PROFFESSIONAL INFORMATION:

ACTORDENE

SCHEDULING STATUS **S3**

1. NAME OF THE MEDICINE

ACTORDENE 0,075 mg / 0,02 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The 28-day pack (Every-day calendar pack) contains 21 active hormonal white or off-white tablets plus 7 inactive non-hormonal (placebo) green film-coated tablets.

Each active white or off-white tablet contains gestodene 0,075 mg and ethinylestradiol 0,02 mg. The inactive green film-coated tablets are placebo and do not contain any active ingredients.

Contains sugar: each active white or off-white tablet contains 59,12 mg lactose monohydrate and each inactive green film-coated tablet contains 55,50 mg lactose monohydrate.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Active tablets

21 round, white or off-white tablets, with a diameter of approximately 5,7 mm, debossed with ‘C’ on one side and ‘34’ on the other.

Inactive film-coated tablets (placebo)

7 round, green film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACTORDENE is indicated for the prevention of pregnancy (oral contraception).

4.2 Posology and method of administration

ACTORDENE, when taken correctly, has a failure rate of approximately 1 % per year. The failure rate may increase when tablets are missed or taken incorrectly.

How to take ACTORDENE

Tablets must be taken every day at about the same time with some liquid as needed. The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. "MO" for Monday).

Following the directions shown by the arrows, one tablet must be taken daily, for 28 consecutive days, until the pack is finished.

Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts 2 to 3 days after starting the inactive tablets and may not have finished before the next pack is started. If a patient starts ACTORDENE during the latter part of the week, the very first cycle may be slightly shortened.

How to start ACTORDENE

No preceding hormonal contraceptive use (in the post month)

Tablet taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2 to 5 of the menstrual cycle is allowed, but during the first cycle an additional barrier method is recommended in addition for the first 7 days of tablet-taking.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

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

The woman should start with ACTORDENE preferably on the day after the last active tablet (the last tablet containing the active substance) of her previous combined oral contraceptive, but at the latest on the day following the usual placebo tablet interval of her previous combined oral contraceptive.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

In case a vaginal ring or transdermal patch has been used, the woman should start using ACTORDENE preferably on the day of removal, but at the latest when the next application would have been due.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

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

The woman may switch on any day from the minipill (from an implant or the intrauterine system on the day of its removal, from an injectable when the next injection would be due) but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

Following first trimester abortion

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

Following delivery or second-trimester abortion

For breastfeeding women see **section 4.6**. Women should be advised to start 21 to 28 days after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of ACTORDENE use, or the woman must wait for her first menstrual period.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

Management of missed tablets

The green tablets are inactive tablets and missing these can be disregarded. However, they should be discarded to avoid unintentionally prolonging the inactive tablet phase. The following advice only refers to missed active tablets:

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

If she is ***more than 12 hours*** late in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. Active tablet-taking must never be discontinued for longer than 7 days;
2. 7 days of uninterrupted active tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly, the following advice can be given in dally practice

First 7 days of active tablet-taking

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 that are missed and the closer they are to the inactive tablet phase, the higher the risk of a pregnancy.

Second 7 days of active tablet-taking

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra

contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Third 7 days of active tablet-taking

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

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 7 inactive tablets must be discarded. The next pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on active tablet-taking days.
2. The woman may also be advised to discontinue active tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack, starting in the silver section with the tablet for the appropriate day of the week.

If the woman missed active tablets and subsequently has no withdrawal bleed in the inactive tablet phase, the possibility of a pregnancy should be considered.

Advice in case of gastrointestinal disturbances

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3 to 4 hours after active tablet-taking, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she must take the extra tablet(s) needed from another pack.

How to delay a period

To delay a period the woman should continue with another pack of ACTORDENE without taking the inactive tablets from her current pack. The extension can be carried on for as long as wished until the end of the active tablets in the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of ACTORDENE is then resumed after the inactive tablet phase.

Additional information on special populations

Children and adolescents

ACTORDENE is only indicated after menarche.

Geriatric patients

Not applicable. ACTORDENE is not indicated after menopause.

Patients with hepatic impairment

ACTORDENE is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See **section 4.3**

Patients with renal impairment

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

Method of administration

ACTORDENE tablets are for oral administration with a drink of water.

4.3 Contraindications

Hypersensitivity to gestodene or ethinylestradiol, or to any of the excipients of ACTORDENE listed in **section 6.1**.

ACTORDENE should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during ACTORDENE use, ACTORDENE should be stopped immediately.

- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident;
- presence or history of prodromata of a thrombosis (e.g. transient ischaemic attack, angina pectoris);
- history of migraine with focal neurological symptoms;
- diabetes mellitus with vascular involvement;
- the presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (such as e.g. hypertension, a family history of thromboembolic events, prolonged immobilisation - see further risk factors for thromboembolism in **section 4.4** "Circulatory disorders") may also constitute a contraindication;
- pancreatitis or a history thereof if associated with severe hypertriglyceridemia;
- 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 sex-steroid influenced malignancies (e.g. of the genital organs or the breasts);
- undiagnosed vaginal bleeding;
- known or suspected pregnancy (see **section 4.6**).

4.4 Special warnings and precautions for use

If any of the conditions/risk factors mentioned below are present, the benefits of ACTORDENE use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it.

In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her medical practitioner. The medical practitioner should then decide on whether its use should be discontinued.

Circulatory disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives, such as ACTORDENE, and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism.

The risk of venous thromboembolism (VTE) is highest during the first year of use. This increased risk is present after initially starting combined oral contraceptives, such as ACTORDENE, or restarting (following a 4 week or greater pill free interval) the same or different combined oral contraceptives. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months. Overall, the risk for venous thromboembolism (VTE) in users of low oestrogen dose (< 50 µg ethinylestradiol) combined oral contraceptives, such as ACTORDENE, is higher than for non-users of combined oral contraceptives.

VTE may be fatal.

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of combined oral contraceptives, such as ACTORDENE.

Thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in combined oral contraceptive users, such as ACTORDENE.

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.

The risk venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- Age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age. If a hereditary predisposition is suspected, the woman should be referred to a

specialist for advice before deciding about any combined oral contraceptive use; obesity (body mass index over 30 kg/m^2);

- dyslipoproteinemia;
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue ACTORDENE (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

The increased risk of thromboembolism in the puerperium must be considered (see **section 4.6**). Other medical conditions that have been associated with thrombotic incidents include diabetes mellitus, systemic lupus erythematosus, haemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

The onset of or increase in frequency or severity of migraine during ACTORDENE use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of ACTORDENE.

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

When considering risk/benefit, the medical practitioner should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis, and that the risk associated with pregnancy is higher than that associated with combined low-dose oral contraceptive use, such as ACTORDENE, (< 0,05 mg ethinylestradiol).

Tumours

An increased risk of cervical cancer in long-term users of combined oral contraceptives, such as ACTORDENE, has been reported in epidemiological studies.

A meta-analysis from epidemiological studies reported that there is an increased relative risk of having breast cancer diagnosed in women who are currently using a combined oral contraceptive such as

ACTORDENE. 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 oral contraceptives.

Benign liver tumours, and rarely, malignant liver tumours have been reported in users of combined oral contraceptives such as ACTORDENE. 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 ACTORDENE.

Other conditions

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

Small increases in blood pressure have been reported in many women taking combined oral contraceptives, such as ACTORDENE; clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of ACTORDENE, then it is prudent for the medical practitioner to withdraw ACTORDENE and treat the hypertension. Where considered appropriate, ACTORDENE use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with combined oral contraceptive use such as ACTORDENE: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis; related hearing loss.

In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of ACTORDENE use until markers of liver function return to normal. The recurrence of cholestatic jaundice that occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of ACTORDENE.

Although ACTORDENE 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 ACTORDENE. However, diabetic women should be carefully observed while taking ACTORDENE.

Crohn's disease and ulcerative colitis have been associated with combined oral contraceptives such as ACTORDENE.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking ACTORDENE.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of ACTORDENE use, guided by the warnings mentioned in this section and the contraindications in **section 4.3**, and should be repeated periodically.

Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of ACTORDENE.

The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests.

Women should be advised that ACTORDENE does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of ACTORDENE may be reduced in the event of e.g. missed active tablets, gastrointestinal disturbances during active tablet-taking (see **section 4.2**) or concomitant medication (see **section 4.5**).

Reduced cycle control

Irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use.

Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

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

In some women withdrawal bleeding may not occur during the inactive tablet phase. If ACTORDENE has been taken according to the directions described in **section 4.2** it is unlikely that the woman is pregnant. However, if ACTORDENE 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 ACTORDENE use is continued.

Psychiatric disorders

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

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, for example combined hormonal contraceptives (CHCs), such as ACTORDENE (see **section 4.5**).

Lactose

ACTORDENE contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ACTORDENE.

4.5 Interaction with other medicines and other forms of interaction

Interactions between ACTORDENE and other medicines may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature:

Hepatic metabolism

Interactions can occur with medicines that induce microsomal enzymes which can result in an increased clearance of ACTORDENE (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, ritonavir, griseofulvin and products containing St John's Wort).

Safety and efficacy of oral combined contraceptives, such as ACTORDENE, may be affected by HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, due to the hepatic metabolism. Other contraceptive mechanisms should be used.

Interference with enterohepatic circulation

Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic medicines are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Women on treatment with any of these medicines should temporarily use a barrier method in addition to ACTORDENE or choose another method of contraception. With microsomal enzyme-inducing medicines, the barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the active tablets in the ACTORDENE pack, the inactive tables should be omitted, and the next ACTORDENE pack should be started.

The first tablet should be taken from the silver section of the calendar pack by selecting the tablet corresponding to the day of the week (e.g. “MO’ for Monday). Then take 1 tablet every day following the directions shown by the arrows.

Substances decreasing the clearance of COCs (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole) and macrolides (e.g. erythromycin) can increase plasma concentrations of the oestrogen or the progestin or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1,4 to 1,6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0,035 mg ethinylestradiol.

ACTORDENE may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin and benzodiazepines) or decrease (e.g. lamotrigine). Note: The prescribing information 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, may increase the risk of ALT elevations (see **section 4.4**).

Therefore, ACTORDENE-users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination medicine regimen. ACTORDENE can be restarted 2 weeks following completion of treatment with this combination medicine regimen.

Laboratory tests

The use of ACTORDENE 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

Pregnancy

ACTORDENE is contraindicated in pregnancy. If pregnancy occurs during treatment with ACTORDENE, further intake should be stopped. See **section 4.3**

Breastfeeding

Lactation may be influenced by ACTORDENE as it may reduce the quantity and change the composition of breastmilk. Therefore, the use of ACTORDENE should generally not be recommended until the breastfeeding mother has completely weaned her child. Small amounts of the active ingredients of ACTORDENE and/or their metabolites may be excreted with the milk.

4.7 Effects on ability to drive and use machines

No or negligible observed effects. However, patients should be advised to exercise caution until they know how ACTORDENE affects them.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occurred in ≥ 1 % of users. Serious adverse reactions are arterial and venous thromboembolism.

Adverse reactions Adverse reactions and their frequencies are reported in **Table 1** by system organ class and by frequency.

Table 1: Tabulated summary of adverse reactions

The following undesirable effects have been reported.

System organ class	ACTORDENE Side effects
Immune system disorders	
Less frequent:	Hypersensitivity.
Metabolism and nutrition disorders	
Less frequent:	Fluid retention.
Psychiatric disorders	
Frequent:	Depressed mood, altered mood.
Less frequent:	Increased libido, decreased libido.
Nervous system disorders	
Frequent:	Headache.
Less frequent:	Migraine.
Eye disorders	
Less frequent:	Contact lens intolerance.
Vascular disorders	
Less frequent:	Venous thromboembolism (VTE), Arterial thromboembolism (ATE).
Gastrointestinal disorders	
Frequent:	Nausea, abdominal pain.
Less frequent:	Vomiting, diarrhoea.
Skin and subcutaneous tissue disorders	
Less frequent:	Rash, urticaria, erythema nodosum, erythema multiforme.
Reproductive system and breast disorders	
Frequent:	Breast pain, breast tenderness.
Less frequent:	Breast hypertrophy, vaginal discharge, breast discharge.
Investigations	
Frequent:	Increased weight.
Less frequent:	Decreased weight.

Table 2: Tabulated summary of adverse reactions (post-marketing)

In post-marketing experience, the following additional undesirable effects have been reported with frequency unknown:

System organ class	ACTORDENE Side effects
Immune system disorders	Exacerbation of hereditary angioedema.
Metabolism and nutrition disorders	Hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance.
Hepato-biliary disorders	Liver function disturbances.
Skin and subcutaneous tissue disorders	Chloasma.
Reproductive system and breast disorders	Reduced menstrual flow, spotting, breakthrough bleeding and missed withdrawal bleeding, post pill amenorrhoea.

Description of selected adverse reactions

The following serious adverse events have been reported in women using COCs, which are discussed in **section 4.4:**

- Venous thromboembolic disorders;
- arterial thromboembolic disorders;
- cerebrovascular accidents;
- hypertension;
- hypertriglyceridemia;
- Changes in glucose tolerance or effect on peripheral insulin resistance;
- Liver tumours (benign and malignant);
- liver function disturbances;
- chloasma;
- in women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema;
- occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis related hearing loss; Crohn's disease; ulcerative colitis; cervical cancer.

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see **section 4.3 "Contraindications"** and **section 4.4 Warnings and special precautions"**.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website

or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in case of taking an overdose of active tablets are nausea; vomiting; and, in young girls, slight vaginal bleeding.

There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 18.8 Ovulation controlling agents

Pharmacotherapeutic group: Sex hormones and modulators of the genital system,

progestogens and oestrogens, fixed combinations.

ATC code: G03AA10

ACTORDENE is a combined low-dose monophasic oral contraceptive with estrogenic (ethinylestradiol) and progestogenic (gestodene) peripheral effects.

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

5.2 Pharmacokinetic properties

Gestodene

Absorption

Orally administered gestodene is rapidly and completely absorbed. Peak serum concentrations of 3,5 ng/ml are reached at about 1 hour after single dose ingestion. Bioavailability is about 99 %.

Distribution

Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1 to 2 % of the total serum gestodene concentrations are present as free steroid, 50 to 70 % are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the proportion of gestodene bound to the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of gestodene is 0,7 L/kg.

Metabolism

Gestodene is completely metabolised by the known pathways of steroid metabolism. The clearance rate from serum is 0,8 mL/min/kg. No interaction was found with the co-administered ethinylestradiol.

Elimination

Gestodene serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 12 hours. Gestodene is not excreted in its unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 6:4. The half-life of metabolite excretion is about 24 hours.

Steady-state conditions

Gestodene pharmacokinetics are influenced by SHBG levels, which are increased about twofold when co-administered with ethinylestradiol. Following daily ingestion, gestodene serum levels increase about fourfold, reaching steady-state conditions during the second half of a treatment cycle.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 65 pg/mL are reached at 1,7 hours. During absorption and first liver passage, ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of about 45 % with a large interindividual variation of about 20 to 65 %.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2,8 to 8,6 L/kg was reported.

Metabolism

Ethinylestradiol is subject to presystemic conjugation in both the small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulphate. The clearance rate was reported to be 2,3 to 7 mL/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases characterised by half-lives of about 1 hour and 10 to 20 hours, respectively. Unchanged substance is not excreted; ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 24 hours.

Steady-state conditions

According to the variable half-life of the terminal disposition phase from serum and the daily ingestion, steady-state serum levels of ethinylestradiol will be reached after about 1 week.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active white or off-white tablets

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Polacrilin potassium

Povidone K-30

Inactive green film-coated tablets (placebo)

Tablet core:

Lactose monohydrate

Magnesium stearate

Maize starch

Povidone K-30

Silica, colloidal anhydrous

Tablet coat:

FD&C blue 2 aluminium lake

Hypromellose 2910

Polysorbate 80

Titanium dioxide

Triacetin

Yellow iron oxide

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C in a cool, dry place.

Keep the blisters in the outer carton to protect from light and moisture.

Store all medicines out of reach of children.

6.5 Nature and contents of container

The tablets are contained in PVC-PVDC/aluminium blisters. Aluminium foil is a foil of push-through aluminium with a lacquered dull side, and a heat sealable bright side lacquered for sealing to PVC.

The blisters are contained in an outer cardboard carton.

Pack size: The 28-day pack (Every-day calendar pack) contains 21 active hormonal white or off-white tablets plus 7 inactive non-hormonal (placebo) green film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

48/18.8/1352

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10. DATE OF REVISION OF THE TEXT

17 December 2024