1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ORALCON 0,15 mg/0,03 mg (tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each active white tablet of ORALCON contains:

Levonorgestrel 0,15 mg

Ethinyl oestradiol 0,03 mg

Contains sugar:

Sucrose: 21,19 mg

Lactose monohydrate: 47,44 mg

Preservative: Methyl hydroxybenzoate 0,08 % *w/w*

The 7 red tablets are inert.

Each red inert tablet contains:

Contains sugar:

Sucrose: 24,5 mg

Lactose monohydrate: 71,38 mg

Preservative: Methyl hydroxybenzoate 0,1 % *w/w*

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

Each course of ORALCON comprises of 21 active white and 7 red inert, sugar-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ORALCON is indicated for fertility control in women and for the control of certain menstrual irregularities i.e. symptomatic treatment of primary dysmenorrhoea where contraception is also desired, and cases of dysfunctional uterine bleeding.

4.2 Posology and method of administration

Posology

FOR CONTRACEPTION

ORALCON tablets must be taken as directed and at intervals not exceeding 24 hours to achieve maximum effectiveness. The tablets are to be taken at the same time every day, preferably after the evening meal or at bedtime. It can be expected to have withdrawal bleeding within 2 to 4 days after the last white tablet has been taken.

If the tablets have been started after day 5 or postpartum, the possibility of pregnancy must be checked prior to commencement of administration as conception or ovulation might have occurred before starting.

1. Beginning on day 1 of the menstrual cycle, i.e. the first day of bleeding.
2. First 21 consecutive days: Take one white tablet daily following the arrows until all the white tablets are finished.
3. Next 7 consecutive days: Take one red inert tablet daily following the arrows until all the red tablets are finished.

4. On the following day start a new package taking the first white tablet of the next course as described under point 2.

NOTE: There must be no delay between finishing one course and starting the next.
The next and all subsequent courses will begin on the day after the last package was completed, even if withdrawal bleeding has not occurred or is still in progress. Each course of ORALCON will start on the same day of the week and follows the same schedule (21 days of white tablets, 7 days of red inert tablets)
During this first cycle, an additional method of contraception (mechanical) should be used until 14 tablets of the first course of ORALCON have been taken.
In the non-lactating mothers, use of ORALCON tablets may be instituted immediately after delivery or at the first postpartum examination, whether or not menstruation has resumed.

Patients changing from another oral contraceptive product:
When changing from another oral contraceptive, begin the first active tablet of ORALCON on the day after the last active tablet of the previous course has been taken. If a tablet-free interval is taken, then extra contraceptive precautions are advised for the first 7 days. If the inert tablets are inadvertently taken first, extra contraceptive precautions are necessary during the first 14 days. If transient spotting or breakthrough bleeding occurs, continue with the course. If the bleeding is persistent or prolonged, consult a physician.

Missed tablets
If a tablet is missed, the risk of pregnancy is greatest when it happens at the beginning or end of a cycle. The missed white tablet should be taken as soon as possible. If tablets are missed for two consecutive days, both tablets should be taken as soon as possible. In either case, the next tablet should be taken at the usual time. Extra contraception methods (mechanical) are required for the next 7 days. If one or more tablets are missed during the

last week of active (white) tablets, the inert red tablets must be discarded and the next cycle of ORALCON started immediately. A period should not be expected until the end of the next cycle.

If three consecutive white tablets are missed, ORALCON should be discontinued, and remaining tablets discarded. A new package should be started on the eighth day after the last tablet was taken. Extra contraception methods (mechanical) are required for the 7 days while no tablets are taken and for 7 days after the new course have been started. If the patient does not have a period at the end of the second pack, she must return to her doctor to exclude the possibility of pregnancy.
Missing any of the inert tablets is not important, but the next course must be started at the right time.

Method of administration

Take ORALCON tablets orally.

4.3 Contraindications

- Hypersensitivity to ORALCON or to any components of the formulation.
- Suspected pregnancy.
- The presence, history or high risk of thromboembolic disease.
- Cerebrovascular disease.
- Previous myocardial infarction.
- Known or suspected coronary artery disease.
- Hyperlipidaemia.
- Known or suspected carcinoma of breast, endometrium or other hormone dependent/responsive neoplasias.
- Hepatic adenoma.

- Abnormal, undiagnosed genital bleeding.
- History or presence of liver tumours or impaired liver functions or cholestasis.
- Acute or chronic liver diseases, including Dubin-Johnson or Rotor syndromes.
- A history during pregnancy of pruritus or cholestatic jaundice.
- Presence of, or multiple risk factors for arterial disease.
- Severe or focal migraine.
- A history during pregnancy of chorea, herpes gestationis, pemphigoid gestationis or deteriorating otosclerosis.
- Depression not well controlled with treatment.
- A history of depression with the use of hormonal contraceptives.

4.4 Special warnings and precautions for use

Use ORALCON with caution in patients with:

• Other forms of migraine headaches. ORALCON should be stopped immediately if a migraine becomes focal. See section 4.3.

• Hypertension.

• Diabetes mellitus. – Monitor carefully as a decrease in glucose tolerance may occur.

• Gallbladder disease.

• Depression. – Discontinue ORALCON if depression recurs.

• Porphyria.

• Conditions influenced by fluid retention, epilepsy and asthma, as the condition may be exacerbated.

• Varicose veins.

The risk of cardiovascular adverse effects such as thromboembolism is increased in women who smoke, especially those over the age of 35 years. The risk is greater if they have used oral contraceptives for longer than 5 years, if they are obese, hypertensive, diabetic or have hypercholesterolaemia. Women who take ORALCON should be advised not to smoke.

Note: ORALCON does not protect against sexually transmitted diseases or the virus that causes acquired immunodeficiency syndrome (AIDS).

ORALCON should be discontinued immediately if any of the following occur:

o Sudden severe chest pain, sudden breathlessness, or severe pain / swelling in calf of one or both legs, as these may indicate thromboembolism or thrombotic disease.

o Unusual, severe prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body or other signs or symptoms suggestive of cerebrovascular accident.

o Hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain. Benign hepatic adenomas have been associated with the use of oral contraceptives, including ORALCON.

o Onset of severe depression. Mood changes and depression are side effects reported with the use of hormonal contraceptives including ORALCON. There is some evidence that hormonal contraceptive use may be associated with severe depression and a higher risk of suicidal thoughts/behaviour (e.g. talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with ORALCON.
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 medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

o A significant rise in blood pressure.

- Clear exacerbation of other conditions known to be capable of deteriorating during oral contraception or pregnancy.

Women undergoing surgery or prolonged bed rest should discontinue ORALCON four to six weeks before and for two weeks thereafter to minimize the possibility of thromboembolism after surgery.

Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, additional non-hormonal contraception is recommended for the duration of antibiotic therapy and for seven days thereafter. Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness.

Oral contraceptive effectiveness may be reduced during vomiting and diarrhoea. Additional contraceptive measures may be necessary during and for 7 days after recovery from such episodes. Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness and additional contraceptive methods should be used. Changing to a product with a different composition may be required to ensure efficacy.

Excipients: Lactose and sucrose warning:

ORALCON contains lactose and sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary condition of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption, fructose intolerance or sucrose-isomaltase insufficiency should not take ORALCON

4.5 Interaction with other medicines and other forms of interaction

Enzyme-inducing medicines may enhance metabolism and clearance of oral contraceptives resulting in failure of the contraceptive effect. This effect is well established for a number of antiepileptics (such as carbamazepine, phenobarbital and phenytoin), griseofulvin, rifamycin antibacterials (such as rifampicin and rifabutin) and has also been suggested for some antivirals and for modafinil.

The following medicines may also interact with ORALCON:

Antibacterials: Broad-spectrum antibacterials have occasionally been reported to decrease oral contraceptive efficacy. See section 4.3.

Antidiabetics: Troglitazone is an enzyme inducer and increases the clearance of estrogens and progestogens.

Antiepileptics: Oral contraceptive failure and breakthrough bleeding have been reported in women on antiepileptic therapy. Phenytoin, phenobarbital, primidone and carbamazepine have been most frequently implicated, and oxcarbazepine, felbamate and topiramate may interact similarly. The effect of these may also be diminished due to the combined oral contraceptive.

Antifungals: Menstrual irregularities and pregnancies have been reported in women receiving oral contraceptives including ORALCON and griseofulvin concurrently. Anecdotal reports have also been received of contraceptive failure with fluconazole, itraconazole and ketoconazole.

Antivirals: Antivirals are likely to accelerate the metabolism of estrogen and progestogens and this has been suggested for the protease inhibitors such as nelfinavir and ritonavir, and for nevirapine.

Hypericum/St John's Wort: May decrease blood concentrations of oral contraceptives resulting in intermenstrual and altered menstrual bleeding and contraceptive failure.

Stimulants: Modafinil may reduce the efficacy of oral contraceptives.

In addition to the above interactions, several medicines may be affected by concomitant use with ORALCON

- paracetamol and morphine – analgesic effects antagonised
- anticoagulants – increased or decreased effects
- antidepressants – both reduced effectiveness and increased toxicity reported with some antidepressants
- antidiabetics such as sulfonylureas and insulin – antagonism of the effect
- antihypertensives – antagonism of the effect
- benzodiazepines – increased or decreased clearance
- ciclosporin – increased plasma concentration resulting in toxicity
- clofibrate – increased clearance and antagonism of the effect
- corticosteroids – enhanced effect due to reduced clearance
- lignocaine – increased free fraction
- selegiline – decreased clearance
- thyroxine – reduced free fraction
- xanthines – decreased clearance

Laboratory tests:

ORALCON may influence results such as liver, thyroid, adrenal and renal function tests, plasma concentrations of binding proteins and lipid/lipoprotein fractions, and fibrinolysis and coagulation parameters.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oral contraceptives are contra-indicated during pregnancy. See section 4.3. Pregnancy should be ruled out before a course of ORALCON is initiated.

If the correct dosing schedule was followed and two consecutive menstrual cycles have been missed, the use of ORALCON should be discontinued, until the possibility of pregnancy has been ruled out.

If the correct dosing schedule was not followed, pregnancy should be ruled out after the first missed menstrual period.

It is recommended that conception be delayed for 3 months after discontinuation of ORALCON or until after the first regular menses.

Breastfeeding

ORALCON may diminish the quantity, quality or the length of time of lactation. ORALCON is recommended to begin after the third postpartum month for mothers who are exclusively breastfeeding and in the third postpartum week for mothers who are only partially or not breastfeeding.

4.7 Effects on ability to drive and use machines

Based on the side effect profile of ORALCON, no effect is expected on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated summary of adverse reactions:

The undesirable effects are listed by system organ classes.

System organ class	
Frequency	**Adverse reaction**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Less frequent:	Breast tumours, hepatocellular carcinoma, benign hepatic tumours (adenomas)
Frequency unknown:	Increased risk of cervical cancer
Metabolism and nutrition disorders	

Frequent:	Water retention
Less frequent:	Reduced glucose tolerance, changes in lipid metabolism, weight gain
Psychiatric disorders:	
Less frequent:	Depression and other mental changes
Nervous system disorders:	
Less frequent:	Worsening or increasing frequency of headache or migraines, chorea
Eye disorders:	
Frequency unknown:	Intolerance to contact lenses has been reported and vision may deteriorate in myopic patients
Cardiac disorders:	
Less frequent:	Hypertension
Vascular disorders:	
Less frequent:	Venous thromboembolism, thrombosis, stroke
Gastrointestinal disorders:	
Frequent:	Nausea and/or vomiting, bloating, abdominal cramps
Hepato-biliary disorders:	
Frequency unknown:	Impaired liver function, gall bladder disease
Skin and subcutaneous tissue disorders:	
Frequent:	Acne
Less frequent:	Chloasma (melasma), skin rashes, gain or loss of body or facial hair
Reproductive system and breast disorders:	
Frequent:	Breast tenderness and menstrual irregularities such as spotting, breakthrough bleeding or amenorrhoea
Less frequent:	Changes in libido, vaginal candidiasis

Post marketing reported side effects:

The following side effects have been reported with the post marketing use of hormonal contraceptives: Severe depression with a higher risk of suicidal thoughts/behaviour and suicide

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 "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdose:

See section 4.8

Nausea and withdrawal bleeding may occur.

Treatment of overdose:

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class: 18.8 Ovulation controlling agent

Pharmacotherapeutic group: Hormonal contraceptives for systemic use, progestogens and estrogens, fixed combinations

ATC code: G03AA07

Oestrogen-progestogen combination oral contraceptives act primarily through the mechanism of gonadotrophin (luteinising hormone and follicle stimulating hormone) suppression, resulting in the prevention of ovulation. The viscosity of the cervical mucosa is

increased, hindering penetration of the sperm. An endometrium which is less receptive for implantation is formed.

5.2 Pharmacokinetic properties

The pharmacokinetics of Levonorgestrel and Ethinyl oestradiol were determined in a bioequivalence study of ORALCON on 24 healthy women, in a randomized, single dose, two treatments, two period, two sequence, open label, crossover study with a 27 day wash out period.

Levonorgestrel

Levonorgestrel is rapidly absorbed from the gastrointestinal tract and is completely bioavailable.

It is highly bound to plasma protein that is to sex hormone binding globulin (SHBG) and albumin. The half-life is approximately 24 hours. The percentage ratios of least square means of ORALCON to reference were found to be comparable for Cmax (105,21 %), AUC0-120 (103,89 %) and AUC0-inf(103,82
%). The main path of metabolism is by reduction of the A ring followed by glucuronidation. The excretion is by urine and faeces.

Ethinyl oestradiol

Ethinyl oestradiol is rapidly and well absorbed from the gastrointestinal tract. The presence of an ethinyl group at the 17-position greatly reduces hepatic first-pass metabolism and the mean bioavailability is only about 40 – 45 %. Ethinyl oestradiol is highly protein bound. It is principally bound to Albumin and enhances the binding capacity of the SHBG. The percentage ratio of least square means of ORALCON to reference product were found to be comparable for Cmax (102,78 %) < AUC0-120(103,38 %) and AUC0- inf(102,89 %). It is metabolised in the liver and excreted in urine and faeces.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active ORALCON tablets:

Acacia,

disodium edetate,

ethyl cellulose,

lactose monohydrate,

magnesium stearate,

maize starch,

methyl hydroxybenzoate,

microcrystalline cellulose,

polacrilin potassium,

polyethylene glycol,

purified talc,

sucrose,

titanium dioxide (CI no. 77891).

Inactive ORALCON tablets:

Carnauba wax,

disodium edetate,

gum acacia,

lactose monohydrate,

magnesium stearate,

maize starch,

methyl hydroxybenzoate,

polacrilin potassium,

ponceau 4R lake (CI no. 16255),

purified talc,

sodium benzoate,

sucrose,

titanium dioxide (CI no. 77891).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Protect from light.

KEEP THE BLISTERS IN THE CARTON UNTIL REQUIRED FOR USE.

6.5 Nature and contents of container

Alu/PVdC/PVC foil blister packs of 28 tablets (21 white and 7 red tablets) packed in a cardboard carton together with a leaflet.

6.6 Special precautions for disposal

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

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Kempton Park,

Johannesburg, 1600

Republic of South Africa

8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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