

Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ROZILAT (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROZILAT film-coated tablets containing 2,5 mg letrozole.
Contains sugar: 48,70 mg lactose monohydrate.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Dark yellow, film-coated, round, slightly biconvex, with bevelled edges tablet debossed with 'L2.5' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ROZILAT is indicated for:

- 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 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 **ROZILAT** is 2,5 mg once daily.
In the adjuvant and extended adjuvant setting, treatment with **ROZILAT** should continue for 5 years or until tumour relapse occurs, whichever comes first.
In patients with metastatic disease treatment with **ROZILAT** should continue until tumour progression is evident.

Patients with renal impairment
No dosage adjustment is required for patients with mild to moderate 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 sections 4.4 and 5.2).

Patients with hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child Pugh grade A and B).

ROZILAT should not be used in patients with severe hepatic impairment (Child-Pugh score C).

Elderly patients
No dose adjustment is required for elderly patients.

Paediatric population
Not applicable.

Method of administration
ROZILAT should be taken orally and can be taken with or without food.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Premenopausal endocrine status.
- Pregnancy or lactation (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 **ROZILAT**. Only women of postmenopausal endocrine status should receive **ROZILAT**.

Renal impairment
ROZILAT has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10 mL/min. **ROZILAT** is therefore contraindicated in patients with severe renal impairment (creatinine clearance < 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. **ROZILAT** is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see section 4.3).

Bone effects
ROZILAT 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).

Other warnings
Co-administration of **ROZILAT** 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).

ROZILAT contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, or severe lactase deficiency or of glucose-galactose malabsorption should not take this medicine.

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.

There is no clinical experience to date on the use of **ROZILAT** 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 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 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).

4.6. Fertility, pregnancy and lactation

Women of peri-menopausal status or child-bearing potential
ROZILAT 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 **ROZILAT** 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), **ROZILAT** may cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity.

ROZILAT is contraindicated during pregnancy (see sections 4.3).

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

ROZILAT 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

ROZILAT has minor influence on the ability to drive and use machines. Since fatigue and dizziness have been observed with the use of **ROZILAT** and somnolence has been reported, caution is advised when driving or using machines.

4.8. Undesirable effects

a. *Summary of the safety profile*

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

Important additional adverse reactions that may occur with **ROZILAT** 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 Table 1.

b. *Tabulated list of adverse reactions*

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

The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post-marketing experience with **ROZILAT**:

Table 1: Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Frequent, less frequent and frequency unknown.

Infections and infestations Less frequent: Urinary tract infection
Neoplasms, benign, malignant and unspecified (including cysts and polyps) Less frequent: Tumour pain[1]
Blood and the lymphatic system disorders Less frequent: Leukopenia
Immune system disorders Frequency unknown: Anaphylactic reaction
Metabolism and nutrition disorders Frequent: Hypercholesterolaemia, anorexia, appetite increase
Psychiatric disorders Frequent: Depression Less frequent: Anxiety (including nervousness), irritability
Nervous system disorders Frequent: Headache, dizziness Less frequent: Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), taste disturbance, cerebrovascular accident, carpal tunnel syndrome
Eye disorders Less frequent: Cataract, eye irritation, blurred vision
Cardiac disorders Less frequent: Palpitations[1], tachycardia, 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), pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders Less frequent: Dyspnoea, cough
Gastrointestinal disorders Frequent: Nausea, dyspepsia[1], constipation, abdominal pain, diarrhoea, vomiting Less frequent: Dry mouth, stomatitis[1]
Hepatobiliary disorders Less frequent: Increased hepatic enzymes Frequency unknown: Hepatitis
Skin and subcutaneous tissue disorders Frequent: Increased sweating, alopecia, rash (including erythematous, maculopapular, psoriaform, and vesicular rash), dry skin Less frequent: Pruritus, urticarial Frequency unknown: Angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders Frequent: Arthralgia, myalgia, bone pain[1], osteoporosis, bone fractures Less frequent: Arthritis Frequency unknown: Trigger finger
Renal and urinary disorders Less frequent: Increased urinary frequency
Reproductive system and breast disorders Frequent: Vaginal bleeding Less frequent: Vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions Frequent: Fatigue (including asthenia, malaise), peripheral oedema Less frequent: General oedema, mucosal dryness, thirst, pyrexia
Investigations Frequent: Weight increase Less frequent: Weight loss

[1] Adverse drug reactions reported only in the metastatic setting

Description of selected adverse reactions

Cardiac adverse reactions
The following cardiac adverse events were reported for **ROZILAT**:
Angina requiring surgery; cardiac failure; hypertension and cerebrovascular accident/transient ischaemic attack.
New or worsening angina, myocardial infarction thromboembolic event, stroke/transient ischaemic attack were also reported.

Skeletal adverse reactions
In the extended adjuvant setting, significantly more patients treated with **ROZILAT** experienced bone fractures or osteoporosis (bone fractures, 10,4 % and osteoporosis, 12,2 %) than patients in the placebo-arm (5,8 % and 6,4 %, respectively). Median duration of treatment was 5 years for **ROZILAT**, compared with 3 years for placebo.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8.

4.9. Overdose

Isolated cases of overdose with **ROZILAT** have been reported.
No specific treatment for overdose is known; treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 21.12 Hormone inhibitors
Endocrine therapy. Hormone antagonist and related agents: aromatase inhibitor, ATC code: L02BG04.

Pharmacodynamic properties

Mechanism of action
The elimination of oestrogen-mediated growth stimulation is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens and endocrine therapy is used. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone and oestradiol. 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 aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where present.

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 %, 78 % and 78 % from baseline respectively. Maximum suppression is achieved in 48 - 78 hours.

In postmenopausal patients with advanced breast cancer, daily doses of 0,1 mg to 5 mg suppressed plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75 – 95 % from baseline in all patients treated. With doses of 0,5 mg and higher, many values of oestrone and oestrone sulphate were 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 highly 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-hydroxyprogesterone, 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 mg 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 is thyroid function as evaluated by TSH, T4, and T3 uptake test.

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_{D} = 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 and Hepatic impairment
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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablets content: lactose monohydrate, cellulose microcrystalline, maize starch, sodium starch glycolate, magnesium stearate and silica colloidal anhydrous. Coating: hypromellose, talc, macrogol, titanium dioxide and iron oxide yellow.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.
Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

Packed in clear PVC/PVC film - aluminium foil blister pack
Packs of 30 film-coated tablets

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd
Woodhill Office Park, Building 1, First Floor
53 Phillip Engelbrecht Avenue
Meyersdal, Ext. 12, 1448
Johannesburg
South Africa

8. REGISTRATION NUMBER

55/21.12/0204

9. DATE OF FIRST AUTHORISATION

29 June 2021

DETACH BEFORE DISPENSING

PATIENT INFORMATION LEAFLET
SCHEDULING STATUS

S4

ROZILAT (film-coated tablet)
Letrozole
Contains sugar: 48,70 mg lactose monohydrate.

Read all of this leaflet carefully before you take ROZILAT

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist, nurse or other healthcare provider.
- **ROZILAT** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet:

1. What **ROZILAT** is and what it is used for
2. What you need to know before you are given **ROZILAT**
3. How to use **ROZILAT**
4. Possible side effects
5. How to store **ROZILAT**
6. Contents of the pack and other information

1. What ROZILAT is and what it is used for

ROZILAT belongs to a group of medicines called hormone inhibitors.
ROZILAT is indicated for:

- The treatment of breast cancer in women who have gone through menopause i.e cessation of periods
- The treatment of postmenopausal women with early breast cancer who have had prior standard treatment with tamoxifen (another medicine used to treat breast cancer).
- First-line treatment in postmenopausal women with hormone dependent advanced breast cancer (breast cancer that has a significant number of oestrogen or progesterone receptors).
- Treatment of advanced breast cancer in women who have previously been treated with antioestrogens and have either experienced menopause naturally or have had it induced.
- **ROZILAT** is used as therapy before surgery in postmenopausal women with localised hormone receptor positive breast cancer.

2. What you need to know before you take ROZILAT

Do not take ROZILAT:

- If you are hypersensitive (allergic) to letrozole or any of the ingredients of **ROZILAT** (listed in section 6);
- If you still have periods, i.e. if you have not yet gone through the menopause;
- If you are pregnant;
- If you are breastfeeding;
- If you have severe liver disease;
- If you have severe kidney disease.

Warnings and special precautions
Talk to your doctor before taking **ROZILAT**:

- If you are unsure if you are postmenopausal (do not have periods), so that tests can be done;
- If you have a severe kidney disease;
- If you have a severe liver disease;
- If you have a history of osteoporosis (bone disorder characterised by loss of bone density) or bone fractures;
- If you are taking tamoxifen or any other anti-oestrogen or oestrogen-containing treatment;

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

Children and adolescents
ROZILAT has not been studied in children or adolescents and therefore should not be used in this patient population.

Other medicine and ROZILAT:
Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines). The use of **ROZILAT** with these medicines may cause undesirable interactions.

In particular tell your doctor if you are using medicines containing the following active substances:

- Tamoxifen (used to treat breast cancer)
- Oestrogen (used to treat the symptoms of menopause)
- Phenytoin (an anticonvulsant)
- Clopidrogel (used to prevent blood clots)

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking this medicine.

- You should only take **ROZILAT** when you have gone through the menopause. However, you should discuss your doctor effective contraception as you may still have the potential to become pregnant during treatment with **ROZILAT**.
- You must not take **ROZILAT** if you are pregnant or breastfeeding as it may harm your baby.

Driving and using machines
ROZILAT might cause tiredness, dizziness, fainting or sleepiness. Do not drive or operate tools or machines if you experience such side effects.
It is not always possible to predict to what extent **ROZILAT** may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which **ROZILAT** affects them.

ROZILAT contains lactose.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take ROZILAT

Do not share medicines prescribed for you with any other person.
Always take **ROZILAT** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose **ROZILAT** is one tablet daily.

ROZILAT should be taken orally and can be taken with or without food.

Your doctor will tell you how long your treatment with **ROZILAT** will last. Do not stop any treatment unless your doctor tells you to do so.

If you have the impression that the effect of **ROZILAT** is too strong or too weak, tell your doctor or pharmacist.

If you take more ROZILAT than you should
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you forget to take ROZILAT
If you forget to take a dose, it should be taken as soon as you remember. However, if it is almost time for the next dose (within 2 or 3 hours), then the missed dose should be skipped, and you should go back to your regular dosage schedule.
Do not take a double dose to make up for forgotten individual doses.

4. Possible side effects

ROZILAT can have side effects.
Not all side effects reported for **ROZILAT** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **ROZILAT**, please consult your doctor, pharmacist or other healthcare professional for advice.
If any of the following happens, stop taking **ROZILAT** and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Swelling around the eyes or face, throat or tongue, (which may be a serious allergic reaction)
- Yellow skin and eyes, nausea, loss of appetite, dark coloured urine (which may be signs of hepatitis)
- Rash, red skin, blistering of eyes or mouth, skin peeling, fever (which may be signs of skin disorder)

These are all very serious side effects. If you have them, you may have had a serious reaction to **ROZILAT**. You may need urgent medical attention or hospitalisation.

Tell your doctor if you notice any of the following:
Frequent side effects:

- Hot flushes
- Increased sweating
- Joint pain
- Tiredness
- Loss or increase of appetite
- Depression
- Headache
- Dizziness
- Hypertension (high blood pressure)
- High cholesterol
- Gastrointestinal disorders such as nausea, indigestion, constipation, abdominal pain, diarrhoea, vomiting
- Hair loss
- Skin rash
- Dry skin
- Muscle pain
- Loss of bone mass leading to bone fractures
- Vaginal bleeding
- Swelling of arms, hands, feet, ankles, legs
- Weight increase

Less frequent side effects:

- Urinary tract infection
- Breast pain
- Low white blood cell count as shown in blood tests
- Nervous disorders such as anxiety, nervousness, irritability
- Tingling or pins and needles
- Impairment of sensation especially of touch
- Pain or burning sensation in hands (carpal tunnel syndrome)
- Taste disorder, dry mouth, thirst
- Eye disorders such as blurred vision or irritation
- Palpitations
- Fast heart beat
- Chest pains
- Blood clots
- Shortness of breath
- Inflammation of the mouth
- Skin disorders such as itching
- Increased urinary frequency
- Vaginal discharge
- Vaginal dryness
- Generalised swelling
- Fever
- Weight loss

Frequency unknown:

- Allergic reaction
- Inflammation of the liver
- Swelling of face, tongue, throat, abdomen (this is a medical emergency)
- Severe skin reactions, which may have blisters and involve the mouth, throat, eyes and genitals that can be life-threatening (toxic epidermal necrolysis)
- Trigger finger (finger is stuck in a bent position)

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects via https://www.sahpra.org.za/Publications/Index/8.
By reporting side effects, you can help provide more information on the safety of **ROZILAT**.

5. How to store ROZILAT

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.
ROZILAT will be stored in the pharmacy:
Store at or below 25 °C.
Keep the container in the outer carton in order to protect from light.
Do not use after the expiry date stated on the blister and the carton.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets)

6. Contents of the pack and other information

What ROZILAT looks like and contents of the pack
ROZILAT is a dark yellow, film-coated, round, slightly biconvex, with bevelled edges tablet debossed with 'L2.5' on one side and plain on the other side.
ROZILAT is packed in clear PVC/PVC film - aluminium foil blister pack in a carton with a professional information.
It is packed in packs of 30 film-coated tablets (3 x blister packs of 10 tablets each)

HOLDER OF THE CERTIFICATE OF REGISTRATION
AUROGEN SA (Pty) Ltd
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Johannesburg
South Africa

Registration number:
55/21.12/0204

This leaflet was last revised in
29 June 2021

Professionele inligting oor medisyne vir menslike gebruik

SKEDULERINGSTATUS

S4

1. NAAM VAN DIE MEDISYNE

ROZILAT filmbedekte tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

ROZILAT filmbedekte tablette bevat 2,5 mg letrosool.
Bevat suiker: 48,70 mg laktosemonohidraat.
Raadpleeg afdeling 6.1 vir die volledige lys hulpstowwe.

3. FARMASEUTIESE VORM

Filmbedekte tablet
Donkergeel, filmbedekte, ronde, effens bikonvekse, tablet met skuins kante met "L2.5" aan die een kant en glad aan die ander kant.

4. KLINIESE BESONDERHEDE

4.1. Terapeutiese indikasies

ROZILAT is aangedui vir:

- Adjuvantbehandeling van postmenopousale vroue met hormoonreseptorpositiewe vroeë borskanker.
- Voortgesette adjuvantbehandeling van vroeë borskanker in postmenopousale vroue wat voorheen standaard adjuvantbehandeling met tamoksifeen ontvang het.
- Eersteliniebehandeling vir postmenopousale vroue met hormoonafhanklike gevorderde borskanker.
- Die behandeling van gevorderde borskanker in vroue met natuurlike of kunsmatig geïnduseerde postmenopousale status wat voorheen met anti-estrogene behandel is.
- Pre-operatiewe behandeling vir postmenopousale vroue met gelokaliseerde hormoonreseptorpositiewe borskanker om 'n operasie met die behoud van die bors moontlik te maak vir vroue wat voorheen nie vir hierdie tipe operasie oorweeg sou word nie. Opvolgbehandeling na die operasie moet volgens standaardsorg wees.

4.2. Dosis en metode van toediening

Dosering
Volwasse en bejaarde pasiënte
Die aanbevole dosis **ROZILAT** is 2,5 mg een keer per dag.
Vir langdurige adjuvantbehandeling moet met **ROZILAT** vir 5 jaar aangehou word of totdat 'n terugval in die tumor voorkom, wat ook al eerste gebeur.
Vir pasiënte met metastatiese siekte moet behandeling met **ROZILAT** aangaan totdat progressie in die tumor sigbaar is.

Pasiënte met swak nierfunksie

Geen aanpassing in die dosis is vir pasiënte met ligte tot matige swak nierfunksie (kreatinienopruiming ≥ 10 mL/min) nodig nie. Daar is onvoldoende data om aanbevelings oor die dosis te maak vir pasiënte met 'n kreatinienopruiming van < 10 mL/min (kyk afdelings 4.4 en 5.2).

Pasiënte met swak lewerfunksie
Geen aanpassing in die dosis is vir pasiënte met ligte tot matige swak lewerfunksie (Child-Pugh-klas A en B) nodig nie.
ROZILAT moet egter nie gebruik word vir pasiënte met erge swak lewerfunksie (Child-Pugh graad C) nie.

Bejaarde pasiënte
Geen dosisaanpassing is vir bejaarde pasiënte nodig nie.

Pediatriese populasie
Nie van toepassing nie.

Metode van toediening
ROZILAT moet oraal gedrink word en kan met of sonder voedsel geneem word.

4.3. Kontra-indikasies

- Hipersensitiwiteit vir die aktiewe bestanddeel of vir enige van die hulpstowwe in afdeling 6.1 gelys.
- Pre-menopousale endokrienstatus.
- Swangerskap en borsvoeding (kyk afdeling 4.6)
- Erge swak lewerfunksie (Child-Pugh graad C).
- Erge swak nierfunksie (kreatinienopruiming < 10 mL/min).

4.4. Spesiale waarskuwings en voorsorgmaatreëls tydens gebruik

Menopousale status
In pasiënte wie se menopousale status onbekend is, moet vlakke van luteïniserende hormoon (LH), follikelstimulerende hormoon (FSH) en/of estradiol gemeet word voordat behandeling met **ROZILAT** begin. Slegs vroue met postmenopousale endokriene status kan **ROZILAT** kry.

Swak nierfunksie
ROZILAT is nie in 'n voldoende aantal pasiënte met 'n kreatinienopruiming laer as 10 mL/min ondersoek nie. **ROZILAT** is dus teenaangedui vir pasiënte met erge swak nierfunksie (kreatinienopruiming < 10 mL/min). (kyk afdeling 4,3).

Swak lewerfunksie
Sistemiese blootstelling en terminale halfleeftyd is ongeveer dubbel in pasiënte met erge swak lewerfunksie (Child-Pugh graad C) vergeleke met gesonde persone. **ROZILAT** is teenaangedui vir pasiënte met erge swak lewerfunksie (Child-Pugh graad C) (kyk afdeling 4.3).

Effekte op skeletbene
ROZILAT is 'n sterk estrogeenverlagende middel. Vroue met 'n geskiedenis van osteoporose en/of frakture, of met 'n groot risiko vir osteoporose, moet hul beenmineraaldigtheid formeel voor die aanvang van adjuvant- en voortgesette adjuvantbehandeling laat meet en moet tydens en na behandeling met letrosool gemonitor word. Behandeling of profilakse vir osteoporose moet, soos toepaslik, begin en noukeurig gemonitor word. Afhangende van die pasiënt se veiligheidsprofiel kan 'n opeenvolgende behandelingskedule (letrosool vir 2 jaar gevolg deur tamoksifeen vir 3 jaar) ook in 'n adjuvantopset oorweeg word (kyk afdelings 4.2, 4.8 en 5.1).

Ander waarskuwings
Toediening van **ROZILAT** saam met tamoksifeen, ander anti-estrogene of estrogeenbevattende medisyne moet vermy word, aangesien hierdie stowwe die farmakologiese werking van letrosool kan verminder (kyk afdeling 4.5).

ROZILAT bevat laktosemonohidraat. Pasiënte met die skaars oorerflike probleem van onverdraagbaarheid van galaktose, of erge laktasetekort of wanabsorpsie van glukose/galaktose, moet nie hierdie medisyne gebruik nie.

4.5. Interaksies met ander medisyne en ander vorms van interaksie:

Metabolisme van letrosool word deels via CYP2A6 en CYP3A4 bewerkstellig. Simetidien, 'n swak, nonspesifieke remmer van CYP 450 -ensieme, beïnvloed nie die plasmakonsentrasies van letrosool nie. Die effek van kragtige CYP 450-remmers is onbekend.

Tot op datum is daar geen kliniese ondervinding met die gebruik van **ROZILAT** in kombinasie met estrogene of antikankermiddels behalwe tamoksifeen nie. Tamoksifeen, ander anti-estrogene of estrogeenbevattende medisyne kan die farmakologiese werking van letrosool verswak. Daarbenewens is bewys dat gelyktydige toediening van tamoksifeen en letrosool die plasmakonsentrasies van letrosool aansienlik verlaag. Toediening van letrosool saam met tamoksifeen, ander anti-oestrogene of estrogene moet vermy word.

In vitro rem letrosool die sitochroom P450 iso-ensieme 2A6 en, matig, 2C19, maar die kliniese relevansie is onbekend. Wees dus versigtig as letrosool gegee word saam met medisinale produkte waarvan die eliminasie hoofsaaklik van hierdie iso-ensieme afhang en waarvan die terapeutiese indeks nou is (bv. fenitoïen, klopidogrel).

4.6. Fertiliteit, swangerskap en borsvoeding

Vroue met peri-menopousale status of wat vrugbaar is
ROZILAT moet slegs gebruik word deur vroue met 'n duidelik gevestigde postmenopousale status (kyk afdeling 4.4). Aangesien daar berigte is van vroue wat tydens die behandeling met **ROZILAT** werking van hulle eierstokke herwin het ten spyte van 'n duidelike postmenopousale status met die aanvang van die terapie, moet die mediese praktisyn, indien nodig, voldoende voorbehoeding bespreek.

Swangerskap
Op grond van ervaring mense waar daar geïsoleerde gevalle van geboortedefekte (labiale samesmelting, dubbelsinnige geslagsdele) was, kan **ROZILAT** aangebore misvormings veroorsaak as dit tydens swangerskap gebruik word. Studies met diere het toksisiteit op voortplanting aangetoon.

ROZILAT is teenaangedui tydens swangerskap (kyk afdeling 4.3)

Borsvoeding
Dit is onbekend of letrosool en sy metaboliete in menslike melk uitgeskei word. 'n Risiko vir die pasgeborenes/babas kan nie uitgesluit word nie.

ROZILAT is teenaangedui tydens swangerskap (kyk afdeling 4.3)

Fertiliteit
Die farmakologiese werking van letrosool is om estrogeenproduksie te verminder deur aromatase te rem. In premenopousale vroue lei die remming van estrogeensintese deur terugkoppeling tot stygings in gonadotropienvlakke (LH, FSH). Hoë FSH-vlakke stimuleer weer groei van die follikels en kan ovulasie veroorsaak.

4.7. Effek op vermoë om 'n voertuig te bestuur en masjiene te gebruik

ROZILAT het 'n klein effek op die vermoë om 'n voertuig te bestuur of masjinerie te hanteer. Aangesien moegheid en duiseligheid met die gebruik van **ROZILAT** waargeneem is en slaperigheid aangemeld is, word aanbeveel dat bestuur van 'n voertuig of gebruik van masjiene versigtig gedoen moet word.

4.8. Ongewensde effekte

a. *Opsomming van die veiligheidsprofiel*
Die newe-reaksies wat die meeste in kliniese studies aangemeld is, is warm gloede, hipercholesterolemie, artralgie, moegheid, meer sweet en naarheid.

Ander belangrike newe-reaksies wat met **ROZILAT** kan voorkom, is: effekte op die skelet soos osteoporose en/of beenbreuke en kardiovaskulêre voorvalle (waaronder serebrovaskulêre en trombo-emboliese effekte). Die frekwenskategorie vir hierdie newe-reaksies word in Tabel 1 gegee.

b. *Getabuleerde opsomming van nadelige reaksies*
Die frekwensies van newe reaksies van **ROZILAT** is hoofsaaklik gebaseer op data wat in kliniese toetse versamel is.

Die volgende lys nadelige geneesmiddelreaksies, gegee in Tabel 1, is saamgestel uit kliniese studies en ondervinding na bemarking van **ROZILAT**:

Tabel 1: Nadelige reaksies word onder die hoofde van frekwensie gegee met die mees algemenes eerste, volgens hierdie konvensie: Dikwels, minder dikwels en frekwensie onbekend.

Infeksies en infestasies Minder dikwels: Urienweginfeksie
Goedaardige, kwaadaardige en ongespesifiseerde neoplasmas (waaronder siste en poliepe) Minder dikwels: Tumorpyn[1]
Versteurings van bloed en limfstelsel Minder dikwels: Leukopenie
Versteurings van die immuunstelsel Frekwensie onbekend: Anafilaktiese reaksie
Versteurings in metabolisme en voeding Dikwels: Hipercholesterolemie, anoreksie, groter eetlus
Psigiatriese versteurings Dikwels: Depressie Minder dikwels: Angs (waaronder senuagtigheid), geïrriteerdheid
Versteurings van die senustelsel Dikwels: Hoofpyn, duiseligheid Minder dikwels: Lomerigheid, slaaploosheid, swak geheue, disestesie (waaronder parestesie, hipoëstesie), smaakversteuring, serebrovaskulêre ongeluk, karpaletonnelsindroom
Oogversteurings Minder dikwels: Katarak, oogirritasie, dowwe visie
Hartversteurings Minder dikwels: Hartkloppings[1], tagikardie, iskemiese harteffekte (waaronder nuwe of verergerende angina, angina wat operasie benodig, miokardiale infarksie en miokardiale iskemie)
Vaskulêre versteurings Dikwels: Warm gloede, hipertensie Minder dikwels: Tromboflebitis (waaronder oppervlakkige en diep veneuse tromboflebitis), longembolie, arteriële trombose, serebrovaskulêre infarksie
Respiratoriese, toragiese en mediastinale versteurings Minder dikwels: Dispnee, hoes
Gastro-intestinale versteurings Dikwels: Naarheid, slegte spysvertering[1], hardlywigheid, buikpyn, diarree, braking Minder dikwels: Droë mond, stomatitis[1]
Hepatobiliêre versteurings Minder dikwels: Toename in lewerensieme Frekwensie onbekend: Hepatitis
Versteurings van die vel en subkutane weefsel Dikwels: Meer sweet, alopesie, uitslag (insluitend eriteemagtig, makulopapulêr, psoria-agtig en vesikulêre uitslag), droë vel Minder dikwels: Pruritus, urtikarie Frekwensie onbekend: Angioedeem, toksiese epidermale nekrolise, multivorme eriteem
Versteurings van die muskuloskeletale stelsel en van bindweefsel Dikwels: Artralgie, mialgie, beenpyn[1], osteoporose, beenbreuke Minder dikwels: Artritis Frekwensie onbekend: Snellervinger
Versteurings van die niere en urienweg Minder dikwels: Toename in frekwensie van urinering
Versteurings in die voortplantingstelsel en borste Dikwels: Vaginale bloeding Minder dikwels: Vaginale bloeding, vaginale droogheid, borspyn
Algemene versteurings en effekte by die plek van toediening Dikwels: Moegheid (waaronder astenie, malaise), perifere edeem Minder dikwels: Algemene edeem, droogheid van die slymvlies, dors, pireksie
Laboratoriumtoetse Dikwels: Toename in gewig Minder dikwels: Gewigsverlies

[1] Nadelige geneesmiddelreaksies wat slegs in die metastatiese omgewing aangemeld is

Beskrywing van spesifieke nadelige reaksies
Hart nadelige reaksies
Die volgende ernstige nadelige effekte is met **ROZILAT** aangemeld:
Angina wat chirurgie benodig, hartversaking, hipertensie en serebrovaskulêre ongeluk/verbygaande iskemiese aanval.
Nuwe of erger angina, miokardiale infarksie, trombo-emboliese voorvalle, beroerte/verbygaande iskemiese aanval is ook aangemeld.

Skeletale nadelige reaksies
In die voortgesette adjuvantomgewing het aansienlik meer pasiënte wat met **ROZILAT** behandel is, beenbreuke of osteoporose (beenfrakture, 10,4 % en osteoporose, 12,2 %) opgedoen as pasiënte in die plasebo-arm (onderskeidelik 5,8 % en 6,4 %). Die mediaan duur van behandeling was 5 jaar vir **ROZILAT**, vergeleke met 3 jaar vir plasebo.

Aanmeld van vermeende nadelige reaksies
Dit is belangrik om vermeende nadelige reaksies wat na magtiging van die medisinale produk voorkom, aan te meld. Dit maak voortgesette monitering van die balans tussen voordeel en risiko van die medisinale produk moontlik. Gesondheidspraktisyns word versoek om alle vermeende nadelige reaksies by SAHPRA aan te meld met die vorm "6.04 Adverse Drug Reaction Reporting Form" wat aanlyn by SAHPRA se publikasies gekry kan word: https://www.sahpra.org.za/Publications/Index/8.

4.9. Oordosis

Geïsoleerde gevalle van oordosering met **ROZILAT** is aangemeld.
Geen spesifieke behandeling vir oordosering is bekend nie; behandeling is dus simptomaties en ondersteunend.

5. FARMAKOLOGIESE EIENSKAPPE

5.1. Farmakodinamiese eienskappe

Farmakologiese klassifikasie: A 21.12 Hormoonremmers
Endokriene terapie. Hormoonantagoniste en verwante middels: aromataseremmers ATC kode: L02BG04.

Farmakodinamiese eienskappe

Werkingsmeganisme
Die uitsluiting van stimulasie van groei deur estrogeen is 'n voorvereiste vir tumorrespons in gevalle waar die groei van die tumorweefsel van estrogeen afhanklik is en endokrienterapie gebruik word. In postmenopousale vroue is estrogene hoofsaaklik afkomstig van 'n proses waardeur aromatase adrenale androgene (hoofsaaklik androsteendioon en testosteroon) na estroon en estradiol omskakel. Die biosintese van estrogeen in perifere weefsel asook die groei van kankerweefsel self kan dus onderdruk word deur spesifieke remming van die aromatase-ensiem.

Letrosool is 'nie-steroïed aromataseremmer. Dit rem die aromatase-ensiem deur kompetitief aan die heem van die sitochroom P450-subeenheid te bind en die biosintese van estrogeen in alle weefsel sodoende te verminder.

In gesonde postmenopousale vroue onderdruk enkeldosisse van 0,1 mg, 0,5 mg of 2,5 mg letrosool estroon en estradiol in die serum met 75 %, 78 % en 78 % van die basiswaardes, onderskeidelik. Die maksimum onderdrukking word binne 48 - 78 uur bereik.

In postmenopousale pasiënte met gevorderde borskanker onderdruk daaglikse dosisse van 0,1 tot 5 mg letrosool plasmakonsentrasies van estradiol, estroon en estroonsulfaat in alle behandelde pasiënte met 75 % tot 95 % van die basisvlak. Met dosisse van 0,5 mg en hoër, is baie estroon- en estroonsulfaatkonsentrasies onder die deteksievlak van die analisemetode, wat aantoon dat 'n hoër estrogeenonderdrukking met hierdie dosisse verkry word. In al hierdie pasiënte is estrogeenonderdrukking dwarsdeur die behandeling volgehou.

Letrosool rem die aktiwiteit van aromatase baie spesifiek. Onderdrukking van adrenale steroïedgenese is nie waargeneem nie. Daar is geen klinies relevante veranderinge gevind in die plasmakonsentrasies van kortisol, aldosteroon, 11-deoksikortisol, 17-hidroksiprogesteroon en ACTH of in plasmarenienaktiwiteit in postmenopousale pasiënte wat behandel is met 'n daaglikse dosis van 0,1 tot 5 mg letrosool nie Die ACTH-stimulasietoets uitgevoer na 6 en 12 weke van behandeling met daaglikse dosisse van 0,1 mg, 0,25 mg, 0,5 mg, 1 mg, 2,5 mg of 5 mg het geen verhoging van aldosteroon- of kortisolproduksie aangetoon nie. Glukokortikoïed- of mineralokortikoïedaanvulling is dus nie nodig nie.

Geen veranderings in plasmakonsentrasies van androgene (androsteendioon en testosteroon) is waargeneem in gesonde postmenopousale vroue na toediening van 0,1 mg; 0,5 mg of 2,5 mg letrosool as enkeldosisse nie, en ook nie in plasmakonsentrasies van androsteendioon in postmenopousale pasiënte wat met daaglikse dosisse van 0,1 tot 5 mg behandel is nie, wat aantoon dat die blokkade van estrogeenbiosintese nie tot 'n akkumulasie van androgeenvoorlopers lei nie. Plasmavlakke van LH en FSH word nie deur letrosool beïnvloed nie, en ook nie tiroïedfunksie nie, soos deur opname van TSH, T4 en T3 aangetoon.

5.2. Farmakokinetiese eienskappe

Absorpsie
Letrosool word vinnig en volledig vanuit die gastro-intestinale kanaal geabsorbeer (gemiddelde absolute biobeskikbaarheid 99,9 %). Voedsel verminder die absorpsietempo effens, maar die mate van absorpsie (AOK) word nie aangetas nie. Dit word nie gereken dat hierdie klein effek op die absorpsietempo van kliniese waarde is nie, en letrosool kan dus met of sonder maaltye geneem word.

Verspreiding
Ongeveer 60 % van die letrosool is aan plasmaproteïene gebonde en hoofsaaklik aan albumien (55 %). Die konsentrasie van letrosool in eritrosiete is ongeveer 80 % van dié in plasma. Na toediening van 2,5 mg ^{14}C-gemerkte letrosool word ongeveer 82 % van die radioaktiwiteit as onveranderde verbinding in die plasma gevind. Sistemiese blootstelling aan metaboliete is dus laag. Letrosool versprei vinnig en wyd in weefsel. Die skynbare volume van verdeling by ewewig is ongeveer 1,87 ± 0,47 L/kg.

Biotransformasie
Metaboliese omskakeling na 'n farmakologies onaktiewe karbinolmetaboliet is die belangrikste eliminasieroete van letrosool (Cl_m = 2,1 L/h), maar dit is relatief stadig in vergelyking met hepatiese bloedvloei (ongeveer 90 L/h). Dit is gevind dat die sitochroom P450-iso-ensieme 3A4 en 2A6 in staat is om letrosool na hierdie metaboliet om te skakel. Die vorming van enkele ongeïdentifiseerde metaboliete en direkte renale en fekale ekskresie speel slegs 'n ondergeskikte rol in die totale eliminasie van letrosool. Binne 2 weke na toediening van 2,5 mg ^{14}C-gemerkte letrosool aan gesonde postmenopousale vrywilligers, was 88,2 ± 7,6 % van die radioaktiwiteit in die urien en 3,8 ± 0,9 % in die feses gevind. Minstens 75 % van die radioaktiwiteit (84,7 ± 7,8 % van die dosis) wat tot op 216 uur in die urien teruggevind is, wis toegeskryf aan die glukuronied van die karbinolmetaboliet, ongeveer 9 % aan twee ongeïdentifiseerde metaboliete en 6 % aan onveranderde letrosool.

Uitskeiding
Die skynbare terminale eliminasiehalfleeftyd in plasma is ongeveer 2 dae. Na daaglikse toediening van 2,5 mg word gelykvlakke binne 2 tot 6 weke bereik. Plasmakonsentrasies by die ewewigstoestand is ongeveer 7 keer hoër as konsentrasies na 'n enkele dosis van 2,5 mg terwyl dit 1,5 tot 2 keer hoër is as die gelykvlakwaardes wat vanaf die konsentrasies van enkeldosisse voorspel is, wat 'n effense nie-lineêriteit in die farmakokinetika van letrosool na daaglikse toediening van 2,5 mg aantoon. Aangesien gelykvlakke oor tyd volgehou word, kan afgelei word dat geen kontinue akkumulasie van letrosool voorkom nie.

Spesiale populasies

Bejaardes
Ouderdom het geen effek op die farmakokinetika van letrosool nie.

Swak nierfunksie en lewerfunksie
Geen effek op die farmakokinetika van letrosool na 'n enkele dosis van 2,5 mg is in 'n studie met vrywilligers met wisselende grade van nierfunksie (24 uur kreatinienopruiming 9 tot 116 mL/min) gevind nie. In 'n soortgelyke studie met pasiënte met wisselende grade van lewerfunksie, was die gemiddelde AOK-waardes van die vrywilligers met matige swak lewerfunksie (Child-Pugh graad B) 37 % hoër as in normale pasiënte, maar steeds binne die spektrum waargeneem in pasiënte sonder lewerwanfunksie.

In 'n studie wat die farmakokinetika van letrosool na 'n enkele orale dosis in agt pasiënte met lewersirrose en erge swak lewerfunksie (Child-Pugh graad C) vergelyk het met dié van gesonde persone (N=8), is gevind dat die AOK en $t_{½}$ onderskeidelik 95 % en 187 % hoër is. Borskankerpasiënte met erge swak lewerfunksie word dus aan hoër vlakke letrosool blootgestel as pasiënte sonder erge swak lewerfunksie.

6. FARMASEUTIESE BESONDERHEDE

6.1. Lys van hulpstowwe
Inhoud van tablette: laktosemonohidraat, mikrokristallyne sellulose, mieliestysel, natriumstyselglikolaat, magnesiumstearaat en kolloïdale watervrye silika. Bedekking: hipromellose, talk, makrogol, titaandioksied en geel ysteroksied.

6.2. Onverenigbaarhede
Nie toepaslik nie

6.3. Rakleeftyd
24 maande

6.4. Spesiale voorsorgmaatreëls vir bewaring
Bêre by of onder 25 °C.
Bêre in die oorspronklike houer totdat dit vir gebruik benodig word.

HOU BUITE BEREIK VAN KINDERS.

6.5. Aard en inhoud van die houer
Verpak in stulpstroke van helder PVC/PVC-film-aluminiumfolie
Pakke met 30 filmbedekte tablette.

6.6. Spesiale voorsorgmaatreëls vir die wegdoen van gebruikte medisyne of afvalstowwe wat uit sodanige medisyne verkry word, en ander hantering van die produk
Geen spesiale vereistes nie.

7. NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT

AUROGEN SA (Edms) Bpk
Woodhillkantoorpark, Gebou 1, Eerste vloer
Phillip Engelbrechtlaan 53
Meyersdal Uitbr. 12, 1448
Johannesburg
Suid-Afrika

8. REGISTRASIENOMMER

55/21.12/0204

9. DATUM VAN EERSTE MAGTIGING

29 Junie 2021

P1528449

DETACH BEFORE DISPENSING

Sê vir u dokter as u enige van die volgende opmerk:
Newe-effekte wat dikwels voorkom:
- Warm gloede
- Meer sweet
- Gewrigspyn
- Moegheid
- Verlies of toename in eetlus
- Depressie
- Hoofpyn
- Duiseligheid
- Hipertensie (hoë bloeddruk)
- Hoë cholesterolvlakke.
- Gastro-intestinale versteurings soos naarheid, spysvertering, hardlywigheid, buikpyn, diarree, braking
- Haarverlies
- Veluitslag
- Droë vel
- Spierpyn
- Verlies van beenmassa wat tot beenbreuke lei
- Vaginale bloeding
- Swelling van die arms, hande, voete, enkels, bene
- Toename in gewig

Newe-effekte wat minder dikwels voorkom:
- Urienweginfeksie
- Pyn in die borste
- Lae witbloedseltelling soos in bloedtoetse gesien
- Senustoormisse soos angs, senuagtigheid, prikkelbaarheid
- Tinteling of naalde en spelde
- Vermindering van gevoel, veral aanraking
- Pyn of brandgevoel in die hande (karpaletonnelsindroom)
- Smaakstoornis, droë mond, dors
- Oogaftwykings soos versteurde visie of irritasie
- Palpitasies
- Vinnige hartklop
- Pyn in die borskas
- Bloedklonte
- Kortasemheid
- Inflammasie in die mond
- Velafwykings soos jeuk
- Toename in frekwensie van urinering
- Vaginale afskeiding
- Vaginale droogheid
- Algemene swelling
- Koors
- Gewigsverlies

Frekwensie onbekend:
- Allergiese reaksie
- Inflammasie van die lewer
- Swelling van gesig, tong, keel, buik (dit is 'n mediese noodgeval)
- Erge velreaksies, wat blase kan vorm en die mond, keel, oë en geslagsdele kan betrek wat lewensgevaarlik kan wees (toksiese epidermale nekrolise)
- Snellervinger (wanneer 'n vinger in 'n gebuigde posisie vasgevang word)

As u enige newe-effekte opmerk wat nie in hierdie blad genoem word nie, moet u u dokter of apteker asseblief in kennis stel.

Aanmeld van newe-effekte
Praat met u dokter, apteker of verpleegkundige as u newe-effekte kry. Dit sluit alle moontlike newe-effekte in wat nie in hierdie blad gelys word nie. U kan newe-effekte ook via https://www.sahpra.org.za/Publications/Index/8 aanmeld. Deur newe-effekte aan te meld, kan u help om meer inligting oor die veiligheid van **ROZILAT** te gee.

5. Hoe om ROZILAT te bêre
HOU ALLE MEDISYNE BUITE BEREIK VAN KINDERS.
ROZILAT sal in die apteek gestoor word
Bêre by of onder 25 °C.
Hou die houer in die buitenste karton om dit teen lig te beskerm.
Moenie na die vervaldatum op die stulpstrook en die karton gebruik nie.
Gee alle ongebruikte medisyne terug aan u apteker.
Ongebruikte medisyne moet nie in dreinering- of rioolstelsels (bv. toilette) gegooi word nie.

6. Inhoud van die pak en ander inligting
Wat ROZILAT bevat
Die aktieve bestanddeel is letrosool.
Elke filmbedekte tablet bevat 2,5 mg letrosool.

Die ander bestanddele van **ROZILAT** is laktosemonohidraat, mikrokristallyne sellulose, mieliestysel, natriumstyselglikolaat, magnesiumstearaat en watervrye silika. Bedekking: hipromellose, talk, makrogol, titaandioksied en geel ysteroksied.

ROZILAT bevat laktosemonohidraat.
As u dokter dus vir u gesê het dat u 'n onverdraagbaarheid teenoor sekere suikers het, moet u dokter skakel voordat u hierdie medisyne drink.

Hoe ROZILAT lyk en die inhoud van die pakkie

ROZILAT is donkergeel, filmbedekte, ronde, effens bikonvekse, tablette met skuins kante met "L2.5" aan die een kant en glad aan die ander kant

ROZILAT is verpak in stulpstroke van helder PVC/PVC-film en aluminiumfoelie in 'n karton met 'n voubiljet.

Dit word verpak 30 filmbedekte tablette in 'n pak (3 x stulpstroke met 10 tablette elk)

HOUER VAN DIE REGISTRASIESERTIFIKAAT
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Registrasienommer:
55/21.12/0204

Hierdie blad is laas hersien op
29 Junie 2021

PASIËNTINLIGTINGSBLAD
SKEDULERINGSTATUS

S4

ROZILAT (filmbedekte tablette)
Letrosool
Bevat suiker: 48,70 mg laktosemonohidraat.

Lees hierdie hele blad noukeurig deur voordat u ROZILAT drink.
- Hou hierdie blad. Dit mag nodig wees dat u dit weer moet lees.
- As u nog enige vrae het, moet u u dokter, apteker, verpleegkundige of ander gesondheidsorgverskaffer asseblief vra.
- **ROZILAT** is vir u persoonlik voorgeskryf en u moet nie u medisyne vir ander mense gee nie. Dit kan hulle skaad, selfs al is hulle simptome dieselfde as u s'n.

Wat in hierdie blad is:
1. Wat **ROZILAT** is en waarvoor dit gebruik word
2. Wat u moet weet voordat u **ROZILAT** kry
3. Hoe om **ROZILAT** te gebruik
4. Moontlike newe-effekte
5. Hoe om **ROZILAT** te bêre
6. Inhoud van die pak en ander inligting

1. Wat ROZILAT is en waarvoor dit gebruik word
ROZILAT behoort aan 'n groep medisyne bekend as hormoonremmers.
ROZILAT is aangedui vir:
- Die behandeling van borskanker in vroue wat deur menopouse gegaan het, d.w.s. die staking van menstruasie
- Behandeling van postmenopousale vroue met vroeë borskanker wat voorheen standaardbehandeling met tamoksifeen gehad het (ander medisyne wat gebruik word om borskanker te behandel).
- Eersteliniebehandeling van postmenopousale vroue met hormoonafhanklike gevorderde borskanker (borskanker wat 'n, beduidende aantal estrogeen- of progesteronreseptore het).
- Behandeling van gevorderde borskanker in vroue wat voorheen met anti-estrogene behandel is en of natuurlike of geïnduseerde menopouse het.
- **ROZILAT** word gebruik as terapie voor chirurgie in postmenopousale vroue met gelokaliseerde hormoonreseptorpositiewe borskanker.

2. Wat u moet weet voordat u ROZILAT drink
Moenie ROZILAT drink nie:
- as u hipersensitief (allergies) vir letrosool of vir enige van die ander bestanddele van **ROZILAT** (gelys in afdeling 6) is;
- as u nog menstrueer, d.w.s. as u nog nie deur menopouse gegaan het nie;
- as u swanger is;
- as u borsvoed;
- as u 'n ernstige lewersiekte het;
- as u 'n erge niersiekte het;

Waarskuwings en spesiale voorsorgmaatreëls
Praat met u dokter voordat u **ROZILAT** drink:
- as u nie seker is of u postmenopousaal is nie (sonder menstruasies), sodat toetse doen kan word ;
- as u aan 'n erge niersiekte ly
- as u 'n erge lewersiekte het
- as u 'n geskiedenis van osteoporose (beenafwyking wat gekenmerk word deur verlies aan beendigtheid) of beenbreuke het
- as u tamoksifeen gebruik of enige behandeling met ander estrogene of anti-estrogene kry

As u nie seker is of enige van die bogenoemde op u van toepassing is nie, moet u met u dokter of apteker praat voordat u hierdie medisyne drink.

Kinders en adolessente

ROZILAT is nie in kinders of adolessente bestudeer nie en moet dus nie vir hierdie pasiëntpopulasie gebruik word nie.

Ander medisyne en ROZILAT:
Sê altyd vir u gesondheidspraktisyn as u enige ander medisyne gebruik (waaronder aanvullende en tradisionele medisyne).
Gebruik van **ROZILAT** saam met hierdie medisyne kan ongewensde interaksies veroorsaak.

Sê veral vir u dokter as u medisyne gebruik wat die volgende aktiewe bestanddele bevat:
- Tamoksifeen (om borskanker te behandel)
- Oestrogeen (om die simptome van menopouse te behandel)
- Fenitoïen ('n antikonvulsant)
- Klopidogrel (om bloedklonte te voorkom)

Swangerskap, borsvoeding en vrugbaarheid
As u swanger is of borsvoed, dink dat u dalk swanger kan wees of beplan om 'n baba te hê, moet u u dokter, apteker of ander gesondheidsorgverskaffer asseblief om advies raadpleeg voordat u hierdie medisyne drink.
- U moet **ROZILAT** slegs drink as u deur menopouse gegaan het.
- U moet egter effektiewe voorbehoeding met u dokter bespreek, aangesien u tydens die behandeling met **ROZILAT** moontlik steeds swanger kan raak.
- U moet **ROZILAT** nie drink as u swanger is of u baba borsvoed nie.

Motorbestuur en gebruik van masjinerie
ROZILAT kan moegheid, duiseligheid, floutes of lomerigheid veroorsaak. Moenie 'n voertuig bestuur of gereedskap of masjiene hanteer as u sulke newe-effekte ervaar nie.

Dit is nie altyd moontlik om te voorspel tot watter mate **ROZILAT** met die daaglikse aktiwiteite van 'n pasiënt kan inmeng nie. Pasiënte moet sorg dat hulle, totdat hulle weet hoe **ROZILAT** hulle beïnvloed, nie aan bogenoemde aktiwiteite deelneem nie.

ROZILAT bevat laktosemonohidraat.
As u dokter dus vir u gesê het dat u 'n onverdraagbaarheid teenoor sekere suikers het, moet u u dokter skakel voordat u hierdie medisyne drink.

3. Hoe om ROZILAT te drink
Moenie medisyne wat vir u voorgeskryf is vir enige ander persoon gee nie. Gebruik **ROZILAT** altyd presies soos vat u dokter vir u gesê het. Raadpleeg u dokter of apteker as u nie seker is nie.

Die gewone dosis van **ROZILAT** is een tablet per dag.

ROZILAT moet oraal gedrink word en kan met of sonder voedsel geneem word.

U dokter sal vir u sê hoe lank u behandeling met **ROZILAT** sal duur. Moenie ophou om **ROZILAT** te drink tensy u dokter so sê nie.

Sê vir u dokter of apteker as u die indruk het dat die effek van **ROZILAT** te sterk of te swak is.

As u meer ROZILAT gedrink het as wat u moes
Raadpleeg u dokter of apteker in geval van oordosering. As nie een beskikbaar is nie, kontak die naaste hospitaal of gifsentrum.

As u vergeet om ROZILAT te drink
As u vergeet het om 'n dosis te drink, drink dit sodra as wat u onthou. As dit egter byna tyd vir die volgende dosis is (binne 2 tot 3 uur), slaan die dosis wat u gemis het oor en gaan met u gewone doseerskedule aan.

Moenie 'n dubbele dosis gebruik om vir vergete individuele dosisse op te maak nie.

4. Moontlike newe-effekte
ROZILAT kan newe-effekte veroorsaak.
Nie al die newe-effekte wat vir **ROZILAT** aangemeld is, is in hierdie blad opgeneem nie. As u algemene gesondheidstoestand vererger of as u newe-effekte ervaar terwyl u **ROZILAT** kry, moet u u dokter, apteker of ander gesondheidspraktisyn asseblief om advies raadpleeg.

Indien enige van die volgende voorkom, moet u ophou om **ROZILAT** te drink en onmiddellik vir u dokter sê of na die ongevalle-afdeling van u naaste hospitaal gaan:
- Swelling om die oë of gesig, keel of tong (wat 'n ernstige allergiese reaksie kan wees)
- Geel vel en oë, naarheid, verlies van eetlus, donkerkleurige urien (wat tekens van hepatitis kan wees)
- Uitslag, rooi vel, blase van oë of mond, velafskilfering, koors (wat tekens van 'n velafwyking kan wees)

Hierdie is almal baie ernstige newe-effekte. As u dit ervaar, kan dit wees dat u 'n ernstige reaksie op **ROZILAT** het. Dit mag wees dat u dringende mediese aandag of hospitaalsorg nodig het.