Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alesse film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 microgram levonorgestrel and 20 microgram ethinylestradiol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.

Round pink biconvex film coated tablets with “W” embossed on one side and “912” embossed on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oral contraception.

4.2 Posology and method of administration

How to take Alesse
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 days 2-3 after the last tablet and may not have finished before the next pack is started.

How to start Alesse
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 Alesse 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 Alesse the next day. She should start Alesse 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 sections 4.4 and 4.6.)

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 in 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 nonhormonal 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 Alesse 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 Alesse is then resumed after the usual 7-day, tablet-free interval.

Paediatric population
Safety and efficacy was evaluated in subjects aged 18 years and above.

4.3 Contraindications

Combined oral contraceptives (COCs) should not be used in women with any of the following conditions listed below. Should any of the conditions appear for the first time during COC use the product must be stopped immediately:

- Venous thrombosis present or history (deep venous thrombosis, pulmonary embolism) or other diseases, associated with an increased thromboembolic risk such as thrombogenic valvulopathies and

thrombogenic rhythm disorders (current or history)

- Arterial thrombosis present or in history (e.g. myocardial infarction) or prodromal conditions (e.g. angina pectoris and transient ischaemic attack)
- Presence or history of a prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris)
- Cerebrovascular accident present or in history
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4)
- Known or suspected carcinoma of the breast
- Known or suspected carcinoma of the endometrium or other estrogen-dependent neoplasia
- Undiagnosed vaginal bleeding
- Severe hepatic disease, current or previous, as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant)
- Uncontrolled hypertension
- Diabetes mellitus associated with vascular involvement
- History of migraine with focal neurological symptoms
- Known or suspected pregnancy
- Hypersensitivity to the active substances (levonorgestrel, ethinylestradiol) or to any of the excipients of Alesse listed in section 6.1

4.4 Special warnings and precautions for use

Warnings

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 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.

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 quite 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 COCs 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.

• *Circulatory Disorders*

Epidemiological studies have shown that the incidence of 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 venous thromboembolism (VTE) compared with no use.

The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies.
VTE is fatal in 1-2 % of the cases.

The overall absolute risk (incidence) of VTE for levonorgestrel containing combined oral contraceptives with 30 µg ethinylestradiol is approximately 20 cases per 100,000 women-years of use. Epidemiological studies have also associated the use of combined COCs with an increased risk for myocardial infarction, transient ischaemic attack and

for stroke. 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.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, retinal veins and arteries, in contraceptive pill users. There is no consensus as to whether the occurrence of these events is associated with the use of hormonal contraceptives.

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include:
• unusual unilateral leg pain and/or swelling
• sudden severe pain in the chest, whether or not it radiates to the left arm
• sudden breathlessness
• sudden onset of coughing
• vertigo
• collapse with or without focal seizure
• weakness or very marked numbness suddenly affecting one side or one part of the body
• motor disturbances
• 'acute' abdomen.

The risk for venous thromboembolic complications in COCs users increases with:
• increasing age
• a positive family history (venous 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.
• prolonged immobilisation, 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 to resume until two weeks after complete remobilisation.
• obesity (body mass index over 30 kg/m²).
• there is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases with:

• increasing age
• smoking (women over 35 years should be strongly advised not to smoke if they wish to use an COC)
• dyslipoproteinemia
• hypertension
• migraine
• valvular heart disease
• atrial fibrillation
• obesity (body mass index over 30 kg/m^2)

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (transient ischaemic attacks, 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.

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

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.

The increased risk of thromboembolism in the puerperium must be considered (see Section 4.6 Pregnancy and Lactation).

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

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

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.

Carcinoma of the reproductive organs

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 behavior and other factors such as human papilloma virus (HPV).

Breast cancer

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 COCs. 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 COCs, or a combination of both. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Hepatic neoplasia/ liver disease

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.

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.

Other Conditions

Carbohydrate and lipid metabolic effects

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. However, diabetic women should be carefully monitored, particularly in the early stage of COC use.

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

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

Non-hormonal contraception may be considered in women with uncontrolled dyslipidemias.

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.

Gallbladder disease

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

Hypertension

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

Women with a history of hypertension, 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.

Headache

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. Development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of the COC and investigation of the cause.

Bleeding irregularities

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. 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 tablet-free interval. If the COC has been taken according to the directions described in section 4.2 Posology 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.

Precautions for use

Medical examination/consultation

Prior to the initiation or reinstitution of ethinylestradiol/levonorgestrel a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (see section 4.3 Contraindications) and warnings (see section 4.4 Special Warnings and special precautions for use'). The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

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

Liver function

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

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.

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.

St. John's wort

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

Other

Reduced efficacy
The efficacy of COCs may be reduced, in the event of missed tablets vomiting or diarrhea or concomitant medication.

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, gallstones, porphyria, systemic lupus erythematosus, 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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Worsening of Crohn's disease and of ulcerative colitis has been reported during 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.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between COCs and other drugs may impair the contraceptive efficacy and/or lead to breakthrough bleeding and/or contraceptive failure.

Women on treatment with any of these drugs should temporarily use a barrier method or another method of contraception in addition to the COC. After discontinuation of substances that may lead to decreased EE serum concentrations, use of a nonhormonal back-up method is recommended for at least 7 days.With liver enzyme inducing drugs, the barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

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

Hepatic metabolism: Interactions can occur with drugs that induce hepatic microsomal enzymes, resulting in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, phenylbutazone, carbamazepine, oxycarbamazepine, rifampicin, rifabutin, modafinil and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing the herbal remedy St. John's wort (*Hypericum perforatum*)). The inducing effect can 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.

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.

Enterohepatic circulation: Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents (e.g. penicillins, tetracyclins) are given at the same time, which may reduce ethinylestradiol concentrations in serum. Women on treatment with antibiotics should use a barrier method during the use of the antibiotics and until 7 days after their discontinuation. Women on treatment with the antibiotics rifampicin and griseofulvin should follow the liver enzyme inducing drugs recommendation above).

Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs.

Oral contraceptives may interfere with the metabolism of certain other drugs. Increased plasma concentrations of cyclosporin have been reported with concomitant administration of OCs. COCs have been shown to induce metabolism of lamotrigine resulting in sub-therapeutic plasma concentrations of lamotrigine.

Competitive inhibitors for sulfation in the gastrointestinal wall may increase serum EE concentrations, such as ascorbic acid (vitamin C) and paracetamol

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

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.

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

4.6 Fertility, pregnancy and lactation

Fertility
There are no clinical safety data on the effects of Alesse on fertility.

Pregnancy
Alesse is not indicated during pregnancy.

If the woman becomes pregnant while using Alesse further intake must 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 at unintentional intake of contraceptive pills in

early pregnancy

Breastfeeding
Lactation may be influenced by COCs, as they may reduce the amount and change the composition of breast milk, therefore, the use of COCs should generally not be recommended until the nursing mother has weaned her child off breast milk. Small amounts of contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

The impact of Alesse on the ability to drive and use machines has not been systematically evaluated. Patients should exercise caution until they know that Alesse does not affect these abilities.

4.8 Undesirable effects

For serious adverse effects when taking COCs, see section 4.4. *Special warnings and precaution for use*. For venous and arterial thromboemebolic events, lipid disorders, gallbladder diseases, breast cancer, hypertension, liver tumours, Crohn's disease, ulcerative colitis, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice see also section 4.4.

The frequency of diagnosis of breast cancer is 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 4.3 Contraindications and 4.4 Special warnings and precautions for use**.**

The most frequently (greater than 10%) reported adverse events during phase III studies and postmarketing surveillance in women using Alesse are headache, including migraines, dysmenorrhoea, abdominal pain, nausea, and breakthrough bleeding/spotting.

Other adverse events have been reported in women taking Alesse:

System organ class	**Frequency of adverse events**			
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Frequency not known (cannot be estimated from the available data)**
Infections and infestations	Vaginitis, including candidiasis			
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Hepatic neoplasm, malignant, Hepatic adenoma
Blood and lymphatic system disorders				Haemolytic uraemic syndrome
Immune system disorders				Anaphylactic/anaphylactoid reaction, angioedema***
Metabolism and		Glucose		

nutrition disorders		tolerance impaired, increased appetite, decreased appetite		
Psychiatric disorders	Mood altered including depression; nervousness, change in libido			
Nervous system disorders	Dizziness			Optic neuritis*, chorea aggravated
Eye disorders				Retinal vascular thrombosis, contact lens intolerance
Vascular Disorders		Aggravation of varicose veins		
Gastrointestinal disorders	Vomiting, diarrhoea, bloating			Pancreatitis, colitis ischaemic, inflammatory bowel disease (Crohn's disease, colitis ulcerative) abdominal cramps
Hepatobiliary disorders		Cholelithiasis	Jaundice cholestatic	Gallbladder disorder**
Skin and subcutaneous tissue disorders	Rash, acne	Urticaria, chloasma which may persist, hirsutism, alopecia	Erythema nodosum	Erythema multiforme
Musculoskeletal and connective tissue disorders				Excerbation of systemic lupus erythematosus
Reproductive system and breast disorders	Breast pain, breast tenderness, breast secretion, change in menstrual flow, change in cervical ectropion and secretion, amenorrhoea, breast enlargement			Vaginal discharge
Congenital, familial and genetic disorders				Excerbation of porphyria
General disorders and	Fluid retention, oedema			

administration site conditions				
Investigations	Weight increased, weight decreased, lipids increased including hypertriglyceridemia	Blood pressure increased		Blood folate decreased (serum folate levels may be depressed by COC therapy)

* may lead to partial or complete loss of vision
** COC's may worsen or accelerate gallbladder disease
*** In women with hereditary angioedema, exogenous oestrogens may induce or exacerbate symptoms of angioedema

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

There have been no reports of serious effects from overdose. Symptoms that may be caused by overdose are nausea, vomiting, drowsiness/fatigue, and slight vaginal bleeding in young girls. There are no antidotes and the treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestin/estrogen combined oral contraceptive

ATC code: G03A07

Pearl Index (excluding pregnancies after missing 3 or more pills) is 0.93 and Pearl Index for method failure is 0.64 (26,554 cycles).

ALESSE is a combination oral contraceptive (COC) containing ethinylestradiol (EE) and levonorgestrel. COCs have been shown to exert their effect by decreasing gonadotropin secretion to suppress ovarian activity, to suppress proliferation of the endometrium and to cause thickening of cervical mucus.

5.2 Pharmacokinetic properties

Pharmacokinetics

Absorption
No specific investigation of the absolute bioavailability of Alesse in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract, but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

After a single dose of Alesse to 22 women under fasting conditions, maximum serum concentrations of levonorgestrel are 2.8 ± 0.9 ng/mL (mean ± SD) at 1.6 ± 0.9 hours. At steady state, attained from day 19 onwards, maximum levonorgestrel concentrations of 6.0 ± 2.7 ng/mL are reached at 1.5 ± 0.5 hours after the daily dose. The minimum serum levels of levonorgestrel at steady state are 1.9 ± 1.0 ng/mL. Observed levonorgestrel concentrations increased

from day 1 (single dose) to days 6 and 21 (multiple doses) by 34% and 96%, respectively. Unbound levonorgestrel concentrations increased from day 1 to days 6 and 21 by 25% and 83%, respectively. The kinetics of total levonorgestrel are non-linear due to an increase in binding of levonorgestrel to sex hormone binding globulin (SHBG), which is attributed to increased SHBG levels that are induced by the daily administration of ethinyl estradiol.

Following a single dose, maximum serum concentrations of ethinyl estradiol of 62 ± 21 pg/mL are reached at 1.5 ± 0.5 hours. At steady state, attained from at least day 6 onwards, maximum concentrations of ethinyl estradiol were 77 ± 30 pg/mL and were reached at 1.3 ± 0.7 hours after the daily dose. The minimum serum levels of ethinyl estradiol at steady state are 10.5 ± 5.1 pg/mL. Ethinyl estradiol concentrations did not increase from days 1 to 6, but did increase by 19% from days 1 to 21.

Table I provides a summary of levonorgestrel and ethinyl estradiol pharmacokinetic parameters.

TABLE I: MEAN (SD) PHARMACOKINETIC PARAMETERS OF Alesse OVER A 21-DAY DOSING PERIOD

Day	C_{max} ng/mL	T_{max} h	AUC ng•h/mL	CL/F mL/h/kg	$V_{\lambda z}$/F L/kg	SHBG nmol/L
Levonorgestrel						
1	2.75 (0.88)	1.6 (0.9)	35.2 (12.8)	53.7 (20.8)	2.66 (1.09)	57 (18)
6	4.52 (1.79)	1.5 (0.7)	46.0 (18.8)	40.8 (14.5)	2.05 (0.86)	81 (25)
21	6.00 (2.65)	1.5 (0.5)	68.3 (32.5)	28.4 (10.3)	1.43 (0.62)	93 (40)
Unbound Levonorgestrel						
	pg/mL	H	pg•h/mL	L/h/kg	L/kg	fu %
1	51.2 (12.9)	1.6 (0.9)	654 (201)	2.79 (0.97)	135.9 (41.8)	1.92 (0.30)
6	77.9 (22.0)	1.5 (0.7)	794 (240)	2.24 (0.59)	112.4 (40.5)	1.80 (0.24)
21	103.6 (36.9)	1.5 (0.5)	1177 (452)	1.57 (0.49)	78.6 (29.7)	1.78 (0.19)
Ethinyl estradiol						
	pg/mL	H	pg•h/mL	mL/h/kg	L/kg	
1	62.0 (20.5)	1.5 (0.5)	653 (227)	567 (204)	14.3 (3.7)	
6	76.7 (29.9)	1.3 (0.7)	604 (231)	610 (196)	15.5 (4.0)	
21	82.3 (33.2)	1.4 (0.6)	776 (308)	486 (179)	12.4 (4.1)	

Distribution

Levonorgestrel in serum is primarily bound to SHBG. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis.

Biotransformation

Levonorgestrel: The most important metabolic pathway occurs in the reduction of the Δ4−3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α,5β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17β-sulfate. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

Ethinyl estradiol: Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of cytochrome P450 (CYP3A) vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation.

Excretion
The elimination half-life for levonorgestrel is approximately 36 ± 13 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in feces. The elimination half-life of ethinyl estradiol is 18 ± 4.7 hours at steady state.

5.3 Preclinical safety data

The toxicity profiles of ethinylestradiol and levonorgestrel alone and in combination are well known. Because of marked species differences, preclinical results possess a limited predictive value for the application of estrogens in humans.

In experimental animals, ethinylestradiol displayed an embryotoxic effect; malformation of the urogenital tract and feminisation of male fetuses were observed.

Levonorgestrel displayed an embryotoxic effect in animal experiments a virilising effect on female fetuses. Reproduction toxicology studies in rats, mice and rabbits provided no other evidence of teratogenicity.

Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risk beyond those discussed in other sections of the SmPC. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Polacrilin potassium
Magnesium stearate

Film coating material:
Hydroxypropyl methylcellulose
Macrogol 1500
Titanium dioxide (E171)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Primary container
PVC/aluminium foil blister pack

Secondary container
Cardboard carton or vinyl wallet in cardboard carton. Each blister strip is packaged in an aluminium foil pouch together with a silica gel desiccant sachet.

Presentation
Pack containing 1x21, 3x21, 6x21 and 13x21 tablets. Not all packs may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 822/65/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 January 2003

Date of last renewal: 07 December 2008

10 DATE OF REVISION OF THE TEXT

December 2014