SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ambelina 150/30 microgram film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ambelina tablet contains:

0.15 mg levonorgestrel and 0.03 mg ethinylestradiol

Excipient with known effect: Each tablet contains 84 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Yellow, round tablet, with a diameter of 6 mm and thickness less than 4 mm approximately.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral Contraception.

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

4.2 Posology and method of administration

Route of administration: oral use

Posology

How to take Ambelina

Tablets must be taken at approximately the same time each day, with some liquid if 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 usually occurs.

The bleeding usually starts within 2 to 3 days after the last tablet and may not end before the next pack is started.

How to start Ambelina

• No preceding hormonal contraceptive use [in the past month]:

Tablet-taking is started on day 1 of the woman's natural cycle (the first day of menstrual bleeding). Starting on day 2-day 5 is allowed, but in that case an additional nonhormonal contraceptive method (barrier method) should be used during the first 7 days of treatment.

• Changing from another combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, transdermal patch): The use of Ambelina tablets is preferably started on the day after the last active tablet of the previous COC (or after removal of the ring or patch), but at the latest on the day following the usual tablet-free (ring-free, patch-free) break or the last placebo tablet of the previous hormonal contraceptive.

• Changing from a progestogen-only method (oral contraceptive with only progesterone, injection, implant) or progestogen-releasing intrauterine system (IUS)

If the oral contraceptive with only progesterone was used previously, the change can take place on any day; the change from an implant or IUS must take place on the day of removal, and from an injectable contraceptive at the time when the next injection would be due. In each case, the use of an additional nonhormonal contraceptive method (barrier method) is necessary during the first 7 days taking Ambelina.

• Following first-trimester abortion

Ambelina may be started immediately. In this case, no additional contraceptive method is required.

• Following childbirth or second-trimester abortion

The use of the tablets is started 21 to 28 days after delivery or second-trimester abortion. When starting later, an additional non-hormonal contraceptive method (barrier method) should be used during the first 7 days of tablet-taking If intercourse has already taken place, pregnancy must be ruled out before starting the use of Ambelina, or the woman must wait until her first menstrual period.

For breast-feeding, see Section 4.6 Pregnancy and Lactation.

Management of missed tablets

If **one tablet is missed, but remembered and taken within 12 hours** of the usual time, then contraceptive protection is not reduced. The subsequent tablets should be taken at the usual time.

If the usual tablet-taking time is missed by more than 12 hours, full contraceptive protection is no longer assured. The following two basic rules apply when a tablet is missed:

1. Tablet-taking must never be discontinued for longer than 7 days.
2. Tablets must be taken regularly for a minimum of 7 days in order to effectively suppress the hypothalamic-pituitary-ovarian axis.

Therefore, the following procedures should be followed in the event that tablets are missed:

• Week 1

The last tablet missed should be taken as soon as possible, even if this means taking 2 tablets in one day. The remaining tablets are then taken at the usual time. In addition, a nonhormonal contraceptive method such as a condom should be used for the next 7 days. If intercourse took place in the 7 days before missing the tablet, the possibility of a pregnancy must be considered. The more tablets missed and the closer they are to the usual tablet-free interval, the higher the risk of pregnancy.

• Week 2

The last tablet missed should be taken as soon as possible, even if this means taking 2 tablets at the same time. The remaining tablets are then taken at the usual time. Provided that the user has taken the tablets correctly in the 7 days prior to the first missed tablet, it is not necessary to use additional contraceptive measures. However, if this is not the case or she has missed more than one tablet, the user should be advised to take additional contraceptive precautions for the next 7 days.

• Week 3

The risk of reduced reliability is imminent because of the forthcoming tablet-free interval. However, by adjusting the tablet-taking schedule, reduced contraceptive protection can still be prevented. Therefore, by adhering to one of the following two options, there is no need to take additional contraceptive precautions, provided that in the 7 days prior to the first missed tablet the user has taken all the tablets correctly. If this is not the case, the user should be advised to follow the first of these two options and take additional precautions for the next 7 days:

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 the tablets at the usual time. The next pack must be started as soon as the current pack is finished, i.e. without a break between packs. The user is unlikely to have withdrawal bleeding until the end of the second pack but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. It is also possible to stop taking tablets from the current pack. The woman must then have a tablet-free break of 7 days, including the days she missed tablets, and then continue with the next pack.

If the user misses several tablets and subsequently has no withdrawal bleeding in the first normal tablet-free interval, the possibility of pregnancy should be considered.

Advice in case of gastrointestinal disorders

In case of severe gastrointestinal disorders (vomiting or diarrhea), absorption of the active ingredients may not be complete and additional contraceptive measures should be taken.

If vomiting or severe diarrhea occurs within 3 to 4 hours after taking a tablet, a new 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 woman should apply the advice given for missed tablets. If the woman does not want to change her normal tablet schedule, she has to take the extra tablets from another pack.

Changing the starting day of a withdrawal bleeding or delaying the withdrawal bleeding

To delay the withdrawal bleeding, the user should go directly to the next blister pack without a tablet-free interval. The withdrawal bleeding can be delayed as long as wished, but not later than till the end of the second pack. During this time, the woman may experience breakthrough bleeding or spotting. After the subsequent usual 7-day tablet-free interval, Ambelina tablets should be continued as usual.

To change the starting day of her periods to another day of the week, the user can be advised to shorten the next tablet-free interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have withdrawal bleeding and will experience breakthrough bleeding and spotting during the next pack (just as when delaying a period).

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. If any of the conditions appear for the first time during CHC use, the product should 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 anti-phospholipid 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, as long as liver function values have not returned to normal,
- presence or history of liver tumors (benign or malignant),
- known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts),
- undiagnosed vaginal bleeding,
- hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Ambelina is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, or medicinal product containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

4.4 Special warnings and precautions for use

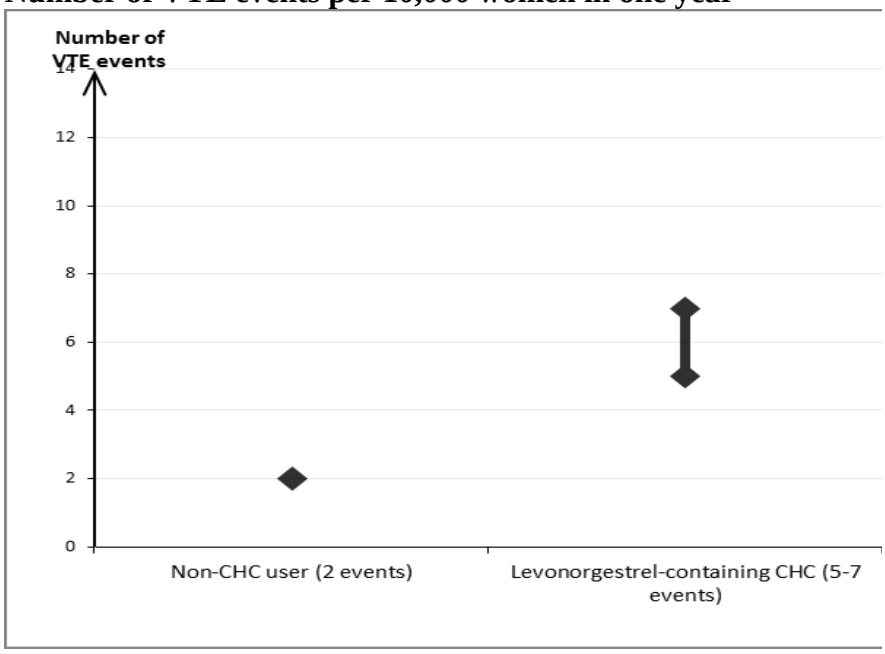
Warnings

If any of the conditions or risk factors mentioned below is present, the suitability of Ambelina 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 Ambelina should be discontinued.

Risk of venous thromboembolism (VTE)
The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, such as Ambelina, norgestimate or norethisterone are associated with the lowest risk of VTE. The decision to use Ambelina should be taken after a discussion with the woman to ensure she understands the risk of VTE with Ambelina, 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.

Number of VTE events per 10,000 women in one year



[1] Mild-point of rango 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).
Ambelina 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 pill (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 Ambelina 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 "Fertility, 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). Ambelina 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/m^2)	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

ALT elevations
During clinical trials with patients treated for hepatitis C virus infections (HCV) with the 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 frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

Tumors

Some epidemiological studies have reported an increased risk of cervical cancer in long-term COC users but there continues to be controversy about the extent to which this finding is attributable to the influence of confounding factors such as sexual behaviour and human papilloma virus (HPV).

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 combined oral contraceptive. This excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation.

The increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less clinically advanced than those diagnosed in never users.

In rare cases, benign, and even more rarely, malignant liver tumors have been reported in COC users. In isolated cases, these tumors have led to life-threatening intra-abdominal bleeding. The possibility of a liver tumor should be considered in the differential diagnosis of women taking COCs who report sever upper abdominal pain, liver enlargement or signs of intra-abdominal bleeding.

Other conditions

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

Although small increases in blood pressure have been observed 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.

The following conditions have been reported to occur or deteriorate during 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 uraemic syndrome, Sydenham's chorea, herpes gestationis and otosclerosis-related hearing loss.

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

Acute or chronic liver function disorders require discontinuation of COC use until liver function markers return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus that first occurred during pregnancy or during previous sex hormone use requires discontinuation of COCs.

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

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

Chloasma may particularly occur, especially in women with a history of chloasma gravidarum. If there is a tendency to chloasma, sunlight and ultraviolet radiation should be avoided when using combined oral contraceptive.

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.

Medical examination/consultation

Prior to the initiation or reinstitution of Ambelina 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) and warnings (see section 4.4.). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Ambelina compared with other CHCs, 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 informed that hormonal contraceptives do not protect against HIV infection (AIDS) and other sexually transmissible diseases.

Reduced efficacy

The contraceptive efficacy of Ambelina combined oral contraceptive may be reduced

o if tablets are missed (see section 4.2.),

o in the event of gastrointestinal disorders (see section 4.2.),

o if certain other drugs are being taken concomitantly (see section 4.5).

Reduced cycle control

When using any COC, 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, possible non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancies 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 instructions given in section 4.2, it is

unlikely that the woman is pregnant. However, if the COC has not been taken according to these instructions prior to the first missed withdrawal bleed, or if two withdrawal bleeds are missed, pregnancy must be ruled out before continuing with COC use.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the 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 medicinal products on Ambelina

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may impair the contraceptive efficacy and/or lead to breakthrough bleeding and/or contraceptive failure.

Management
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.

Short-term treatment
Women on treatment with enzyme inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. 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 right after the previous one without the usual tablet-free interval.

Long-term treatment
In women on long-term treatment with enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.
The following interactions have been reported in the literature.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:
Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (*Hypericum perforatum*).

Substances with variable effects on the clearance of COCs
When co-administered with COCs, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases. Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by

women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Substances decreasing the clearance of COCs (enzyme inhibitors)
The clinical relevance of potential interactions with enzyme inhibitors remains unknown.
Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the oestrogen or the progestin or both.

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

- Effects of Ambelina on other medicinal products

Oral contraceptives may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporine) or decrease (e.g. lamotrigine)

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

- 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 ethinylestradiolcontaining 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, Ambelina users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with these drug regimens. Ambelina can be restarted 2 weeks following completion of treatment with these drug regimens.

- 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 blood coagulation and fibrinolysis. The changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ambelina is not indicated in pregnancy.

If the woman becomes pregnant while using Ambelina tablets, further intake must be stopped immediately.

However, most epidemiological studies have revealed neither an increased risk for birth defects in children born to women who used COCs before pregnancy, nor any teratogenic effects at unintentional intake of contraceptive pills in early pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting Ambelina (see section 4.2 and 4.4).

Breast-feeding

Breast-feeding may be influenced by contraceptive pills as they may reduce the amount of breast milk and change its composition. Therefore, the use of combined oral contraceptives should generally not be recommended until the nursing mother has weaned her child off breast milk.Small amounts of contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts may affect the child.

4.7 Effects on ability to drive and use machines

Ambelina has no or negligible influence on the ability to drive and use machines**.**

4.8 Undesirable effects

The following undesirable effects have been observed with use of combined oral contraceptives containing ethinylestradiol/levonorgestrel:

Organ system	**Adverse events reported in clinical trials**			
	Common (≥ 1/100 to < 1/10)	**Uncommon (≥ 1/1,000 to <1/100)**	**Rare (≥1/10,000 to < 1/1,000)**	**Unknown**
Eye disorders			Contact lens intolerance	
Gastrointestinal disorders	Nausea abdominal pain	Vomiting Diarrhea		
Immune system disorders			Hypersensitivity	Exacerbation of symptoms of hereditary and acquired angioedema.
Investigations	Weight increased		Weight decreased	
Metabolism and nutrition disorders		Fluid retention		
Nervous system disorders	Headache	Migraine		
Vascular			Venous	

Organ system	Adverse events reported in clinical trials			
	Common (≥ 1/100 to < 1/10)	**Uncommon (≥ 1/1,000 to <1/100)**	**Rare (≥1/10,000 to < 1/1,000)**	**Unknown**
system disorders			thromboembolism (VTE) Arterial thromboembolism (ATE)	
Psychiatric disorders	Depressed mood Mood altered	Libido decreased	Libido increased	
Reproductive system and breast disorders	Breast tenderness Breast pain	Breast enlargement	Breast discharge Vaginal discharge	
Skin and subcutaneous tissue disorders		Rash Urticaria	Erythema nodosum Erythema multiforme	

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 4.3 and 4.4:

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. For
further information, see sections 4.3 and 4.4**.**

- Liver tumors (benign and malignant)

Other conditions

- Increased risk of pancreatitis in women with hypertriglyceridemia
- 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
- 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 4.5).

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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
No serious adverse reactions due to overdose have been reported. Symptoms of overdose of a combined oral contraceptive may include: nausea, vomiting; in adolescents, slight vaginal bleeding may occur. There is no specific antidote. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: progestogen and estrogens, fixed combinations

ATC code: G03AA07

Overall Pearl Index (method failure + patient failure): 0.59 (upper tow-sided 95% confidence limit: 0.85).

The contraceptive effect of COCs is based on the interaction of various factors. The most important are the inhibition of ovulation and changes in the cervical mucus.

5.2 Pharmacokinetic properties

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed rapidly and completely.
Peak serum concentrations of about 100 pg/ml are reached within 1–1.5 hours after taking 30 microgram ethinylestradiol. During absorption and first-pass hepatic

metabolism ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 40-60% (interindividual variation).

Distribution

Ethinylestradiol is highly (approximately 98%) but nonspecifically bound to serum albumin, and induces an increase in the serum concentrations of sex hormone binding globulin (SHBG). The absolute volume of distribution of ethinylestradiol is 5 L/kg.

Biotransformation

Ethinylestradiol is subject to significant gut and hepatic first-pass metabolism. Ethinylestradiol and its oxidative metabolites are primarily conjugated with glucuronide or sulfate. The metabolic clearance rate was reported to be about 2.3–7 ml/min/kg.
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.

Elimination

Ethinylestradiol levels in serum decrease in two phases characterized by half-lives of about 1-2 hours and about 20 hours, respectively. Ethinylestradiol is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of 4:6. The elimination half-life is about 1 day.

Steady-State

Ethinylestradiol concentration in serum increases about 40% after continuous use of tablets containing 150 microgram levonorgestrel and 30 microgram ethinylestradiol. Due to the variable half-life of the terminal phase in serum clearance and the daily administration, steady-state conditions are reached after approximately 5 daily administrations

Levonorgestrel

Absorption

Orally administered levonorgestrel is absorbed rapidly and completely. Peak serum levonorgestrel levels of about 3 ng/ml are reached around 1 hour after taking 150 microgram levonorgestrel. The bioavailability of levonorgestrel after oral administration is nearly 100%.

Distribution

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only 1.5% of the total serum drug concentrations are present as free steroid, approximately 65% are specifically bound to SHBG and approximately 35% are non-specifically bound to albumin. The ethinylestradiol-induced increase in the SHBG concentration influences the relative distribution of levonorgestrel into different protein fractions. Induction of the binding protein causes an increase in the SHBG-bound fraction and a decrease in the albumin-bound fraction.

Biotransformation

Levonorgestrel is completely metabolized. The most important metabolic pathways are the reduction of Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation. Furthermore, CYP3A4 is involved in the oxidative metabolism of LNG, however,
in vitro data suggest that this metabolic route is less relevant than reduction and conjugation. The metabolic clearance rate from serum is approximately 1.0 ml/min/kg.

Elimination

Serum levonorgestrel levels decrease in two phases. The terminal phase is characterized by a half-life of approximately 20 hours. Levonorgestrel is metabolised before being excreted. Its metabolites are at a urinary to biliary (feces) ratio of about 1:1. The elimination half-life of the metabolites is about 1 day.

Steady-state

During the continuous use of Ambelina tablets, serum levonorgestrel levels increase about fourfold reaching steady-state conditions during the second half of the treatment cycle. The pharmacokinetic of levonorgestrel is influenced by SHBG levels in serum, which increase by 1.7-fold after daily ingestion of a combined oral contraception containing estradiol. This effect leads to a reduction of the clearance rate to about 0.7 ml/min/kg at steady state.

5.3 Preclinical safety data

Preclinical data for ethinylestradiol and levonorgestrel from conventional studies of general toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction have not revealed other effects than those which can be explained bases on the known hormone profile of ethinylestradiol and levonorgestrel. However, it should be remembered that sex steroids can promote the growth of certain hormone-dependent tissues and tumors.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Povidone

Crospovidone

Magnesium stearate

Coating:

Polyvinyl alcohol, partial hydrolized

Titanium dioxide (E171)

Macrogol

Talc (E553b)

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 30ºC.

6.5 Nature and contents of container

Blisters of aluminium push-thru foil and PVC/PVDC film.

It is available in boxes of 1, 3, 6 and 13 packs (blisters), each one containing 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Ltd.

Key House, Sarum Hill,

Basingstoke,

RG21 8SR,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0667

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/12/2023

10 DATE OF REVISION OF THE TEXT

08/11/2024