Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Violite 100/20 micrograms film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 micrograms levonorgestrel and 20 micrograms ethinylestradiol.

For the full list of excipients, see section 6.1.
Excipients with known effect:
Each film-coated tablet contains 66.94 mg of lactose

3 PHARMACEUTICAL FORM

Film coated tablets.

Pink, cylindrical, biconvex, film coated tablet of 6 mm approximately.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

The decision to prescribe Violite should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Violite compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

How to take Violite
Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

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 Violite
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 2-5 is allowed, but during the first cycle a barrier method of birth control is recommended in addition for the first 7 days of tablet-taking.

Changing from another combined oral contraceptive (COC), vaginal ring, or transdermal patch)
The woman should start Violite 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. In case a vaginal ring or transdermal patch has been used, the woman should start using Violite preferably on the day of removal, but at the latest when the next application would have been due.

Changing from a progestin-only method (progestin-only pill, injection, implant) or from a progestogen releasing intrauterine system (IUS)
The woman may switch any day from the progestogen-only pill (from an implant or the IUS on the day of its removal, from an injectable when 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.

Accordingly the following advice can be given in daily practice.
Week 1
The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

Week 2
The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Week 3
The risk of reduced reliability is imminent because of the forthcoming tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the current pack is finished, i.e., no gap should be left between packs. 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.
2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the first normal tablet-free interval, the possibility of a pregnancy should be considered.

In case of gastrointestinal upset
In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, the advice concerning missed tablets, as given in section 4.2 "management of missed tablets", is applicable.

How to shift periods or how to delay a period
To delay a period, the woman should continue with another pack of Violite 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 Violite is then resumed after the usual 7-day, tablet-free interval.

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

Special populations
Paediatric population
Violite is only indicated after menarche.

Elderly
Not applicable. Violite is not indicated after menopause.

Hepatic impairment
Violite is contraindicated in women with severe hepatic diseases. See also section 'Contraindications'.

Renal impairment
Violite has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

Method of administration
Oral use

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:

- Presence or risk of venous thromboembolism (VTE)
    - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
    - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
    - Major surgery with prolonged immobilisation (see section 4.4)
    - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)
- Presence or risk of arterial thromboembolism (ATE)
    - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
    - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).

- History of migraine with focal neurological symptoms.
- A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:

- diabetes mellitus with vascular symptoms
- severe hypertension
- severe dyslipoproteinaemia

- Presence or history of severe hepatic disease, e.g. active viral hepatitis and severe cirrhosis, as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Known or suspected pregnancy
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substances (levonorgestrel, ethinylestradiol) or to any of the excipients of Violite listed in section 6.1.
- Violite is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, medicinal products containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special warnings and precautions for use

Warnings
If any of the conditions or risk factors mentioned below is present, the suitability of Violite should be discussed with the woman.
In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Violite should be discontinued.

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

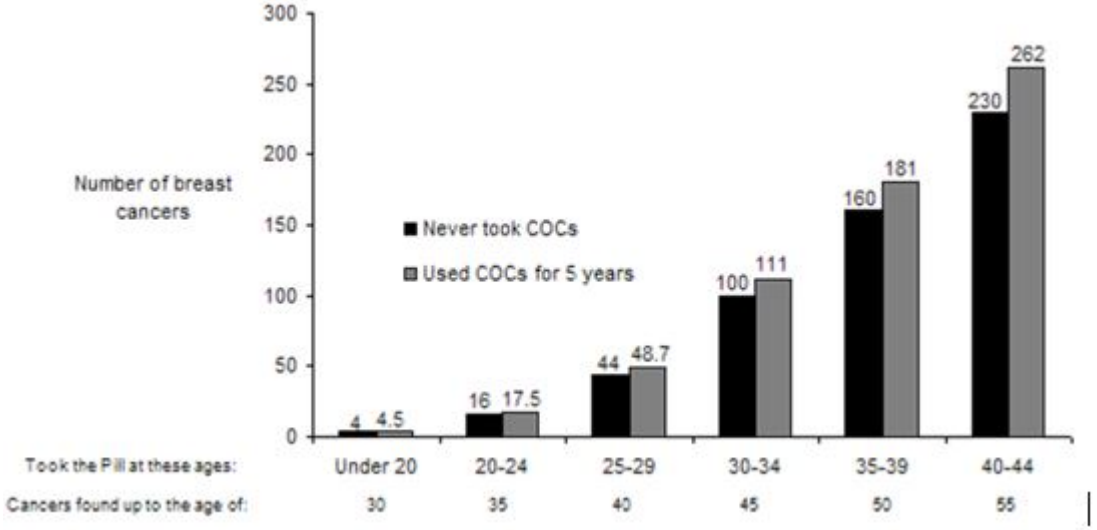
The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel (including Violite), norgestimate or norethisterone are associated with the lowest risk of VTE. The decision to use Violite should be taken after a discussion with the woman to ensure she understands the risk of VTE with Violite, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.**

In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

It is estimated that out of 10,000 women who use a CHC that contains levonorgestrel, about 6[1] will develop a VTE in a year**.**

This number of VTEs per year is fewer than the number expected in women during pregnancy or in the postpartum period.

VTE may be fatal in 1-2% of cases **.**



[1] Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6
Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

Risk factors for VTE
The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).
Violite is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the patch/pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Violite has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.
The increased risk of thromboembolism in pregnancy, and particularly the 6 week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking,
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).
Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.
If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)
Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE
The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Violite is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).
Table: Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE
In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

Arterial thromboembolic events may be life threatening or may have a fatal outcome.
The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A COC should not be prescribed in case of a negative risk benefit assessment (see section 4.3).

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

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (<0.05 mg ethinylestradiol).
Conditions which require strict medical supervision
The decision to prescribe the COC must be made using clinical judgement and in consultation with the woman. Exacerbation or first appearance of any of these conditions or risk factors may indicate that use of the oral contraceptive should be discontinued. The woman should contact her physician, who should then decide on whether COC use should be discontinued:

- diabetes mellitus with mild vascular disease or mild nephropathy, retinopathy or neuropathy
- hypertension that is adequately controlled, i.e. systolic >140 to159 mmHg or diastolic >90 to 94 mmHg (see also Section 4.4 'Reasons for stopping oral contraception immediately')
- porphyria
- obesity
- migraine
- cardiovascular diseases

Reasons for stopping oral contraception immediately:
When stopping oral contraception non-hormonal contraception should be used to ensure contraceptive protection is maintained.

1. Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches
2. Sudden disturbances of vision, of hearing or other perceptual disorders
3. First signs of thrombosis or blood clots (e.g. unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason). Feeling of pain and tightness in the chest
4. At least four weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Do not restart

until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin

5. Onset of jaundice, hepatitis, itching of the whole body
6. Significant rise in blood pressure
7. Severe upper abdominal pain or liver enlargement
8. Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy (see section 4.4 'Conditions which deteriorate in pregnancy or during previous COC use' under 'Other conditions')

Tumours

Numerous epidemiological studies have been reported on the risks of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives. The evidence is clear that high dose combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer. However, it is not clear whether low dose COCs confer protective effects to the same level.

Cervical cancer

The most important risk factor for cervical cancer is persistent HPV infection. 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

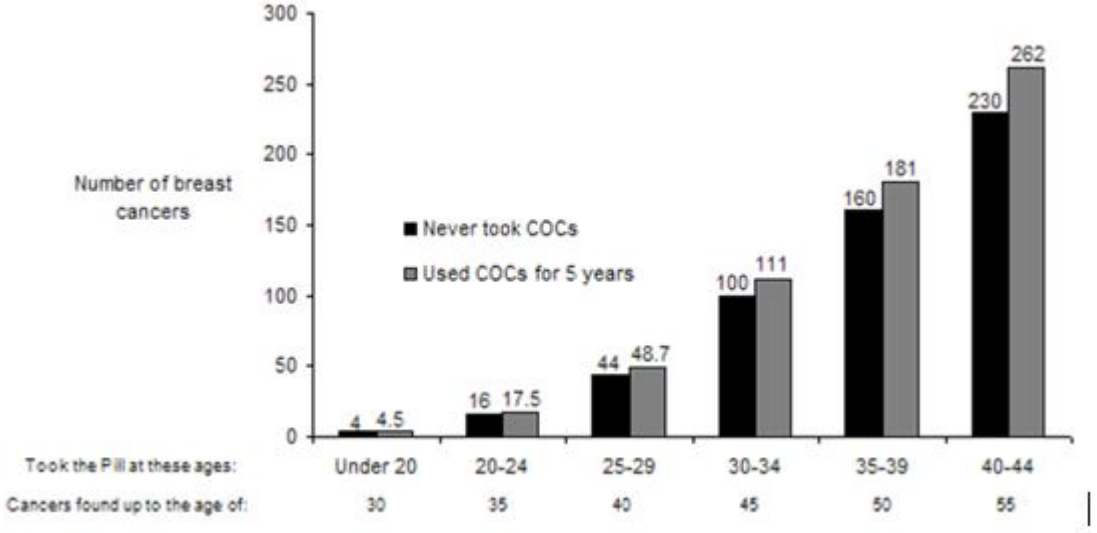
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.

Breast cancer is rare among women under 40 years of age whether or not they take COCs. Whilst this background risk increases with 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 (see bar chart).

The most important risk factor for breast cancer in COC users is the age women discontinue the COC; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess.

The possible increase in risk of breast cancer should be discussed with the user and weighed against the benefits of COCs taking into account the evidence that they offer substantial protection against the risk of developing certain other cancers (e.g. ovarian and endometrial cancer).

Estimated cumulative numbers of breast cancers per 10,000 women diagnosed in 5 years of use and up to 10 years after stopping COCs, compared with numbers of breast cancers diagnosed in 10,000 women who had never used COCs.



Liver cancer

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

Malignancies may be life threatening or may have a fatal outcome.

Other conditions
The possibility cannot be ruled out that certain chronic diseases may occasionally deteriorate during the use of combined oral contraceptives.

Known hyperlipidaemias
Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs. Women with hyperlipidaemias are at an increased risk of arterial disease (see section 4.4 'Risk of arterial thromboembolism (ATE)'). However routine screening of women on COCs is not appropriate.

Blood pressure
Hypertension is a risk factor for stroke and myocardial infarction (see section 4.4 'Risk of arteria thromboembolism (ATE)'). Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if sustained hypertension develops during the use of a COC, antihypertensive treatment should normally be instigated at a level of 160/100 mm Hg in uncomplicated patients or at 140/90 mm Hg in those with target organ damage, established cardiovascular disease, diabetes or with increased cardiovascular risk factors. Decisions about the continued use of the COC should be made at lower BP levels, and alternative contraception may be advised. If, during the use of a COC in preexisting 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.

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. Consideration should be given to stopping Violite if any of the following occur during use:

- jaundice and/or pruritus related to cholestasis;
- gallstones;
- porphyria;
- systemic lupus erythematosus;
- haemolytic uremic syndrome;
- Sydenham's chorea;
- herpes gestationis;
- otosclerosis-related hearing loss;
- sickle cell anaemia
- renal dysfunction
- depression
- any other condition an individual woman has experienced worsening of during pregnancy or previous use of COCs.

Angioedema
Exogenous estrogens may induce or exacerbate symptoms of hereditary and aquired angioedema.

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

Diabetes (without vascular involvement)
Insulin-dependent diabetics without vascular disease can use COCs. However it should be remembered that all diabetics are at an increased risk of arterial disease and this should be considered when prescribing COCs. Diabetics with existing vascular disease are contraindicated from using COCs (see section 4.3 Contraindications).

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed, particularly in the early stage of COC use.

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

Chloasma
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.

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) should not be used while taking Violite due to the risk of decreased plasma concentrations and reduced clinical effects of Violite (see section 4.5 Interactions).

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.

Medical examination/consultation
Prior to the initiation or reinstitution of Violite 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'). Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

It is important to draw the woman's attention to the information on venous and arterial thrombosis, including the risk of Violite compared with other CHC, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

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.

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

Reduced cycle control
Reduction of menstrual flow is not abnormal and it is to be expected in some patients. Indeed, it may be beneficial where heavy periods were previously experienced.

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in Section 4.2, 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.

Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of oral contraceptives, especially when these conditions existed prior to use. Women should be informed of this possibility.

Psychiatric disorders
Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medications on Violite
Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.
Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

Reduced absorption:
Drugs that increase gastrointestinal motility, e.g. Metoclopramide, may reduce hormone absorption.

Enzyme induction (increase of 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*)). Enzyme induction can already be observed after a few 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 about 4 weeks. The inducing effect with St John's Wort can persist for at least 2 weeks after cessation of treatment. If COC's and St John's Wort are used concomitantly, a non-hormonal backup method of birth control is recommended.

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

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

Substances decreasing the clearance of COCs (enzyme inhibitors):
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole) verapamil, diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestin or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

Pharmacodynamic interactions
During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing 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 ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3).
Therefore, Violite users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these drug regimens. Violite can be restarted 2 weeks following completion of treatment with these drug regimens.

Effects of COCs on other medication
Oral contraceptives may interfere with the metabolism of certain other drugs. Increased plasma concentrations of cyclosporin, tizanidine, theophylline 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.

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism-based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while

plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

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. Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

4.6 Fertility, pregnancy and lactation

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

Pregnancy
Violite is not indicated during pregnancy.
If the woman becomes pregnant while using Violite 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.
The increased risk of VTE during the postpartum period should be considered when re-starting Violite (see section 4.2 and 4.4).

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 Violite on the ability to drive and use machines has not been systematically evaluated. Patients should exercise caution until they know that Violite 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 reported adverse events during phase III studies and postmarketing surveillance in women using Violite are headache, including migraines, depressed mood, altered mood, dysmenorrhea, abdominal pain, increased weight, nausea, breast pain, breast tenderness and breakthrough bleeding/spotting. They occur in ≥ 1 % of users.

Other adverse events have been reported in women taking Violite*:

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)	Not known (Frequency cannot be estimated from the available data)
Immune system disorders			Hypersensitivity	Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
Metabolism and		Fluid retention		Hypertriglyceridemia

nutrition disorders				
Psychiatric disorders	Depressed mood, Mood altered	Libido decreased	Libido increased	
Nervous system disorders	Headache	Migraine		Exacerbation of chorea
Eye disorders			Contact lens intolerance	
Vascular system disorders			Venous thromboembolism (VTE)**, Arterial thromboembolism (ATE)	
Hepatobiliary disorders				Liver function disturbances
Gastrointestinal disorders	Nausea, Abdominal pain	Vomiting, Diarrhoea		Crohn's disease, Ulcerative colitis
Skin and subcutaneous tissue disorders		Rash, Urticaria	Erythema nodosum, Erythema multiforme	Chloasma
Reproductive system and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge, Breast discharge	Reduced menstrual flow, spotting, breakthrough bleeding and missed withdrawal bleeding, post pill amenorrhoea
Investigations	Weight increased		Weight decreased	

* - The most appropriate MedDRA term (version 12.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed but should be taken into account as well.
** - Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives.
'Venous and arterial thromboembolic events' summarizes the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/ Cerebral infarction and stroke not specified as hemorrhagic.

Description of selected adverse reactions
An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections "Contraindications", "Special warnings and precautions for use"):

Tumors

- The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.
- Liver tumors (benign and malignant)

Other conditions

- Women with hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- Hypertension

- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema
- Liver function disturbances
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis.
- Chloasma

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 'Interaction with other medicinal products and other forms of interaction')

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, Website: www.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: Progestogens and estrogens, fixed combinations
ATC code: G03AA07

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

Violite is an oestrogen-progestogen combination which acts by inhibiting ovulation by suppression of the mid-cycle surge of luteinising hormone, the inspissation of cervical mucus producing a barrier to sperm, and the rendering of the endometrium unreceptive to implantation.

Post Authorization Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges between 7-10 per 10,000 woman years in low estrogen dose (< 50 µg ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4 per 10,000 woman years in non-pregnant non-COC users, and ranges between 20 to 30 per 10,000 pregnant women or post partum.
As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and the bleeding is lighter.
The latter may result in a decrease in the occurrence of iron deficiency. Apart from this, there is evidence of a reduced risk of endometrial cancer and ovarian cancer. Furthermore, the higher dosed COCs (0.05 mg ethinylestradiol) have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to lower-dosed COCs remains to be confirmed.

5.2 Pharmacokinetic properties

Levonorgestrel
Absorption
Orally administered levonorgestrel is rapidly and completely absorbed. Peak serum concentrations of 2.3 ng/mL are reached at about 1.3 hours after single ingestion. Levonorgestrel is almost completely bioavailable after oral administration. Maximum active substance levels of approx 3 ng/mL were reached in serum just one hour after ingestion of levonorgestrel/ethinylestradiol tablets. The serum concentrations subsequently fell in 2 phases with half-lives of around 0.5 hours and 20 hours. The metabolic clearance rate from plasma is approx. 1.5 mL/min/kg.

Distribution
Levonorgestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1.1% of the total serum drug concentrations are present as free steroid, approximately 65% are specifically bound to SHBG and about 34% are non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG influences the proportion of levonorgestrel bound to the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is 129 L.

Biotransformation
Levonorgestrel is extensively metabolized. The major metabolites in the plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydro-levonorgestrel. Based on *in vitro* and *in vivo* studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel. The clearance rate from serum is approximately 1.0 mL/min/kg.

Elimination
Levonorgestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 25 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:1. The half-life of metabolite excretion is about 1 day.

Steady-state conditions
Following daily ingestion drug serum levels increase about threefold reaching steady-state conditions during the second half of a treatment cycle. Levonorgestrel pharmacokinetics are influenced by SHBG levels, which are increased 1.5-1.6 fold when co-administered with ethinylestradiol. At steady-state, clearance rate and volume of distribution are slightly reduced to 0.7 mL/min/kg and about 100 L, respectively.

Ethinylestradiol
Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 50 pg/mL are reached within 1-2 hours. During absorption and first-liver passage, ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of about 45% with a large interindividual variation of about 20-65%.

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

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

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

Steady-state conditions
Ethinylestradiol serum concentrations increase about two-fold after daily oral administration of levonorgestrel/ethinylestradiol. According to the variable half-life of the terminal disposition phase from serum and the daily ingestion, steady-state serum levels of ethinylestradiol will be reached after about one week.

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 Summary of Product Characteristics. 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,
Polacrilin potassium,
Microcrystalline cellulose,
Magnesium stearate.

Tablet coating:
Opadry II pink, consisting of:
Macrogol 3350,
Titanium dioxide (E171)
Polyvinyl alcohol,
Talc (E533b),
Iron oxide red (E172),
Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Violite is packed in PVC/PVDC/Aluminium blister packs of 21 tablets.
Each pack may contain either:
1 × 21 film-coated tablets or
3 × 21 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product of waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc
Gyömroi út 19-21
H-1103, Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th June 2016

Date of last renewal: 21st April 2021

10 DATE OF REVISION OF THE TEXT

April 2024