PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

This medicine is dispensed with a doctor's prescription only

Koselugo™ 10 mg

Hard capsules

Each hard capsule contains:
Selumetinib (as hyd-sulfate) 10 mg

Koselugo™ 25 mg

Hard capsules

Each hard capsule contains:
Selumetinib (as hyd-sulfate) 25 mg
For inactive ingredients in the medicine - please see section 6 "Further Information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have any further questions, ask your doctor or pharmacist.
This medicine has been prescribed for you/your child. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

1. WHAT THE MEDICINE INTENDED FOR?

Koselugo is indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

Therapeutic group
Koselugo is protein Kinase inhibitor.

2. BEFORE USING THE MEDICINE:

Do not use the medicine if:
- You or your child are/is sensitive (allergic) to the active ingredient Selumetinib or to any of the other ingredients of this medicine (see section 6).

Special warnings regarding use of Koselugo
Before treatment with Koselugo, tell the doctor if:
- you or your child suffers from heart problems (see section 4 "Side effects").
- you or your child suffers from eye problems such as: blurred vision, sensitivity to light, cataracts or increased intraocular pressure (see section 4 "Side effects").
- you or your child suffers from gastrointestinal problems such as diarrhea (see section 4 "Side effects").
- you or your child suffers from skin problems such as rash (see section 4 "Side effects").
- you or your child suffers from muscle pain (which can be caused by increase creatinine phosphokinase enzyme) (see section 4 "Side effects").
- you or your child suffers from an increased risk of bleeding .
- you are pregnant or planning to become pregnant. Koselugo may harm the fetus. See section "Pregnancy, breast-feeding and fertility".
- you are breast-feeding or planning to breast-feed. See section "Pregnancy, breast-feeding and fertility".

Children and adolescents:
This medicine is not intended for children under 2 years of age. There is no information regarding the safety and efficacy of the use of this medicine in children under the age of 2.

Tests and follow ups:
Your doctor will conduct to you or to your child blood tests to check the levels of creatine phosphokinase enzyme in the blood, before and during treatment with Koselugo.
The doctor will check your or your child vision before and during the treatment of Koselugo.
The doctor will conduct to you or to your child cardiac functions tests before and during the treatment of Koselugo.
The doctor will check occasionally you or your child for the development of rashes on the skin.
The doctor will check occasionally if you or your child have/has hemorrhages and blood clotting functions.
The doctor will check if you are pregnant before starting treatment with Koselugo (see section "Pregnancy, breast-feeding and fertility").

Drug interactions:
If you/your child are/is taking, or have/has recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking or your child is taking:
- aspirin, blood thinners (such as vitamin K antagonists like Warfarin) or other medicines to treat blood clots.
- Supplements containing vitamin E. Koselugo contains vitamin E which may increase the risk of bleeding.
- Strong or moderate inhibitors of the enzyme CYP3A4 or Fluconazole, because they may increase the levels of Koselugo in the blood. This may increase the risk of side effects.
- Strong or moderate inducers of the enzyme CYP3A4 such as the Hypericum plant (St. John's Wort), because they may decrease the levels of Koselugo in the blood. This may decrease the efficacy of Koselugo.
- Supplements containing grapefruits.

Use of the medicine and food:
Take Koselugo on an empty stomach. Do not eat for 2 hours before taking your dose and 1 hour after taking your dose. Do not drink grapefruit juice or eat grapefruits during the treatment with Koselugo.

Pregnancy, breast-feeding and fertility:
Pregnancy
Do not take Koselugo if you are pregnant or might be pregnant, since Koselugo can harm your fetus. Before starting treatment with Koselugo, the attending doctor will check if you are pregnant.
Tell your doctor immediately if you become pregnant or think you may be pregnant during treatment with Koselugo.

Breast-feeding
Do not breast-feed during treatment with Koselugo and for 1 week after the last dose of Koselugo. It is not known whether Koselugo passes into the breast milk. Talk to the attending doctor about the best way to feed your baby during this time period.

Fertility
It is recommended that women of childbearing age will use effective contraceptives during the treatment of Koselugo and for 1 week after the last dose of Koselugo.
It is recommended that males with female partners of child-bearing age will use effective
contraceptives during the treatment with Koselugo and for 1 week after your last dose of Koselugo.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use this medicine according to your doctor's instructions.
Check with the doctor or pharmacist if you are uncertain about the dosage and manner of treatment with this medicine.
The dosage and manner of treatment will be determined only by your doctor.
The attending doctor will decide on the appropriate dosage for you or your child and how many capsules of Koselugo you or your child should take, based on the surface area of your body or your child's body.
The recommended dosage is usually: 25 mg/m^2, twice a day.
- It is possible that the doctor will change the dosage, stop the treatment temporarily or permanently, if you or your child experiences side effects.
- The medicine should be taken around the same time every day, 12 hours apart between each dose.
- Koselugo must be taken on an empty stomach. Do not eat two hours before taking the dose and one hour after taking the dose.
- Take the capsules whole with water. Do not chew, dissolve or open the capsules. In order not to harm the absorption of Koselugo and thereby reduce the effectiveness of the medicine.
- Do not take Koselugo if you or your child are unable to swallow a whole capsule .
- If you or your child vomits at any time after taking Koselugo, do not take an additional dose. Take the next dose at the scheduled time.

Do not exceed the recommended dose.

If you have taken or your child accidentally took a higher dose or if a child has accidentally swallowed the medicine, immediately refer to the doctor or to a hospital emergency room and bring the package of the medicine with you.

If you forgot or your child forgot to take the medicine:
If you forget or your child forgot to take the medicine at the scheduled time, take the dose as soon as you remember. If you remember less than six hours before the next dose you or your child supposed to take, the next dose should be taken at the schedule time. Do not take a double dose to compensate the forgotten dose.

If you or your child stops taking the medicine:
Do not change the dosage or stop treatment without consulting with the attending doctor.
Continue treatment as recommended by your doctor.

Do not take medicines in the dark! Check the label and dose each time you take the medicine. Wear glasses if you need them.

If you have any further questions on the use of this medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Koselugo may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Taking Koselugo may cause serious side effects, such as:
- **Heart Problems** - Koselugo may decrease the amount of blood pumped by the heart. This is common and can also be severe. Your doctor will perform heart function tests before and during treatment with Koselugo. **Tell your doctor immediately if you or your child gets any of the following symptoms:**
  - persistent coughing or wheezing
  - shortness of breath
  - swelling of the ankles and feet
  - tiredness
  - increased heart rate
- **Eye Problems** - Koselugo may cause eye problems that can lead to blindness. **Tell your doctor immediately if you or your child gets any of the following symptoms:**
  - blurred vision
  - loss of vision
  - dark spots in your vision (floaters)
  - other changes in the vision
- **Severe diarrhea** - Diarrhea is common when taking Koselugo and may also be severe. Tell your doctor immediately the first time that you or your child gets diarrhea during treatment with Koselugo. Your doctor may give you or your child medicine to treat the diarrhea and may tell you or your child to drink more fluids.
- **Skin rash** - Skin rashes are common during treatment with Koselugo and may also be severe. **Tell your doctor if you or your child gets any of the following symptoms:**
  - rash covers a large areas of your body
  - peeling skin
  - blisters
- **Muscle problems (rhabdomyolysis)** - Muscle problems are common during treatment with Koselugo and may also be severe. Treatment with Koselugo may increase the level of creatine phosphokinase enzyme (CPK) in the blood and may be a sign of muscle damage. **Tell your doctor immediately if you or your child gets any of the following symptoms:**
  - muscle pain
  - muscle spasms and weakness
  - dark and reddish urine

It is possible that the doctor will change the dosage, stop the treatment with Koselugo temporarily or permanently, if you or your child experiences one of those side effects.

Very common side effects appear in more than 1 in every 10 users:
- Vomiting
- Abdominal pain
- Diarrhea
- Nausea
- Mouth sores (stomatitis)
- Constipation
- Rash
- Inflammation around the fingernails (Paronychia)
- Pruritus
- Dermatitis
- Hair changes
- Dry skin
- Feeling tired ,weak or lack of energy
- pain in the muscles and bones
- Fever
- Edema
- Headache
- Nosebleed
- Blood in the urine
- Protein in the urine
- Decreased appetite
- Decreased heart function
- Visual disturbances
- Dry mouth
- Facial edema
- Increased weight
- Acute kidney injury
- Shortness of breath at exertion or at rest
- Hypertension
- Changes in laboratory tests:
  - Increase levels of: creatinine phosphokinase enzyme, AST, ALT, lipase, potassium, alkaline phosphatase, amylase, sodium
  - Decrease levels of: albumin, potassium, sodium, hemoglobin, white blood cells (neutrophils, lymphocytes)

If a side effect appears, if any of the side effects worsens, or when you suffer from a side effect not mentioned in the leaflet, consult the doctor.

Reporting of side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

- Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor!
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month. In any case of doubt, consult the pharmacist who provided the medicine to you.
- Do not store different medicines in the same package.

Storage condition:
- Do not store above 25°C.
- Store in the original bottle to protect from moisture and light.
- Use within 60 days after first opening and no later than the expiry date of the product.
- The package contains desiccant. Do not swallow or remove it from the bottle.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Vitamin E polyethylene glycol succinate, Printed hard hypromellose capsule shell, Hypromellose
Composition of printed white hard hypromellose capsule shell:
Body and Cap
10 mg: Hypromellose, Purified Water, Titanium Dioxide, Potassium Chloride, Carrageenan
25 mg: Hypromellose, Purified Water, Titanium Dioxide, Potassium Chloride, Carrageenan, FD&C Blue 2, Ferric oxide yellow
Ink
10 mg: Shellac Glaze, Iron Oxide Black, Propylene Glycol, Ammonium Hydroxide 28%.
25 mg: White shellac, FD&C Blue 2 Aluminium lake, Ferric oxide yellow, Ferric oxide red, Carnauba wax, Glyceryl monooleate

What the medicine looks like and the content of the package?
10 mg: hard capsule colored white - off white, marked with "SEL 10" in black.
25 mg: hard capsule colored blue, marked with "SEL 25" in black.
Each bottle contains 60 hard capsules and pack in carton box.

Manufacturer: AstraZeneca UK limited, Macclesfield, UK**.**

License Holder and importer: AstraZeneca (Israel) Ltd.,
1 Atirei Yeda St.,
Kfar Saba 4464301.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Koselugo 10 mg - 167-72-36526
Koselugo 25 mg - 167-75-36527

Approved in June 2021 according to the MoH guidelines.

AstraZeneca