SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Synphase 500 microgram / 35 microgram tablets and 1 milligram / 35 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

7 blue tablets containing norethisterone 500 micrograms and ethinylestradiol 35 micrograms; 9 white tablets containing norethisterone 1.0 milligram and ethinylestradiol 35 micrograms; 5 blue tablets containing norethisterone 500 micrograms and ethinylestradiol 35 micrograms.

Excipients with known effect:
Each tablet contains lactose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.
Synphase consists of 7 blue tablets marked 'BX' on one side and 'SEARLE' on the other; 9 white tablets marked 'SEARLE' on one face and 'BX' on the other; 5 blue tablets marked 'BX' on one side and 'SEARLE' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Synphase is indicated for oral contraception, with the benefit of a low intake of estrogen.

4.2 Posology and method of administration

Posology

The dosage of Synphase for the initial cycle of therapy is 1 tablet taken at the same time each day from the first day of the menstrual cycle. For subsequent cycles, no tablets are taken for 7 days, then a new course is started of 1 tablet daily for the next 21 days. This sequence of 21 days on treatment, seven days off treatment is repeated for as long as contraception is required.

Patients unable to start taking Synphase tablets on the first day of the menstrual cycle may start treatment on any day up to and including the 5th day of the menstrual cycle.

Patients starting on day 1 of their period will be protected at once. Those patients delaying therapy up to day 5 may not be protected immediately and it is recommended that another method of contraception is used for the first 7 days of tablet-taking. Suitable methods are condoms, caps plus spermicides and intra-uterine devices.

The rhythm, temperature and cervical-mucus methods should not be relied upon.

Tablet omissions

Tablets must be taken daily in order to maintain adequate hormone levels and contraceptive efficacy.

If a tablet is missed within 12 hours of the correct dosage time then the missed tablet should be taken as soon as possible, even if this means taking 2 tablets on the same day, this will ensure that contraceptive protection is maintained. If one or more tablets are missed for more than 12 hours from the correct dosage time it is recommended that the patient takes the last missed tablet as soon as possible and then continues to take the rest of the tablets in the normal manner. In addition, it is recommended that extra contraceptive protection, such as a condom, is used for the next 7 days.

Patients who have missed one or more of the last 7 tablets in a pack should be advised to start the next pack of tablets as soon as the present one has finished (i.e. without the normal seven day gap between treatments). This reduces the risk of contraceptive failure resulting from tablets being missed close to a 7 day tablet free period.

Changing from another oral contraceptive

In order to ensure that contraception is maintained it is advised that the first dose of Synphase tablets is taken on the day immediately after the patient has finished the previous pack of tablets.

Use after childbirth, miscarriage or abortion

Providing the patient is not breast feeding the first dose of Synphase tablets should be taken on the 21st day after childbirth. This will ensure the patient is protected immediately. If there is any delay in taking the first dose, contraception may not be established until 7 days after the first tablet has been taken. In these circumstances patients should be advised that extra contraceptive methods will be necessary.

After a miscarriage or abortion patients can take the first dose of Synphase tablets on the next day; in this way they will be protected immediately.

Method of administration

Oral administration.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
As with all combined progestogen/oestrogen hormonal contraceptives, the following conditions should be regarded as contra-indications:

i. History of confirmed venous thromboembolic disease (VTE), family history of idiopathic VTE and other known risk factors of VTE
ii. Thrombophlebitis, cerebrovascular disorders, coronary artery disease, myocardial infarction, angina, hyperlipidaemia or a history of these conditions.
iii. Acute or severe chronic liver disease, including liver tumours, Dubin-Johnson or Rotor syndrome.
iv. History during pregnancy of idiopathic jaundice, severe pruritus or pemphigoid gestationis.
v. Known or suspected breast or genital cancer.
vi. Known or suspected oestrogen-dependent neoplasia.
vii. Undiagnosed abnormal vaginal bleeding.
viii. A history of migraines classified as classical, focal or crescendo.
ix. Pregnancy.

Synphase 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

Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

Women taking oral contraceptives require careful observation if they have or have had any of the following conditions: breast nodules; fibrocystic disease of the breast or an abnormal mammogram; uterine fibroids; a history of severe depressive states; varicose veins; sickle-cell anaemia; diabetes; hypertension; cardiovascular disease; migraine; epilepsy; asthma; otosclerosis; multiple sclerosis; porphyria; tetany; disturbed liver functions; gallstones; kidney disease; chloasma; any condition that is likely to worsen during pregnancy. The worsening or first appearance of any of these conditions may indicate that the oral contraceptive should be stopped. Discontinue treatment if there is a gradual or sudden, partial or complete loss of vision or any evidence of ocular changes, onset or aggravation of migraine or development of headache of a new kind which is recurrent, persistent or severe.

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

Gastro-intestinal upsets, such as vomiting and diarrhoea, may interfere with the absorption of the tablets leading to a reduction in contraceptive efficacy. Patients should continue to take Synphase, but they should also be encouraged to use another contraceptive method during the period of gastro-intestinal upset and for the next 7 days.

Progestogen oestrogen preparations should be used with caution in patients with a history of hepatic dysfunction or hypertension.

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 norethisterone (including Synphase) are associated with the lowest risk of VTE. The decision to use Synphase should be taken after a discussion with the woman to ensure she understands the risk of VTE with Synphase, 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 low dose CHC that contains levonorgestrel, about 6[1] will develop a VTE in one year.

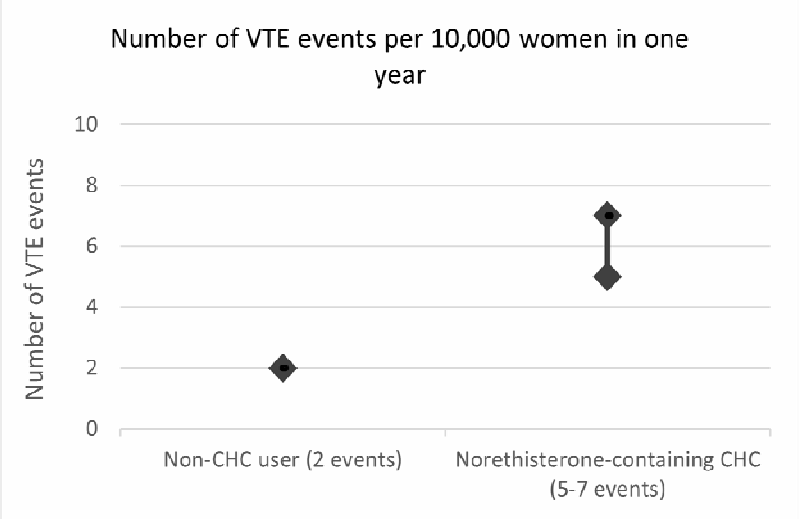
Current evidence suggests that the risk of VTE with use of norethisterone-containing CHCs is similar to the risk with levonorgestrel-containing CHCs.

[1] Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-sue of approximately 2.3 to 3.6.

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



The level of all of these risks of VTE increases with age and is likely to be further increased in women with other known risk factors for VTE such as obesity.

Patients receiving oral contraceptives should be kept under regular surveillance, in view of the possibility of development of conditions such as thromboembolism.

The risk of coronary artery disease in women taking oral contraceptives is increased by the presence of other predisposing factors such as cigarette smoking, hypercholesterolaemia, obesity, diabetes, history of pre-eclamptic toxaemia and increasing age. After the age of thirty-five years, the patient and physician should carefully re-assess the risk/benefit ratio of using combined hormonal contraceptives as opposed to alternative methods of contraception.

Synphase should be discontinued at least four weeks before, and for two weeks following, elective operations and during immobilisation. Patients undergoing injection treatment for varicose veins should not resume taking Synphase until 3 months after the last injection.

Benign and malignant liver tumours have been associated with oral contraceptive use. The relationship between occurrence of liver tumours and use of female sex hormones is not known at present. These tumours may rupture causing intra-abdominal bleeding. If the patient presents with a mass or tenderness in the right upper quadrant or an acute abdomen, the possible presence of a tumour should be considered.

The risk of arterial thrombosis associated with combined hormonal contraceptives increases with age, and this risk is aggravated by cigarette smoking. The use of combined hormonal contraceptives by women in the older age group, especially those who are cigarette smokers, should therefore be discouraged and alternative methods advised.

The use of this product in patients suffering from epilepsy, migraine, asthma or cardiac dysfunction may result in exacerbation of these disorders because of fluid retention. Caution should also be observed in patients who wear contact lenses.

Decreased glucose tolerance may occur in diabetic patients on this treatment, and their control must be carefully supervised.

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

The use of oral contraceptives has also been associated with a possible increased incidence of gall bladder disease.

Women with a history of oligomenorrhoea or secondary amenorrhoea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrhoeic after discontinuation of oral contraceptives. Women with these pre-existing problems should be advised of this possibility and encouraged to use other contraceptive methods.

Numerous epidemiological studies have been reported on the risks of ovarian, endometrial, cervical and breast cancer in women using combined hormonal contraceptives. The evidence is clear that combined hormonal contraceptives offer substantial protection against both ovarian and endometrial cancer.

An increased risk of cervical cancer in long-term users of combined hormonal contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects of sexual behaviour and other factors.

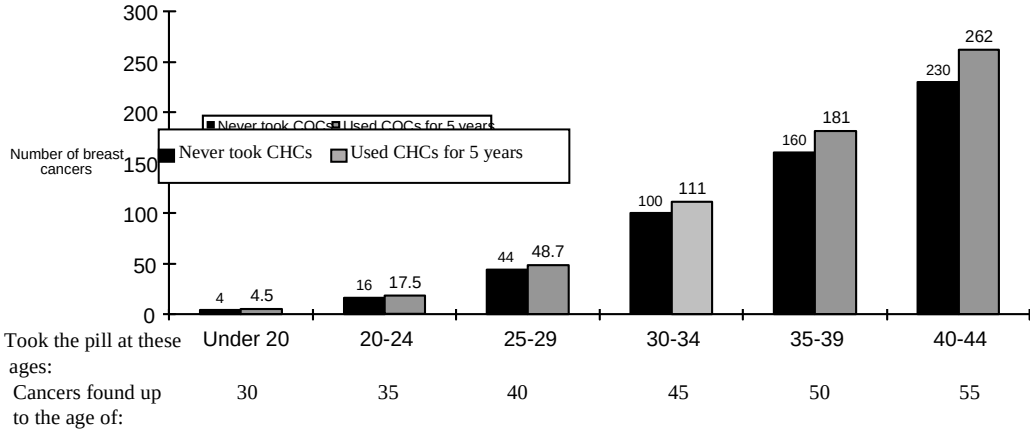
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined hormonal contraceptives (CHCs). The observed pattern of increased risk may be due to an earlier diagnosis of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

Breast cancer is rare among women under 40 years of age whether or not they take CHCs. Whilst this background risk increases with age, the excess number of breast cancer diagnoses in current and recent CHC users is small in relation to the overall risk of breast cancer (see bar chart).

The most important risk factor for breast cancer in CHC users is the age women discontinue the CHC; 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 CHC 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 CHCs 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 CHCs, compared with numbers of breast cancers diagnosed in 10,000 women who had never used CHCs.



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.

4.5 Interaction with other medicinal products and other forms of interaction

The herbal remedy St John's wort (*Hypericum perforatum*) should not be taken concomitantly with this medicine as this could potentially lead to a loss of contraceptive effect.

Some drugs may modify the metabolism of Synphase reducing its effectiveness; these include certain sedatives, antibiotics, anti-epileptic and anti-arthritic drugs. During the time such agents are used concurrently, it is advised that mechanical contraceptives also be used.

The results of a large number of laboratory tests have been shown to be influenced by the use of oestrogen containing oral contraceptives, which may limit their diagnostic value. Among these are: biochemical markers of thyroid and liver function; plasma levels of carrier proteins, triglycerides, coagulation and fibrinolysis factors.

Pharmacodynamic interactions

During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir, 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 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, Synphase-users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with these combination drug regimens. Synphase can be restarted 2 weeks following completion of treatment with these combination drug regimens.

4.6 Fertility, pregnancy and lactation

Pregnancy

Synphase is not indicated during pregnancy. If pregnancy occurs during medication with Synphase, treatment should be withdrawn immediately. Like all norethisterone derivatives used for contraception, Synphase has slight androgenic activity. At doses higher than normally used in OC and HRT formulations, masculinisation of female foetuses has been observed. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens with progestogens, indicate no teratogenic or foetotoxic effects.

Breast-feeding

Patients who are fully breast-feeding should not take Synphase tablets since, in common with other combined hormonal contraceptives, the oestrogen component may reduce the amount of milk produced. In addition, active ingredients or their metabolites have been detected in the milk of mothers taking oral contraceptives. The effect of Synphase on breast-fed infants has not been determined.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

As with all oral contraceptives, there may be slight nausea at first, weight gain or breast discomfort, which soon disappear.

Other side-effects known or suspected to occur with oral contraceptives include gastro-intestinal symptoms, changes in libido and appetite, headache, exacerbation of existing uterine fibroid disease, depression, and changes in carbohydrate, lipid and vitamin metabolism.

Spotting or bleeding may occur during the first few cycles. Usually menstrual bleeding becomes light and occasionally there may be no bleeding during the tablet-free days.

Hypertension, which is usually reversible on discontinuing treatment, has occurred in a small percentage of women taking oral contraceptives.

Exacerbation of symptoms of hereditary and acquired angioedema. (Frequency 'Not known' (cannot be estimated from the available data)).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdosage may be manifested by nausea, vomiting, breast enlargement and vaginal bleeding. There is no specific antidote and treatment should be symptomatic. Gastric lavage may be employed if the overdose is large and the patient is seen sufficiently early (within four hours).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormones and modulators of the genital system, progestogens and oestrogens, sequential preparations, ATC code: G03AB04

The mode of action of Synphase is similar to that of other progestogen/oestrogen hormonal contraceptives.

CHC suppress gonadotropins in a manner that inhibits ovulation, which leads to contraception. Such activity is exerted through a combined effect on one or more of the following: hypothalamus, anterior pituitary, ovary, endometrium and cervical mucus.

5.2 Pharmacokinetic properties

Norethisterone is rapidly and completely absorbed after oral administration, peak plasma concentrations occurring in the majority of subjects between 1 and 3 hours. Due to first-pass metabolism, blood levels after oral administration are 60% of those after i.v. administration. The half life of elimination varies from 5 to 12 hours, with a mean of 7.6 hours. Norethisterone is metabolised mainly in the liver. Approximately 60% of the administered dose is excreted as metabolites in urine and faeces.

Ethinylestradiol is rapidly and well absorbed from the gastro-intestinal tract but is subject to some first-pass metabolism in the gut-wall. Compared to many other oestrogens it is only slowly metabolised in the liver. Excretion is via the kidneys with some appearing also in the faeces.

5.3 Preclinical safety data

The toxicity of norethisterone is very low. Reports of teratogenic effects in animals are uncommon. No carcinogenic effects have been found even in long-term studies.

Long-term continuous administration of oestrogens in some animals increases the frequency of carcinoma of the breast, cervix, vagina and liver.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Polyvidone

Magnesium stearate

Lactose

The blue tablets also contain E132.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Pvc/foil blister packs of 21 and 63 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich

Kent

CT13 9JN

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/05/1996 / 26/02/2009

10 DATE OF REVISION OF THE TEXT

10/06/2025

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