SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bimizza 150 microgram/20 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 micrograms desogestrel and 20 micrograms ethinylestradiol.

Excipients: 1 uncoated tablet contains 58 mg of lactose anhydrous

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Each tablet is round, white to off-white, 5.00 mm, uncoated, biconvex, debossed with '141' on one side and other side plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

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

4.2 Posology and method of administration

Route of administration: Oral use

How to take Bimizza

Tablets must be taken every day at about the same time, with some liquid as needed, in the order shown on the blister pack. 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 bleeding usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to start Bimizza

No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding) in which case no extra contraceptive precaution are necessary.

If menstruation has already begun, (that is 2, 3, or 4 days previously), tablet taking should commence on day 5 of the menstrual period. In this case additional contraceptive precautions must be taken for the first 7 days of tablet taking. If menstruation began more than 5 days previously then the patient should be advised to wait until her next menstrual period before starting to take Bimizza.

Changing from a 21 day pill or another 22 day pill to Bimizza:
All tablets in the old pack should be finished. The first Bimizza tablet is taken the next day i.e. no gap is left between taking tablets nor does the patient need to wait for her period to begin. Tablets should be taken as instructed in 'How to take Bimizza'. Additional contraceptive precautions are not required. The patient will not have a period until the end of the first Bimizza pack, but this is not harmful, nor does it matter if she experiences some bleeding on tablet-taking days.

Changing from a combined Every Day Pill (28 day tablets) to Bimizza:
Bimizza should be started after taking the last active tablet from the 'Every Day Pill' pack (i.e. after taking 21 or 22 tablets). The first Bimizza tablet is taken the next day i.e. no gap is left between taking tablets nor does the patient need to wait for her period to begin. One tablet is taken daily at the same time, without interruption for 21 days, followed by a 7 day tablet-free period. Each subsequent pack is started after the 7 day tablet-free period has elapsed. Additional contraceptive precautions are not required. Remaining tablets from the Every Day (ED) pack should be discarded. The patient will not have a period until the end of the first Bimizza pack, but this is not harmful, nor does it matter if she experiences some bleeding on tablet-taking days.

Changing from a Progestogen -only Pill (POP or Mini Pill) to Bimizza:
The first Bimizza tablet should be taken on the first day of the period, even if the patient has already taken a mini pill on that day. One tablet is taken daily at the same time, without interruption for 21 days, followed by a 7 day tablet-free period. Each subsequent pack is started after the 7 day tablet-free period has elapsed. Additional contraceptive precautions are not then required. All the remaining Progestogen-only pills in the mini pill pack should be discarded. If the patient is taking a (mini) pill, then she may not always have a period, especially when she is breast feeding. The first Bimizza tablet should be taken on the day after stopping the mini pill. All remaining pills in the mini pill packet must be discarded. Additional contraceptive precautions must be taken for the first seven days.

- *Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch)*

The woman should start taking Bimizza 150 microgram/20 microgram Tablets preferably on the day after the last active tablet (the last tablet containing the active

substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or a transdermal patch has been used, the woman should start using Bimizza 150 microgram/20 microgram Tablets preferably on the day of removal, but at the latest when the next application would have been due.

- *Changing from a progestogen-only-method (injection, implant) or from a progestogen-releasing intrauterine system (IUS)*

The woman may switch any day from the progestogen-only pills (from an implant or the IUS on the day of its removal; from an injectable when the next injection would be due) but should be advised to additionally use a contraceptive precautions for the first 7 days of tablet-taking in all of these cases.

- *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*

The woman should be advised **to start** at day 21 to 28 after delivery (non-breast feeding) or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days. 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.

For breastfeeding women - see section 4.6.

Additional contraceptive precautions:
When additional contraceptive precautions are required the patient should be advised either not to have sex, or to use a cap plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the pill disrupts the usual cyclical changes associated with the natural menstrual cycle e.g. changes in temperature and cervical mucus.

How to skip a period:
To skip a period, a new pack of Mercilon should be started on the day after finishing the current pack (the patient skips the tablet-free days). Tablet-taking should be continued in the usual way. During the use of the second pack she may experience slight spotting or breakthrough bleeding but contraceptive protection will not be diminished provided there are no tablet omissions. The next pack of Mercilon is started after the usual 7 tablet-free days, regardless of whether the period has completely finished or not.

Management of missed tablets

If the user is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced.
The woman should take the tablet as soon as she remembers, and should take further tablets at usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The patient should take the last forgotten tablet, even if this means taking

two tablets in one day, and then continue to take tablets at the normal time. Additional contraceptive precautions should be taken for the next seven days. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days

2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamus-pituitary-ovarian-axis.

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 she has 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 7-day 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, she should follow the first of these two options and 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 blister pack must be started as soon as the current blister 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 blister 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 blister 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.

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. Unless diarrhoea is extremely severe, it does not affect steroidal absorption.

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, under section "Management of missed tablets", is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed
To delay a period the woman should continue with another blister pack of Bimizza 150 microgram/20 microgram Tablets 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 Bimizza 150 microgram/20 microgram Tablets 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 subsequent pack (just as when delaying a period).

Paediatric population

The safety and efficacy of desogestrel in adolescents below 18 years has not yet been established. No data are available.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first 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 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
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected estrogen-dependent tumours, (See 4.4 Special warnings and special precautions for use: The Pill and Cancer).
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients of Bimizza 150 microgram/20 microgram Tablets listed in section 6.1.

Bimizza is contraindicated for concomitant use with the 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

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

Circulatory disorders

Risk of venous thromboembolism (VTE)

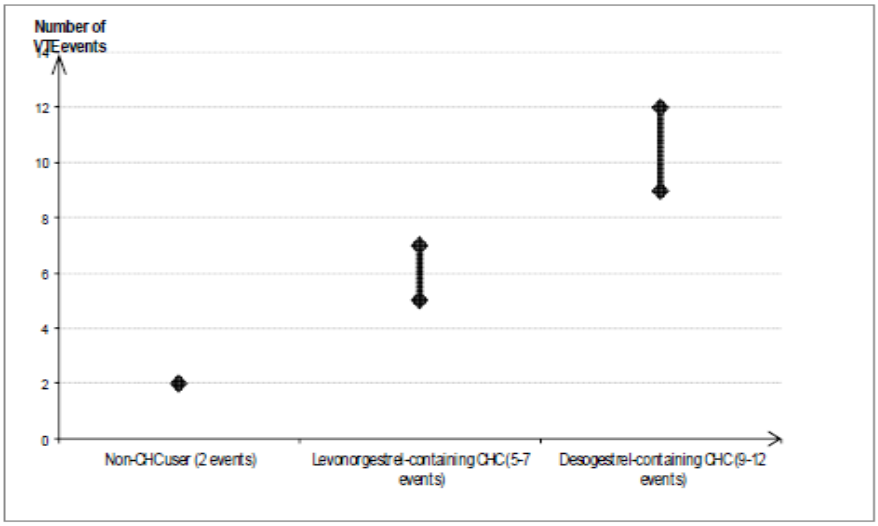
The use of any combined hormonal contraceptive (CHC) carries an increased risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Bimizza may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with Bimizza, 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[1] that out of 10,000 women who use a CHC containing desogestrel between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in women who use a levonorgestrel-containing CHC.
In both cases, the number of VTEs per year is fewer than the number expected 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] These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.

[2] 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 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).

Bimizza 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/m²)	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	In these situations it is advisable to discontinue use of the patch/pill/ring (in the

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.	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 Bimizza 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). Bimizza 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).

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 a 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 thechest, 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.

Tumours

An increased risk of cervical cancer in long-term users of COCs (> 5 years) 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 behaviour and other factors such as human papilloma virus (HPV).

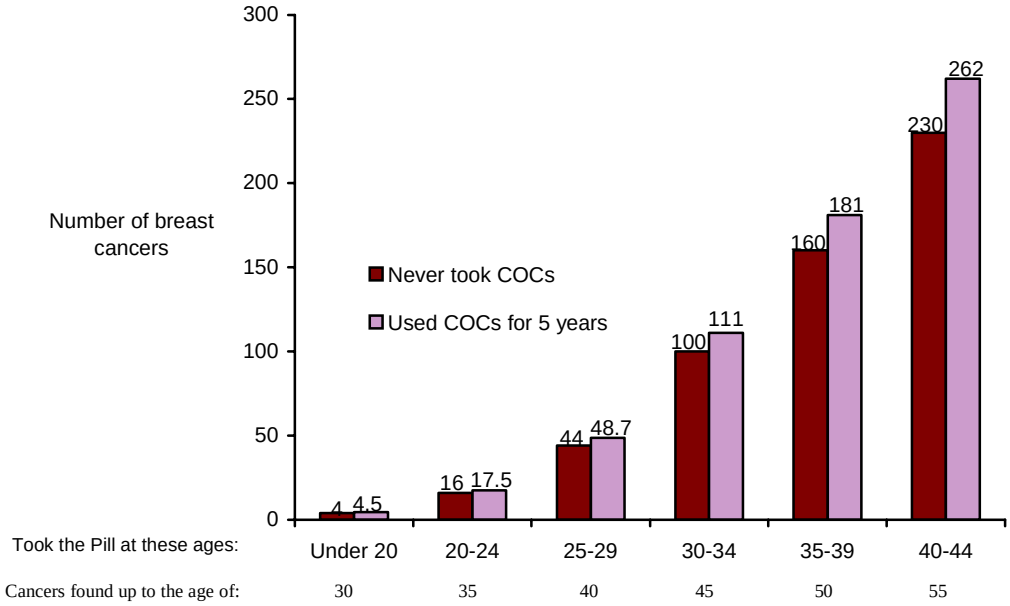
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological 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



In rare cases, benign liver tumours, and even more rarely malignant liver tumours have been reported in users of CHCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic 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 CHCs.

With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Other conditions Women with hypertriglyceridaemia or a family history thereof may be at increased risk of pancreatitis when using CHCs.

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

However, if a sustained clinically significant hypertension develops during the use of a CHC then it is prudent for the physician to withdraw the CHC and treat the hypertension.

The following conditions have been reported to occur or deteriorate with both pregnancy and CHC use, but the evidence of an association with CHC use is inconclusive: Jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

Acute or chronic disturbances of liver function may necessitate discontinuation of CHC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which previously occurred during pregnancy or during previous use of sex steroids necessitates the discontinuation of CHCs.

Although CHCs 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 CHCs (containing <0.05 mg ethinylestradiol). However, diabetic women should be carefully observed, particularly in the early stage of CHC use.

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

Chloasma may occasionally occur, especially in women with a medical history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to sunlight or ultra-violet radiation whilst taking CHCs.

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

Relative Contraindications
Severe depression or a history of this condition.

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 Bimizza 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 contra-indications (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 Bimizza 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 advised that hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method.

Reduced efficacy

The efficacy of Bimizza may be reduced in the event of missed tablets (section 4.2.), gastro-intestinal disturbances (section 4.2.) or concomitant medication that decrease the plasma concentration of etonogestrel, the active metabolite of desogestrel (section 4.5.).

Reduced cycle control/irregular bleeding

With all CHCs, irregular bleeding (spotting and 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 3 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 CHC has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if the CHC 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 CHC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Influence of other medical products on Bimizza Tablets

Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism:

Interactions can occur with medicinal or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance reducing plasma concentrations of sex hormones and may decrease the effectiveness of combined oral contraceptives, including Bimizza. These products include phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, rifabutin and possibly also oxcarbazepine, modafinil, topiramate, felbamate, griseofulvin, some HIV protease inhibitors (e.g., ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz) and products containing the herbal remedy St. John’s wort.

Enzyme induction can occur after a few days of treatment. Maximal enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days.

Women receiving any of the above mentioned hepatic enzyme-inducing medicinal or herbal products should be advised that the efficacy of Bimizza may be reduced. A barrier contraceptive method should be used in addition to Bimizza during administration of the hepatic enzyme-inducing medicinal product, and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product. If concomitant drug administration runs beyond the end of the tablets in the current

COC pack, the next COC pack should be started right away without the usual tablet-free interval.

For women on long-term therapy with enzyme-inducing medicinal products, an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

- When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g., nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g., boceprevir, telaprevir), can increase or decrease plasma concentrations of progestins, including etonogestrel, the active metabolite of desogestrel, or estrogens. The net effect of these changes may be clinically relevant in some cases.

- Concomitant administration of strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of estrogens or progestins, including etonogestrel, the active metabolite of desogestrel.

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

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

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, Bimizza users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with these combination drug regimens. Bimizza can be restarted 2 weeks following completion of treatment with these combination 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 coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Bimizza is not indicated for use during pregnancy.If pregnancy occurs during the use of Bimizza the preparation should be withdrawn immediately.

However, most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used CHCs prior to pregnancy, nor a teratogenic effect when CHCs were taken inadvertently during early pregnancy.

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

Lactation may be influenced by CHCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of CHCs should generally not be recommended until the breast-feeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk but there is no evidence that this adversely affects infant health.

Fertility

No relevant supporting data/evidence is available to suggest short or long term infertility effects of this product. However, in patients receiving similar oral contraceptive products, an adverse reaction of temporary infertility after discontinuance of treatment has been seen infrequently.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed

4.8 Undesirable effects

Description of selected adverse reactions
As with all COCs, changes in vaginal bleeding patterns may occur, especially during the first months of use. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration.

An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Possibly related undesirable effects that have been reported in users of Bimizza or CHC users in general are listed in the table below[1]. All ADRs are listed by system organ class and frequency; common (≥1/100) , uncommon (≥1/1,000 to < 1/100), and rare (<1/1000) and not known (cannot be estimated from the available data).

Organ systems	***common***	***Uncommon***	***Rare***	***Not Known***
Immune system			Hypersensitivity	Exacerbation of symptoms

disorders				of hereditary and acquired angioedema.
Metabolism and nutrition disorders		Fluid retention		
Psychiatric disorders	Depressed mood, mood altered	Libido decreased	Libido increased	
Nervous system disorders	Headache	Migraine		
Eye disorders			Contact lens Intolerance	
Vascular disorders			Venous thromboembolism[2] Arterial thromboembolism[2]	
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting diarrhoea		
Hepatobiliary disorders				Transaminases increased
Skin and subcutaneous tissue disorders		Rash Urticaria	Erythema Nodosum, Erythema multiforme	
Reproductive system and breast disorders	Breast pain, breast tenderness	Breast enlargement	Vaginal Discharge, Breast discharge	
Investigations	Weight increased		Weight decreased	

[1] The most appropriate MedDRA term (version 11) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed,but should be taken into account as well.
[2] Incidence in observational cohort studies of ≥1/10000 to 1/1000 women-years.

4.9 Overdose

There have been no reports of serious deleterious effects from overdose.Symptoms that may possibly occur in this case are: nausea, vomiting and slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations

ATC code: G03AA09

The contraceptive action of COCs is based on interaction of different factors, out of which the most important is the inhibition of ovulation and changes in the cervical secretion. Besides 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 bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. In the largest multicenter trial (n=23 258 cycles), the uncorrected Pearl Index is estimated at 0.1 (95% confidence interval 0.0-0.3). Furthermore, 4.5% of the women reported absence of withdrawal bleeding and 9.2% reported occurrence of irregular bleeding after 6 treatment cycles.

Bimizza is a COC with ethinylestradiol and the progestogen desogestrel.

Ethinylestradiol is a well known synthetic estrogen.

Desogestrel is a synthetic progestogen. After oral administration it has a strong ovulation-inhibiting activity, a strong progestational and anti-estrogenic activity, no estrogenic activity, very weak androgenic/anabolic activity

With the use of the higher-dosed COCs (50μg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Paediatric population

No clinical data on efficacy and safety are available in adolescents below 18years.

5.2 Pharmacokinetic properties

Desogestrel

Absorption

After oral administration of Bimizza150 microgram/20 microgram Tablets, desogestrel is rapidly and completely absorbed and converted intoetonogestrel. Peak plasma levels are reached at about1.5 hours. The bioavailability is 62-81%.

Distribution

Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2 -4 % of the total serum drug concentrations are present as free steroid, 40 -70 % are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution over 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 desogestrel is 1.5 l/kg.

Biotransformation

Etonogestrel is completely metabolized by the known pathways of steroid metabolism, including cytochrome P450 3A4. The metabolic clearance rate from serum is about 2 ml/min/kg. No interaction was found with the co-administered ethinylestradiol."

Elimination

Etonogestrel is eliminated with a mean half-life of approx. 31 hours (24-38 hours), plasma clearance varies from 5.0-9.5 l/hour. Desogestrel and its metabolites are eliminated via the urine and in the faeces, either as free steroids or conjugates. Ratio for elimination in urine or faeces is 1.5:1.

Steady-State Conditions

In steady-state conditions the serum level of 3-keto-desogestrel is elevated by two- to threefold. Etonogestrel pharmacokinetics are influenced by SHBG levels, which are increased threefold by ethinylestradiol. Following daily ingestion, drug serum levels increase about two-to threefold, reaching steady state conditions during the second half of a treatment cycle."

Ethinylestradiol

Absorption

Ethinyl estradiol is rapidly and completely absorbed. Peak plasma levels are reached within 1-2 hours. As a consequence of presystemic conjugation and first-pass metabolism the absolute bioavailability is 60%.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 l/kg was determined.

Biotransformation

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized 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 sulfate. The metabolic clearance rate is about 5 ml/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. 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

Steady-state conditions are obtained after 3 to 4 days, when the serum drug level is approx. 30 to 40% higher than after the administration of a single dose.

5.3 Preclinical safety data

Toxicological studies have not revealed other effects than those, which can be explained, based on the hormone profile of Bimizza 150 microgram/20 microgram Tablets. Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. However, it must be borne in mind that sex steroids can promote the growth of various hormone-dependent tissues and tumours.The results of pre-clinical studies do not add to the information included in the other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

all-*rac*-alpha-tocopherol

Potato starch

Povidone (E1201)

Stearic acid (E570)

Silica, colloidal anhydrous (E551)

Lactose, anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C and store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Clear transparent PVC/PVDC-Al blister of 21 tablets per calendar blister strip available in packs containing 1x21, 3x21 or 6x21 tablets. Each blister is packed in trilaminated pouch, either with a 2g molecular sieve (desiccant) or without the desiccant.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Ethinylestradiol is expected to pose a risk to the aquatic environment, especially to fish populations.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

29/01/2025