PROPOSED PACKAGE INSERT FOR CASTRA 1 TABLETS

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

CASTRA 1 TABLETS film coated tablet

COMPOSITION:

Active ingredient: Each film coated tablet contains 1 mg anastrozole.

Inactive ingredients: Lactose monohydrate, povidone, isopropyl alcohol, sodium starch glycolate, magnesium stearate, hypromellose, macrogol, titanium dioxide, purified water.

Contains sugar: lactose.

PHARMACOLOGICAL CLASSIFICATION:

A 21.12 Hormone inhibitors

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Anastrozole is a selective non-steroidal inhibitor of the aromatase (oestrogen synthetase) system, which converts adrenal androgens to oestrogen in peripheral tissue. The conversion of androstenedione to oestrone is inhibited by anastrozole in peripheral tissues where oestrone is subsequently converted to oestradiol. Anastrozole does not exhibit any oestrogenic, androgenic or progestogenic activity. Additionally no effect on cortisol or aldosterone secretion was found before or after standard ACTH challenge testing upon anastrozole treatment.

Pharmacokinetic properties:

Anastrozole is rapidly and almost completely absorbed from the gastrointestinal tract after doses with peak plasma concentrations occur after 2 hours of dosing under fasted conditions. Food decreases the rate but not the extent of absorption, though this is not considered clinically significant. The terminal half-life is approximately 50 hours and steady-state concentrations are achieved after about 7 days in patients receiving once-daily doses. Anastrozole pharmacokinetics is independent of age in postmenopausal women. Anastrozole is moderately bound (40 %) to plasma proteins. Anastrozole is metabolized in the liver primarily by N-dealkylation, hydroxylation, and glucoronidation to inactive metabolites, with a triazole as the primary metabolite. Approximately 10 % unchanged anastrozole is excreted via the urine within 72 hours of dosing. The metabolites are excreted primarily via the urine. Anastrozole treatment achieves an 80 % reduction in serum oestradiol concentrations after 14 days. The plasma concentrations of anastrozole in volunteers with mild stable hepatic cirrhosis or mild renal impairment were within the limits found in patients with normal hepatic and renal function.

INDICATIONS:

CASTRA 1 TABLETS is indicated in the treatment of early as well as advanced breast cancer in postmenopausal women.

Efficacy of **CASTRA 1 TABLETS** has not been demonstrated in oestrogen receptor negative patients unless they have had a previous positive clinical response to tamoxifen.

CONTRAINDICATIONS:

CASTRA 1 TABLETS is contraindicated in:

- patients with hypersensitivity to anastrozole or to any of the ingredients
- premenopausal women
- pregnant/lactating women
- patients with severe renal impairment (creatinine clearance less than 20 ml/min)
- patients with moderate or severe hepatic disease.

WARNINGS AND SPECIAL PRECAUTIONS:

Reduction in bone mineral density can occur during treatment with **CASTRA 1 TABLETS** due to the lowering of circulating oestrogen levels. Patients with a risk of osteoporosis have a consequent increased risk of bone fractures and should be appropriately and carefully monitored.

CASTRA 1 TABLETS is not recommended for use in premenopausal women or in children as safety and efficacy have not been established in these patients. In the event that there is doubt about hormonal status of a patient, menopause should be defined biochemically in such a patient.

Anastrozole has not been studied in patients with moderate or severe hepatic impairment or patients with severe impairment of renal function (creatinine clearance less than 20 ml/min) to support its safe use (see **CONTRAINDICATIONS**).

CASTRA 1 TABLETS contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take **CASTRA 1 TABLETS**.

Effects on ability to drive and use machines:

Caution should be observed when driving or operating machinery as anastrozole has been reported to cause asthenia and somnolence

INTERACTIONS:

Oestrogen and/or tamoxifen containing medications should not be used concomitantly with **CASTRA 1 TABLETS** as they would diminish pharmacological action of **CASTRA 1 TABLETS**. Concomitant use of **CASTRA 1 TABLETS** with other medicines is unlikely to result in clinically significant interactions mediated by cytochrome P450 enzyme system. No clinically significant interactions were revealed in patients treated concomitantly with anastrozole and other commonly prescribed medicines as well as with bisphosphonates.

PREGNANCY AND LACTATION:

CASTRA 1 TABLETS is contraindicated in pregnant or lactating women.

DOSAGE AND DIRECTIONS FOR USE:

Adults including the elderly:

Take one tablet **CASTRA 1 TABLETS** orally once a day.

Children:

CASTRA 1 TABLETS is not recommended for use in children.

Renal impairment:

No dose change is recommended in patients with mild or moderate renal impairment.

Hepatic impairment:

No dose change is recommended in patients with mild hepatic disease.

SIDE EFFECTS:

Blood and the lymphatic system disorders:

Less frequent: Thromboembolism, thrombophlebitis, anaemia, leukopenia with or without infection.

Metabolism and nutrition disorders:

Less frequent: Anorexia, hypercholesterolaemia, fluid retention, increased appetite, weight gain.

Nervous system disorders:

Frequent: Headache, dizziness.

Less frequent: Somnolence, insomnia, anxiety, confusion, nervousness, paraesthesia, depression.

Vascular disorders:

Frequent: Hot flushes, flushing, hypertension, peripheral oedema.

Respiratory, thoracic and mediastinal disorders:

Frequent: Chest pain, dyspnoea, cough, pharyngitis.

Less frequent: Bronchitis, sinusitis or rhinitis.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea, constipation, abdominal pain, dry mouth.

Less frequent: Vomiting.

Skin and subcutaneous tissue disorders:

Frequent: Hair thinning, rash.

Less frequent: Erythema multiforme, Stevens-Johnson syndrome, pruritus, allergic reactions including angioedema, urticaria, anaphylaxis.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Joint pain/stiffness, back and bone pain, bone fractures.

Less frequent: Arthralgia, myalgia.

Hepato-biliary disorders:

Less frequent: Increased gamma-GT and alkaline phosphatase.

Reproductive system and breast disorders:

Frequent: Vaginal dryness.

Less frequent: Vaginal bleeding.

General disorders:

Frequent: Asthenia, pain, pelvic pain.

Less frequent: Flu syndrome.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Refer to **SIDE EFFECTS** for possible symptoms of overdosage.

Treatment is essentially symptomatic and supportive and should consider the possibility that multiple agents may have been taken. Emptying the stomach via induction of emesis if the patient

is alert and dialysis may be helpful. Treatment of overdose involves general supportive care, including frequent monitoring of vital signs and close observation of the patient.

IDENTIFICATION:

CASTRA 1 TABLETS: White, biconvex, round coated tablets, debossed with ‘A7’ on one side and plain on other side. The tablets should be free of all physical detects.

PRESENTATION:

CASTRA 1 TABLETS are packed 10 tablets into a silver-grey aluminium/transparent PVC/PVDC blister strip. 1 or 3 blister strips (10 or 30 tablets) into an outer carton box.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep blisters in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

42/21.12/0995

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Zydus Healthcare SA (Pty) Ltd.

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion

0157

DATE OF PUBLICATION OF THE PACKAGE INSERT:

September 2011