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Certificate of registration of the medicinal product
No. 20387 of 24.02.2014
No. 20388 of 24.02.2014
Annex 1

Ministry of Health of the Republic of Moldova

INSTRUCTION FOR ADMINISTRATION

ANASTROZOLE

tablets

TRADE NAME
Anastrozole
INN of the active substance
Anastrozolum
COMPOSITION
1 tablet contains:
active substance: anastrozole 0,25 mg or 1,0 mg;
excipients: magnesium stearate, Kollidon CL (crospovidone), FD&C Yellow No. 5, Ludipress (lactose, polyvidone, crospovidone).
PHARMACEUTICAL FORM
Tablets.
DESCRIPTION OF THE DRUG
Tablets 0.25 mg
Yellow tablets, square in shape, compact and homogeneous structure, with a dividing line and the inscription 'BP' on one side of the tablet, with bevelled edges, lateral surface with rounded edges. Marking on the surface of the tablet is allowed.
Tablets 1 mg
Yellow tablets, square in shape, compact and homogeneous structure, with a dividing line and the inscription 'BP' on one side of the tablet and with the inscription '1' on the other side of the tablet, with bevelled edges, side surface with rounded edges. Marbling on the surface of the tablets is allowed.
PHARMACOTHERAPY GROUP and ATC code
Hormone antagonist and related substances. Aromatase inhibitor, L02BG03.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Anastrozole refers to a new generation of nonsteroidal selective aromatase inhibitors used in the treatment of disseminated breast cancer in women after menopause. Anastrozole inhibits the endogenous oestrogen-dependent multiplication and growth of mammary gland cells. The mechanism of action of anastrozole is reduced to the selective inhibition of the activity of aromatase, a cytochrome P450 enzyme.
The main source of oestrogens in menopausal women are androgens, mainly androatendione and testosterone. Aromatase provides multiple hydroxylation of these with conversion to estrone and then to estradiol in adipose and muscle tissue, liver, adrenal and tumour tissue.
Anastrozole selectively inhibits aromatase by interacting with the iron atom of heme cytochrome P-450. Thus, the preparation provides a marked inhibition of the enzyme activity, which contributes to maximally reduce the level of estrogen both in the peripheral circulation and in the tumor, which provides the therapeutic effect in women with breast cancer. In postmenopausal women, anaesthesiol at a dose of 1 mg/day causes an 80% decrease in oestradiol levels. Anastrozole has no progestogenic, androgenic or oestrogenic activity. The preparation does not influence cortisol and aldosterone secretion. Therefore, corticosteroid supplementation is not necessary.
Pharmacokinetic properties
Absorption of anastrozole is rapid and peak plasma concentrations are usually reached within the first two hours after administration (under fasting conditions). Food slightly decreases the rate but not the extent of absorption. It is not expected that a minor change in the rate of absorption will have a clinically significant effect on the steady-state plasma concentration during administration of a single daily dose of ana- strozole 1 mg tablets. Approximately 90 to 95% of the steady-state plasma concentration of anastrozole is reached after 7 days of daily administration. There is no evidence of time or dose dependence of anastrozole pharmacokinetic parameters.
Anastrozole pharmacokinetics are independent of age in post-menopausal women.
Anastrozole binds only 40% of plasma proteins. Anastrozole is slowly eliminated, with a plasma elimination half-life of 40 to 50 hours. It is highly metabolised in post-menopausal women, with less than 10% of the dose being excreted unchanged in the urine within 72 hours of administration.
Metabolisation of anastrozole occurs via N-dealkylation, hydroxylation and glu- curonoconjugation. The metabolites are excreted mainly via the urine. Triazole, the main metabolite present in plasma, does not exhibit the inhibitory effect of aromatase.
Kidney or liver failure
The apparent clearance (Cl/F) of anastrozole after oral administration was approximately 30% lower in volunteers with stabilised liver cirrhosis compared to the control group (Study 1033IL/0014).
However, plasma anastrozole concentrations in volunteers with cirrhosis of the liver were within the range of concentrations observed in normal subjects in other clinical studies. Anastrozole plasma concentration values observed during long-term efficacy studies in patients with hepatic impairment were within the range of plasma concentrations observed in patients without hepatic impairment.
The apparent clearance (Cl/F) of anastrozole was not altered in volunteers with severe renal impairment (RFG <30 ml/min) in study 1033IL/0018, which is consistent with the fact that anastrozole is eliminated mainly by metabolism. The plasma concentrations of anastrozole observed during long-term efficacy studies in patients with renal impairment were within the range of plasma concentrations observed in patients without renal impairment. In patients with severe renal impairment anastrozole should be administered with caution.
THERAPEUTIC INDICATIONS
Treatment of advanced breast neoplasm with estrogen receptors present in post-menopausal women.
Adjuvant treatment for incipient invasive breast neoplasm with estrogen receptors present in post-menopausal women. Adjuvant treatment for early invasive breast neoplasm with estrogen receptors present in post-menopausal women who have received adjuvant tamoxifen for 2 to 3 years. **DOSAGE AND ADMINISTRATION**
The tablets are taken internally with water, without chewing. It is recommended that the preparation is taken at the same time.
Post-menopausal women, including the elderly, are given 1 mg once a day for a long time. When the disease progresses, the preparation should be discontinued. Dosage adjustment in patients with mild to moderate disturbances of liver and kidney function is not necessary.
ADVERSE REACTIONS
The adverse reactions listed below are classified by frequency, by device, system and organ. Frequency groups according to convention

MedDRA: very common (≥1/10), common (≥ 1/100 and < 1/10), less common (≥ 1/1000 and < 1/100), rare (≥1/10000 and <1/1000) and very rare (<1/10000).
The most commonly reported side effects were headache, hot flushes, nausea, transient rash, arthralgia, joint stiffness, arthritis and asthenia.
Metabolic and nutritional disorders
Frequent: anorexia, hypercholesterolemia.
Nervous system disorders
Very common: headache.
Common: drowsiness, carpal tunnel syndrome.
Vascular disorders
Very common: hot flushes.
Gastrointestinal disorders *Very common*: nausea.
Common: diarrhoea, vomiting
Hepatobiliary disorders
Frequent: increased plasma al- caline phosphatase, AST and ALT concentrations.
Less common: increased plasma γ-GT and bilirubin concentrations, hepatitis.
Skin and subcutaneous tissue disorders
Very common: transient rash.
Common: thinning of hair/alopecia, allergic reactions
Less common: hives
Rare: polymorphic erythema, anaphylactoid reactions, cutaneous vasculitis (including some reports of Henoch-Schönlein purpura).
Very rare: Stevens-Johnson syndrome, angioedema.
Musculoskeletal and connective tissue disorders
Very common: arthralgia/joint pain, arthritis, osteoporosis.
Frequent: bone pain.
Less common: digital tenosynovitis.
Genital and breast disorders
Frequent: dryness of the vaginal mucosa, vaginal bleeding.
General and site of administration disorders *Very common:* asthenia.

CONTRAINDICATIONS

Hypersensitivity to anastrozole or any of the components of the preparation.
Pre-menopausal women.
Severe renal failure (creatinine clearance below 20 ml/min)
Moderate or severe liver impairment (harmlessness and efficacy not confirmed).
Pregnancy and breastfeeding.

SUPRADOZAJ

No cases of overdose have been reported.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Not recommended for women of childbearing age. In women with uncertain hormonal status, confirmation of menopausal status by hormonal methods is recommended.
There are insufficient data on the harmlessness of anastrozole in patients with moderate to marked impairment of liver function or severe renal impairment (creatinine clearance below 20 ml/min).
Anastrozole is not recommended for administration to children, as its harmlessness and efficacy is not established.
If metrorrhagia persists against the background of taking anastrozole, the gynaecologist should be consulted.
Anastrozole, by lowering circulating estradiol levels, may decrease bone mineral density. In patients suffering from osteoporosis or at risk of developing osteoporosis, it is recommended to determine bone mineral density at the initiation of treatment and during treatment by densiometric method (DEXA scan). If necessary, treatment or prophylaxis of osteoporosis should be carried out under medical supervision.
This medicine contains lactose. Patients with rare hereditary conditions of galactose intolerance, lactase deficiency (Lapp) or glucose-galactose malabsorption syndrome should not use this medication.
Contains FD&C Yellow No. 5 (E102). May cause allergic reactions.
Administration during pregnancy or lactation
Anastrozole is contraindicated in pregnancy and during breastfeeding. ***Influence on ability to drive vehicles or use machinery***
Because of the adverse reaction profile of the drug, the ability to drive vehicles and use machinery may be impaired.

INTERACTIONS WITH OTHER MEDICINES, OTHER TYPES OF INTERACTIONS

In vitro, anostrozole inhibits CYP 1A2, 2C8/9 and 3A4 isoenzymes. Clinical studies with antipyrine and warfarin have demonstrated that anastrozole administered at a dose of 1 mg does not significantly inhibit the metabolism of antipyrine and R- and S-warfarin, thus it is unlikely that co-administration of anastrozole with other drugs would produce clinically significant drug interactions mediated by CYP enzymes.
Enzymes that mediate anastrazole metabolism have not been identified. Cimentidine, a weak, non-specific inhibitor of CYP enzymes, does not influence plasma concentrations of anastrozole. The effect of strong CYP inhibitors is unknown.
No clinically significant interactions were observed in anastrozole-treated patients receiving concomitant therapy with other drugs. There were no clinically significant interactions with biophosphonates.
Concomitant administration with tamoxifen or oestrogen-containing drugs should be avoided, as a reduction in pharmacological action may occur.

PRESENTATION, PACKAGING

Tablets 0.25 mg and 1 mg.
20 tablets in blister pack. 3 blisters each with instructions for administration in carton box.

PUBLICATION

Store at temperatures below 25°C.
Keep out of the reach and sight of children!

SHELF LIFE

3 years. Do not use after the expiry date indicated on the packaging.

LEGAL STATUS

By prescription.

DATE OF LAST REVISION OF THE TEXT

February 2014

HOLDER OF THE REGISTRATION CERTIFICATE

SC Balkan Pharmaceuticals SRL, Republic of Moldova,
N. Grădescu str., 4, mun. Chisinau

NAME AND ADDRESS OF MANUFACTURER

SC Balkan Pharmaceuticals SRL, Republic of Moldova,
N. Grădescu str., 4, mun. Chisinau

In the event of any adverse reaction, inform the pharmacovigilance section of the Agency for Medicinal Products and Medical Devices (tel.: 022-88-43-38).