MINESSE®

1. NAME OF THE MEDICINAL PRODUCT

MINESSE®

2. QUANTITATIVE AND QUALITATIVE COMPOSITION

Gestodene: .... ……60 micrograms
Ethinylestradiol:..... ……15 micrograms
For one pale-yellow, film-coated tablet (active tablet)
Excipient with known effect: lactose

The white, film-coated tablets do not contain any active ingredients (placebo).
Excipient with known effect: lactose

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

The active tablet is a pale-yellow round tablet with convex faces embossed with “60” on one side and “15” on the other.

The placebo tablet is a white round tablet with convex faces.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral hormonal contraception.

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

4.2 Posology and method of administration

Posology

Take regularly and without omission, one tablet daily at the same time of the day, for 28 consecutive days (one pale-yellow, active tablet during the first 24 days, one white, inactive tablet during the 4 following days) with no free interval between each blister pack. A withdrawal bleed usually starts on day 2-3 after the last active tablet and may not have finished before the next pack is started.

How to start Minesse®

- No preceding hormonal contraceptive use in the past month:

- Take the first tablet on the first day of menstrual bleeding.

– Changing from another combined oral contraceptive (COC):
The woman should start Minesse® on the day after the last active tablet of her previous COC.

- Changing from a progestin-only method (minipill, injection, implant):
The woman may switch any day from the minipill and should begin Minesse® the next day. She should start Minesse® on the day of an implant removal or, if using an injection, the day the next injection would be due. In all of these situations, the woman should be advised to additionally use a non-hormonal back-up method for the first 7 days of tablet-taking.

- Following first-trimester abortion:
The woman may start Minesse® immediately. Additional contraceptive measures are not needed.

- Following delivery or second-trimester abortion:
Since the immediate post-partum period is associated with an increased risk of thromboembolism, COCs should be started no earlier than days 21 to 28 after delivery or second-trimester abortion. The woman should be advised to additionally use a non-hormonal 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.

- For breastfeeding women, see section 4.6.

Omission of one or more tablets

Contraceptive reliability may be reduced if pale-yellow tablets are missed, and particularly if tablets are missed during the first days of the pack.

- If the woman becomes aware of the omission of a pale-yellow tablet **within 12 hours** of the normal time of intake, the tablet should be taken immediately and treatment pursued normally, the next tablet being taken at the usual time.

- If the woman becomes aware of the omission of a pale-yellow tablet **more than 12 hours after the normal time of intake**, contraception is no longer assured. The last forgotten tablet should be taken immediately, even if this means taking two tablets in one day, and oral contraceptive treatment pursued to the end of the blister pack, together with a non-hormonal back-up method of contraception (condoms, spermicides, etc.) which should be used for the next seven days. If the seven days where a back-up method is required run beyond the last active tablet in the current pack, the next pack must be started on the day following the intake of the last active tablet in the current pack and all inactive tablets should be discarded. The user is unlikely to have a withdrawal bleed until the inactive-tablet interval of the second pack, but she may experience spotting or breakthrough bleeding. If the user does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be excluded before resuming tablet-taking.

Errors in taking one or more white tablets have no consequence, provided the interval between the last pale-yellow tablet of the current pack and the first pale-yellow tablet of the following pack does not exceed four days.

In case of gastrointestinal upset:

The onset of intercurrent digestive disorders within four hours after taking the tablet, such as vomiting or severe diarrhoea, may cause transient inefficacy of the method by reducing COC hormone absorption and such events should be dealt with in the same way as the case where a tablet has been forgotten for less than 12 hours. The extra tablet should be taken from a back-up pack. If these episodes recur over several days, a non-hormonal back-up contraceptive method should then be used, (condom, spermicide, etc.) until the beginning of the next blister pack.

Paediatric population
Safety and efficacy was evaluated in subjects aged 18 years and above.
Limited data available for use in adolescents below 18 years.

Elderly patients
Minesse ®is not indicated after menopause.

Patients with hepatic impairment
Minesse® is contraindicated in women with severe hepatic diseases. See also section 'Contraindications'.

Patients with renal impairment
Minesse® has not been specifically studied in renally impaired patients.

Method of administration
Oral use.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. If one of these disorders occurs during the use of Minesse®, Minesse® must be discontinued immediately.

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- 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
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Hepatic adenomas or carcinoma, or active liver disease, as long as liver function tests have not returned to normal
- Undiagnosed genital bleeding

Minesse® is contraindicated for concomitant use with certain anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir/paritaprevir/ritonavir, dasabuvir and glecaprevir/pibrentasvir (see sections 4.4 and 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 Minesse® 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 Minesse® 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, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Minesse® 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 Minesse®, 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).

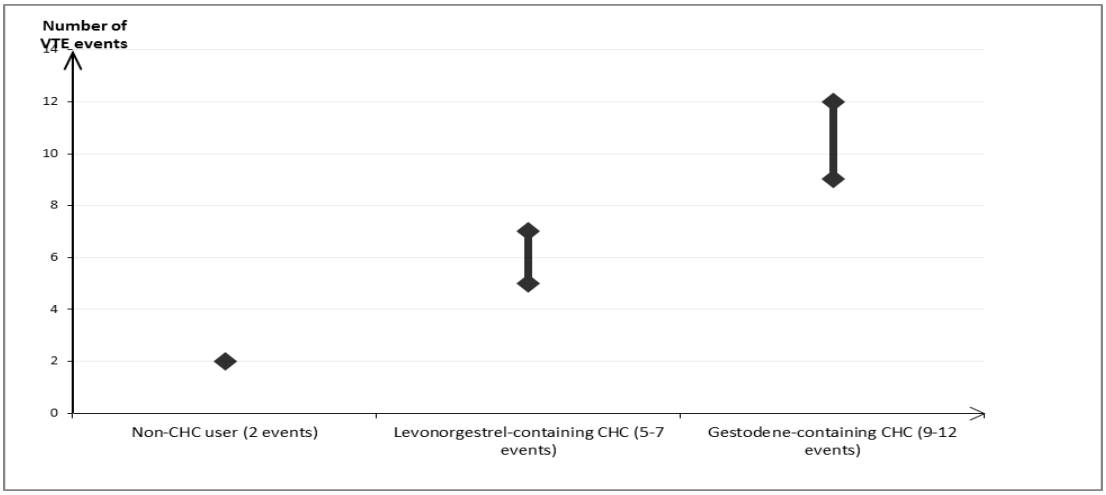
It is estimated[1] that out of 10,000 women who use a CHC containing gestodene between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in women who use a levonorgestrel-containing CHC.

In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.

[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

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

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



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).

Minesse® 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 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 Minesse® 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). Minesse® 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.

GYNAECOLOGICAL CANCERS

A meta-analysis of data from 54 international studies demonstrated a slightly higher risk of breast cancer diagnosis among users of oral contraceptives. This increased risk does not appear to be dependent upon the duration of use. The influence of risk factors such as nulliparity or a family history of breast cancer is not established.

This increased risk is transient and disappears 10 years after the oral contraceptive is discontinued.

It is possible that the more regular clinical monitoring of women taking oral contraceptives, with increased likelihood of earlier diagnosis, may play an important role in the higher number of breast cancers diagnosed.

Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies. However, there continues to be controversy about the extent to which these findings may be due to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

The published data do not compromise the use of oral contraceptives, as the potential risks appear to be outweighed by the benefits.

In addition, oral contraception decreases the risk of ovarian and endometrial cancers.

HEPATIC NEOPLASIA /LIVER DISEASE

In rare cases benign liver tumours (e.g. focal nodular hyperplasia, hepatic adenomas) 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 haemorrhage.

Cholestasis has been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive.

Hepatic and hepatobiliary disorders have been reported with COC use. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of COCs and evaluation of the cause.

HYPERTENSION

Although uncommon, increases in blood pressure have been reported in women taking COCs.
In women with hypertension, a history of hypertension or hypertension related diseases (including certain renal diseases), another method of contraception may be preferable. If COCs are used in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, COCs should be discontinued.

OTHER

Medical examination/consultation
Prior to the initiation or reinstitution of Minesse® 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 Minesse® 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.

Caution should be exercised in women with:

- Metabolic disorders such as uncomplicated diabetes.
- Hyperlipidemia (hypertriglyceridemia, hypercholesterolemia). Women who are being treated for hyperlipidemias should be followed closely if they elect to use COCs. Persistent hypertriglyceridemia may occur in a small proportion of COC users.

In patients with elevated triglycerides, estrogen-containing preparations may be associated with rare but large elevations of plasma triglycerides that may lead to pancreatitis.

Obesity (body mass index=Weight/Height2≥30)

Benign tumours of the breast and uterine dystrophy (hyperplasia, fibroma)

Hyperprolactinemia with or without galactorrhea.

Close surveillance should also be ensured in the presence of conditions, which have been reported to occur or deteriorate with pregnancy or COC use, respectively in patients presenting or with a history of: epilepsy, migraine, otosclerosis, asthma, family history of vascular disease, varicose veins, herpes gestationis, gallstones, systemic lupus erythematosus, cardiac, renal or hepatic dysfunction, depression, hypertension, chorea, haemolytic uremic syndrome.

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

In clinical trials, amenorrhea, not linked to pregnancy, was observed in 7% of cycles (occurring in 24% of women over the total duration of the clinical trials) and 3.6% of women experienced consecutive amenorrheic cycles. In the clinical trials, only and 1% of women discontinued because of amenorrhea.

When Minesse® is taken according to directions, in the occurrence of one amenorrheic cycle, there is no reason for discontinuation and performance of a pregnancy test. If Minesse® is not taken according to directions or if amenorrhea occurs after a long period of regular menstrual bleeding, pregnancy should be ruled out.

Some women may encounter post-therapeutic amenorrhea (possibly with anovulation) or oligomenorrhea, especially when such a condition was pre-existing. It usually resolves spontaneously. If prolonged, investigations should be carried out into the possibility of pituitary disorders before any further prescription.

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. Further diagnostic measures may include curettage.

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.
If melasma/chloasma has appeared during pregnancy or with previous COC use, exposure to sunlight should be avoided to minimize exacerbation of this condition.

Diarrhea and/or vomiting may reduce COC hormone absorption (see Section 4.2).

Women should be advised that hormonal contraceptives do not protect against HIV infection (AIDS) or other sexually transmitted diseases.

Due to the presence of lactose, this medicinal product is not recommended for use in women with lactose intolerance.

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 frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). There is also a risk of substantial ALT elevations with concomitant use of glecaprevir/pibrentasvir (see sections 4.3 and 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between ethinylestradiol or gestodene and other substances may lead to decreased or increased plasma and tissue concentrations of ethinylestradiol or gestodene.

Decreased ethinylestradiol serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the COC.

Concomitant use not recommended:
*Enzyme inducing agents such as: anticonvulsants (phenobarbital, phenytoin, primidone, carbamazepine, topiramate, felbamate); rifabutin; rifampicine; griseofulvine, and possibly St. John’s Wort. Reduction in the efficacy of contraception through increased hepatic metabolism during treatment and for one cycle following treatment discontinuation. Preference should be given to a nonhormonal contraceptive method.

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. Please see the corresponding SmPC of each HIV or HCV protease inhibitors and nonnucleoside reverse transcriptase inhibitors for specific recommendation.

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), macrolides (e.g. clarithromycin, erythromycin), 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.
The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

*Modafinil: risk of a decreased contraceptive efficacy during treatment and for one cycle following treatment discontinuation.

*Flunarizine: risk of galactorrhea due to increased sensitivity of mammary tissue to prolactin through the action of flunarizine.

*Troleandomycin may increase the risk for intrahepatic cholestasis during co-administration with COCs.

Effects of COCs on other medicinal products:

Oral contraceptives may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) 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 to moderate (e.g., tizanidine) increase in their plasma concentration.

The labelling of concomitant medications should be consulted to identify potential interactions.

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin or glecaprevir/pibrentasvir may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, Minesse® users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with anti-viral HCV medicinal products such as ombitasvir, paritaprevir, ritonavir, dasabuvir, glecaprevir, pibrentasvir. Minesse® can be restarted 2 weeks following completion of treatment with certain anti-viral HCV medicinal products and their combinations.

4.6 Fertility,pregnancy and lactation

Fertility
Minesse® is indicated for the prevention of pregnancy.
Women may experience post treatment amenorrhoea following discontinuation of treatment (see section 4.4).

Pregnancy
This medicine is not indicated during pregnancy.

In clinical use to date, and in contrast with diethylstilbestrol, the results of numerous epidemiological studies have made it possible to discount the risk of malformation with estrogen administered alone or in combination during early pregnancy.
In addition, the risks concerning foetal sex differentiation (particularly female) which were

described with early, highly androgenomimetic progestogens cannot be extrapolated to more recent progestogens (such as that employed in this proprietary medicinal product) which are markedly less androgenomimetic, if at all.

Consequently, the discovery of pregnancy in a woman receiving an estrogen-progestogen combination does not justify an abortion.

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

Breast-feeding
The use of this medicine in breast-feeding mothers is not advisable since estrogen-progestogens can be found in breast milk.
During lactation a different method of contraception should be proposed.

4.7 Effects on ability to drive and use machines

The impact of Minesse® on the ability to drive and use machines has not been systematically evaluated. Minesse® is not expected to influence the ability to drive or use machines. Cases of dizziness have been reported. Patients should exercise caution until they know that Minesse ®does not affect these abilities.

4.8 Undesirable effects

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.

The following undesirable effects have been reported in users of COCs:

For serious adverse effects in COC users see section 4.4.

The occurrence of amenorrhea was reported in 15% of women during clinical trial, see section 4.4. Some most frequently (greater than 10 %) reported adverse events during phase III studies and postmarketing surveillances in women using Minesse® are headache, including migraines, abdominal pain, breast pain, breast tenderness.

Other adverse events have been reported in women taking COC:

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	***Not known (cannot be estimated from the available data)***
Infections and Infestations	Vaginitis, including candidiasis			
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Hepatocellular carcinoma and benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic

				adenoma)
Immune system disorders				Anaphylactic/anaphylactoid reaction, including very rare cases of angioedema, severe reactions with respiratory and circulatory symptoms and urticaria. Exacerbation of symptoms of hereditary and acquired angioedema.
Metabolism and nutrition disorders		Increased appetite, decreased appetite		Glucose tolerance impaired
Psychiatric disorders	Mood altered, including depression, nervousness, change in libido			
Nervous system disorders	Dizziness			Optic neuritis, chorea aggravated
Eye disorders				Contact lens intolerance
Vascular disorders		Aggravation of varicose veins	Venous thromboembolism and arterial thromboembolism	
Gastrointestinal disorders	Vomiting, nausea, bloating		Pancreatitis	Colitis ischaemic, possible aggravation of inflammatory bowel disease, abdominal cramps
Hepato-biliary disorder			Hepatic and hepatobiliary disorders (e.g. hepatitis, hepatic function abnormal), biliary lithiasis[1], gallbladder disease[2]	Jaundice cholestatic, cholestasis[1]
Skin and subcutaneous tissue disorders	Acne, rash, alopecia	Chloasma which may persist, hirsutism		Erythema multiforme, erythema nodosum

Musculoskeletal and connective tissue disorders				Exacerbation of systemic lupus erythematosus
Renal and urinary disorders				Haemolytic uraemic syndrome
Reproductive system and breast disorders	Breakthrough bleeding, spotting, dysmenorrhoea, change in menstrual flow, change in cervical ectroption and secretion.	Breast secretion, breast enlargement		
Congenital, familial and genetic disorders				Exacerbation of porphyria
General disorders and administration	Fluid retention/oedema			
Investigations	Weight increased, weight decreased	Blood pressure increased, lipids increased		

[1]COCs may worsen existing biliary lithiasis and cholestasis
[2]COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Symptoms of oral contraceptive overdose in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness / fatigue; withdrawal bleeding may occur in females. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PROGESTOGENS AND ESTROGENS IN FIXED COMBINATION
ATC Code: G03AA10 (genitourinary system and sex hormones).
Minesse® is a combination oral contraceptive (COC) containing ethinyl estradiol (EE) and gestodene. COCs have been shown to exert their effect by decreasing gonadotropin secretion to suppress ovarian activity. The resulting contraceptive effect is based on various mechanisms, the most important of which is the inhibition of ovulation.

5.2 Pharmacokinetic properties

Ethinylestradiol:

Absorption

Ethinylestradiol is rapidly and completely absorbed after oral ingestion. After administration of 15 µg, peak plasma concentrations of 30 pg/mL are reached after 1- 1.5 hours. Ethinylestradiol undergoes an extensive first pass effect, which displays great interindividual variation. The absolute bioavailability is approximately 45%.

Distribution

Ethinylestradiol has an apparent volume of distribution of 15 L/kg and binding to plasma proteins is approximately 98%. Ethinylestradiol induces the hepatic synthesis of sex-hormone binding globulins (SHBG) and corticoid-binding globulins (CBG). During treatment with 15 µg ethinylestradiol the plasma concentration of SHBG increases from 86 to about 200 nmol/L.

Biotransformation

Ethinylestradiol is metabolised completely (metabolic plasma clearance approximately 10 mL/min/kg). The metabolites formed are excreted in the urine (40%) and feces (60%).
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

The elimination half-life of ethinylestradiol is approximately 15 hours. Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary to biliary ratio of 4 : 6.

Steady state conditions

Steady state conditions are reached during the second half of the treatment cycle and serum levels of ethinylestradiol accumulate by a factor of about 1.4 to 2.1.

Gestodene:

Absorption

After oral administration gestodene is rapidly and completely absorbed. The absolute bioavailability is about 100%. After oral intake of a single 60 µg gestodene dose, peak plasma concentrations of 2 ng/mL are reached in about 60 minutes. The plasma concentrations are strongly dependent on the SHBG concentrations.

Distribution

Gestodene has an apparent volume of distribution of 1.4 L/kg following a single 60 µg dose. It is 30% bound to plasma albumin and 50 – 70% bound to SHBG.

Biotransformation

Gestodene is extensively metabolised by the steroid metabolic pathway. The metabolic clearance is about 0.8 mL/min/kg following a single 60 µg dose. The non-active metabolites formed are excreted in urine (60%) and faeces (40%).

Elimination

The apparent elimination half-life of gestodene is about 13 hours. The half-life is prolonged to 20 hours after concomitant administration with ethinylestradiol.

Steady state conditions

After multiple dosing concomitantly with ethinylestradiol the plasma concentration increases approximately by a factor of 2-4.

5.3 Preclinical safety data

Toxicological studies have been performed on all components individually and on their combination.
Acute toxicity studies in animals showed no evidence of a risk of acute symptoms arising after accidental overdosage.

General safety studies with repeated administration have shown no evidence of any effects suggesting any unexpected risks in man.

Long term and repeated dose carcinogenicity studies have not demonstrated any carcinogenic potential; however, it is important to remember that sex steroids are capable of promoting the development of certain tissues into hormone-dependent tumours.

Teratogenicity studies have not indicated any particular risk when estrogen-progestogen combinations are used correctly; it is however essential to discontinue treatment immediately if taken in error at the beginning of pregnancy.

Mutagenicity studies have not revealed any mutagenic potential for ethinylestradiol or gestodene.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Pale-yellow tablet (active):
lactose monohydrate,
microcrystalline cellulose,
OPADRY yellow YS-1-6386-G,
polacrilin potassium,
magnesium stearate,
polyethylene glycol 1450,
wax E (montanglycol wax).

White tablet (placebo):
lactose monohydrate,
microcrystalline cellulose,
OPADRY white Y-5-18024-A,
polacrilin potassium,
magnesium stearate,
polyethylene glycol 1500,
wax E (montanglycol wax).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of the container

24 pale-yellow tablets and 4 white tablets in blister pack (PVC/Aluminium).

The pack sizes are 1 x 28 and 3 x 28.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd. 9 Shenkar St. Hertzliya Pituach 46725

8. LICENSE NUMBER

122-57-30271

Revised in 09/2022 according to MOHs guidelines.