SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Primolut N 5 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 5 mg norethisterone.

Excipient with known effect: lactose monohydrate 70.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Product description: White, round, cross-scored tablet with an emblem 'AN' in a hexagon on one side (diameter 7 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Method of administration

Tablets are meant to be swallowed whole with liquid.

The effect of Primolut N may be reduced if you forget to take a tablet. Only the last forgotten tablet should be taken as quickly as possible, and the next tablet is taken at the normal time the next day.

If contraception is required, an additional non-hormonal method of contraception must be used (barrier method).

Posology

Dysfunctional bleeding
A uterine bleeding with no associated organ lesions will stop within 1–3 days at a dosage of 1 tablet 3 times daily over 10 days. For the treatment to be successful, the use of Primolut N tablets must be continued for a total of 10 days. About 2–4 days after the discontinuation of treatment, withdrawal bleeding will occur resembling normal menstruation in intensity and duration.

Slight bleeding during treatment
Occasionally slight bleeding may occur even after the initial arrest of bleeding. Tablet taking is not to be interrupted even if there is slight bleeding.

Continued bleeding, heavy breakthrough bleeding
If the bleeding does not stop in spite of regular tablet taking, the possibility of an organic or extragenital cause (e.g. polyps, carcinoma of the cervix, endometrial cancer, myoma, residua in the uterus after abortion, extrauterine pregnancy, clotting disorders) must be considered to decide on further measures. This also applies if heavy bleeding recurs after the arrest of bleeding during continued tablet taking.

Prevention of recurring dysfunctional bleeding
To prevent recurrence of dysfunctional bleeding, the recommendation is to use Primolut N tablets prophylactically during an anovulatory cycle: 1 tablet 1–2 times daily from the 16th to the 25th day of the cycle (1st day of cycle = 1st day of bleeding). Withdrawal bleeding starts a few days after the tablet taking is stopped.

Primary and secondary amenorrhea
The possibility of pregnancy must be excluded before treating secondary amenorrhea with hormone preparations.

A prolactin-producing pituitary tumor should be excluded before starting the treatment since according to current knowledge the possibility that macroadenomas increase in size cannot be excluded when high estrogen doses are used in long-term treatment.

To induce menstrual type bleeding, estrogen should be administered (e.g. for 14 days) before starting treatment with Primolut N. Estrogen is then combined with Primolut N at a dose of 1 tablet 1–2 times daily for 10 days. Withdrawal bleeding starts a few days after the tablet taking is stopped.

If adequate endogenous estrogen production has been achieved, administration of estrogen can be stopped and Primolut N can be used at a dosage of 1 tablet 2 times daily between the 16th and 25th day of the cycle in an attempt to induce cycle bleeding.

Premenstrual syndrome, mastopathy
Premenstrual symptoms such as headache, depressive moods, fluid retention and breast tenderness can be relieved at a dosage of 1 tablet 1–3 times daily during the luteal phase of the cycle.

Timing of menstruation
Primolut N tablets can be used to postpone menstruation but only in such cycles when there is no possibility of pregnancy.

Dosage: 1 tablet 2–3 times daily for no more than 10–14 days, beginning about 3 days before the expected menstruation. Bleeding will start 2–3 days after the medication is stopped.

Endometriosis
Treatment is commenced between the 1st and 5th day of the cycle at a dosage of 1 tablet twice daily. If spotting appears, the dose is increased to 2 tablets twice daily. If the bleeding ceases, the initial dosage can be resumed. The treatment is continued for at least 4–6 months. During the daily treatment, there will usually be no ovulation nor menstruation.

Withdrawal bleeding will start once the hormone treatment is stopped.

4.3 Contraindications

Primolut N is contraindicated if the patient has any of the conditions mentioned below; related data have also been collected from the use of progestin-only preparations and combined contraceptives. Should any of the conditions mentioned below appear during the use of Primolut N, use of the product should be stopped immediately:

- Known or suspected pregnancy
- Breastfeeding
- Active or previous venous or arterial thrombotic/thromboembolic event (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or cerebrovascular accident
- Active or previous prodrome of a thrombosis (e.g. transient ischemic attack, angina pectoris)
- Increased risk of venous or arterial thrombosis (see section 4.4)
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular complications
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of malignant or benign liver tumors
- Known or suspected sex hormone dependent malignancies (e.g. of the genital organs or the breasts)
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Primolut N is contraindicated for concomitant use with the medicinal products containing the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

If the patient has any of the diseases or conditions listed below or it worsens, the risks and benefits must be analyzed before treatment with Primolut N is initiated or continued.

Circulatory disorders

Results from epidemiological studies indicate that the use of ovulation-preventing oral preparations containing estrogen and progestin is associated with an increased risk of thromboembolic diseases. The increase in thromboembolic risk should be kept in mind, especially if the patient has previously had a thromboembolic disease.

Known risk factors for venous thromboembolism include positive personal or family history (venous thromboembolism in a sibling or parent at a relatively young age), age, overweight, long-term immobilization, major surgery or trauma.

The increased risk of venous thromboembolism in the puerperium must be considered.

The treatment must be discontinued immediately if there are symptoms of venous or arterial thromboembolism or suspicion thereof.

Tumors

In rare cases benign and in even rarer cases malignant liver tumors have been reported in users of hormones such as norethisterone. In isolated cases these tumors have led to life-threatening intraabdominal hemorrhages. The possibility of a liver tumor should be included in the differential diagnosis considerations if the user of Primolut N presents with severe upper abdominal pain, liver enlargement, or signs of intraabdominal hemorrhage.

Other

Strict medical supervision during Primolut N treatment is required in patients with diabetes.

Chloasma may occasionally occur, especially in women with a history of chloasma during pregnancy. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Primolut N.

Patients with a history of depression should be carefully monitored, and the use of the preparation must be stopped if depressive symptoms more severe than before occur during the treatment.

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Physical examination

Before the use of Primolut N is started, the patient's medical history has to be taken and she must undergo a thorough medical and gynecological examination, with attention being paid to contraindications (see section 4.3) and warnings (see section 4.4). These examinations should be repeated during the treatment with Primolut N. The frequency and nature of the examinations will depend on the individual patient but they usually include blood pressure measurement, examination of the breasts, pelvis and genital organs, and a cervical smear.

Tablet taking must be discontinued immediately if the patient presents with one of the conditions listed below:

Occurrence for the first time of migrainous headache or more and more frequent occurrence of exceptionally severe headache, sudden perceptual disorder (e.g. disturbances in vision or hearing), first signs of thrombophlebitis or thromboembolic events (for example, unusual pain or swelling in the legs, a stabbing pain on breathing or coughing for no apparent reason), pain and a feeling of tightness in the chest, scheduled surgery (6 weeks prior), immobilization (for example, in connection with an accident), jaundice, or hepatitis with no associated jaundice, generalized itching, significant increase in blood pressure, pregnancy.

Additional warnings based on partial metabolism of norethisterone into ethinyl estradiol

Norethisterone is metabolized partly into ethinyl estradiol after oral administration. This leads to a dose of 4–6 micrograms ethinyl estradiol / 1 mg norethisterone (after oral administration) (see section 5.2).

Due to the partial transformation of norethisterone into ethinyl estradiol, Primolut N tablets are assumed to have similar pharmacological effects than combined contraceptives. Therefore, the following general warnings associated with the use of combined contraceptives must be taken into account as well:

Circulatory disorders
The increased risk of venous thromboembolism (VTE) is highest during the first year a woman uses a combined oral contraceptive (COC), when the use is started for the first time or continued after a break of at least one month.

Epidemiological studies have shown that the incidence of VTE in users of combined oral contraceptives with low estrogen content (< 50 micrograms ethinyl estradiol) ranges from about 20 to 40 cases per 100,000 woman-years, and the risk estimate varies depending on the progestogen used in the product. Correspondingly, the incidence ranges from 5 to 10 cases per 100,000 woman-years for non-users. The use of all COCs is associated with an increased risk of VTE compared with non-users. This increased risk is smaller than that associated with pregnancy, estimated at 60 cases per 100,000 pregnancies.

Venous thromboembolism can be life-threatening or fatal (1–2% of cases).

Venous thromboembolism manifesting as a deep venous thrombosis and/or pulmonary embolism can occur during the use of any combined contraceptive.

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

Symptoms of a venous or arterial thrombotic/thromboembolic event or a stroke 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
- any unusual, severe, prolonged headache
- sudden, partial or complete loss of vision
- diplopia
- slurred speech or aphasia
- vertigo
- collapse with or without focal epileptic seizure
- weakness or very marked numbness suddenly affecting one side or one part of the body
- motor disturbances
- "acute" abdomen.

A possible increased synergistic risk of thrombosis must be considered in women with several risk factors or with high severity of a single risk factor. A single increased risk factor may pose a higher risk than accumulation of several factors. Combined contraceptives must not be prescribed if the risk/benefit assessment is negative (see section 4.3).

The risk of venous or arterial thromboembolic complications or of a cerebrovascular accident increases with:
- age
- obesity (body mass index over 30 kg/m^2)
- positive family history (venous or arterial thromboembolism 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 use of combined oral contraceptives.
- prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue the use of oral contraceptives (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilization.
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- dyslipoproteinemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation.

There is no consensus about the possible connection between varicose veins or superficial thrombophlebitis and venous thrombosis.

Other conditions associated with adverse circulatory events include diabetes, SLE, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell anemia.

An increase in the frequency or severity of migraine attacks (which may be a prodrome of a cerebrovascular event) during the use of combined oral contraceptives may be a reason to stop their use immediately.

Biochemical factors that may indicate a hereditary or acquired predisposition for venous or arterial thrombosis include APC resistance, hyperhomocysteinemia, antithrombin III deficiency, protein C and S deficiency, antiphospholipid antibodies (cardiolipin antibody, lupus anticoagulant).

In the risk/benefit assessment, it should be noted that appropriate care may reduce the related risk of thrombosis and that the risk of thrombosis associated with pregnancy is greater than that of low dose combined contraceptives (< 0.05 mg ethinyl estradiol).

Tumors
The most important risk factor for cervical cancer is a prolonged human papilloma virus (HPV) infection. An increased risk of cervical cancer in long-term users of combined oral contraceptives (COCs) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to confounding effects such as screening for cervical cancer and sexual behavior, including the use of barrier methods for contraception.

A meta-analysis of 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. This risk gradually disappears during the course of 10 years after cessation of COC use. Since 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 during the whole life time. These studies do not provide evidence for causality. 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 users also tend to be less advanced clinically than the cancers diagnosed in never-users.

Malignant tumors can be life-threatening or fatal.

Other conditions
Women with hyperglyceridemia, 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 significant increases are rare.

However, if a sustained clinically significant hypertension develops during the use of a COC, then the use of COCs must be stopped and the hypertension treated. 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; SLE; hemolytic uremic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis-related hearing loss.

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

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until liver function tests return to normal. Discontinuation of COCs is necessary if cholestatic jaundice has occurred previously during pregnancy or earlier use of sex hormones and/or pruritus recurs.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on Primolut N

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

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

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme induction):
Phenytoin, barbiturates, bosentan, primidone, carbamazepine, rifampicin and HIV medications ritonavir, nevirapine and efavirenz, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and herbal products containing St. John's wort (*Hypericum perforatum*).

Substances with variable effects on the clearance of sex hormones
When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors may increase or decrease the plasma concentrations of estrogen or progestin. These changes may be clinically relevant in certain cases.

Substances decreasing the clearance of sex hormones (enzyme inhibitors):
The clinical relevance of potential interactions between enzyme inhibitors and sex hormones remains unknown.
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase the plasma concentrations of estrogen and/or progestin.
Etoricoxib doses of 60 to 120 mg/day have been shown to increase the plasma concentrations of ethinyl estradiol 1.4 to 1.6-fold when taken concomitantly with a combined hormonal medicinal product containing 0.035 mg ethinyl estradiol.

Effects of Primolut N on other medicinal products

Progestins may interfere with the metabolism of other drugs. Accordingly, their plasma and tissue concentrations may either increase (e.g. cyclosporine) or decrease (e.g. lamotrigine).
Clinical research data suggest that ethinyl estradiol inhibits the clearance of CYP1A2 substrates, leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentrations.

Pharmacodynamic interactions

Concomitant use with the medicinal products containing the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, may increase the risk of ALT elevations (see sections 4.3 and 4.4). Use of Primolut N can be restarted 2 weeks following completion of this treatment.

Other forms of interaction

Laboratory tests
Use of progestins may influence the results of certain laboratory tests, including biochemical parameters of the 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 blood coagulation and fibrinolysis. Changes generally remain within the normal range.

4.6 Fertility, pregnancy and lactation

Pregnancy
The product is not to be used during pregnancy.

Breastfeeding
The product should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

No studies have been conducted on how the product affects the ability to drive and use machines.

4.8 Undesirable effects

Adverse effects are more common during the first months of treatment and disappear gradually when the treatment is continued. In addition to the adverse drug reactions mentioned in 4.4 (Special warnings and precautions for use), the adverse reactions listed in the table below have been reported in connection with the use of Primolut N but their causal relationship with the product has not always been established.

The table below presents a summary of adverse reactions by MedDRA system organ classes. The frequency of the adverse reactions is based on post-marketing data and research results.

System Organ Class (MedDRA)	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**
Immune system disorders				Hypersensitivity reactions	
Nervous system disorders		Headache	Migraine		
Eye disorders					Disturbances in vision
Respiratory, thoracic and mediastinal disorders					Dyspnea
Gastrointestinal disorders		Nausea			

System Organ Class (MedDRA)	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)
Skin and subcutaneous tissue disorders				Urticaria Rash	
Reproductive system and breast disorders	Uterine and vaginal bleeding, including spotting* Hypomenorrhea*	Amenorrhea*		Breast tenderness Changes in libido	
General disorders and administration site conditions		Edema			

* In the endometriosis indication

The most appropriate MedDRA term is used in the table to describe a certain reaction and its synonyms and related conditions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 to the following address:

website: www.fimea.fi
Finnish Medicines Agency Fimea
Lääkkeiden haittavaikutusrekisteri [*register of adverse drug reactions*]
PO Box 55
00034 FIMEA

4.9 Overdose

Acute toxicity studies have not indicated a risk of acute adverse effects even in case of inadvertent intake of a multiple therapeutic dose of norethisterone acetate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens, estren derivatives
ATC code: G03DC02

Norethisterone is a potent progestin. In women receiving appropriate estrogen therapy, the complete transformation of the endometrium from the growth phase to the secretion phase is achieved with oral norethisterone doses of 100–150 mg. The effect of Primolut N in the treatment of dysfunctional bleeding, primary and secondary amenorrhea and endometriosis is based on the progestin activity directed at the endometrium.

Secretion of gonadotropin and ovulation are suppressed with a daily 0.5-mg dose of norethisterone. The positive effects of Primolut N on premenstrual symptoms are based on the suppression of ovulatory function.

Due to the endometrial effects, norethisterone can be used to postpone the menstruation.

Norethisterone increases the basal body temperature just like progesterone.

5.2 Pharmacokinetic properties

Absorption

After oral administration norethisterone is absorbed rapidly and completely at a wide dose range. The peak plasma levels of norethisterone (about 16 ng/ml) are reached within about 1.5 hours of taking a Primolut N tablet. Due to high first-pass metabolism, the bioavailability of orally administered norethisterone is about 64%.

Distribution

Norethisterone is bound to serum albumin and to sex hormone-binding globulin (SHBG). Only about 3–4% of the total drug content in serum is found as unbound steroid, 35% is bound to SHBG and 61% to albumin. The distribution volume of norethisterone is 4.4 ± 1.3 l/kg. The concentration in serum after an oral dose decreases in a biphasic way with half-lives of 1-2 hours and about 5–13 hours.

Norethisterone is excreted in breast milk, and its concentration in breast milk is about 10% of the drug content in the mother's plasma regardless of the route of administration. If the average drug peak concentration in the mother's serum is assumed to be about 16 ng/ml and the child receives about 600 ml of milk each day, no more than about 1 μg of the drug (0.02% of the mother's dose) can enter the child's blood circulation.

Biotransformation

Norethisterone is metabolized predominantly as the A-ring double bond is saturated and a 3-keto group is reduced into a hydroxyl group, which leads to conjugation into corresponding sulfates and glucuronides. Some of the metabolites are eliminated relatively slowly from plasma ($t_{1/2}$ about 67 h) and are therefore cumulated in plasma during long-term daily use of norethisterone.

Norethisterone or norethisterone acetate is metabolized partly into ethinyl estradiol in humans after oral administration. This leads to a dose of 4–6 micrograms ethinyl estradiol / 1 mg norethisterone or norethisterone acetate (after oral administration).

Elimination

No significant amounts of norethisterone are excreted unchanged. Predominantly A-ring-reduced and hydroxylated metabolites as well as their conjugates (glucuronides and sulfates) appear in urine and feces in a ratio of 7:3. The majority of renally excreted metabolites are excreted within 24 hours and their half-life is about 19 hours.

Steady state

Even if norethisterone is administered in several doses daily, it is not likely to cumulate in the body due to the relatively short half-life. However, if norethisterone is used concurrently with SHBG inducing substances, such as ethinyl estradiol, the serum content of norethisterone may increase since it binds to SHBG.

5.3 Preclinical safety data

Non-clinical data for norethisterone and its esters reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenicity in addition to what has been described in other sections. However, it should be kept in mind that sex steroids may stimulate the growth of hormone-dependent tissues and tumors.

Studies on toxicity to reproduction and development showed that using the product in high doses at the time of the development of the external genitalia leads to masculinization in female fetuses. Since epidemiological studies show that this effect occurs in humans as well with high doses, it must be noted that Primolut N may provoke virilization in female fetuses if administered during the hormone-sensitive stage of somatic sexual differentiation (from day 45 of pregnancy onwards). However, no indications of teratogenic effects were obtained from the studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
maize starch
magnesium stearate

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

30 tablets in a blister pack (PVC/Aluminum).

6.6 Special precautions for disposal and other handling

No special requirements.

Store all medicines appropriately and keep them out of the reach and sight of children.

7. MARKETING AUTHORIZATION HOLDER

Bayer Oy
Pansiontie 47
20210 Turku

8. MARKETING AUTHORIZATION NUMBER

3817

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 3 August 1966
Date of latest renewal: 24 June 2008

10. DATE OF REVISION OF THE TEXT

17 December 2018