if the condition recurs, the COC should be discontinued.

4. Ocular Lesions
There have been case reports of retinal thrombosis with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

5. Gallbladder Disease

An increased relative risk of gallbladder disease in users of oral contraceptives and estrogens has been reported in some studies.

6. Carbohydrate and Lipid Metabolic Effects

Glucose intolerance has been reported in oral contraceptive users. Some progestins are known to increase insulin secretion and create insulin resistance, while estrogens (> 75 micrograms) may create a state of hyperinsulinism. Women with impaired glucose tolerance or diabetes mellitus should be carefully observed while taking oral contraceptives.

Due to alterations of glucose tolerance, the required dose of insulin or other antidiabetic agents might change.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents.

7. Hypertension

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestins.

Women with a history of hypertension or hypertension-related diseases, or renal diseases should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued.

8. Headache

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

9. Bleeding Irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestin may be important. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, continued use of the oral contraceptive or a change to another formulation may solve the problem. In some women, withdrawal bleeding may not occur during the usual tablet free interval. If the COC has been taken according to directions, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to directions prior to the first missed withdrawal bleed or if two consecutive withdrawal bleeds are missed, pregnancy should be ruled out.

PRECAUTIONS FOR USE

1. Physical Examination and Follow-up

A complete personal and family medical history and physical examination should be taken prior to the initiation of COC use, and should be repeated periodically during the use of COC's. The physical examination should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Patients should be counselled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

2. Lipid Disorders

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Persistent hypertriglyceridemia may occur in a small proportion of COC users. Elevations of plasma triglycerides may lead to pancreatitis and other complications. Women who are being treated for hyperlipidemias should be followed closely if

they elect to use oral contraceptives. Some progestins may elevate low-density lipoprotein (LDL) levels and may render the control of hyperlipidemias more difficult. Non-hormonal contraception should be considered in women with uncontrolled dyslipidemias (See WARNINGS).

3. Liver function
Acute or chronic liver dysfunction may necessitate the discontinuation of COC use until liver function returns to normal. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. Emotional disorders
Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

5. Folate levels
Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

6. St. John's Wort
If combined oral contraceptives (COC's) and St. John's Wort are used concomitantly, a non-hormonal back-up method of birth control is recommended (see 4.5).

7 Other
Diarrhoea and/or vomiting may reduce hormone absorption resulting in decreased serum concentration (see 4.5).

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, porphyria, systemic lupus erythematosus, haemolytic uremic syndrome, Sydenham´s chorea, herpes gestationis, otosclerosis-related hearing loss.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between ethinylestradiol (EE) and other substances may lead to decreased or increased serum EE concentrations.

Decreased EE serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the COC.

During concomitant use of EE-containing products and substances that may lead to decreased EE serum concentrations, it is recommended that a non-hormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of NORDETTE. In the case of prolonged use of such substances COC's should not be considered the primary contraceptive.

Examples of substances that may decrease serum EE concentrations:
- Ritonavir.
- Any substance that reduces gastrointestinal transit time and, therefore, EE absorption.
- Substances that induce hepatic microsomal enzymes, such as carbamazepine, oxycarbamazepine, rifampicin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, griseofulvin, topiramate and modafinil.
- Certain antibiotics (eg, ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of estrogens.
- St. John's Wort: Breakthrough bleeding and unintended pregnancies have been reported in women taking COC's and St. John's Wort (*Hypericum perforatum*). St. John's Wort may induce microsomal enzymes, which theoretically may result in reduced clinical efficacy of COC's. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's Wort. If COC's and St. John's Wort are used concomitantly, a

non-hormonal backup method of birth control is recommended.

After discontinuation of substances that may lead to decreased EE serum concentrations, use of a non-hormonal back-up method is recommended for at least 7 days. Longer use of a back-up method is advisable after discontinuation of substances that have lead to induction of hepatic microsomal enzymes, resulting in decreased EE serum concentrations. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance.

Examples of substances that may increase serum EE concentrations:

- Atorvastatin.

- Competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol.

- Substances that inhibit cytochrome P450 3A4 isoenzymes, such as indinavir, fluconazole and troleandomycin.

Troleandomycin may increase the risk of intrahepatic cholestasis during co-administration with COC's.

EE may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes, or by inducing hepatic drug conjugation, particularly glucuronidation. Accordingly, plasma and tissue concentrations may either be increased (e.g. ciclosporin and theophylline,) or decreased (e.g. lamotrigine).

In patients treated with flunarizine, use of oral contraceptives has been reported to increase the risk of galactorrhea.

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

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.

4.6 Pregnancy and lactation

NORDETTE is not indicated during pregnancy.

Before commencing a treatment with NORDETTE pregnancy has to be excluded. If pregnancy occurs during use with NORDETTE treatment should be withdrawn immediately.

Extensive epidemiological studies have revealed no increased risk of birth defects in children born to women who used COC's prior to pregnancy. Most epidemiological studies also do not suggest a teratogenic effect; particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when combinations of estrogens and progestogens in dose levels relevant for NORDETTE or other COC's were taken inadvertently during early pregnancy. Studies in animals have shown reproductive toxicity, including adverse effect on the development of the female urogenital system.

LACTATION
Lactation may be influenced by COC's as they may reduce the quantity and change the composition of breast milk, therefore, the use of COC's should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

For serious adverse effects when taking COC's, see section 4.4. "Special warnings and precautions for use. For thromboembolic events, lipid disorders, gallbladder diseases, breast cancer, see also section 4.4. "Special warnings and precautions for use". The most frequently (greater than 10%) reported adverse events during phase III studies and post-marketing surveillance in women using NORDETTE are headache, including migraines and breakthrough bleeding/spotting.

Other adverse events have been reported in women taking NORDETTE:

System organ class	Frequency of adverse events		
	Common ≥1% and <10%	Uncommon ≥0.1% and <1%	Rare ≥0.01% and <0.1%
Infections and infestations	Vaginitis, including candidiasis		
Immune system disorders			Anaphylactic/anaphylactoid reactions including very rare cases of urticaria, angioedema and severe reactions with respiratory and circulatory symptoms
Metabolism and nutrition disorders		Changes in appetite (increase or decrease)	Glucose intolerance
Psychiatric disorders	Mood changes, including depression; changes in libido		
Nervous system disorders	Nervousness; dizziness		
Eye disorder			Intolerance to contact lenses
Gastrointestinal disorders	Nausea, vomiting, abdominal pain	Abdominal cramps, bloating	
Hepato biliary disorder			Cholestatic jaundice
Skin and subcutaneous tissue disorders	Acne	Rash, chloasma (melasma) which may persist, hirsutism, alopecia	Erythema nodosum
Reproductive system breast disorders	Breast pain, tenderness, enlargement, secretion, dysmenorrhea, change in menstrual flow, change in cervical ectropion and secretion, amenorrhea		
General disorders	Fluid retention/edema		
Investigations	Change in weight (increase or decrease)	Increase in blood pressure, changes in serum lipid levels, including hypertriglyceridemia	Decrease in serum folate levels (Serum folate levels may be depressed by COC therapy.)

The following adverse events have been classified as very rare adverse events (<0.01%):

- Exacerbation of systemic lupus erythematosus.
- Exacerbation of porphyria.
- Exacerbation of chorea.
- Optic neuritis (optic neuritis may lead to partial or complete loss of vision).
- Aggravation of varicose veins.
- Retinal vascular thrombosis.

- Pancreatitis.
- Hepatic adenomas.
- Hepatocellular carcinomas.
- Gallbladder disease, including gallstones (COC's may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.).
- Erythema multiforme.
- Haemolytic uremic syndrome.

4.9 Overdose

Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote, and further treatment of overdose, if necessary, is directed to the symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group:
Progestogens and estrogens, fixed combinations.
ATC Code: G03AA07

Nordette is a combined oral contraceptive containing the oestrogen ethinylestradiol and the progestogen, levonorgestrel. It acts primarily through the mechanism of gonadotrophin suppression resulting in the suppression of ovulation.

5.2 Pharmacokinetic properties

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal-tract but is subject to first pass metabolism in the gut wall. Compared to other estrogens it is only slowly metabolised in the liver. Excretion is via the kidneys with some appearing also in the faeces.

Levonorgestrel is absorbed from the gastrointestinal tract. Metabolites are excreted in the urine and faeces as glucuronide and sulphate conjugates.

5.3 Preclinical safety data

A carcinogenic effect can be produced in certain strains of mice and rats when progestogens, oestrogens and combinations of the hormones are given in high doses throughout their life span. The susceptibility to tumour induction by hormonal contraceptives is not consistent in different strains of mice and rats and such studies have not provided useful predictive information of the potential carcinogenicity in women.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Magnesium stearate
Talc
Glycerol
Sucrose
Macrogol
Calcium carbonate

Titanium dioxide (E171)
Iron oxide yellow pigment (E 172)
Wax E

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Primary container:

Blister packs, formed from moulded clear 250µm PVC film and 20µm aluminium foil coated with heat sealable lacquer.

Secondary container:

Cardboard carton.

Presentation:

Each blister pack contains 21 tablets. Cartons containing 1 and 3 blisters.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

John Wyeth and Brother Limited
Trading as Wyeth Laboratories
Huntercombe Lane South
Taplow
Maidenhead
Berkshire, SL6 0PH
UK

8 MARKETING AUTHORISATION NUMBER

PA 22/66/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 July 1994

Date of last renewal: 21 July 2004

10 DATE OF REVISION OF THE TEXT

September 2006