

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Ava 30 ED, film coated tablets 0.15mg/0.03mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each blister strip holds 21 active hormonal tablets containing 0.15 mg levonorgestrel and 0.03 mg ethinylestradiol and 7 non-hormonal tablets.

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Active hormonal tablets: White, round, sugar coated tablets, diameter 5.6 mm.

Non-hormonal tablets: Yellow, round, sugar coated tablets, diameter 5.6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

4.2 Dose and method of administration

Combined oral contraceptives, such as Ava 30 ED, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

How to take Ava 30 ED

Tablets must be taken in the order directed on the package every day at about the same time with some water as needed. Tablet-taking is continuous. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack following the directional arrows. Withdrawal bleeding usually occurs while taking the 7 yellow non-hormonal tablets. This usually starts on day 2 - 3 after starting the yellow non-hormonal tablets and may not have finished before the next pack is started.

How to start Ava 30 ED

The following instructions are given for starting Ava 30 ED, depending on the woman's contraception history:

START WITH THE FIRST TABLET FROM THE BLUE SECTION MARKED WITH THAT DAY OF THE WEEK, in accordance with one of the following:

- **No preceding hormonal contraceptive use (in the past month)**

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

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

The woman should start with Ava 30 ED preferably on the day after her last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or non-hormonal tablet interval of her previous COC.

In case a vaginal ring or transdermal patch has been used, the woman should start taking Ava 30 ED preferably on the day of removal, but at the latest when the next application would have been due.

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

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

- **Following first-trimester abortion**

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

- **Following delivery or second-trimester abortion**

The woman should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later than this, the woman should be advised to additionally use a barrier contraceptive method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before starting Ava 30 ED or the woman has to wait for her first menstrual period.

Management of Missed Tablets

Errors in taking the yellow non-hormonal tablets contained in Ava 30 ED can be ignored. However, they should be discarded to avoid unintentionally prolonging the non-hormonal tablet phase. The following advice only refers to missed white active tablets:

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

If she is **more than 12 hours** late in taking any white active tablet, contraceptive protection may be reduced.

There is a particularly high risk of pregnancy if tablets are missed just before or immediately after taking the yellow non-hormonal tablets. If tablets are missed in the first week of taking the white active tablets following the non-hormonal tablets and intercourse took place in the preceding 7 days, the possibility of pregnancy should be considered.

The management of missed tablets can be guided by the following two basic rules:

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

These rules form the basis of the instructions to patients provided in the package insert.

Extra Contraceptive Precautions

When you need extra contraceptive precautions, either:

- don't have sex; or
- use a cap plus spermicide; or
- use a condom

Do not use the rhythm or temperature methods as extra contraceptive precautions. This is because oral contraceptives alter the usual menstrual cycle changes, such as changes in temperature and cervical mucus.

The 7 Day Rule

- Continue taking your Pills.
- You will not be protected from pregnancy until you have taken your daily white active Pill for the next 7 days in a row.
- Use another method of contraception (see “*Extra Contraceptive Precautions*”) such as condoms or do not have sexual intercourse for these next 7 days.
- If there are fewer than 7 white active Pills left in the pack, or before the yellow non-hormonal Pills in the pack, go straight on to the active Pills in the blue section of the next pack. This means that you miss out the yellow non-hormonal Pills. You may not have a period until the end of the next pack. This is not harmful.

If the user missed tablets and subsequently has no withdrawal bleed in the yellow non-hormonal tablet phase, the possibility of a pregnancy should be considered.

Advice in case of Vomiting or severe Diarrhoea

If vomiting or severe diarrhoea occurs within 3 - 4 hours after taking the white active tablet, absorption may not be complete and additional barrier contraceptive measures should be used. In such an event, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet taking schedule, she has to take the extra tablet(s) needed from another pack.

How to Shift Periods or How to Delay a Period

To delay a period the woman should continue with the white active tablets from another pack of Ava 30 ED without taking the yellow non-hormonal tablets from her current pack. The extension can be carried on for as long as desired until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Ava 30 ED is then resumed after the non-hormonal tablet phase.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming non-hormonal tablet phase by as many days as she likes. The shorter the hormone-free interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the second pack (just as when delaying a period).

4.3 Contraindications

Combined oral contraceptives 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 their use, the product should be stopped immediately.

- Presence or 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 prodromi of a thrombosis (e.g. transient ischemic attack, angina pectoris)
- Diabetes mellitus with vascular involvement
- Disturbed lipometabolism
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see also Special warnings and precautions for use).

- 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)
- History of migraine with focal neurological symptoms
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the active substances or excipients of Ava 30 ED

Ava 30 ED is contraindicated for use with the Hepatitis C combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or with ribavirin (see Special warnings and precautions for use).

4.4 Special warnings and precautions for use

The clinical and epidemiological evidence for COCs like Ava 30 ED is predominantly based on experience with COCs in general. Therefore, the following warnings related to the use of COCs apply also to the use of Ava 30 ED.

If any of the conditions/risk factors mentioned below are present, the benefits of COC 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 physician. The physician should then decide whether the COC should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs. The risk for venous thromboembolism is highest during the first year a woman takes a COC. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

This study has shown that the frequency of VTE diagnosis range from 8 to 10 per 10,000 woman years in low oestrogen dose (< 50 µg ethinylestradiol) COC users.

The most recent data suggests that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman years in non-pregnant non-COC users and range from 20 to 30 per 10,000 women or post-partum.

Overall the risk of VTE in users of low oestrogen dose (< 50 µg ethinylestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

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

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of venous (includes pulmonary embolism (PE) and deep venous thrombosis (DVT)) or arterial thrombosis/thromboembolic (includes myocardial infarction (MI), vascular occlusion and

cerebrovascular accident) events can include: unilateral leg pain and/or swelling; 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; sudden, severe pain in the chest which may increase with deep breathing; 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; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe, prolonged headache with no known cause; sudden, partial or complete loss of vision; diplopia; sense of anxiety; dizziness; sudden confusion; 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; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

Some of these symptoms (e.g. "shortness of breath", "coughing") are nonspecific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Arterial thromboembolic events may be fatal.

The risk of 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 COC use
- obesity (body mass index over 30 kg/m²)
- 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 COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The increased risk of thromboembolism in the puerperium must be considered.

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

An increase in frequency or severity of headaches during COC use, in particular the onset of migraine which may be prodromal of a cerebrovascular event, may be a reason for immediate discontinuation of the COC.

Biochemical factors that may be indicative of 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 physician 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 low-dose COCs (< 0.05 mg ethinylestradiol).

Tumours

The most important risk factor for cervical cancer is persistent HPV infection.

Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use.

Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign, 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 haemorrhages. A liver 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 COCs.

Hepatitis C

During clinical trials with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings.

Ava 30 ED must be discontinued 2 weeks prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin. Ava 30 ED can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

Other Conditions

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC, then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: 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 or kidney function may necessitate the discontinuation of COC use until markers of liver or kidney function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

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

Crohn's disease and ulcerative colitis have been associated with COC use.

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 COCs.

Each white active tablet contains 47.4 mg of lactose and each yellow non-hormonal tablet contains 52.5 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstatement of Ava 30 ED, guided by the "Contraindications" and "Special warnings and precautions for use" sections. This should be repeated at least annually during the use of Ava 30 ED. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischemic 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 Ava 30 ED. 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.

Sexually Transmitted Diseases including HIV infections and AIDS

Women should be advised that preparations like Ava 30 ED do not protect against HIV infections (AIDS) and other sexually transmissible diseases. The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs.

Reduced Efficacy

The efficacy of Ava 30 ED may be reduced in the event of missed active tablets (see "Management of Missed Tablets"), vomiting or severe diarrhoea (see "Advice in Case of Vomiting or Severe Diarrhoea") or concomitant medication (see Interaction with other medicines and other forms of interaction).

Reduced Cycle Control

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. These may include curettage.

In some women withdrawal bleeding may not occur while taking the 7 yellow non-hormonal tablets. If the COC has been taken according to the directions described under “Dose and method of administration”, it is unlikely that the woman is pregnant. However, if the COC 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 COC use is continued.

Paediatric Use

Ava 30 ED is only indicated after menarche.

Use in the Elderly

Ava 30 ED is not indicated after menopause.

Patients with hepatic impairment

Ava 30 ED is contraindicated in women with severe hepatic diseases as long as the liver function values have not returned to normal (see Contraindications).

Patients with renal impairment

Ava 30 ED has not been specifically studied in renal impaired patients. There is no data suggesting the need for a dosage adjustment in patients with renal impairment.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on Ava 30 ED

Interactions can occur with medicines that induce microsomal enzymes which result in an increased clearance of sex hormones and which can lead to breakthrough bleeding and/or oral contraceptive failure.

Women on treatment with any of these medicines should temporarily use a barrier method in addition to the COC or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after its discontinuation. If the period during which the barrier method is used runs beyond the end of the white active tablets in the Ava 30 ED pack, the yellow non-hormonal tablets should be omitted and the next Ava 30 ED pack should be started.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme induction) eg.:

Interactions can occur with medicines that induce microsomal enzymes (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John’s Wort (*hypericum perforatum*)) which can result in increased clearance of sex hormones.

Substances with variable effects on the clearance of COCs:

When co-administered with COCs, many human immunodeficiency virus (HIV)/hepatitis C (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of oestrogen and progestogen. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of COCs (enzyme inhibitors):

Strong and moderate CYP3A4 inhibitors such as azole antifungals (eg. itraconazole, voriconazole, fluconazole) verapamil, macrolides (eg. clarithromycin, erythromycin), diltiazem and grapefruit juice 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 ethinyloestradiol 1.4 to 1.6 fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinyloestradiol.

Influence of Ava 30 ED on other medication

Oral contraceptives such as Ava 30 ED may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

In vitro, ethinylloestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinylloestradiol lead to no, or a weak, increase in CYP3A4 substrates (eg. midazolam) and a weak (eg. theophylline) to moderate (eg. melatonin, tizanidine) increase of CYP1A2 substrates.

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

Laboratory Tests

The use of preparations like Ava 30 ED 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 (Category B3)

The administration of Ava 30 ED is contraindicated during pregnancy (see Contraindications).

If pregnancy occurs during treatment with Ava 30 ED, further intake must be stopped.

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

Lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk. Therefore the use of COCs should generally not be recommended until the nursing mother has completely weaned her child.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

4.8 Undesirable effects

Serious undesirable effects of Ava 30 ED have been referred to under the “Contraindications” and “Special warnings and precautions for use” sections.

Serious adverse reactions are arterial and venous thromboembolism.

In addition, the following undesirable effects have been reported in users of COCs such as Ava 30 ED, although the causal relationships have not been confirmed.

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and < 1/100)	Rare (< 1/1000)
Eye Disorders			Contact lens intolerance
Gastrointestinal Disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Immune System Disorders			Hypersensitivity
Investigations	Increased weight		Decreased weight
Metabolism and Nutrition Disorders		Fluid retention	
Nervous System Disorders	Headache	Migraine	
Psychiatric Disorders	Depressed mood, altered mood	Decreased libido	Increased libido
Reproductive System and Breast Disorders	Breast pain, breast tenderness	Breast hypertrophy	Vaginal discharge, breast discharge
Skin and Subcutaneous Tissue Disorders		Rash, urticaria	Erythema nodosum, erythema multiforme
Vascular Disorders			Venous and arterial thromboembolic events**

** Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives. 'Venous and arterial thromboembolic events' summarises the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction/cerebral infarction and stroke not specified as haemorrhagic.

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

4.9 Overdose

There have been no reports of serious deleterious effects from overdose.

Symptoms

Symptoms that may occur in case of taking an overdose of active tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding.

Treatment

There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogen and estrogens, fixed combinations, ATC code: G03AA07

The contraceptive effect of Ava 30 ED is 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. When Ava 30 ED is taken according to instructions, the egg cells are prevented from maturing to the point at which they can be fertilised, the cervical mucus remains thick so as to constitute a barrier to sperm, and the endometrium is rendered unreceptive to implantation.

As well as protection against pregnancy, oestrogen/progestogen combinations have several positive properties which, next to the negative properties (see "Special warnings and precautions for use" and "Undesirable effects"), can be useful in deciding on the method of birth control.

With combined oral contraceptives (COCs) the cycle is more regular and menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this there is evidence of a reduced risk of endometrial cancer and ovarian cancer. With the higher-dosed combined oral contraceptives containing 0.05 mg ethinylestradiol, there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease and ectopic pregnancy. This may also apply to lower-dosed COCs.

5.2 Pharmacokinetic properties

Levonorgestrel

Absorption

Orally administered levonorgestrel is rapidly and completely absorbed. Peak serum concentrations of 3 – 4 ng/mL are reached 1 hour after single ingestion.

Levonorgestrel is almost completely bioavailable after oral administration.

Distribution

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only around 1.3% of the total serum medicine concentrations are present as free steroid, approximately 64% are specifically bound to SHBG and about 35% non-specifically bound to albumin. The ethinylestradiol induced increase in SHBG influences the proportion of levonorgestrel 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 levonorgestrel is 184 L after single administration.

Metabolism

Levonorgestrel is completely metabolized by known pathways of steroid metabolism. The metabolic clearance rate from serum is approximately 1.3 – 1.6 mL/min/kg.

Elimination

Levonorgestrel serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 20 – 23 hours. Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of approximately 1:1. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Following daily ingestion, medicine serum levels increase approximately three- to four-fold reaching steady-state conditions during the second half of the treatment cycle.

Levonorgestrel pharmacokinetics are influenced by SHBG levels, which are increased about 1.7 fold after daily oral administration of levonorgestrel 0.15 mg and ethinylestradiol 0.03 mg tablets. This effect leads to a reduction of the clearance rate to approximately 0.7 mL/min/kg at steady state.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 95 pg/mL are reached within 1 - 2 hours. During absorption and first-pass liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of approximately 45% with a large interindividual variation of about 20 - 65%.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approx. 98%), and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2.8 - 8.6 L/kg was reported.

Metabolism

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate was reported to be 2.3 - 7 mL/min/kg.

Elimination

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

Steady-state Conditions

Ethinylestradiol serum concentrations increase slightly after daily oral administration of levonorgestrel 0.15 mg and ethinylestradiol 0.03 mg tablets. The maximum concentrations are approximately 114 pg/mL at the end of a treatment cycle.

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 approximately one week.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active tablets

Lactose
Polacrillin Potassium
Magnesium Stearate
Ethyl Cellulose
Talc
Gum Aacacia
Disodium Edetate
Sucrose
Microcrystalline Cellulose
Titanium Dioxide
Macrogol 6000
Maize Starch
Methyl hydroxybenzoate

Non-hormonal tablets

Lactose
Glycerol
Macrogol 6000
Calcium Carbonate
Talc
Povidone K-90
Povidone K-25
Sucrose
Titanium Dioxide
Magnesium Stearate
Carnuaba Wax
Maize Starch
Yellow Oxide of Iron

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/PVdC/Aluminium foil blister strips. Pack size of 84 tablets (3 strips of 28 tablets).

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited

PO Box 128 244

Remuera

Auckland 1541

Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

22 April 2010

10. DATE OF REVISION OF THE TEXT

10 February 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	Update to the SPC-style format
4.3 & 4.4	Updated due to risk of hepatotoxicity when medicines containing ethinylestradiol are taken with HCV combination drug regimens (ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin).
4.5, 4.6, 4.8	Updated
8.	Sponsor company name and address details updated