Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

CRYSVITA 10 mg
CRYSVITA 20 mg
CRYSVITA 30 mg
Solution for subcutaneous injection

Active ingredient:
Each vial contains 1 ml of burosumab 10 mg, 20 mg, or 30 mg solution, respectively.

Inactive ingredients and allergens in this medicine: see section 2 "Important information about some of this medicine's ingredients" and section 6 "Additional Information".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine.
If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. What is this medicine intended for?

1.1 CRYSVITA is intended for treating adults, and children 6 months and older who have XLH.
XLH (X-linked hypophosphatemia) is a genetic disease. People with this disease have high levels of a hormone called fibroblast growth factor 23 (FGF23) which lowers the amount of phosphate in the blood and may lead to bones that cannot grow and harden properly.
1.2 CRYSVITA is indicated for the treatment of tumor induced osteomalacia (TIO), in cases when the tumor cannot be located or removed, in adult and pediatric patients 2 years of age and older.
Patients with TIO have higher levels of a hormone called FGF23 produced by certain types of tumors. FGF23 lowers the amount of phosphate levels in the blood. The low levels of phosphate may lead to softening of the bones, muscle weakness, tiredness, bone pain and fractures.

Therapeutic group:
CRYSVITA belongs to a group of medicines intended for treating bone diseases and of other medicines that affect bone structure and mineralization (minerals such as calcium and phosphate depositing in bone)

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient (burosumab) or to any of the other ingredients in this medicine (see section 6 "Additional Information").
- You are being treated with oral phosphate medicines or supplements, or with vitamin D medicines or supplements (active vitamin D analogs such as calcitriol, paricalcitol, doxercalciferol, calcifediol) (see the section “Other medicines and CRYSVITA”).
- The level of phosphate in your blood is normal or high (hyperphosphatemia) for your age.
- You have severe kidney disease or kidney failure.

Special warnings about using this medicine
Before starting CRYSVITA, tell your doctor if:

- You are taking phosphate supplements.
- You are taking vitamin D supplements (such as calcitriol). There are vitamin D supplements that you may be able to continue or start taking. Your doctor will guide you.

Children and adolescents:
XLH -The safety and effects of the medicine have not been studied in children with XLH under 6 months of age.
TIO - The safety and effects of the medicine have not been studied in children with TIO under 18 years of age. The safety and efficacy of Crysvita in children 2 years and older with TIO is based on evidence from studies in adults with TIO.

Tests and follow-up:

Before you start taking this medicine, and while you are taking it, your doctor will order a blood test for phosphate. You may also have a vitamin D test.
In case of an overdose, you may be sent for tests of phosphate level, calcium level, and kidney function.

Other medicines and CRYSVITA:
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:
phosphate supplements or active vitamin D. These medicines will increase your level of phosphate further than can be expected from treatment with CRYSVITA alone. This increase may cause hyperphosphatemia which can result in calcium deposits in your kidneys. This is why you are not allowed to take these medicines and dietary supplements together with CRYSVITA.

Pregnancy and breastfeeding:
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, consult your doctor before taking this medicine.
Pregnancy:
- There is no information about use of this medicine in pregnant women.
- CRYSVITA is not recommended in pregnancy because it's effect on your baby is not known.

Breastfeeding:
- It is not known if CRYSVITA passes into breast milk or whether it can affect your baby.

Driving and using machines:
Do not drive or operate dangerous machines. Avoid riding a bike and playing near the road because CRYSVITA could cause dizziness. If you think you are affected by this, tell your doctor.

Important information about some of this medicine's ingredients:
Each vial of CRYSVITA contains 45.91 mg of sorbitol (equivalent to 45.91 mg/ml)

3. How to use this medicine?

Always use this medicine according to your doctor's instructions.
Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
Only your doctor will determine your dose and how you should take this medicine.
The recommended starting dosage is usually:

Treatment of XLH
Children:
- The recommended starting dose in children who weigh less than 10 kg is 1 mg/kg of body weight rounded to the nearest 1 mg, every two weeks.
- The recommended starting dose in children who weigh 10 kg or more is 0.8 mg per kg body weight rounded to the nearest 10 mg, every two weeks. Accordingly, the minimum starting dose is 10 mg and **the maximum starting dose is 90 mg**.

Adults
- The recommended starting dose in adults is 1 mg per kg body weight rounded to the nearest 10 mg, every 4 weeks. The maximum permitted dose is 90 mg.

Your subsequent dosage will be adjusted by your doctor.

Treatment of Tumor induced Osteomalacia (TIO)
Children (two years to less than 18 years)
- The recommended starting dose for pediatrics is 0.4 mg/kg body weight administered every 2 weeks, rounded to the nearest 10mg, up to a maximum dose of 2 mg/kg not to exceed 180mg, administered every 2 weeks.

Adults (18 years and over)

- The recommended starting dose for adults is 0.5 mg/kg body weight administered every 4 weeks, rounded to the nearest 10 mg, up to a maximum dose of 2 mg/kg not to exceed 180mg, administered every 2 weeks

Do not exceed the recommended dose.
This medicine is for injection under the skin.

If you have accidentally taken a higher dose, if you are given an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine at the scheduled time, consult your doctor immediately. The missed dose should be given as soon as possible, and your doctor will re-arrange your next doses accordingly. Even if your health improves, do not stop taking this medicine without consulting your doctor.
Adhere to the treatment as recommended by your doctor.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take a medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>

Like with all medicines, using CRYSVITA may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Allergic reactions:
Stop treatment and consult a doctor immediately if you experience any of the following side effects which may be a sign of an allergic reaction:

- rash and itching all over the body
- shortness of breath
- rapid heartbeat
- perspiration
- hives (urticaria, itchy raised lumps)

Consult your doctor if:

- you get acute skin reactions in the injection area such as redness, rash, swelling, pain, itching, hives (urticaria), or hematoma (bad bruising)
- you get a side effect called restless legs syndrome (irresistible urge to move your legs to stop uncomfortable, painful or odd sensations in the legs especially prior to sleep or at night time)

In XLH

Children:

Very common side effects (may affect more than 1 in 10 children)

- headache
- reactions in the injection area, which may include
  - itching
  - swelling
  - pain
  - prickling
  - wound
  - change or loss of color
  - discomfort
  - hematoma (bad bruise)
  - bleeding
  - stiffness
  - spots
  - hives

  These injection site reactions are usually mild; they occur within a day after the injection and usually get better in 1 to 3 days.

- fever
- vomiting
- pain in extremities
- low vitamin D in your blood
- rash
- infected tooth
- tooth abcess
- toothache
- muscle pain
- dizziness

Adults:

Common side effects (affect 1-10 in 100 users):

- back pain
- headache
- tooth infection
- restless legs syndrome
- vitamin D decreased
- dizziness
- muscle spasms
- constipation
- increase in blood phosphate level

In Tumor Induced Osteomalacia (TIO)

Adults:

Very common side effects (may affect more than 1 in 10 patients)

- back pain
- tooth infection
- restless legs syndrome
- Low vitamin D in your blood
- muscle spasms
- dizziness
- constipation
- injection site reaction
- increase in blood phosphate level
- rash
- headache

Children:

Side effects in children are not known.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects

You can report side effects to the Ministry of Health by following the link "Reporting Side Effects of Drug Treatment" on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by the doctor. Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions:

- Keep refrigerated (2°C-8°C).
- Do not freeze or shake.
- Keep in the original package, protected from light.
- Do not use this medicine if you notice it is cloudy or discolored or if it contains visible particles.
- CRYSVITA vials are for single use. Discard any remaining unused medicine.

6. Additional information

In addition to the active ingredient, this medicine also contains:
d-sorbitol, l-histidine, l-methionine, polysorbate 80, hydrochloric acid, water for injection.

What the medicine looks like and contents of the pack:
CRYSVITA is a solution for injection under the skin. Each pack contains a 1 ml vial of sterile, clear to slightly opalescent, colorless to pale yellow/brown solution for injection.

Registration holder's name and address:
Medison Pharma Ltd.,10 Hashiloach Street, POB 7090, Petah Tikva.

Manufacturer's name and address:
Piramal Healthcare UK Ltd.
Whalton Road, Morpeth, Northumberland NE61 3YA

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Registration number of the medicine in the Ministry of Health's National Drug Registry:
CRYSVITA 10 mg: **164-58-35724-00**
CRYSVITA 20 mg: **164-59-35725-00**
CRYSVITA 30 mg: **164-60-35726-00**

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