1.3.1.1 PACKAGE INSERT

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

ACCORD LETROZOLE 2,5 mg. Film-coated tablet.

Each film-coated tablet contains 2,5 mg letrozole.

Contains sugar: Lactose monohydrate

For the full list of excipients, see Section 6.1

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Quantitative and qualitative declaration:

Each **ACCORD LETROZOLE 2,5 mg** film-coated tablet contains 2,5 mg letrozole.

3. PHARMACEUTICAL FORM

ACCORD LETROZOLE 2,5 mg are yellow, round, biconvex, film coated tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with antioestrogens.
- Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast- conserving surgery in women not originally considered candidates for this type of surgery. Subsequent treatment after surgery should be in accordance with standard of care.

4.2 Posology and method of administration:

Posology:

Adults and elderly patients: The recommended dose of **ACCORD LETROZOLE 2,5 mg** once daily.

In the adjuvant and extended adjuvant setting, treatment with **ACCORD LETROZOLE 2,5 mg** should continue for 5 years or until tumour relapse occurs, whichever comes first.

In patients with metastatic disease, treatment with **ACCORD LETROZOLE 2,5 mg** should continue until tumour progression is evident.

Elderly patients:

No dose adjustment is required for elderly patients.

Paediatric population:

Not applicable.

Patients with hepatic and/or renal impairment:

No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child Pugh grade A and B) or renal impairment (creatinine clearance ≥ 10 ml/min).

Insufficient data are available to establish dosage recommendations for patients with a creatinine clearance of < 10 ml/min (see section 4.3 *Contra-indications*).

However, **ACCORD LETROZOLE 2,5 mg** should not be used in patients with severe hepatic impairment (Child-Pugh score C).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Premenopausal endocrine status, pregnancy or lactation.
- Severe impairment of hepatic function (Child-Pugh grade C).
- Severe impairment of renal function (creatinine clearance < 10 ml/min).

4.4 Special warnings and precautions for use

Menopausal status

In patients whose menopausal status is unclear, luteinising hormone (LH), follicle-stimulating hormone (FSH) and/or oestradiol levels should be measured before initiating treatment with **ACCORD LETROZOLE 2,5 mg**. Only women of postmenopausal endocrine status should receive **ACCORD LETROZOLE 2,5 mg**.

Impaired renal function

ACCORD LETROZOLE 2,5 mg has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10 ml/min.

Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. The potential risk/benefit to such patients should be carefully considered before administration of **ACCORD LETROZOLE 2,5 mg**.

Bone effects

ACCORD LETROZOLE 2,5 mg is a potent oestrogen-lowering agent. Women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, should have their bone mineral density formally assessed prior to the commencement of adjuvant and extended adjuvant treatment and monitored during and following treatment with letrozole.
Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered depending on the patient's safety profile. (see sections 4.2, 4.8)

Other warnings

Co-administration of **ACCORD LETROZOLE 2,5 mg** with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole (see section 4.5).

As the tablets contain lactose, **ACCORD LETROZOLE 2,5 mg** is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

4.5 Interaction with other medicines and other forms of interaction

Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of **ACCORD LETROZOLE 2,5 mg** with these medicines does not result in clinically significant drug interactions.

Additionally, in a large clinical trial there was no evidence of clinically relevant interaction in patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).

There is no clinical experience to date on the use of **ACCORD LETROZOLE 2,5 mg** in combination with other anti-cancer agents other than tamoxifen.

Tamoxifen, other anti-oestrogens or oestrogen-containing therapies may diminish the pharmacological action of letrozole. In addition, co-administration of tamoxifen with letrozole has been shown to substantially decrease plasma concentrations of letrozole. Co-administration of letrozole with tamoxifen, other anti- oestrogens or oestrogens should be avoided.

ACCORD LETROZOLE 2,5 mg inhibits the cytochrome P450-isozymes 2A6, and moderately 2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow (e.g. phenytoin, clopidrogel).

CYP2A6 does not play a major role in medicine metabolism.

In studies, letrozole was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady state.

Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. However, caution should be used in the concomitant administration of medicines whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

4.6 Fertility. Pregnancy and lactation

ACCORD LETROZOLE 2,5 mg is contra-indicated during pregnancy and lactation. (Refer to Section 4.3)

4.7 Effects on ability to drive and use machines

Fatigue and dizziness have been observed with the use of **ACCORD LETROZOLE 2,5 mg** and somnolence has been reported. Patients should be advised that their physical and/or mental abilities required for operating machinery or driving a car may be impaired.

4.8 Undesirable effects

Infections and Infestations

Less frequent: Urinary tract infection

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Less frequent: Tumour pain (in metastatic/neoadjuvant setting only)

Blood and lymphatic system disorders

Less frequent: Leucopoenia

Immune system disorders:

Frequency unknown: Angioedema, anaphylactic reactions

Metabolism and nutrition disorders

Frequent: Anorexia, appetite increase, hypercholesterolemia

Less frequent: General oedema

Psychiatric disorders

Frequent: Depression

Less frequent: Anxiety, (including nervousness, irritability)

Nervous system disorders

Frequent: Headache, dizziness.

Less frequent: Somnolence, insomnia, memory impairment, dysesthesia (paraesthesia, hypaesthesia), taste disturbance, cerebrovascular accident, carpal tunnel syndrome.

Eye disorders

Less frequent: Cataract, eye irritation, blurred vision

Cardiac disorders

Frequent: Palpitations

*Less frequent: T*achycardia, ischaemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischaemia)

Vascular disorders

Frequent: Hot flushes, hypertension

Less frequent: Thrombophlebitis (including superficial and deep vein thrombophlebitis), ischemic cardiac events, pulmonary embolism, arterial thrombosis, cerebrovascular infarction

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea, cough

Gastrointestinal disorders

Frequent: Nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain

Less frequent: Stomatitis, dry mouth

Hepato-biliary disorders

Less frequent: Increased hepatic enzymes hyperbilirubinemia, jaundice

Frequency not known: Hepatitis

Skin and subcutaneous tissue disorders

Frequent: Hyperhidrosis, alopecia, increased sweating, rash, (erythematous, maculopapular, psoriaform and vesicular rash) dry skin

Less frequent: Pruritus, urticaria

Frequency not known: Angioedema, toxic epidermal necrolysis, erythema multiforme

Musculoskeletal and connective tissue disorders

Frequent: Myalgia, bone pain, osteoporosis, bone fractures, arthralgia, arthritis [(1)]

Frequency not known: Trigger finger

Renal and urinary disorders

Less frequent: Increased urinary frequency, pollakiuria

Reproductive system and breast disorders

Frequent: Vaginal bleeding

Less frequent: Vaginal discharge, vaginal dryness, breast pain

General disorders and administration site conditions

Frequent: Hot flushes, fatigue (including asthenia and malaise), peripheral oedema, chest pain

Less frequent: Pyrexia, mucosal dryness, thirst, general oedema

Investigations

Frequent: Weight increase

Less frequent: Weight loss

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Isolated cases of overdosage with **ACCORD LETROZOLE 2,5 mg** have been reported. No specific treatment for overdosage is known; treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

A 21.12 HORMONE INHIBITORS

5.1 Pharmacodynamic properties

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues. Letrozole is specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, and ACTH or in plasma renin activity amongst postmenopausal patients.

5.2 Pharmacokinetic properties

Absorption:

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99,9 %). Food slightly decreases the rate of absorption but the extent of absorption (AUC) is not changed.

The minor effect on the absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken without regard to mealtimes.

Distribution:

Plasma protein binding of letrozole is approximately 60 %, mainly to albumin (55 %). The concentration of letrozole in erythrocytes is about 80 % of that in plasma. After administration of 2,5 mg ^{14}C-labelled letrozole, approximately 82 % of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1,87 ± 0,47 l/kg.

Metabolism and elimination:

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (Cl_m= 2,1 l/h) but is relatively slow when compared to hepatic blood flow (about 90 l/h).

The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2,5 mg ^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88,2 ± 7,6 % of the radioactivity was recovered in urine and 3,8 ± 0,9 % in faeces.

At least 75 % of the radioactivity recovered in urine up to 216 hours (84,7 ± 7,8 % of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9 % to two unidentified metabolites, and 6 % to unchanged letrozole.

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2,5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2,5 mg, while they are 1,5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2,5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs. Age had no effect on the pharmacokinetics of letrozole.

Special populations:

In a study involving volunteers with varying degrees of renal function (24-hour creatinine clearance 9 to 116 ml/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2,5 mg.

In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) was 37 % higher than in normal subjects, but still within the range seen in subjects without impaired function.

In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) to those in healthy volunteers (N = 8), AUC and $t_{1/2}$ increased by 95 and 187 %, respectively. Breast cancer patients with severe hepatic impairment are thus exposed to higher levels of letrozole than patients without severe hepatic dysfunction.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains 61,500 mg of lactose monohydrate.

Tablet core:

Cellulose microcrystalline, colloidal anhydrous silica, hypromellose Type 2910, lactose monohydrate, magnesium stearate, maize starch

sodium starch glycolate Type A

Coating (Opadry 03B82927 yellow):

Hypromellose 6 cp E464, macrogol 400, iron oxide yellow E172, talc E553b, titanium dioxide E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25 °C.

Do not remove the blisters from the outer container until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

ACCORD LETROZOLE 2,5 mg film coated tablets are packed in plain aluminium blister strips of 10 tablets per strip, with a clear PVC coated PVDC film.

3 strips of 10 tablets (30 tablets) are packed in a unit carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park,

6 Coombe Place, Rivonia

Gauteng, South Africa

8. REGISTRATION NUMBER

42/21.12/0323

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine: 26 November 2010

10. DATE OF REVISION OF THE TEXT

5 February 2015, March 2020