PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

LETROZOLE 2,5 mg TABLETS PHARMA-Q film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: lactose monohydrate 85,00 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

Dark yellow coloured, round shaped, slightly biconvex bevel edged film coated tablets debossed with ‘5’ on one side and ‘H’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- Extended adjuvant treatment of early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
- 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 anti-oestrogens.
- 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 LETROZOLE 2,5 mg TABLETS PHARMA-Q is 2,5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with LETROZOLE 2,5 mg TABLETS PHARMA-Q should continue for 5 years or until tumour relapse occurs, whichever comes first. In patients with metastatic disease treatment with LETROZOLE 2,5 mg TABLETS PHARMA-Q should continue until tumour progression is evident.

Special populations

Elderly patients

No dose adjustment is required for elderly patients.

Children

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).

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

Method of administration

LETROZOLE 2,5 mg TABLETS PHARMA-Q should be taken orally and can be taken with or

without food.

4.3 Contraindications

- Hypersensitivity to letrozole or to any of the excipients of LETROZOLE 2,5 mg TABLETS PHARMA-Q listed in section 6.1.
- Premenopausal endocrine status.
- Pregnancy or breastfeeding (see section 4.6)
- 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 LETROZOLE 2,5 mg TABLETS PHARMA-Q. Only women of postmenopausal endocrine status should receive LETROZOLE 2,5 mg TABLETS PHARMA-Q.

Renal impairment

LETROZOLE 2,5 mg TABLETS PHARMA-Q has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10 ml/min (see section 4.3).

Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers (see section 4.3).

Bone effects

LETROZOLE 2,5 mg TABLETS PHARMA-Q is a potent oestrogen-lowering (medicine). 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 and 5.1).

Tendonitis and tendon rupture

Tendonitis and tendon ruptures may occur. Close monitoring of the patients and appropriate measures (e.g. immobilisation) must be initiated for the affected tendon (see section 4.8). [(3)]

Other warnings

Co-administration of LETROZOLE 2,5 mg TABLETS PHARMA-Q 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).

Lactose

LETROZOLE 2,5 mg TABLETS PHARMA-Q tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take LETROZOLE 2,5 mg TABLETS PHARMA-Q.

4.5 Interaction with other medicines and other forms of interaction

Metabolism of letrozole is partly mediated via CYP2A6 and CYP3A4. Cimetidine, a weak, unspecific inhibitor of CYP450 enzymes, did not affect the plasma concentrations of letrozole. The effect of potent CYP450 inhibitors is unknown.

Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of letrozole as in LETROZOLE 2,5 mg TABLETS PHARMA-Q with these medicines does not result in clinically significant interactions.

There was no evidence of clinically relevant interaction in patients receiving other commonly prescribed medicines (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).

There is no clinical experience to date on the use of letrozole as in LETROZOLE 2,5 mg TABLETS PHARMA-Q in combination with oestrogens or other anticancer medicines, 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 2,5 mg TABLETS PHARMA-Q with tamoxifen, other anti-oestrogens or oestrogens should be avoided.

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19, but the clinical relevance is unknown. Caution is therefore advised when giving letrozole as in LETROZOLE 2,5 mg TABLETS PHARMA-Q concomitantly with medicines whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow (e.g. phenytoin, clopidogrel).

4.6 Fertility, pregnancy and lactation

Women of perimenopausal status or child-bearing potential

LETROZOLE 2,5 mg TABLETS PHARMA-Q should only be used in women with a clearly established postmenopausal status (see section 4.4). As there are reports of women regaining ovarian function during treatment with letrozole as in LETROZOLE 2,5 mg TABLETS PHARMA-Q despite a clear postmenopausal status at start of therapy, the medical practitioner needs to discuss adequate contraception when necessary.

Pregnancy

Based on human experience in which there have been isolated cases of birth defects (labial fusion, ambiguous genitalia), letrozole as in LETROZOLE 2,5 mg TABLETS PHARMA-Q may cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3).

LETROZOLE 2,5 mg TABLETS PHARMA-Q is contraindicated during pregnancy (see sections 4.3 and 5.3).

Breastfeeding

It is unknown whether letrozole and its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

LETROZOLE 2,5 mg TABLETS PHARMA-Q is contraindicated during breast-feeding (see section 4.3).

Fertility

The pharmacological action of letrozole is to reduce oestrogen production by aromatase inhibition. In premenopausal women, the inhibition of oestrogen synthesis leads to feedback increases in gonadotropin (LH, FSH) levels. Increased FSH levels in turn stimulate follicular growth and can induce ovulation.

4.7 Effects on ability to drive and use machines

LETROZOLE 2,5 mg TABLETS PHARMA-Q may cause fatigue, dizziness and somnolence, which may affect the ability of patients to drive and use machines. Patients should not drive and use machines before they know how treatment with LETROZOLE 2,5 mg TABLETS PHARMA-Q affects their ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The frequencies of adverse reactions for letrozole are mainly based on data collected from clinical trials.

Up to approximately one third of the patients treated with letrozole in the metastatic setting and approximately 80 % of the patients in the adjuvant setting as well as in the extended adjuvant setting experienced adverse reactions. The majority of the adverse reactions occurred during the first few weeks of treatment.

The most frequently reported adverse reactions in clinical studies were hot flushes, hypercholesterolaemia, arthralgia/arthritis, fatigue, increased sweating and nausea.

Important additional adverse reactions that may occur with letrozole are skeletal events such as osteoporosis and/or bone fractures and cardiovascular events (including cerebrovascular and thromboembolic events). The frequency category for these adverse reactions is described in the table below.

b. Tabulated summary of adverse reactions

The frequencies of adverse reactions for letrozole are mainly based on data collected from clinical trials.

The following adverse drug reactions, listed in the table below, were reported from clinical studies and from post-marketing experience with letrozole:

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: frequent, less frequent or frequency unknown.

System organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Less frequent	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Less frequent	Tumour pain
Blood and lymphatic system disorders	Less frequent	Leukopenia
Immune system disorders	Frequency unknown	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders	Frequent	Hypercholesterolaemia, decreased appetite, increased appetite, anorexia
Psychiatric disorders	Frequent	Depression
	Less frequent	Anxiety (including nervousness), irritability
Nervous system disorders	Frequent	Headache, dizziness

System organ class	Frequency	Adverse reactions
	Less frequent	Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Eye disorders	Less frequent	Cataract, eye irritation, blurred vision
Cardiac disorders	Frequent	Palpitations
	Less frequent	Tachycardia, ischaemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischaemia), cardiac failure
Vascular disorders	Frequent	Hot flushes, hypertension
	Less frequent	Thrombophlebitis (including superficial and deep vein thrombophlebitis), pulmonary embolism, arterial thrombosis, cerebral infarction, transient ischaemic attack
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, cough
Gastrointestinal disorders	Frequent	Nausea, dyspepsia, constipation, abdominal pain, diarrhoea, vomiting
	Less frequent	Dry mouth, stomatitis
Hepato-biliary disorders	Less frequent	Increased hepatic enzymes, hyperbilirubinemia, jaundice
	Frequency unknown	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, alopecia, rash (including erythematous, maculopapular, psoriaform,

System organ class	Frequency	Adverse reactions
		and vesicular rash), dry skin
	Less frequent	Pruritus, urticaria
	Frequency unknown	Toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, myalgia, bone pain[1], osteoporosis, bone fractures, arthritis
	Less frequent	Tendonitis and tendon rupture
	Frequency unknown	Trigger finger
Renal and urinary disorders	Less frequent	Pollakiuria
Reproductive system and breast disorders	Frequent	Vaginal haemorrhage
	Less frequent	Vaginal discharge, vulvovaginal dryness, breast pain, endometrial proliferative disorders (endometrial hyperplasia/ endometrial cancer)
General disorders and administration site conditions	Frequent	Fatigue (including asthenia, malaise), peripheral oedema, chest pain
	Less frequent	General oedema, mucosal dryness, thirst, pyrexia
Investigations	Frequent	Weight increased
	Less frequent	Weight decreased

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 & Quality Problem Reporting Form”, found online under SAHPRA’s publications: https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

Isolated cases of overdose with letrozole have been reported.

No specific treatment for overdose is known; treatment should be symptomatic and supportive.

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.12 Hormone Inhibitors

Pharmacotherapeutic group: Endocrine therapy. Hormone antagonist and related agents: aromatase inhibitor, ATC code: L02BG04.

The elimination of oestrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to estrone (E1) and oestradiol (E2). The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

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.

In healthy postmenopausal women, single doses of 0,1 mg, 0,5 mg and 2,5 mg letrozole suppress serum oestrone and oestradiol by 75 to 78 % and 78 % from baseline respectively. Maximum suppression is achieved in 48 to 78 hours.
In postmenopausal patients with advanced breast cancer, daily doses of 0,1 to 5 mg suppress plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75 to 95 % from baseline in all patients treated. With doses of 0,5 mg and higher, many values of oestrone and oestrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.

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 among postmenopausal patients treated with a daily dose of letrozole, 0,1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0,1 mg, 0,25 mg, 0,5 mg, 1 mg, 2,5 mg and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation is not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0,1 mg; 0,5 mg and 2,5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0,1 to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor are thyroid function as evaluated by TSH, T4 and T3 uptake.

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.

Biotransformation

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.

Elimination

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.

Special populations

Elderly

Age had no effect on the pharmacokinetics of letrozole.

Renal impairment

It was reported that 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.

Therefore, no dose adjustment is required for patients with renal impairment (CL_{cr} ≥10 ml/min). Little information is available in patients with severe impairment of renal function (CL_{cr} <10 ml/min) (see section 4.2).

Hepatic impairment

It was reported that in a 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. It was reported that 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 (see sections 4.2 and 4.3).

5.3 Preclinical safety data

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of systemic or target organ toxicity.

Letrozole showed a low degree of acute toxicity in rodents exposed up to 2 000 mg/kg. In dogs letrozole caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings observed can be attributed to the pharmacological action of the compound. The no-adverse-effect level was 0,3 mg/kg in both species.

Oral administration of letrozole to female rats resulted in decreases in mating and pregnancy ratios and increases in pre-implantation loss.

Both in vitro and in vivo investigations of letrozole's mutagenic potential revealed no indications of any genotoxicity.

In a 104-week rat carcinogenicity study, no treatment-related tumours were noted in male rats. In female rats, a reduced incidence of benign and malignant mammary tumours at all the doses of letrozole was found.

In a 104-week mouse carcinogenicity study, no treatment-related tumors were noted in male mice. In female mice, a generally dose-related increase in the incidence of benign ovarian granulosa theca cell tumors was observed at all doses of letrozole tested. These tumors were considered to be related to the pharmacological inhibition of oestrogen synthesis and may be due to increased LH resulting from the decrease in circulating oestrogen.

Letrozole was embryotoxic and foetotoxic in pregnant rats and rabbits following oral administration at clinically relevant doses. In rats that had live foetuses, there was an increase in the incidence of foetal malformations including domed head and cervical/centrum vertebral fusion. An increased incidence of foetal malformations was not seen in the rabbit. It is not known whether this was an indirect consequence of the pharmacological properties (inhibition of oestrogen biosynthesis) or a direct medicine effect (see sections 4.3 and 4.6).

Preclinical observations were confined to those associated with the recognised pharmacological action, which is the only safety concern for human use derived from animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Povidone

Silica colloidal anhydrous.

Tablet coating

Opadry yellow 03B82401 (hypromellose, E464, titanium dioxide, E171, iron oxide yellow, E172, macrogol 400 and talc, E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Keep blisters in the outer carton until required for use.

6.5 Nature and contents of container

Blister packs of 10 tablets per blister, packed in aluminium/clear PVC/PE/PVDC blisters or Alu-

Alu blisters. 30 tablets are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

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Industria West 2003

Johannesburg

South Africa

8 REGISTRATION NUMBER

47/21.12/0511

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 April 2021

10 DATE OF REVISION OF THE TEXT

13 April 2021