ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CRYSVITA 10 mg solution for injection

CRYSVITA 20 mg solution for injection

CRYSVITA 30 mg solution for injection

CRYSVITA 10 mg solution for injection in pre-filled syringe

CRYSVITA 20 mg solution for injection in pre-filled syringe

CRYSVITA 30 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CRYSVITA 10 mg solution for injection

Each vial contains 10 mg of burosumab in 1 ml solution.

CRYSVITA 20 mg solution for injection

Each vial contains 20 mg of burosumab in 1 ml solution.

CRYSVITA 30 mg solution for injection

Each vial contains 30 mg of burosumab in 1 ml solution.

CRYSVITA 10 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 10 mg of burosumab in 0.33 ml solution.

CRYSVITA 20 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 20 mg of burosumab in 0.67 ml solution.

CRYSVITA 30 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 30 mg of burosumab in 1 ml solution.

Burosumab is a recombinant human monoclonal IgG1 antibody for FGF23 and is produced by recombinant DNA technology using Chinese hamster ovary (CHO) mammalian cell culture.

Excipient with known effect

Each vial contains 45.91 mg sorbitol.

Each 10 mg pre-filled syringe contains 15.30 mg sorbitol.
Each 20 mg pre-filled syringe contains 30.61 mg sorbitol.
Each 30 mg pre-filled syringe contains 45.91 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear to slightly opalescent, colourless to pale brownish-yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CRYSVITA is indicated for the treatment of X-linked hypophosphataemia, in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.

CRYSVITA is indicated for the treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in children and adolescents aged 1 to 17 years and in adults.

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the management of patients with metabolic bone diseases.

Posology

Oral phosphate and active vitamin D analogues (e.g. calcitriol) must be discontinued 1 week prior to initiation of treatment. As burosumab however increases active vitamin D synthesis (see section 5.1), patients' requirements for replacement or supplementation with inactive vitamin D should be assessed. Vitamin D replacement or supplementation with inactive forms may be started or continued as per local guidelines under monitoring of serum calcium and phosphate. At initiation, fasting serum phosphate level should be below the reference range for age (see section 4.3).

Serum calcium concentration should be monitored before initiation of treatment, and 1-2 weeks after initiation and dose adjustments in addition to regular monitoring during treatment (see section 4.4).

X-linked hypophosphataemia (XLH)

Dosing in Children and Adolescents with XLH aged 1 to 17 years
The recommended starting dose in children and adolescents aged 1 to 17 years is 0.8 mg/kg of body weight given every two weeks. Doses should be rounded to the nearest 10 mg. The maximum dose is 90 mg.

Fasting serum phosphate should be monitored as appropriate during treatment with burosumab, including after any dose adjustment, to ensure that it remains within the reference range for age. Blood samples for measurement of serum phosphate must always be obtained approximately 2 weeks post dose.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. If fasting serum phosphate is within the reference range for age, the same dose should be maintained.

If fasting serum phosphate is not within the reference range, dose adjustment (dose increase/dose decrease) may be required (see below). Fasting serum phosphate should be re-measured 4 weeks after any dose adjustment. If fasting serum phosphate is within reference range at remeasurement, the new dose should be maintained, otherwise further dose adjustment should be considered.

Dose increase
If fasting serum phosphate is below the reference range for age, the dose may be increased stepwise by 0.4 mg/kg up to a maximum dose of 2.0 mg/kg (maximum dose of 90 mg). Fasting serum phosphate should be measured 4 weeks after dose adjustment. Burosumab should not be adjusted more frequently than every 4 weeks.

Dose decrease
If fasting serum phosphate is above the reference range for age, the next dose should be withheld and the fasting serum phosphate reassessed within 2 weeks. The patient must have fasting serum phosphate below the reference range for age to restart burosumab at half of the previous dose, rounding the amount as described above. If the level remains below the reference range after the first re-initiation dose, the dose can be increased as described under "Dose increase" (above).

Dose Conversion at age 18 years
Children and adolescents aged 1 to 17 years should be treated using the dosing guidance outlined above. At 18 years of age the patient should convert to the adult dose and dosing regimen as outlined below.

Dosing in Adults with XLH
The recommended starting dose in adults is 1.0 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, given every 4 weeks.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. Fasting serum phosphate should be measured 2 weeks after the previous dose of burosumab. If serum phosphate is within the normal range, the same dose should be continued.

Dose decrease
If serum phosphate is above the upper limit of normal range, the next dose should be withheld and the serum phosphate level reassessed within 2 weeks. The patient must have serum phosphate below the normal range before restarting burosumab. Once serum phosphate is below the normal range, treatment may be restarted at half the initial starting dose up to a maximum dose of 40 mg every 4 weeks. Serum phosphate should be reassessed 2 weeks after any change in dose.

If the level remains below the reference range after the first re-initiation dose, the dose can be increased at the discretion of the physician in increments up to 1.0 mg/kg, rounded to the nearest 10 mg (to a maximum (total) administration dose of 90 mg), administered every 4 weeks. Serum phosphate levels should be reassessed 2 weeks after dose adjustment.

Tumour-induced osteomalacia (TIO)
The posology in children and adolescents with TIO aged 1 to 17 years has been determined from pharmacokinetic modelling and simulation (see section 5.2)

Dosing in Children with TIO aged 1 to 12 years

The recommended starting dose for children aged 1 to 12 years is 0.4 mg/kg of body weight, given every 2 weeks. Doses should be rounded to the nearest 10 mg. The maximum dose is 90 mg.

Dose increase
If serum phosphate is below the reference range for age, the dose may be increased in a stepwise manner. Doses should be increased by an initial increment of 0.6 mg/kg with subsequent increments, depending on patient's response to treatment, of 0.5 mg/kg (up to a maximum dose of 2.0 mg/kg), rounding the amount as described above, up to a maximum dose of 90 mg, given every 2 weeks. Fasting serum phosphate should be measured 4 weeks after dose adjustment. Burosumab should not be adjusted more frequently than every 4 weeks.

Dosing in Adolescents with TIO aged 13 to 17 years

The recommended starting dose for adolescents aged 13 to 17 years is 0.3 mg/kg of body weight, given every 2 weeks. Doses should be rounded to the nearest 10 mg. The maximum dose is 180 mg.

Dose increase
If serum phosphate is below the reference range for age, the dose may be increased in a stepwise manner. Doses should be increased by an initial increment of 0.3 mg/kg with subsequent increments of between 0.2 mg/kg – 0.5 mg/kg (dose increment dependent on the patient's serum phosphate response to treatment), rounding the amount as described above, up to a maximum dose of 2.0 mg/kg (maximum dose 180 mg), given every 2 weeks. Fasting serum phosphate should be measured 4 weeks after dose adjustment. Burosumab should not be adjusted more frequently than every 4 weeks.

Dosing in Children and Adolescents with TIO aged 1 to 17 years

Fasting serum phosphate should be monitored as appropriate during treatment with burosumab, including after any dose adjustment, to ensure that it remains within the reference range for age. Blood samples for measurement of serum phosphate must always be obtained approximately 2 weeks post dose.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. If fasting serum phosphate is within the reference range for age, the same dose should be maintained. If fasting serum phosphate is not within the reference range, dose adjustment (dose increase/dose decrease) may be required (see below). Fasting serum phosphate should be re-measured 4 weeks after any dose adjustment. If fasting serum phosphate is within reference range at remeasurement, the new dose should be maintained, otherwise further dose adjustment should be considered.

Dose decrease
If serum phosphate is above the reference range for age, the next dose should be withheld and the fasting serum phosphate level reassessed in 2 weeks. Once serum phosphate is below the reference range for age, treatment may be restarted at half the previous dose in rounding the amount as described above. The fasting serum phosphate level should be assessed 4 weeks after the dose adjustment. If the level remains below the reference range for age after the re-started dose, the dose can be further adjusted.

Dose Conversion at age 18 years
At 18 years of age the patient should convert to the adult dose and dosing regimen as outlined below.

Dosing in Adults with TIO
The recommended starting dose for adults is 0.3 mg/kg body weight, rounded to the nearest 10 mg, given every 4 weeks.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 4 weeks, 2 weeks after each dose for the first 3 months of treatment, and thereafter as appropriate. If serum phosphate is within the reference range, the same dose should be maintained.

Dose increase
If serum phosphate is below the reference range, the dose may be increased in a stepwise manner. Doses should be increased by an initial increment of 0.3 mg/kg, with subsequent increments of between 0.2 mg/kg – 0.5 mg/kg (dose dependent on the patient's response to treatment), up to a maximum dose of 2.0 mg/kg (maximum dose 180 mg), given every 4 weeks. Fasting serum phosphate should be measured 2 weeks after dose adjustment.

For patients whose serum phosphate still remains below the reference range, despite providing the maximum dose every 4 weeks, the previous dose may be divided and given every 2 weeks, with

incremental increases as required, as outlined above, up to a maximum dose of 2.0 mg/kg every 2 weeks (maximum dose 180 mg).

Dose decrease
If serum phosphate is above the reference range, the next dose should be withheld and the fasting serum phosphate level reassessed in 2 weeks. The patient must have serum phosphate below the reference range before restarting burosumab. Once serum phosphate is below the reference range, treatment may be restarted at approximately half the previous dose, administered every:

- 4 weeks (for patients dosed every 4 weeks before dose interruption)
- 2 weeks (for patients dosed every 2 weeks before dose interruption)

Serum phosphate should be reassessed 2 weeks after any change in dose.

If the level remains below the reference range after the re-started dose, the dose can be further adjusted.

Dose Interruption in paediatric and adult patients with TIO
If a patient undergoes treatment of the underlying tumour (i.e., surgical excision or radiation therapy) burosumab treatment should be interrupted.

Following completion of the treatment of the underlying tumour, serum phosphate should be reassessed before reinitiating treatment with burosumab. Burosumab treatment should be resumed at the patient's original starting dose if serum phosphate level remains below the lower end of the normal reference range. Follow the recommended dose adjustment outlined above to maintain serum phosphate level within the normal reference range.

For all patients with TIO, treatment should be discontinued if the treating physician considers that no meaningful improvement in biochemical or clinical markers of response are observed, despite the maximum dose being administered.

All Patients
To decrease the risk for ectopic mineralisation, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range (see section 4.4).

Missed dose
Treatments may be administered 3 days either side of the scheduled treatment date if needed for practical reasons. If a patient misses a dose, burosumab should be resumed as soon as possible at the prescribed dose.

Special populations

Renal impairment
No or limited data are available in patients with renal impairment. Burosumab must not be given to patients with severe or end stage renal disease (see section 4.3).

Paediatric population
X-linked hypophosphataemia (XLH)
The safety and efficacy of burosumab in paediatric patients with XLH aged less than one year have not been established in clinical studies.

Tumour-induced osteomalacia (TIO)
The safety and efficacy of burosumab in paediatric patients with TIO have not been established in clinical studies.

Elderly
Limited data is available in patients over 65 years of age.

Method of administration

For subcutaneous use.

Burosumab should be injected in the upper arm, abdomen, buttock or thigh.

The maximum volume of medicinal product per injection site is 1.5 ml. If more than 1.5 ml is required on a given dosing day, the total volume of medicinal product must be split and administered at two or more different injection sites. Injection sites should be rotated and carefully monitored for signs of potential reactions (see section 4.4).

For handling of burosumab before administration, see section 6.6.

For some patients, self/carer-administration with either the vial and/or the pre-filled syringe may be suitable. Once no immediate dose modifications are anticipated, the administration can be performed by an individual who has been trained properly in injection techniques. The first self-administered dose after drug initiation or dose change should be conducted under the supervision of a healthcare professional. Clinical monitoring of the patient, including monitoring of phosphate levels, must continue as required and as outlined below. A detailed 'Instructions for Use' section intended for the patient is provided at the end of the Package Leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concurrent administration with oral phosphate, active vitamin D analogues (see section 4.5).

Fasting serum phosphate above the normal range for age due to the risk of hyperphosphatemia (see section 4.4).

Patients with severe renal impairment or end stage renal disease.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded within the patient's records.

Ectopic mineralisation

Ectopic mineralisation, as manifested by nephrocalcinosis, has been observed in patients with XLH treated with oral phosphate and active vitamin D analogues; these medicinal products should be stopped at least 1 week prior to initiating burosumab treatment (see section 4.2).

Monitoring for signs and symptoms of nephrocalcinosis, e.g. by renal ultrasonography, is recommended at the start of treatment and every 6 months for the first 12 months of treatment, and annually thereafter. Monitoring of plasma alkaline phosphatase, calcium, parathyroid hormone (PTH) and creatinine is recommended every 6 months (every 3 months for children 1-2 years) or as indicated.

Monitoring of urine calcium and phosphate is suggested every 3 months.

Hyperphosphataemia

Levels of fasting serum phosphate should be monitored due to the risk of hyperphosphatemia. To decrease the risk for ectopic mineralisation, it is recommended that fasting serum phosphate is targeted

in the lower end of the normal reference range for age. Dose interruption and/or dose reduction may be required (see section 4.2). Periodic measurement of post prandial serum phosphate is advised.

To prevent hyperphosphataemia, treatment with burosumab should be interrupted in patients with tumour-induced osteomalacia who undergo treatment of the underlying tumour. Burosumab treatment should be reinitiated only if the patient's serum phosphate level remains below the lower end of the normal reference range (see Section 4.2).

Hypercalcaemia and hyperparathyroidism

Increases in serum calcium or parathyroid hormone have been reported in patients treated with burosumab. Factors such as hyperparathyroidism, prolonged immobilisation, dehydration, hypervitaminosis D or renal impairment may increase the risk of hypercalcaemia. In particular, severe hypercalcaemia has been reported in subjects with tertiary hyperparathyroidism. Serum calcium and parathyroid hormone levels should be monitored before and during burosumab treatment (see section 4.2). In patients with moderate to severe hypercalcaemia (>3 mmol/l), burosumab should not be administered until hypercalcaemia is adequately treated.

Injection site reactions

Administration of burosumab may result in local injection site reactions. Administration should be interrupted in any patient experiencing severe injection site reactions (see section 4.8) and appropriate medical therapy administered.

Hypersensitivity

Therapeutic proteins, such as burosumab, may be associated with hypersensitivity reactions. In Clinical Studies, mild or moderate hypersensitivity reactions (e.g., rash, injection site rash) were observed (see section 4.8). Burosumab must be discontinued if serious hypersensitivity reactions occur and appropriate medical treatment should be initiated.

Excipient with known effect

CRYSVITA solution for injection in vials
This medicine contains 45.91 mg of sorbitol in each vial which is equivalent to 45.91 mg/ml. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

This medicine contains 0.5 mg of polysorbate 80 in each vial which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions.

CRYSVITA 10 mg solution for injection in pre-filled syringe
This medicine contains 15.30 mg of sorbitol in each pre-filled syringe which is equivalent to 45.91 mg/ml. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

This medicine contains 0.165 mg of polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions.

CRYSVITA 20 mg solution for injection in pre-filled syringe
This medicine contains 30.61 mg of sorbitol in each pre-filled syringe which is equivalent to 45.91 mg/ml. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

This medicine contains 0.335 mg of polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions.

CRYSVITA 30 mg solution for injection in pre-filled syringe
This medicine contains 45.91 mg of sorbitol in each pre-filled syringe which is equivalent to 45.91 mg/ml. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

This medicine contains 0.5 mg of polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of burosumab with oral phosphate and active vitamin D analogues is contraindicated as it may cause an increased risk of hyperphosphatemia and hypercalcaemia (see section 4.3).

Caution should be exercised when combining burosumab with calcimimetic medicinal products (i.e. agents that mimic the effect of calcium on tissues by activating the calcium receptor). Co-administration of these medicinal products has not been studied in clinical trials, therefore close monitoring of serum calcium levels is recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with burosumab and for at least 14 weeks after stopping treatment.

Pregnancy

There are no or limited amount of data from the use of burosumab in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Burosumab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether burosumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to low concentrations soon afterwards. Consequently a risk to the breast-fed newborn cannot be excluded during this short period. Afterwards, use of burosumab could be considered during breast-feeding only if clinically needed.

Fertility

Studies in animals have shown effects on male reproductive organs (see section 5.3). There are no clinical data available on the effect of burosumab on human fertility. No specific fertility studies in animals with burosumab were conducted.

4.7 Effects on ability to drive and use machines

Burosumab has a minor influence on the ability to drive and use machines. Dizziness may occur following administration of burosumab.

4.8 Undesirable effects

Summary of the safety profile

The most common (> 10%) adverse drug reactions reported in paediatric patients with XLH during clinical trials based on completed long term studies up to a maximum exposure to burosumab of 214 weeks (with variable period of exposure across the safety population) were: cough (55%), injection site reactions (54%), pyrexia (50%), headache (48%), vomiting (46%), pain in extremity (42%), tooth

abscess (40%), vitamin D decreased (28%), diarrhoea (27%), nausea (21%), rash (20%), constipation (12%), and dental caries (11%).

The most common (> 10%) adverse drug reactions reported during clinical trials in adult patients with XLH or adult patients with TIO, based on completed long term studies up to a maximum exposure to burosumab of 300 weeks (with variable period of exposure across the safety population), were: back pain (30%), injection site reaction (29%), headache (28%), tooth infection (28%), vitamin D decrease (28%), muscle spasms (18%), restless legs syndrome (16%), dizziness (16%) and constipation (13%) (see section 4.4 and 'Description of selected adverse reactions' below).

Tabulated lists of adverse reactions

The frequencies of adverse reactions are listed in Table 1 (XLH, paediatric patients), and Table 2 (XLH and TIO adult patients).

The adverse reactions are presented by system organ class and frequency categories, defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported in paediatric patients 1 to 17 years of age with XLH, observed from clinical trials (N=120) and post-marketing

MedDRA System Organ Class	Frequency category	Adverse reaction
Infections and infestations	Very common	Tooth abscess[1]
Endocrine disorders	Not known	Hyperparathyroidism[2] (see section 4.4)
Metabolism and nutrition disorders	Uncommon	Hypercalcaemia[3,4] (see section 4.4)
	Not known	Hypercalciuria[5]
Respiratory, thoracic and mediastinal disorders	Very common	Cough[6]
Nervous system disorders	Very common	Headache
	Very common	Dizziness[7]
Gastrointestinal disorders	Very common	Vomiting Nausea Diarrhoea Constipation Dental Caries
Skin and subcutaneous tissue disorders	Very common	Rash[8]
	Common	Urticaria[4]
Musculoskeletal and connective tissue disorders	Very common	Myalgia
		Pain in extremity
General disorders and administration site conditions	Very common	Injection site reaction[9] Pyrexia
Investigations	Very common	Vitamin D decreased[10]
	Common	Blood parathyroid hormone increased (see section 4.4)[4]
	Not known	Blood phosphorus increased[11]

[1]Tooth abscess includes: *Tooth abscess, Tooth infection and Toothache*
[2]Hyperparathyroidism includes: *Hyperparathyroidism, Hyperparathyroidism secondary and Hyperparathyroidism tertiary*
[3]Hypercalcaemia includes: *Hypercalcaemia and Blood calcium increased*
[4]Seen in clinical trials, confirmed by post-marketing experience
[5]Hypercalciuria includes: *Hypercalciuria and Urine calcium increased*
[6]Cough includes: *Cough, and Productive cough*
[7]Dizziness includes: *Dizziness, and Dizziness exertional*
[8]Rash includes: *Rash, Rash erythematous, Rash generalised, Rash pruritic, Rash maculo-papular, and Rash pustular*

[9]Injection site reaction includes: *Injection site reaction, Injection site erythema, Injection site pruritus, Injection site swelling, Injection site pain, Injection site rash, Injection site bruising, Injection site discolouration, Injection site discomfort, Injection site haematoma, Injection site haemorrhage, Injection site induration, Injection site macule, and Injection site urticaria*
[10]Vitamin D decreased includes: *Vitamin D deficiency, Blood 25-hydroxycholecalciferol decreased, and Vitamin D decreased*
[11]Blood phosphorus increased includes: *Blood phosphorus increased and Hyperphosphataemia*

Table 2: Adverse reactions observed from clinical trials in adults (N=203) with XLH (N=176) and TIO (N=27) and post-marketing

MedDRA System Organ Class	Frequency Category	Adverse Reaction
Infections and infestations	Very common	Tooth infection[1]
Endocrine disorders	Common	Hyperparathyroidism[2,3] (see section 4.4)
Metabolism and nutrition disorders	Common	Hypercalcaemia[3, 4] (see section 4.4) Hypercalciuria[5,6]
Nervous system disorders	Very common	Headache[7]
	Very common	Dizziness
	Very common	Restless legs syndrome
Gastrointestinal disorders	Very common	Constipation
Skin and subcutaneous tissue disorders	Common	Rash[8] Urticaria[5]
Musculoskeletal and connective tissue disorders	Very common	Back pain
	Very common	Muscle spasms
General disorders and administration site conditions	Very common	Injection site reaction[9]
Investigations	Very common	Vitamin D decreased[10]
	Common	Blood phosphorus increased[11] Blood parathyroid hormone increased (see section 4.4)[12]

[1] Tooth infection includes: *tooth abscess, tooth infection and toothache*
[2]Hyperparathyroidism includes: *Hyperparathyroidism, Hyperparathyroidism secondary and Hyperparathyroidism tertiary*
[3]Hypercalcaemia includes: *Hypercalcaemia and Blood calcium increased*
[4]Seen in clinical trials with TIO, confirmed by post-marketing experience
[5]Seen in clinical trials with XLH, confirmed by post-marketing experience
[6]Hypercalciuria includes: *Hypercalciuria and Urine calcium increased*
[7]Headache includes*: headache and head discomfort*
[8]Rash includes: *rash, rash papular and rash erythematous*
[9]Injection site reaction includes: *Injection site reaction, Injection site erythema, Injection site pruritus, Injection site swelling, Injection site pain, Injection site rash, Injection site bruising, Injection site discolouration, Injection site discomfort, Injection site haematoma, Injection site haemorrhage, Injection site induration, Injection site macule, Injection site urticaria, Injection site hypersensitivity and Injection site inflammation*
[10]Vitamin D decreased includes: *Vitamin D deficiency, Blood 25-hydroxycholecalciferol decreased, and Vitamin D decreased*
[11]Blood phosphorus increased includes: *blood phosphorus increased, and hyperphosphataemia*
[12]Seen in clinical trials with XLH and TIO, confirmed by post-marketing experience

Description of selected adverse reactions

Injection site reactions
Paediatric patients with XLH:
Local reactions (e.g. injection site urticaria, erythema, rash, swelling, bruising, pain, pruritus, and haematoma) have occurred at the site of injection. In the paediatric studies, approximately 54% of the patients had an injection site reaction, based on data from clinical studies. The injection site reactions were generally mild in severity, occurred within 1 day of medicinal product administration, mostly lasted 1 to 3 days, required no treatment, and resolved in almost all instances.

Adult patients with XLH or TIO:
Injection site reactions were generally mild in severity, required no treatment, and resolved in almost all instances.
In patients with XLH, in the placebo-controlled treatment period of Study UX023-CL303, the frequency of injection site reactions was 12% in both burosumab and placebo treatment groups (injection site reaction, erythema, rash, bruising, pain, pruritis and haematoma).
In patients with TIO, the frequency of injection site reactions based on data from completed long term clinical studies was 22% (injection site reaction, injection site pain and injection site swelling).

Hypersensitivity
Paediatric patients with XLH:
Hypersensitivity reactions (e.g.: injection site reactions, rash, urticaria, swelling face, dermatitis, etc) were reported in 39% of paediatric patients, based on data from clinical studies. All reported reactions were mild or moderate in severity.

Adult patients with XLH or TIO:
Hypersensitivity reactions were mild or moderate in severity.
In XLH patients, in the placebo-controlled treatment period of Study UX023-CL303, the incidence of potential hypersensitivity reactions was similar (6%) in the burosumab treated and placebo treated adults.
In patients with TIO, the frequency of hypersensitivity reactions (rash, drug eruption, and hypersensitivity) based on data from completed long term clinical studies was 30%.

Vitamin D Decreased
Paediatric patients with XLH:
Reduced serum 25 hydroxy-vitamin D has been observed following initiation of burosumab treatment in approximately 8% of paediatric patients, possibly due to increased conversion to activated 1,25 dihydroxy-vitamin D. Supplementation with inactive vitamin D was successful in restoring plasma levels to normal.

Hyperphosphataemia
Adult patients with XLH or TIO:
In XLH patients, in the placebo-controlled treatment period of Study UX023-CL303 in the burosumab group, 9 subjects (13.2%) had high serum phosphate at least once; 5 of these 9 required protocol-specified dose reduction(s). After initiation of burosumab in the open-label Treatment Continuation Period, 8 subjects (12.1%) in the placebo→burosumab group had high serum phosphate levels. Four of these 8 subjects required protocol-specified dose reduction(s). The dose for all patients meeting the protocol-specified criteria was reduced by 50%. A single patient (1%) required a second dose reduction for continued hyperphosphataemia.
In patients with TIO, based on data from completed long term clinical studies, 11% of patients experienced events of hyperphosphataemia, which were managed with dose reduction.

Restless legs syndrome
Adult patients with XLH or TIO:
In XLH patients, in the placebo-controlled treatment period of Study UX023-CL303 approximately 12% of the burosumab treatment group and 8% in the placebo group had a worsening of baseline restless legs syndrome or new onset restless legs syndrome of mild to moderate severity.
In patients with TIO, based on data from completed long term clinical studies, 11% of patients experienced events of restless legs syndrome of mild to moderate severity.

Immunogenicity:
Paediatric patients with XLH:
Overall, the incidence of anti-drug antibodies (ADA) to burosumab in paediatric patients administered burosumab, based on data from clinical studies was 10%. The incidence of neutralising ADA in paediatric patients was 3%. No adverse events, loss of efficacy, or changes in the pharmacokinetic profile of burosumab were associated with these findings.

Adult patients with XLH and TIO:
The incidence of patients that tested positive for ADAs to burosumab in adult clinical studies with XLH or TIO, based on data from completed long term clinical studies was 15%. None of these patients developed neutralising ADA. No adverse events, loss of efficacy, or changes in the pharmacokinetic profile of burosumab were associated with these findings.

Adverse reactions in paediatric patients with TIO
No data are available in paediatric patients with TIO (see section 5.1).

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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose of burosumab. Burosumab has been administered in paediatric XLH clinical trials without dose limiting toxicity using doses up to 2.0 mg/kg body weight with a maximal dose of 90 mg every two weeks. In adult XLH clinical trials no dose limiting toxicity has been observed using doses up to 1.0 mg/kg or a maximal total dose of 128 mg every 4 weeks. In adult TIO clinical trials no dose limiting toxicity has been observed using doses up to 2.0 mg/kg or a maximal total dose of 184 mg every 4 weeks.

Management

In case of overdose, it is recommended to stop burosumab and to monitor biochemical response.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of bone diseases, other drugs affecting bone structure and mineralisation, ATC code: M05BX05.

Mechanism of action

Burosumab is a recombinant human monoclonal antibody (IgG1) that binds to and inhibits the activity of fibroblast growth factor 23 (FGF23). By inhibiting FGF23, burosumab increases tubular reabsorption of phosphate from the kidney and increases serum concentration of 1,25 dihydroxy-Vitamin D.

Clinical efficacy in paediatric patients with XLH

Study UX023-CL301
In paediatric study UX023-CL301 61 patients aged 1 to 12 years (56% female; 44% male, Age at first dose, mean (SD): 6.3 (3.31) years) were randomised to burosumab (n=29) or active control (n=32; oral phosphate and active vitamin D). At entry to the study all patients had to have had a minimum of 6 months treatment of oral phosphate and active vitamin D. All patients had radiographic evidence of bone disease due to XLH (Rickets severity score ≥ 2). Burosumab was started at a dose of 0.8 mg/kg every 2 weeks and increased to 1.2 mg/kg if there was inadequate response, as measured by fasting serum phosphate. Those patients randomised to active control group received multiple daily doses of oral phosphate and active vitamin D.

The primary efficacy endpoint was the change in severity of rickets at Week 40, as assessed by the RGI-C (Radiographic Global Impression of change) score, compared between the burosumab and active control groups.

The RGI-C is a relative rating scale that compares a patient's rickets before and after treatment utilising a 7-point ordinal scale to evaluate change in the same abnormalities rated in the RSS (as described below). Scores range from -3 (indicating severe worsening of rickets) to +3 (indicating complete healing of rickets).

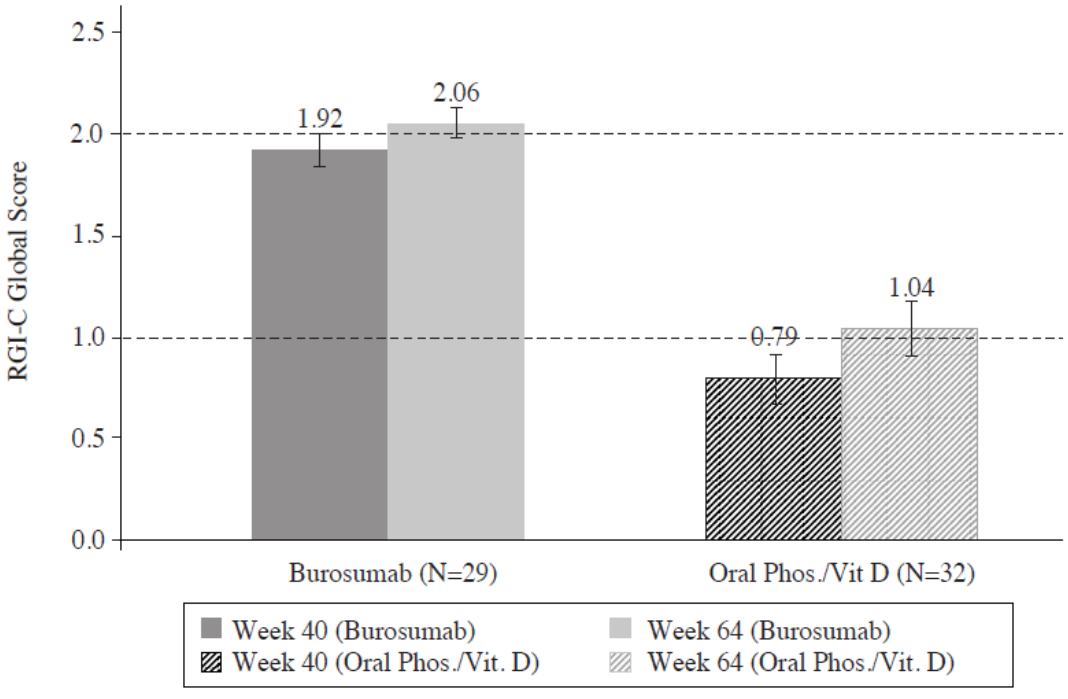
The severity of paediatric rickets was measured using the RSS, a radiographic scoring method based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected. In the UX023-CL301 study, the RSS was scored using a predefined scale looking at specific abnormalities in the wrists and knees.

All patients (n=61) completed the 64 Week randomised Treatment Period. No patients had dose reductions and 8 (28%) of burosumab-treated patients received dose escalations to 1.2 mg/kg. A total of 51 patients entered the Treatment Extension Period, 26 patients in the active control→burosumab group and 25 patients in the burosumab→burosumab group, and were treated with burosumab up to 124 Weeks.

Primary Efficacy Results

Greater healing of rickets at Week 40 was seen with burosumab treatment compared to active control and this effect was maintained at week 64, as shown in Figure 1. These results were sustained to Week 88 (n=21).

Figure 1: RGI-C Global Score (Mean ± SE) – Primary Efficacy Endpoint at Week 40 and 64 (Full Analysis Set)



Week 40 (Primary Analysis)
LS mean difference: +1.14 (95% CI: 0.83, 1.45), p < 0.0001, ANCOVA model

Week 64
LS mean difference: +1.02 (95% CI: +0.72, +1.33), p < 0.0001, GEE model

Secondary Efficacy Results

Key Secondary efficacy endpoint results for Weeks 40 and 64 are presented in Table 3. These results were sustained to Week 88 (n=21).

Table 3: Secondary Efficacy Endpoint Results

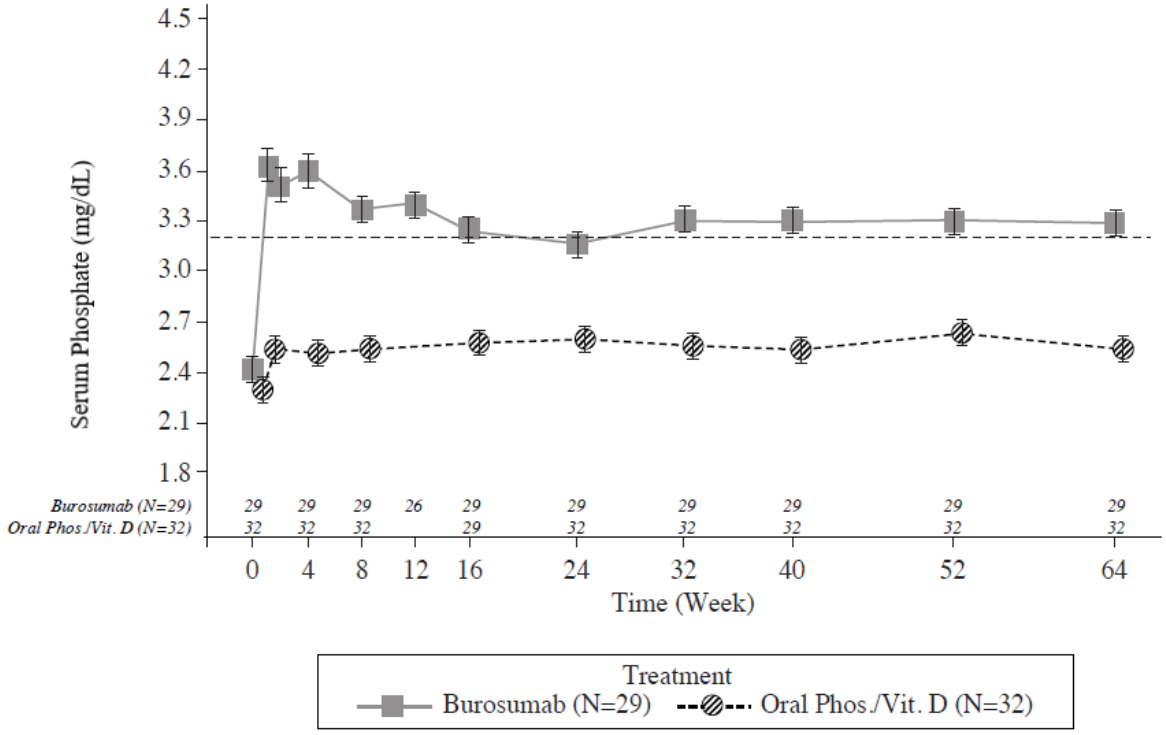
Endpoint	Week	Active Control LS Mean (SE)	Burosumab LS Mean (SE)	Difference (burosumab – active control)
Lower Limb Deformity; assessed by RGI-C (GEE model)	40	+0.22 (0.080)	+0.62 (0.153)	+0.40 [95% CI: 0.07, 0.72] p = 0.0162
	64	+0.29 (0.119)	+1.25 (0.170)	+0.97 [95% CI: +0.57, +1.37] p < 0.0001
Height; Z-score	Baseline	-2.05 (0.87)	-2.32 (1.17)	
	40 [a]	+0.03 (0.031)	+0.16 (0.052)	+0.12 [95% CI: 0.01, 0.24] p = 0.0408
	64 [b]	+0.02 (0.035)	+0.17 (0.066)	+0.14 [95% CI: 0.00, 0.29] p = 0.0490
Rickets severity, RSS total Score	Baseline	3.19 (1.141)	3.17 (0.975)	
	40 [a]	-0.72 (0.162)	-2.08 (0.104)	-1.34 [95% CI: 1.74, -0.94] p < 0.0001
	64 [b]	-1.01 (0.151)	-2.23 (0.117)	-1.21 [95% CI: -1.59, -0.83] p < 0.0001
Serum ALP (U/L)	Baseline	523 (154)	511 (125)	
	40 [a]	489 (189)	381 (99)	-97 [95% CI: -138, -56] p < 0.0001
	64 [b]	495 (182)	337 (86)	-147 [95% CI: -192, -102] p < 0.0001
Six Minute Walk Test (m)	Baseline	450 (106)	385 (86)	
	40 [a]	+4 (14)	+47 (16)	+43 [95% CI: -0.3, 87] p = 0.0514
	64 [b]	+29 (17)	+75 (13)	+46 [95% CI: 2, 89] p = 0.0399

a: the change from Baseline to Week 40 from ANCOVA model.
b: the change from Baseline to Week 64 from GEE Model.

Serum Phosphate
At each study visit at which serum phosphate was assessed in both groups, changes in serum phosphate from Baseline were larger in the burosumab group compared with the active control group ($p < 0.0001$; GEE model) (Figure 2).

Figure 2: Serum Phosphate Concentration and Change from Baseline (mg/dL) (Mean ± SE) by Treatment Group (PD Analysis Set)

Note: Dashed line in figure indicates the lower limit of the normal serum phosphate reference range, 3.2 mg/dL (1.03 mmol/L)



During the Treatment Extension Period (Week 66 to Week 140), prolonger burosumab treatment in both groups (burosumab→burosumab (n=25) and active control→burosumab (n=26) the results were sustained.

Study UX023-CL201

In paediatric Study UX023-CL201, 52 paediatric patients aged 5 to 12 years (mean 8.5 years; SD 1.87) with XLH were treated for an initial period of 64 Weeks and dosed either every two weeks (Q2W) or every four weeks (Q4W). This was followed by two extension periods with dosing Q2W for all patients; the first period up to 96 Weeks (total 160 Weeks) and a further period of up to 56 Weeks for safety analysis.

Nearly all patients had radiographic evidence of rickets at baseline and had received prior oral phosphate and vitamin D analogues for a mean (SD) duration of 7 (2.4) years. This conventional therapy was discontinued 2-4 weeks prior to burosumab initiation. The burosumab dose was adjusted to target a fasting serum phosphate concentration of 3.50 to 5.02 mg/dL (1.13 to 1.62 mmol/L). In the first 64 Weeks, 26 of 52 patients received burosumab Q4W. Twenty six of 52 patients received burosumab Q2W at an average dose (min, max) of 0.73 (0.3, 1.5), 0.98 (0.4, 2.0) and 1.04 (0.4, 2.0) mg/kg at weeks 16, 40 and 64 respectively, and up to a maximum dose of 2.0 mg/kg.

Burosumab increased serum phosphate concentration and increased TmP/GFR. In the Q2W group, mean (SD) serum phosphate concentration increased from 2.38 (0.405) mg/dL (0.77 (0.131) mmol/L) at baseline), to 3.3 (0.396) mg/dL (1.07 (0.128) mmol/L) at Week 40 and was maintained to Week 64 at 3.35 (0.445) mg/dL (1.08 (0.144) mmol/L). The increased serum phosphate levels were sustained to Week 160 (n=52).

Alkaline phosphatase activity

Mean (SD) serum total alkaline phosphatase (ALP) activity was 459 (105) U/L at Baseline and decreased to 369 (76) U/L at Week 64 (-19.6%, $p < 0.0001$); decreases were similar in the two dose groups. Overall, decreased serum ALP levels were sustained to Week 160.

Bone-derived serum alkaline phosphatase (BALP) content was 165 (52) µg/L [mean (SD)] at Baseline and 115 (31) µg/L at Week 64 (mean change: -28.5%); decreases were similar in the two dose groups. Overall, decreased serum BALP levels were sustained to Week 160.

In Study UX023-CL201 the severity of paediatric rickets was measured using the RSS, as described above, which was scored using a predefined scale looking at specific abnormalities in the wrists and knees. As a complement to the RSS assessment, the RGI-C rating scale was used. Results are summarised in Table 4.

Table 4: Rickets Response in Children 5-12 Years Receiving Burosumab in Study UX023-CL201

Endpoint	**Duration of Burosumab (week)**	**Effect Size**	
		Q2W (N=26)	**Q4W (N=26)**
RSS Total Score Baseline Mean (SD) LS Mean change (SE) from baseline in total score[a] (reduced RSS score indicates improvement in rickets severity)	40	1.92 (1.2) -1.06 (0.100) (p < 0.0001)	1.67 (1.0) -0.73 (0.100) (p < 0.0001)
	64	-1.00 (0.1) (p < 0.0001)	-0.84 (0.1) (p < 0.0001)
RGI-C Global Score LS Mean score (SE)[a] (positive indicates healing)	40	+1.66 (0.1) (p < 0.0001)	+1.47 (0.1) (p < 0.0001)
	64	+1.56 (0.1) (p < 0.0001)	+1.58 (0.1) (p < 0.0001)

a) The estimates of LS means and p-values are from the generalized estimation equation model accounting for baseline RSS, visits and regimen and its interaction.

Study UX023-CL205

In paediatric Study UX023-CL205, burosumab was evaluated in 13 XLH patients, aged 1 to 4 years (mean 2.9 years; SD 1.1) for a Treatment Period of 64 Weeks. Twelve patients continued to receive burosumab for an additional 96 Weeks during the Extension Period, for a maximum duration of 160 Weeks. All patients had radiographic evidence of rickets at baseline and 12 patients had received oral phosphate and vitamin D analogues for a mean (SD) duration of 16.7 (14.4) months. This conventional therapy was discontinued 2-6 weeks prior to burosumab initiation. Patients received burosumab at a dose of 0.8 mg/kg every two weeks.

Mean (SD) fasting serum phosphate concentration increased from 2.51 (0.284) mg/dL (0.81 (0.092) mmol/L) at baseline to 3.47 (0.485) mg/dL (1.12 (0.158) mmol/L) at Week 40 and the increased levels were sustained to Week 160.

Serum alkaline phosphatase activity

Mean (SD) serum total alkaline phosphatase activity was 549 (193.8) U/L at baseline and decreased to 335 (87.6) U/L at Week 40 (mean change: -36.3%). Decreased serum total alkaline phosphatase activity was sustained with long-term treatment to Week 160.

Rickets Severity Score (RSS)

Mean total RSS improved from 2.92 (1.367) at baseline to 1.19 (0.522) at Week 40, corresponding to a change from baseline in LS mean (SE) change of -1.73 (0.132) (p <0.0001). The RSS was sustained to Weeks 64, 112 and 160.

Radiographic Global Impression of Change (RGI-C)

After 40 weeks of treatment with burosumab, the LS mean (SE) RGI-C Global score was +2.21 (0.071) in all 13 patients (p < 0.0001) demonstrating healing of rickets. All 13 patients were considered RGI-C responders as defined by RGI-C global score ≥ +2.0. The RGI-C global score was sustained to Weeks 64, 112, and 160.

The European Medicines Agency has deferred the obligation to submit the results of studies with burosumab in one or more subsets of the paediatric population in treatment of X-linked hypophosphataemia. See 4.2 for information on paediatric use.

Clinical efficacy in adults with XLH

Study UX023-CL303
Study UX023-CL303 is a randomised, double-blind, placebo-controlled study in 134 adult XLH patients. The study comprised of a 24-week placebo-controlled treatment phase followed by a 24-week open-label period where all patients received burosumab. Oral phosphate and active vitamin D analogues were not allowed during the study. Burosumab was administered at a dose of 1 mg/kg every 4 weeks. The primary endpoint of this study was normalisation of serum phosphate across the 24-week double-blind period. Key secondary endpoints included worst pain as measured by the Brief Pain Inventory (BPI) scale and stiffness and physical function as measured by the WOMAC (Western Ontario and McMaster Universities Osteoarthritis) Index. Exploratory endpoints included fracture and pseudofracture healing, enthesopathy, 6 Minute Walk Test, BPI Pain interference, Brief Fatigue Inventory (BFI) worst fatigue and BFI global fatigue score.

At study entry, the mean age of patients was 40 years (range 19 to 66 years) and 35% were male. 66 patients were randomised to placebo treatment and 68 to burosumab treatment; at baseline, mean (SD) serum phosphate was 0.62 (0.10) mmol/L [1.92 (0.32) mg/dL] and 0.66 (0.1 mmol/L) [2.03 (0.30) mg/dL] in the placebo and burosumab groups respectively.

For the primary efficacy endpoint, a greater proportion of patients treated with burosumab achieved a mean serum phosphate level above the lower limit of normal (LLN) compared to the placebo group through week 24 (Table 5 and Figure 3).

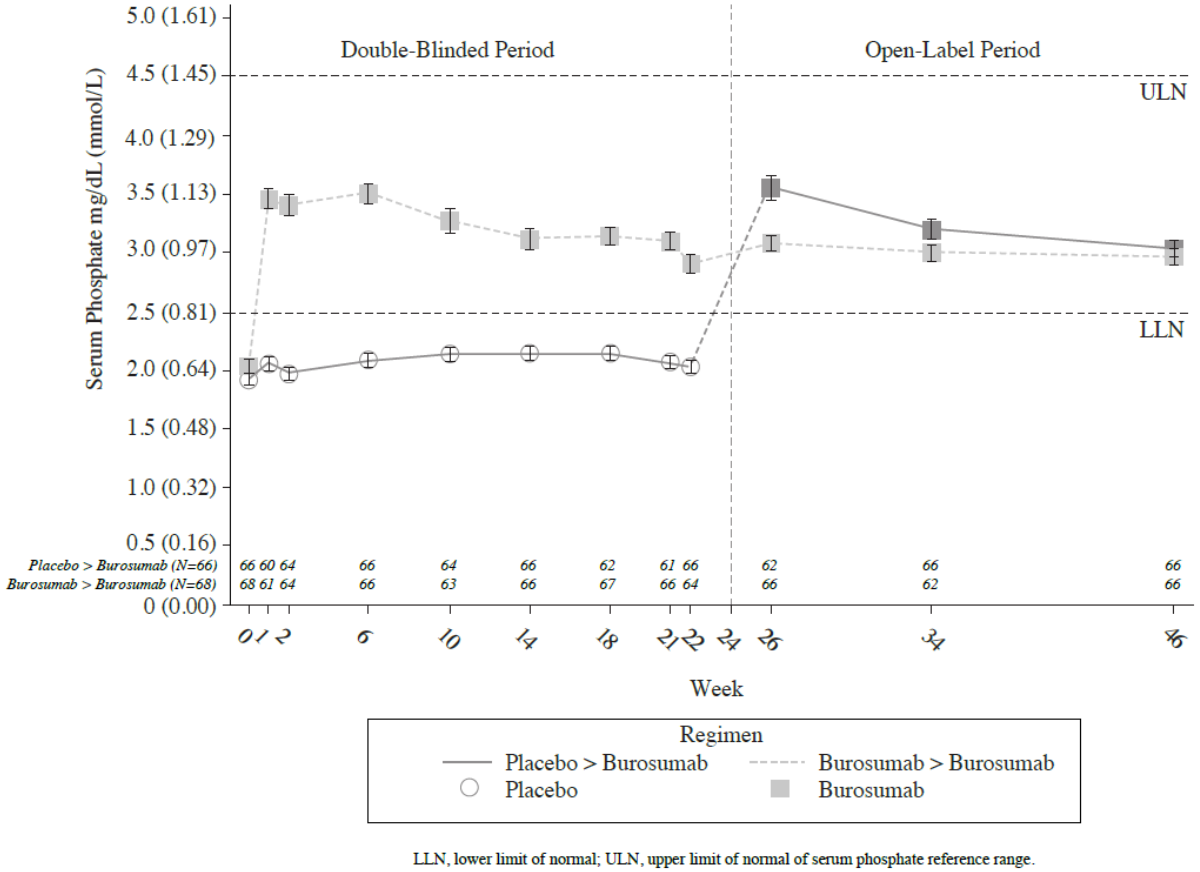
Table 5: Proportion of Adult Patients Achieving Mean Serum Phosphate Levels Above the LLN at the Midpoint of the Dose Interval in Study UX023-CL303 (Double-Blind Period)

	Placebo (N = 66)	**Burosumab (N = 68)**
Achieved Mean Serum Phosphate > LLN Across Midpoints of Dose Intervals Through Week 24 - n (%)	7.6% (5/66)	94.1% (64/68)
95% CI	(3.3, 16.5)	(85.8, 97.7)
p-value[a]		< 0.0001

The 95% CIs are calculated using the Wilson score method.

[a] P-value is from Cochran-Mantel-Haenszel (CMH) testing for association between achieving the primary endpoint and treatment group, adjusting for randomisation stratifications.

Figure 3: Mean (± SE) Serum Phosphate Peak Concentrations (mg/dL [mmol/L])



LLN, lower limit of normal; ULN, upper limit of normal of serum phosphate reference range.

Patient reported pain, physical function and stiffness
Change from baseline at Week 24 showed a larger difference for burosumab relative to placebo in patient reported pain (BPI), physical function (WOMAC Index) and stiffness (WOMAC Index). The mean (SE) difference between treatment groups (burosumab-placebo) reach statistical significance for WOMAC stiffness at Week 24. Details are shown in Table 6.

Table 6: Patient reported pain, physical function and stiffness score changes from baseline to Week 24 and analysis of difference at Week 24

	Placebo	**Burosumab**
	N=66	N=68
BPI worst pain[a]		
LS Mean (SE) change from Baseline	-0.32 (0.2)	-0.79 (0.2)
[95% CIs]	[-0.76, 0.11]	[-1.20, -0.37]
LS Mean (SE) Difference (Burosumab-Placebo)	-0.5 (0.28)	
p-value	0.0919[c]	
WOMAC Index physical function[b]		
LS Mean (SE) change from Baseline	+1.79 (2.7)	-3.11 (2.6)
[95% CIs]	[-3.54, 7.13]	[-8.12, 1.89]
LS Mean (SE) Difference	-4.9 (2.5)	
p-value	0.0478[c]	

	Placebo	Burosumab
	N=66	N=68
WOMAC Index stiffness[b]		
LS Mean (SE) change from Baseline	+0.25 (3.1)	-7.87 (3.0)
[95% CIs]	[5.89, 6.39]	[-13.82, -1.91]
LS Mean (SE) Difference (Burosumab-Placebo)	-8.12 (3.2)	
p-value	0.0122	

[a] BPI worst pain item score ranges from 0 (no pain) to 10 (pain as bad as you can imagine)
[b] WOMAC Index physical function and stiffness domains range from 0 (best health) to 100 (worst health)
[c] Not significant following Hochberg adjustment

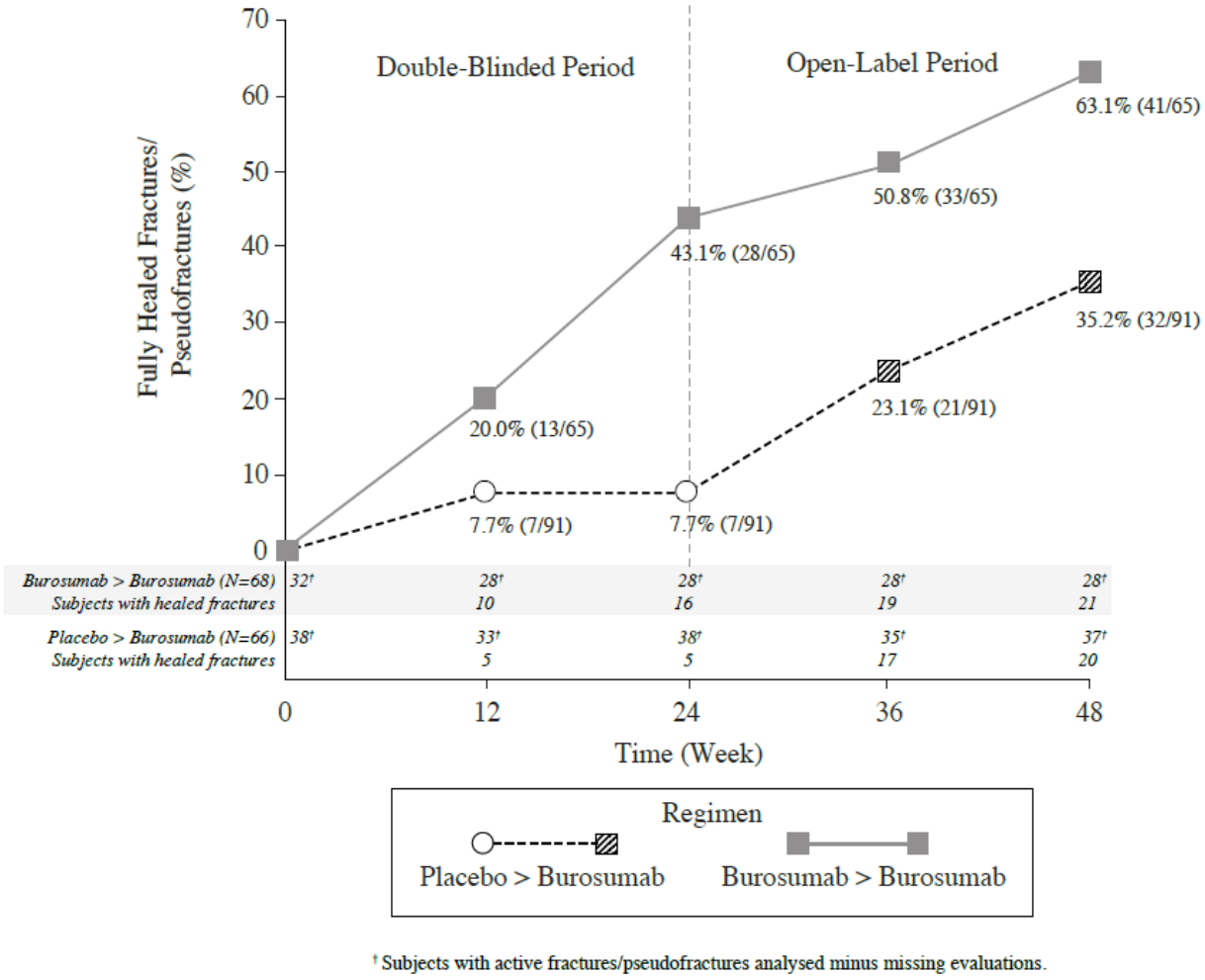
6 Minute Walk Test
This exercise test was conducted in all patients at Baseline, Week 12, 24, 36 and 48 (LS mean difference in change from baseline, burosumab → placebo; Table 7). Improvements continued through to Week 48 where distance walked increased from 357 m at baseline to 393 m at Week 48. Patients who crossed over from placebo to burosumab achieved similar improvements after 24 weeks of treatment.

Table 7: 6 Minute Walk distance (SD) Baseline and Week 24; Least Squares Mean Difference (SE)

6 MWT, m(SD)	**Placebo**	**Burosumab**
Baseline	367 (103)	357 (109)
Week 24	369 (103)	382 (108)
LS Mean difference burosumab-placebo (SE)	20 (7.7)	

Radiographic Evaluation of Fractures and Pseudofractures
In Study UX023-CL303, a skeletal survey was conducted at baseline to identify osteomalacia-related fractures and pseudofractures. There were 52% (70/134) of patients who had either active fractures (12%, 16/134) or active pseudofractures (47%, 63/134) at baseline. Following burosumab treatment more patients showed healing of fractures and pseudofractures compared to the placebo group (Figure 4). During the placebo-controlled treatment period up to week 24, a total of 6 new fractures or pseudofractures appeared in 68 patients receiving burosumab compared to 8 new abnormalities in 66 patients receiving placebo. Of the number of new fractures developed prior to week 48 most (10/18) were healed or partially healed at the end of the study.

Figure 4: Percentage of Healed Active Fractures and Pseudofractures in Study UX023-CL303



† Subjects with active fractures/pseudofractures analysed minus missing evaluations.

At Baseline, the mean (SD) total calcaneal enthesopathy burden (sum of superior and inferior calcaneal spurs) was 5.64 (3.12) cm in the burosumab group and 5.54 (3.1) cm in the placebo group. At Week 24, the mean (SD) total calcaneal enthesopathy burden was 5.90 (3.56) cm in the burosumab→burosumab group and 4.07 (2.38) cm in the placebo→burosumab group.

For the exploratory endpoints of BPI Pain interference, BFI worst fatigue and BFI global fatigue score no meaningful difference were observed between treatment arms.

Bone Histomorphometry in Adults

Study UX023-CL304

Study UX023-CL304 is a 48-week, open-label, single-arm study in adult XLH patients to assess the effects of burosumab on improvement of osteomalacia as determined by histologic and histomorphometric evaluation of iliac crest bone biopsies. Patients received 1.0 mg/kg burosumab every 4 weeks. Oral phosphate and active vitamin D analogues were not allowed during the study.

14 patients were enrolled, and at study entry, the mean age of patients was 40 years (range 25 to 52 years) and 43% were male. After 48 weeks of treatment in Study UX023-CL304 paired biopsies were available from 11 patients; healing of osteomalacia was observed in all ten evaluable patients as demonstrated by decreases in osteoid volume/bone volume (OV/BV) from a mean (SD) score of 26.1% (12.4) at baseline to 11.9% (6.6), Osteoid thickness (O.Th) declined in 11 evaluable patients from a mean (SD) of 17.2 (4.1) micrometres to 11.6 (3.1) micrometres.

Clinical Efficacy in adult patients with Tumour-induced osteomalacia

Burosumab has been evaluated in two single-arm open-label studies which enrolled a total of 27 adult patients with TIO. Oral phosphate and active vitamin D analogues were discontinued between 2-10 weeks before burosumab treatment was initiated. Patients received burosumab every 4 weeks at a weight based starting dose of 0.3 mg/kg to achieve a fasting serum phosphate level of 2.5 to 4.0 mg/dL [0.81 to 1.29 mmol/L].

Study UX023T-CL201 enrolled 14 adult patients with a confirmed diagnosis of FGF23-related hypophosphataemia induced by an underlying tumour that was not amenable to surgical excision or could not be located. Eight patients were male and age range for all patients was from 33 years to 68 years of age (median 59.5 years). The mean (SD) dose of burosumab was 0.83 (0.41) mg/kg at Week 20, 0.87 (0.49) mg/kg at Week 48, 0.77 (0.52) mg/kg at Week 96 and 0.67 (0.54) mg/kg at Week 144.

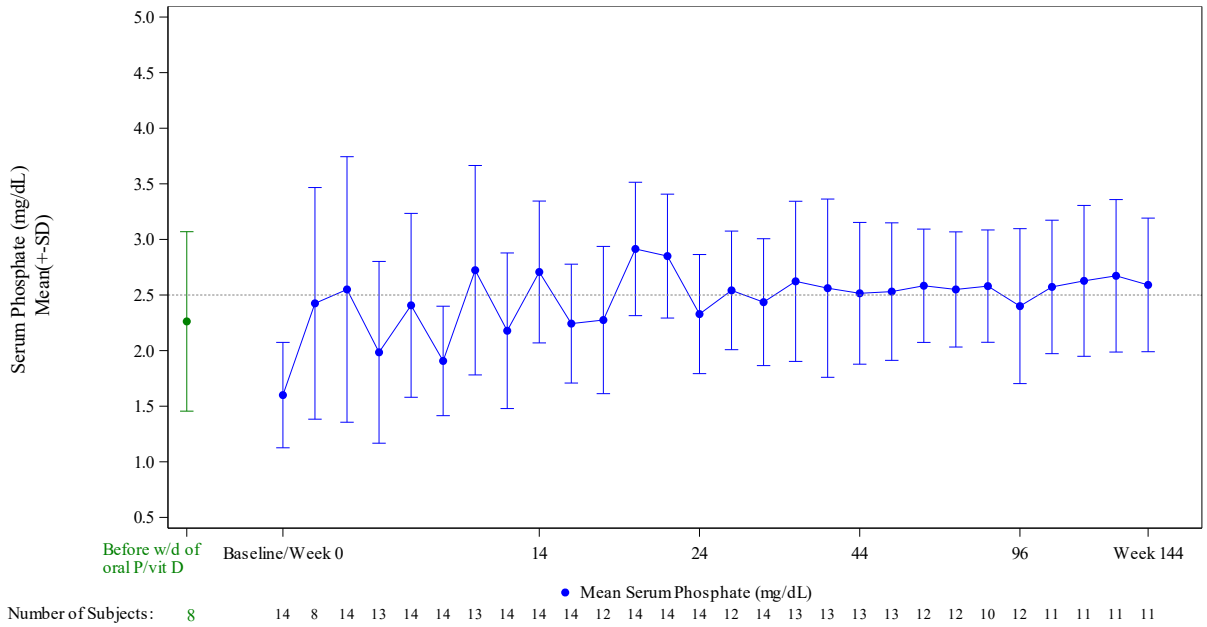
Study KRN23-002 enrolled 13 adult patients from Japan and South Korea with a confirmed diagnosis of TIO. Six patients were male and age range for all patients was from 41 years to 73 years of age (median 58.0 years). The mean (SD) dose of burosumab was 0.91 (0.59) mg/kg at Week 48, and 0.96 (0.70) mg/kg at Week 88.

Serum Phosphate

In both studies, burosumab increased mean serum phosphate levels and these remained stable throughout the study period, as shown in Figures 5 and 6, respectively.

Figure 5: Study UX023T-CL201 Serum Phosphate Concentration (mg/dL) (Mean ± SD)

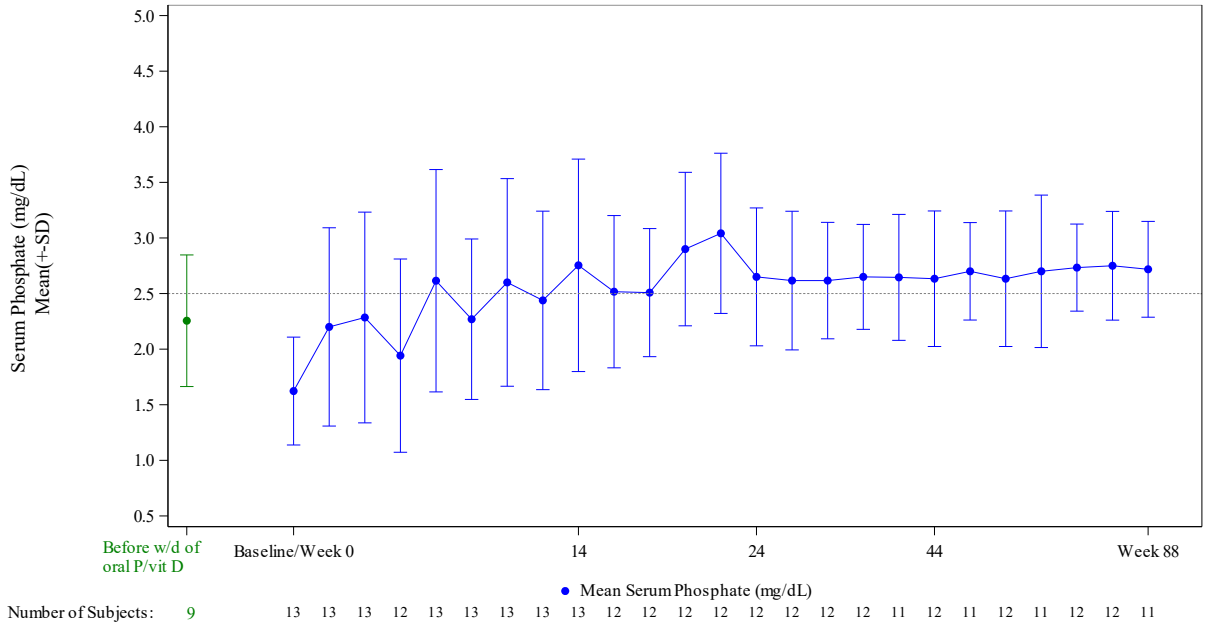
Note: Dashed line in figure indicates the lower limit of the serum phosphate reference range, 2.5 mg/dL (0.81 mmol/L)



*Before withdrawal of oral phosphate/vitamin D; these values were taken before the enrolment in the study

Figure 6: Study KRN23-002 Serum Phosphate Concentration (mg/dL) (Mean ± SD)

Note: Dashed line in figure indicates the lower limit of the serum phosphate reference range, 2.5 mg/dL (0.81 mmol/L)



*Before withdrawal of oral phosphate/vitamin D; these values were taken before the enrolment in the study

In Study UX023T-CL201, the ratio of TmP/GFR increased in these patients from a mean (SD) of 1.12 (0.54) mg/dL [0.36 (0.17) mmol/L] at baseline to 2.12 (0.64) mg/dL [0.68 (0.21) mmol/L] at Week 48 and remained stable through to Week 144. In Study KRN23-002, the ratio of TmP/GFR, increased from a mean (SD) of 1.15 (0.43) mg/dL [0.46 (0.17) mmol/L] at baseline to 2.30 (0.48) mg/dL [0.92 (0.19) mmol/L] at Week 48.

Bone Histomorphometry

In Study UX023T-CL201, 11 patients had paired bone biopsies; changes were assessed after 48 weeks of treatment. Histomorphology parameters are presented below in Table 8 as group mean measurements at baseline and week 48, followed by the mean of relative changes of individualised measurements.

Table 8: Changes in histomorphology parameters in Study UX023T-CL201

Parameter	Group mean (SD) score		Percentage change in group mean values
	Baseline	Week 48	
OV/BV (%)	17.6 (19.5)	12.1 (15.4)	-31.3
OS/BS (%)	56.8 (31.0)	56.6 (26.3)	-0.004
O.Th (µm)	16.5 (12.0)	11.3 (9.2)	-31.5

Radiographic Evaluation

^{99m}technetium-labelled whole body bone scans and x-ray skeletal surveys were conducted at baseline and post-treatment up to Week 144 to assess the number of fractures and pseudofractures. A reduction in fractures and pseudofractures was observed on both bone scans and x-rays.

Paediatric patients with TIO

There are no clinical trials with burosumab in paediatric patients of any age with TIO. The posology of burosumab in paediatric TIO patients has been determined from pharmacokinetic modelling and simulation (see section 5.2).

The European Medicines Agency has waived the obligation to submit the results of studies with burosumab in all subsets of the paediatric population in treatment of Tumour-induced Osteomalacia. See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Burosumab absorption from subcutaneous injection sites to blood circulation is nearly complete. Following subcutaneous administration, the median time to reach maximum serum concentrations (T_{max}) of burosumab is approximately 7-13 days. The peak serum concentration (C_{max}) and area under the concentration-time curve (AUC) of serum burosumab is dose proportional over the dose range of 0.1-2.0 mg/kg.

Distribution

In XLH patients, the observed volume of distribution of burosumab approximates the volume of plasma, suggesting limited extravascular distribution.

Biotransformation

Burosumab is composed solely of amino acids and carbohydrates as a native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination

Due to its molecular size, burosumab is not expected to be directly excreted. The clearance of burosumab is dependent on body weight and estimated to be 0.290 L/day and 0.136 L/day in a typical adult (70 kg) and paediatric (30 kg) XLH patient, respectively, with corresponding disposition half-life ($t_{1/2}$) in the serum ranging from approximately 16 to 19 days. Given the $t_{1/2}$ estimates, the estimated time to reach the plateau of steady-state exposures is approximately 67 days. Following multiple dose administration to paediatric subjects, observed serum trough concentrations reach a plateau by 8 weeks after initiation of treatment.

Linearity/non-linearity

Burosumab displays time-invariant pharmacokinetics that is linear to dose over the subcutaneous dose range of 0.1 to 2.0 mg/kg.

Pharmacokinetic/pharmacodynamic relationship(s)

With the subcutaneous route of administration, in XLH and TIO subjects, a direct PK-PD relationship between serum burosumab concentrations and increases in serum phosphate concentration is observed and well described by an E_{max}/EC_{50} model. Serum burosumab and phosphate concentrations, as well as TmP/GFR, increased and decreased in parallel and reached maximum levels at approximately the same time point after each dose, supporting a direct PK-PD relationship. The AUC for the change from baseline in serum phosphate, TmP/GFR and $1,25(OH)_2D$ increased linearly with increasing burosumab AUC.

Paediatric PK/PD

No significant difference has been observed in paediatric patient pharmacokinetics or pharmacodynamics as compared with PK/PD in the adult population. Burosumab clearance and volume of distribution are body weight dependent.

Paediatric patients with TIO
The starting dose of burosumab for paediatric patients with TIO is based on Population PK/PD modeling and simulations which indicate that a starting dose of 0.4 mg/kg every 2 weeks for children aged 1-12 years and 0.3 mg/kg every 2 weeks for adolescents aged 13-17 years is predicted to result in a

proportion of paediatric patients with TIO reaching normal serum phosphate levels. These can be titrated up to a maximum of 2.0 mg/kg every 2 weeks (the highest dose simulated).

Special Populations

Population PK analyses using data from paediatric and adult subjects who have XLH and adult subjects with TIO indicated that age, sex, race, ethnicity, baseline serum albumin, baseline serum alkaline phosphate, baseline serum alanine aminotransferase, and baseline creatinine clearance ≥ 49.9 mL/min, were not significant predictors of burosumab PK. Based on the population PK analysis, the PK characteristics of burosumab were similar between XLH and TIO patients.

Post-Prandial Effect on Serum Phosphate and Calcium

The effect of burosumab on serum phosphate and calcium levels after food was investigated in two sub-studies (Study UX023-CL301 and UX023-CL303); 13 paediatric patients (aged > 3 years) and 26 adult patients (aged 24-65 years). Serum phosphate and calcium were measured at the end of the treatment interval in paediatric patients and mid-interval in adults. Blood samples were taken after a period of fasting, and again 1-2 hours after a standardised meal.

Burosumab treatment did not cause post-prandial excursions above the age-adjusted upper limits of normal in serum phosphate or serum calcium in any paediatric or adult subject in the sub-studies.

5.3 Preclinical safety data

Adverse reactions in non-clinical studies with normal animals were observed at exposures which resulted in serum phosphate concentration greater than normal limits. These effects were consistent with an exaggerated response to the inhibition of normal FGF23 levels resulting in a supraphysiologic increase in serum phosphate beyond the upper limit of normal.

Studies in rabbits and adult and juvenile cynomolgus monkeys demonstrated dose-dependent elevations of serum phosphate and 1,25 $(OH)_2D$ confirming the pharmacologic actions of burosumab in these species. Ectopic mineralisation of multiple tissues and organs (e.g. kidney, heart, lung, and aorta), and associated secondary consequences (e.g. nephrocalcinosis) in some cases, due to hyperphosphataemia, was observed in normal animals at doses of burosumab that resulted in serum phosphate concentrations in animals greater than approximately 8 mg/dL (2.6 mmol/L). In a murine model of XLH, a significant reduction in the incidence of ectopic mineralisation was observed at equivalent levels of serum phosphate, suggesting that the risk of mineralisation is less in the presence of excess FGF23.

Bone effects seen in adult and juvenile monkeys included changes in bone metabolism markers, increases in thickness and density of cortical bone, increased density of total bone and thickening of long bone. These changes were a consequence of higher than normal serum phosphate levels, which accelerated bone turnover and also led to periosteal hyperostosis and a decrease in bone strength in adult animals, but not in juvenile animals at the doses tested. Burosumab did not promote abnormal bone development, as no changes in femur length or bone strength were noted in juvenile animals. Bone changes were consistent with the pharmacology of burosumab and the role of phosphate in bone mineralization, metabolism and turnover.

In repeat-dose toxicology studies of up to 40 weeks duration in cynomolgus monkeys, mineralisation of the rete testis/seminiferous tubules was observed in male monkeys; however, no changes were observed in semen analysis. No adverse effects on female reproductive organs were observed in these studies.

In the reproductive and developmental toxicology study performed in pregnant cynomolgus monkeys, moderate mineralisation of the placenta was seen in pregnant animals given 30 mg/kg of burosumab and occurred in animals with peak serum phosphate concentration greater than approximately 8 mg/dL (2.6 mmol/L). Shortening of the gestation period and associated increased incidence of premature births were observed in pregnant monkeys at doses of ≥ 0.3 mg/kg which corresponded to burosumab exposures that are ≥ 0.875- to 1.39-fold anticipated clinical levels. Burosumab was detected in serum

from fetuses indicating that burosumab was transported across the placenta to the fetus. There was no evidence of teratogenic effects. Ectopic mineralisation was not observed in foetuses or offspring and burosumab did not affect pre- and postnatal growth including survivability of the offspring.

In preclinical studies, ectopic mineralisation has been observed in normal animals, most frequently in the kidney, given burosumab at doses that resulted in serum phosphate concentrations greater than 8 mg/dL (2.6 mmol/L). Neither new or clinically meaningful worsening of nephrocalcinosis nor ectopic mineralisation have been observed in clinical trials of patients with XLH treated with burosumab to achieve normal serum phosphate levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
D-sorbitol (E 420)
Polysorbate 80 (E 433)
L-methionine
Hydrochloric acid, 10% (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

CRYSVITA solution for injection in pre-filled syringe
Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C when protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

CRYSVITA solution for injection in vials
Clear glass vial with butyl rubber stopper, and aluminium seal.

Pack size of one vial

CRYSVITA solution for injection in pre-filled syringe
Clear type I glass syringe with a staked stainless steel needle. The syringe is closed by a rigid polypropylene and elastomer needle shield and a fluoropolymer-laminated bromobutyl rubber plunger stopper.

The different strengths of the medicinal product can be identified by a different coloured plunger rod: 10 mg (blue), 20 mg (red), and 30 mg (green).

Pack size of one pre-filled syringe.

6.6 Special precautions for disposal and other handling

CRYSVITA solution for injection in vials
Each vial is for single use only.

Do not shake the vial before use.

Before administration, the solution should be inspected visually. The liquid should be clear to slightly opalescent, colourless to pale brown-yellow. If the solution is cloudy, discoloured or contains particles, the solution should not be used.

After removing the vial from the refrigerator, allow the vial to reach room temperature for 30 minutes before injecting burosumab.

Burosumab should be administered using aseptic technique and sterile disposable syringes and injection needles.

CRYSVITA solution for injection in pre-filled syringe
Before administration, the solution should be inspected visually. The liquid should be clear to slightly opalescent, colourless to pale brown-yellow. If the solution is cloudy, discoloured or contains particles, the solution should not be used.

After removing the pre-filled syringe from the refrigerator, allow the syringe to reach room temperature for 45 minutes before injecting burosumab.

Comprehensive instructions for subcutaneous administration of burosumab in a pre-filled syringe is provided at the end of the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands
+31 (0) 237200822
medinfo@kyowakirin.com

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1262/001
EU/1/17/1262/002
EU/1/17/1262/003
EU/1/17/1262/004
EU/1/17/1262/005
EU/1/17/1262/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 February 2018
Date of latest renewal: 21 February 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Kyowa Kirin Co., Ltd.
Takasaki Plant
100-1 Hagiwara-machi
Takasaki
370-0013 Gunma
JAPAN

Name and address of the manufacturer responsible for batch release

allphamed PHARBIL Arzneimittel GmbH
Hildebrandstr. 10-12
37081 Göttingen
GERMANY

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

10 mg CARTON

1. NAME OF THE MEDICINAL PRODUCT

CRYSVITA 10 mg solution for injection
burosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 mg burosumab in 1 ml of solution.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, D- sorbitol (E 420), polysorbate 80 (E 433), L-methionine, hydrochloric acid, 10%, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.
Do not shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1262/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRYSVITA 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 mg VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CRYSVITA 10 mg injection
burosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

20 mg CARTON

1. NAME OF THE MEDICINAL PRODUCT

CRYSVITA 20 mg solution for injection
burosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 20 mg burosumab in 1 ml of solution.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, D- sorbitol (E 420), polysorbate 80 (E 433), L-methionine, hydrochloric acid, 10%, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.
Do not shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1262/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRYSVITA 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

20 mg VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CRYSVITA 20 mg injection
burosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

30 mg CARTON

1. NAME OF THE MEDICINAL PRODUCT

CRYSVITA 30 mg solution for injection
burosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 30 mg burosumab in 1 ml of solution.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, D- sorbitol (E 420), polysorbate 80 (E 433), L-methionine, hydrochloric acid, 10%, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.
Do not shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1262/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRYSVITA 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

30 mg VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CRYSVITA 30 mg injection
burosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 10 mg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

CRYSVITA 10 mg solution for injection in pre-filled syringe
burosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 10 mg of burosumab in 0.33 ml solution.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, D- sorbitol (E 420), polysorbate 80 (E 433), L-methionine, hydrochloric acid, 10%, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.
Do not shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1262/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRYSVITA 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 mg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CRYSVITA 10 mg injection
burosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.33 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 20 mg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

CRYSVITA 20 mg solution for injection in pre-filled syringe
burosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 20 mg burosumab in 0.67 ml of solution.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, D- sorbitol (E 420), polysorbate 80 (E 433), L-methionine, hydrochloric acid, 10%, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.
Do not shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1262/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRYSVITA 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

20 mg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CRYSVITA 20 mg injection
burosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.67 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 30 mg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

CRYSVITA 30 mg solution for injection in pre-filled syringe
burosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 30 mg burosumab in 1 ml of solution.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, D- sorbitol (E 420), polysorbate 80 (E 433), L-methionine, hydrochloric acid, 10%, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.
Do not shake before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1262/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRYSVITA 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

30 mg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CRYSVITA 30 mg injection
burosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

CRYSVITA 10 mg solution for injection
CRYSVITA 20 mg solution for injection
CRYSVITA 30 mg solution for injection

burosumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CRYSVITA is and what it is used for

What CRYSVITA is
CRYSVITA contains the active substance burosumab. This is a type of medicine called a human monoclonal antibody.

What is CRYSVITA used for
CRYSVITA is used to treat X-linked hypophosphataemia (XLH). It is used in children and adolescents aged 1 to 17 years, and in adults.

CRYSVITA is used to treat Tumour-induced Osteomalacia (TIO) where the tumour causing this condition cannot be successfully removed or found, in children and adolescents aged 1 to 17 years and in adults.

What is X-Linked Hypophosphataemia (XLH)
X-Linked Hypophosphataemia (XLH) is a genetic disease.
- People with XLH have higher levels of a hormone called fibroblast growth factor 23 (FGF23).
- FGF23 lowers the amount of phosphate in the blood.
- The low level of phosphate may:
  - lead to bones that may not harden properly and, in children and adolescents, cannot grow properly
  - result in pain and stiffness in bones and joints

What is Tumour-induced osteomalacia (TIO)
- People with TIO have higher levels of a hormone called FGF23 produced by certain types of tumours.
- FGF23 lowers the amount of phosphate in the blood.
- The low level of phosphate may lead to softening of the bones, muscle weakness, tiredness, bone pain and fractures.

How CRYSVITA works
CRYSVITA attaches to FGF23 in the blood which stops FGF23 from working and increases the phosphate levels in the blood so that normal levels of phosphate can be achieved.

2. What you need to know before you use CRYSVITA

Do not use CRYSVITA if
- you are allergic to burosumab or any of the other ingredients of this medicine (listed in section 6)
- you are taking any phosphate supplements or certain vitamin D supplements (that contain so called active vitamin D, e.g. calcitriol)
- you already have a high level of phosphate in your blood ("hyper-phosphataemia")
- you have severe kidney disease or kidney failure.

Allergic reactions
Stop taking CRYSVITA and contact your doctor straight away if you have any of the following side effects, as they could be signs of an allergic reaction:
- rash and itching all over the body
- severe swelling of eyelids, mouth or lips (angio-oedema)
- shortness of breath
- rapid heartbeat
- sweating.

Do not take CRYSVITA if any of the above apply to you. If you are not sure, talk to your doctor before using CRYSVITA.

Warnings and precautions

Skin reactions
You may get skin reactions where the injection is given, see section 4 for more information. If these reactions are severe, tell your doctor.

Tests and checks
Your doctor will check the phosphate and calcium levels in your blood and urine and may also do a renal ultrasound before and during your treatment in order to reduce the risk of hyperphosphataemia (too much phosphate in the blood), hypercalcaemia (too much calcium in the blood) and ectopic mineralisation (a build-up of calcium in tissues such as the kidneys). Your serum parathyroid hormone level will also be checked before and during your treatment in order to reduce the risk of hyperparathyroidism (too much parathyroid hormone in the blood).

Children under 1 year
CRYSVITA should not be given to children under 1 year of age because the safety and effects of the medicine have not been studied in this age group.

Keeping a record
If you are injecting yourself or your child, you should note down the date of administration, name of the medicine and batch number (which is on the packaging after Lot) and keep this information in a safe place. Talk to your doctor, nurse or pharmacist if you are not sure.

Other medicines and CRYSVITA
Tell your doctor if you are taking, have recently taken, or might take any other medicines.

Do not take CRYSVITA and tell your doctor if you are taking:
- phosphate supplements
- certain vitamin D supplements (that contain so called active vitamin D, e.g. calcitriol). There are some vitamin D supplements you can continue or start to use and your doctor will advise which ones these are.

Talk to your doctor before taking CRYSVITA:
- if you are taking medicines that work in the same way as calcium in the body ("calcimimetics"). Your doctor may monitor your calcium levels more closely.
- if you are a patient with TIO and you are about to receive treatment of the underlying tumour (i.e. radiation therapy or surgical removal). In this case, treatment with CRYSVITA will not be started until after the treatment of the underlying tumour and if the serum phosphate levels are low.
- if you have problems with your parathyroid glands.

Pregnancy and breastfeeding
If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. This is because it is not known if CRYSVITA will affect the baby.

CRYSVITA is not recommended in pregnancy.

If you could get pregnant, you must use an effective method of contraception (birth control) while using CRYSVITA and for at least 14 weeks after your last dose. You should discuss this with your doctor.

Monoclonal antibodies like CRYSVITA are known to pass into breast milk during the first few days after birth, but after this first period CRYSVITA could be used. Talk to your doctor about using CRYSVITA while breast-feeding in order to help you decide whether you should stop breast-feeding or stop using CRYSVITA.

Driving, riding a bike and using machines
You or your child may feel dizzy when taking CRYSVITA. If this happens it may be dangerous to do things such as drive, use any tools or machines, ride a bike or horse or climb trees.

CRYSVITA contains sorbitol
This medicine contains 45.91 mg of sorbitol in each vial which is equivalent to 45.91 mg/ml. Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you (or your child) have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

CRYSVITA contains polysorbate
This medicine contains 0.5 mg of polysorbate 80 in each vial which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you or your child have any known allergies.

3. How to use CRYSVITA

CRYSVITA should be given by injection under the skin (subcutaneous use) in the upper arm, abdomen, buttock or thigh. This medicine will be given to you or your child by a healthcare provider. Alternatively, your doctor may recommend that you inject yourself or your child. A healthcare provider will show you how to do this. The first self-injection after start of treatment or after any dose change should be carried out in front of them. A detailed 'Instructions for Use' section is provided at the end of this leaflet. Always follow these instructions carefully when giving yourself or your child the CRYSVITA injection.

Always use this medicine exactly as your doctor, nurse or pharmacist has told you. Check with your doctor, nurse or pharmacist if you are not sure.

How much CRYSVITA you will need
The dose is based on your body weight. Your doctor will work out the right dose for you.

Dose for XLH and TIO
Your CRYSVITA dose will need to be injected:
- every two weeks in children and adolescents aged 1 –17 years
- every four weeks in adults

Your doctor will perform checks to make sure that you are getting the right dose and may change your dose or frequency of dose if needed.

Maximum dose for XLH patients
The maximum dose you will be given for the treatment of XLH is 90 mg.

Maximum dose for TIO patients
The maximum dose you will be given for the treatment of TIO:
- for children aged 1 to 12, is 90 mg
- for adolescents aged 13 to 17 and for adults, is 180 mg

Patients with TIO
If you are a patient with TIO who requires treatment of the underlying tumour (i.e. radiation therapy or surgical removal), treatment with CRYSVITA will be stopped by your doctor. After treatment of the tumour is completed, your doctor will perform checks of your phosphate levels and restart treatment with CRYSVITA if serum phosphate levels are low.

If you have been given more CRYSVITA than you should
If you think that you have been given too much CRYSVITA, tell your doctor straight away.

If you miss a dose of CRYSVITA
If a dose is missed, talk to your doctor straight away. The missed dose should be given as soon as possible and your doctor will re-arrange future doses accordingly.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects in children and adolescents with XLH
Very common (may affect more than 1 in 10 children and adolescents)
- Tooth abscess (infection)
- Cough
- Headache
- Dizziness
- Vomiting
- Nausea
- Diarrhoea
- Constipation
- Tooth decay or cavities
- Rash
- Pain in muscles (myalgia) and hands and feet

- Reactions where the injection was given, which may include:
  - redness or rash
  - pain or itching
  - swelling
  - bleeding or bruising

  These injection site reactions are usually mild and occur within a day after the injection and usually get better in around 1 to 3 days.
- Fever
- Low vitamin D in your blood

Common (may affect up to 1 in 10 children and adolescents)
- Hives
- Increased parathyroid hormone in your blood

Uncommon (may affect up to 1 in 100 children and adolescents)
- High levels of calcium in your blood

Not known (frequency cannot be estimated from the available data)
- High levels of calcium in your urine
- Increased phosphate or high levels of parathyroid hormone in your blood

Side effects in children and adolescents with TIO
Side effects in children and adolescents are not known, as no clinical studies have been carried out.

Side effects in adults with XLH and TIO
Very common (may affect more than 1 in 10 adults)
- Tooth abscess (infection)
- Headache
- Dizziness
- 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)
- Constipation
- Pain in back
- Muscle spasm
- Reactions where the injection was given, which may include pain or swelling.
- Low vitamin D in your blood

Common (may affect up to 1 in 10 adults)
- Increased or high levels of parathyroid hormone in your blood
- High levels of calcium in your blood or urine
- Rash
- Hives
- Increased phosphate in your blood

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CRYSVITA

Keep CRYSVITA out of the sight and reach of children.
Do not use CRYSVITA after the expiry date which is stated on the carton and label after “EXP”.
The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Do not use CRYSVITA if it contains visible particles.
Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.
If self-injecting, see step 5 of the 'Instructions for Use' in the end of the Package Leaflet for instructions on disposal of unused medicines and supplies. If you have questions on how to throw away medicines you no longer use, ask your healthcare provider or pharmacist.

6. Contents of the pack and other information

What CRYSVITA contains
The active substance is burosumab. Each vial contains either 10, 20 or 30 mg of burosumab.
The other ingredients are L-histidine, D-sorbitol (E 420), polysorbate 80 (E 433), L-methionine, 10%, hydrochloric acid, and water for injections. (See "CRYSVITA contains sorbitol" in section 2 for more information).

What CRYSVITA looks like and contents of the pack
CRYSVITA comes as a clear to slightly opalescent, colourless to pale yellow/brown solution for injection in a small glass vial. Each pack contains 1 vial.

Marketing Authorisation Holder
Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands
medinfo@kyowakirin.com

Manufacturer
allphamed PHARBIL Arzneimittel GmbH
Hildebrandstr. 10-12
37081 Göttingen
Germany

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

INSTRUCTIONS FOR USE

Read these Instructions for Use carefully before you use CRYSVITA:

- Only inject yourself or your child if you have been told to do so by your doctor.
- You should only inject after you have been trained in injection technique. The first self-injection after start of treatment or after any dose change should be carried out in front of a healthcare provider.
- Always use this medicine exactly as your doctor, pharmacist or nurse (healthcare provider) has told you. Check with your healthcare provider if you are not sure.
- Your doctor will prescribe your correct dose. Your dose is measured in milligrams (mg). CRYSVITA is available in three different strength vials: 10 mg, 20 mg, and 30 mg. Each vial is for single use only. Always use a new CRYSVITA vial for each injection, see step 5 on how to dispose used vials and other supplies.
- Your healthcare provider will tell you how much CRYSVITA to give yourself or your child. You or your child may be given more than one vial to get the correct dose.
- If your healthcare provider tells you that more than one injection is needed to give your required dose, you must repeat the following Steps 2-5 for each injection. Use new supplies and a different site on the body for each injection.
- Only use the syringe and needles provided or prescribed by your healthcare provider to give the injection.
    - Always use the large needle to withdraw the liquid and remember to change to the small needle to inject the liquid.
    - Using the wrong syringe or needle can lead to a mistake in your dose or make the injection more painful.
- When giving CRYSVITA to a young child, it may be helpful to have another person present to provide support.
- Do not use CRYSVITA if allergic to any ingredients of this medicine. Stop using CRYSVITA if you have any allergic reaction during or after the injection and contact your healthcare provider straightaway. See section 2 of the package leaflet for more information.

Step 1. Gather and Inspect Supplies

Remove the CRYSVITA vials you need from the refrigerator.

Check the strength on the label of each vial.
Make sure that you have the correct number of vials to match the dose in mg as advised by your healthcare provider.
If you are not sure, ask your healthcare provider for advice.

Let the vials warm to room temperature for 30 minutes. Do not warm the vials in any other way, such as with hot water or a microwave oven. Do not put the vials in direct sunlight.

Note down the date of administration, name of the medicine and batch number (which is on the packaging after Lot) and keep this information in a safe place.

Check the expiry date (shown after EXP) on the label of the vial.
Inspect the liquid in the vial. Do not shake.
Do not use the vial if it is:

- past the expiry date
- discoloured, cloudy or contains any particles. CRYSVITA liquid should be clear to slightly opalescent, colourless to pale brown-yellow.

Place all the items you will need on a clean, flat surface. For each injection you will need:

A. Vial of CRYSVITA for injection
B. One syringe with plunger
C. One large syringe needle to withdraw CRYSVITA
D. One small syringe needle to inject CRYSVITA
E. Alcohol wipes
F. Sharps container
G. Plaster (if required)
H. Gauze pad or cotton wool

Contact your healthcare provider if you do not have these supplies.

Your healthcare provider will explain the use of different needles.
The **large needle** is used for withdrawing CRYSVITA from the vial.
The **small needle** is used for injecting CRYSVITA.
If you are not sure, ask your healthcare provider for advice before use.

Do not use any items that have missing pieces or are damaged in any way.

Do not remove the caps from the needles until you are ready to use them.

Wash your hands thoroughly with soap and water before going to Step 2.

Step 2. Withdraw CRYSVITA and Prepare Injection

Remove the sealing cap from the vial to reveal the rubber stopper.

Clean the rubber stopper with an alcohol wipe and let it dry. Don't touch the rubber stopper after cleaning it.

Select the **large** needle and remove from the sterile packaging but do not remove the cap covering the needle.

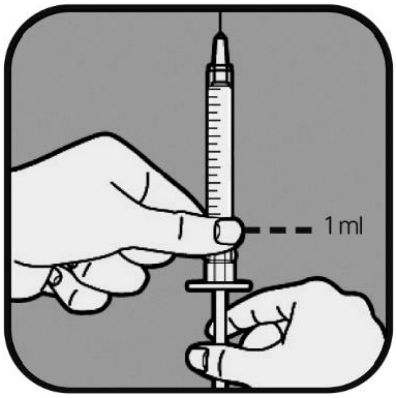
To attach the needle to the syringe, hold the **large** needle by the protective cap in one hand and the syringe by the barrel in the other hand.
Depending on the supplies you have been given;

- you will need to push the needle down and turn clockwise onto the syringe until tight
- **or** push the needle down until it is firmly attached.

Do not touch the needle itself or the end of the syringe where the needle attaches.

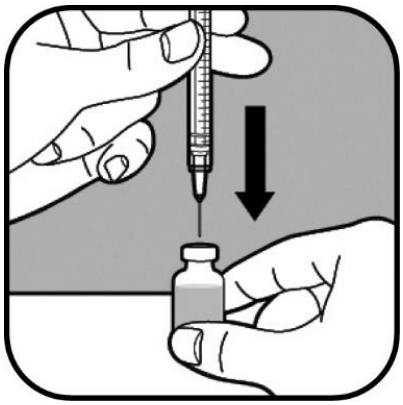
Once the needle is firmly attached, hold the syringe by the barrel with the needle pointing up.
Remove the needle cap by pulling it straight off.
Do not throw the needle cap away.

Do not touch the needle or allow the needle to touch any surface once the cap has been removed.
Do not use the syringe if you drop it after removing the cap or if the needle appears damaged.



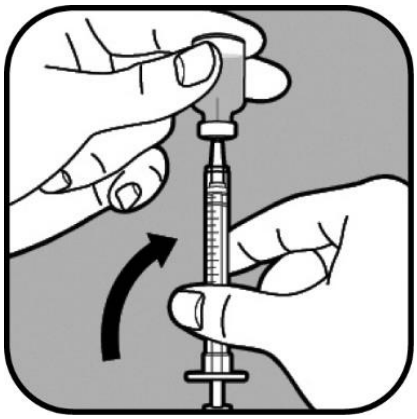
Your healthcare provider will tell you how much liquid you need to inject. This will normally be 1ml for each injection. Your healthcare provider will show you which mark to use if you need to inject less than 1 ml.
Always use the mark equal to your dose. If you are not sure, ask your healthcare provider for advice before use.

Pull back the syringe plunger until the end of the plunger lines up with mark equal to your dose.
This fills the syringe with air.

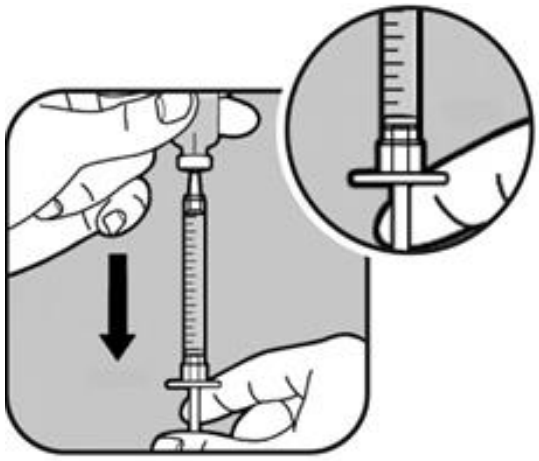


Keep the vial on a flat surface.
Slowly insert the large needle through the rubber stopper and into the vial.
Do not let the tip of the needle touch the liquid in the vial.
If the tip of the needle touches the liquid, slowly pull the needle until it no longer touches the liquid.

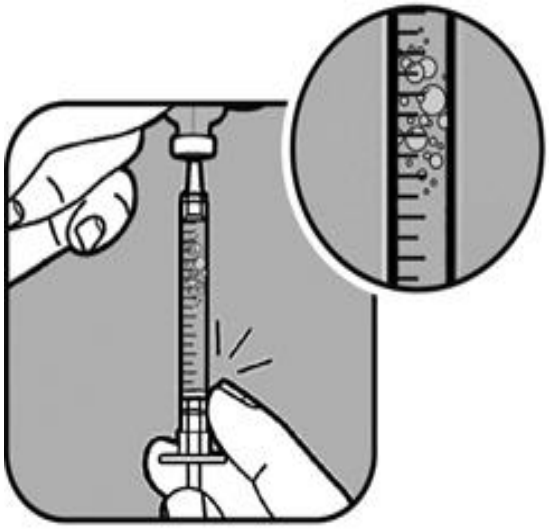
Slowly push the plunger into the syringe.
This pushes air from the syringe into the vial.



Keep the needle in the vial and turn the vial upside down.
Make sure the tip of the needle is at the bottom of the liquid.



Slowly pull back the plunger to fill the syringe until the end of the plunger lines up with the mark equal to your dose.
Keep the tip of the needle in the liquid at all times.



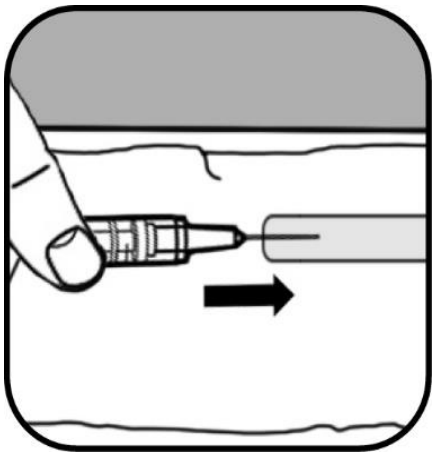
Check the liquid in the syringe for air bubbles.

If you see bubbles,

- keep the syringe upright with the needle still inside the vial,
- gently tap the barrel with your finger to move the air bubbles,
- when the air bubbles are at the top, slowly push the plunger to push out the air bubbles.

Check your dose again against the markings on the syringe.
If required, withdraw some more liquid to line up with the mark equal to your dose.
Check again for bubbles and repeat the process if required.

When there are no bubbles in the syringe, pull the syringe and needle straight down out of the vial.



Remove the large needle from the syringe.

- To do this, take the large needle cap and place on a flat surface.
- Using one hand, slide the large needle into the cap and scoop upward to cover the needle without using your other hand to avoid injury. Then use your other hand to secure the cap and snap into place.
- Depending on your supplies, you will;
    - need to twist the capped large needle anti-clockwise to remove from the syringe
    - or pull the capped large needle straight from the syringe and place in the sharps container.

Select the **small** needle and remove from the sterile packaging but do not remove the cap covering the needle.

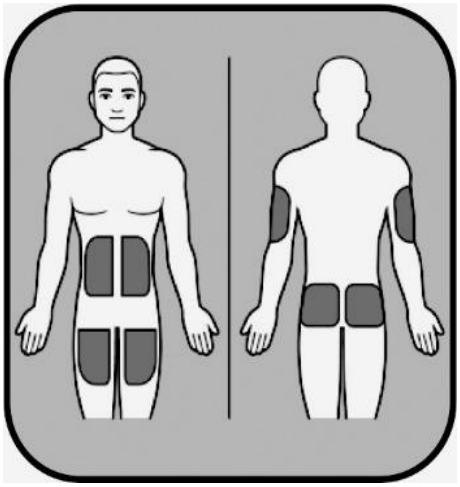
To attach the needle to the syringe, hold the **small** needle by the protective cap in one hand and the syringe by the barrel in the other hand.

Depending on the supplies you have been given,

- you will need to push the needle down and turn clockwise onto the syringe until tight
- **or** push the needle down until it is firmly attached.

Do not touch the needle itself or the end of the syringe where the needle attaches.

Step 3. Prepare the Injection Site



The injection must be given into the fatty layer just below the skin. You will need to choose an injection site. If you are giving the injection to yourself, suitable areas are:

- stomach area, upper thighs

If you are giving the injection to someone else, suitable areas are:

- stomach area, upper thighs, outer area of upper arms, buttocks

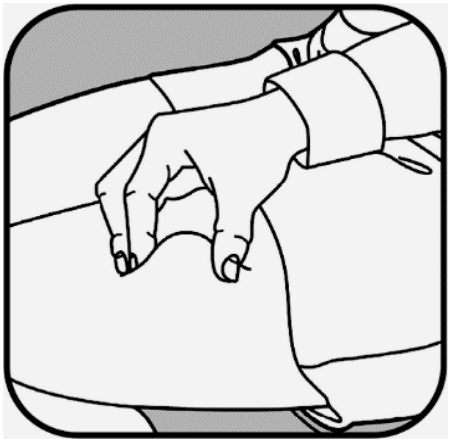
Do not inject:

- an area that is sore, red, bruised or where the skin is broken
- an area that has stretch marks or scars (including burns)
- directly into a mole, or an area around a mole

If you are giving more than one injection, use a different site for each injection. Clean each injection site with a new alcohol wipe and leave the skin to dry.

CRYSVITA should be injected into clean dry skin.

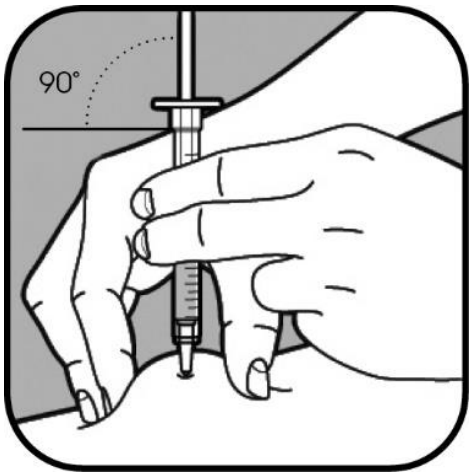
Step 4. Inject CRYSVITA



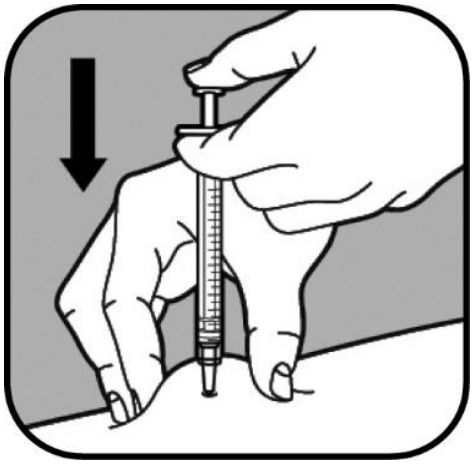
Remove the small needle cap by pulling it straight off.

Pinch the skin firmly between your thumb and fingers, creating an area about 5 cm wide.

Hold the syringe between the thumb and index finger of your dominant hand.
The needle should be inserted into the skin at a 45° angle or 90° angle.
Your healthcare provider will show you which angle you should use.

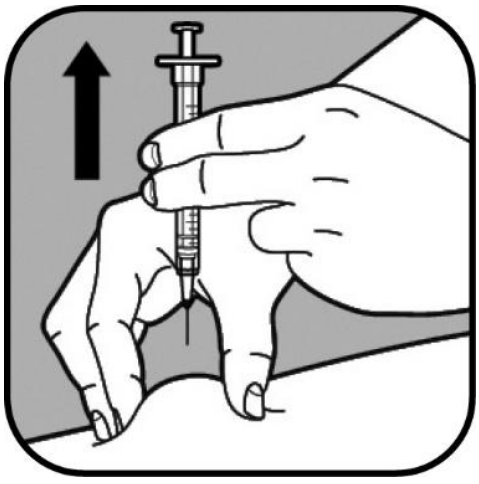


Use a quick ‘dart-like’ motion to insert the needle into the pinched skin.
Do not push the plunger when inserting the needle.



When the needle is inserted do not move it around.

Keep pinching the skin.
Slowly push the plunger into the syringe, for up to 30 seconds, until the syringe is empty.



After you have given the full dose, remove the injection by gently pulling the syringe straight out.

Release the pinched skin.
Press the injection site with a cotton ball or gauze pad for a few seconds to stop bleeding. Apply a plaster if needed.

Do not rub the injection site.

To avoid any injury, do not put the cap back on the small needle. Place the uncapped needle in the sharps disposal container.

Step 5. After each injection

Put your used needles, caps and syringes in the sharps disposal container, vials should be discarded according to your local guidelines.
Do not throw away needles or syringes in your household waste.
Do not save vials with leftover medicine for future use or pass it on to others.

When your sharps container is almost full, you will need to follow your local guidelines to request another container and to dispose of it correctly.

Reminder: If you are giving more than one injection, repeat steps 2-5 for each injection.
Use new supplies for each injection.

Note the date of the injection and all the areas where you have injected so that you use different sites for the next injection.

A video showing you how to prepare and give the injection is available on the following link:
www.myinject.eu

Package leaflet: Information for the user

CRYSVITA 10 mg solution for injection in pre-filled syringe
CRYSVITA 20 mg solution for injection in pre-filled syringe
CRYSVITA 30 mg solution for injection in pre-filled syringe

burosumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CRYSVITA is and what it is used for

What CRYSVITA is
CRYSVITA contains the active substance burosumab. This is a type of medicine called a human monoclonal antibody.

What is CRYSVITA used for
CRYSVITA is used to treat X-linked hypophosphataemia (XLH). It is used in children and adolescents aged 1 to 17 years, and in adults.

CRYSVITA is used to treat Tumour-induced Osteomalacia (TIO) where the tumour causing this condition cannot be successfully removed or found, in children and adolescents aged 1 to 17 years and in adults.

What is X-Linked Hypophosphataemia (XLH)
X-Linked Hypophosphataemia (XLH) is a genetic disease.
- People with XLH have higher levels of a hormone called fibroblast growth factor 23 (FGF23).
- FGF23 lowers the amount of phosphate in the blood.
- The low level of phosphate may:
  - lead to bones that may not harden properly and, in children and adolescents, cannot grow properly
  - result in pain and stiffness in bones and joints

What is Tumour-induced osteomalacia (TIO)
- People with TIO have higher levels of a hormone called FGF23 produced by certain types of tumours.
- FGF23 lowers the amount of phosphate in the blood.
- The low level of phosphate may lead to softening of the bones, muscle weakness, tiredness, bone pain and fractures.

How CRYSVITA works
CRYSVITA attaches to FGF23 in the blood which stops FGF23 from working and increases the phosphate levels in the blood so that normal levels of phosphate can be achieved.

2. What you need to know before you use CRYSVITA

Do not use CRYSVITA if
- you are allergic to burosumab or any of the other ingredients of this medicine (listed in section 6)
- you are taking any phosphate supplements or certain vitamin D supplements (that contain so called active vitamin D, e.g. calcitriol)
- you already have a high level of phosphate in your blood ("hyper-phosphataemia")
- you have severe kidney disease or kidney failure.

Allergic reactions
Stop taking CRYSVITA and contact your doctor straight away if you have any of the following side effects, as they could be signs of an allergic reaction:
- rash and itching all over the body
- severe swelling of eyelids, mouth or lips (angio-oedema)
- shortness of breath
- rapid heartbeat
- sweating.

Do not take CRYSVITA if any of the above apply to you. If you are not sure, talk to your doctor before using CRYSVITA.

Warnings and precautions

Skin reactions
You may get skin reactions where the injection is given, see section 4 for more information. If these reactions are severe, tell your doctor.

Tests and checks
Your doctor will check the phosphate and calcium levels in your blood and urine and may also do a renal ultrasound before and during your treatment in order to reduce the risk of hyperphosphataemia (too much phosphate in the blood), hypercalcaemia (too much calcium in the blood) and ectopic mineralisation (a build-up of calcium in tissues such as the kidneys). Your serum parathyroid hormone level will also be checked before and during your treatment in order to reduce the risk of hyperparathyroidism (too much parathyroid hormone in the blood).

Children under 1 year
CRYSVITA should not be given to children under 1 year of age because the safety and effects of the medicine have not been studied in this age group.

Keeping a record
If you are injecting yourself or your child, you should note down the date of administration, name of the medicine and batch number (which is on the packaging after Lot) and keep this information in a safe place. Talk to your doctor, nurse or pharmacist if you are not sure.

Other medicines and CRYSVITA
Tell your doctor if you are taking, have recently taken, or might take any other medicines.

Do not take CRYSVITA and tell your doctor if you are taking:
- phosphate supplements
- certain vitamin D supplements (that contain so called active vitamin D, e.g. calcitriol). There are some vitamin D supplements you can continue or start to use and your doctor will advise which ones these are.

Talk to your doctor before taking CRYSVITA:
- if you are taking medicines that work in the same way as calcium in the body ("calcimimetics"). Your doctor may monitor your calcium levels more closely.
- if you are a patient with TIO and you are about to receive treatment of the underlying tumour (i.e. radiation therapy or surgical removal). In this case, treatment with CRYSVITA will not be started until after the treatment of the underlying tumour and if the serum phosphate levels are low.
- if you have problems with your parathyroid glands.

Pregnancy and breastfeeding
If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. This is because it is not known if CRYSVITA will affect the baby.

CRYSVITA is not recommended in pregnancy.

If you could get pregnant, you must use an effective method of contraception (birth control) while using CRYSVITA and for at least 14 weeks after your last dose. You should discuss this with your doctor.

Monoclonal antibodies like CRYSVITA are known to pass into breast milk during the first few days after birth, but after this first period CRYSVITA could be used. Talk to your doctor about using CRYSVITA while breast-feeding in order to help you decide whether you should stop breast-feeding or stop using CRYSVITA.

Driving, riding a bike and using machines
You or your child may feel dizzy when taking CRYSVITA. If this happens it may be dangerous to do things such as drive, use any tools or machines, ride a bike or horse or climb trees.

CRYSVITA contains sorbitol
CRYSVITA 10 mg solution for injection in pre-filled syringe: This medicine contains 15.30 mg sorbitol in each pre-filled syringe.
CRYSVITA 20 mg solution for injection in pre-filled syringe: This medicine contains 30.61 mg sorbitol in each pre-filled syringe.
CRYSVITA 30 mg solution for injection in pre-filled syringe: This medicine contains 45.91 mg sorbitol in each pre-filled syringe.
Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you (or your child) have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

CRYSVITA contains polysorbate
CRYSVITA 10 mg solution for injection in pre-filled syringe: This medicine contains 0.165 mg polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/ml.
CRYSVITA 20 mg solution for injection in pre-filled syringe: This medicine contains 0.335 mg polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/ml.
CRYSVITA 30 mg solution for injection in pre-filled syringe: This medicine contains 0.5 mg polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/ml.
Polysorbates may cause allergic reactions. Tell you doctor if you or your child have any known allergies.

3. How to use CRYSVITA

CRYSVITA should be given by injection under the skin (subcutaneous use) in the upper arm, abdomen, buttock or thigh. This medicine can be given to you by a healthcare provider, or alternatively, your doctor may recommend that you or your caregiver can inject CRYSVITA. If you are suggested to self-inject, a healthcare provider will provide training to show you or your caregiver the correct way to use CRYSVITA before the first self-injection.

The first self-injection after start of treatment or after any dose change should be carried out in front of the healthcare provider. A detailed 'Instructions for Use' section for using the pre-filled syringe is provided at the end of this leaflet. Follow these instructions carefully when giving yourself or your child the CRYSVITA injection.

Always use this medicine exactly as your doctor, nurse or pharmacist has told you. Check with your doctor, nurse or pharmacist if you are not sure.

How much CRYSVITA you will need
The dose is based on your body weight. Your doctor will work out the right dose for you.

Dose for XLH and TIO
Your CRYSVITA dose will need to be injected:
- every two weeks in children and adolescents aged 1-17 years
- every four weeks in adults

Your doctor will perform checks to make sure that you are getting the right dose and may change your dose or frequency of dose if needed.

Maximum dose for XLH patients
The maximum dose you will be given for the treatment of XLH is 90 mg.

Maximum dose for TIO patients
The maximum dose you will be given for the treatment of TIO:
- for children aged 1 to 12, is 90 mg
- for adolescents aged 13 to 17 and for adults, is 180 mg

Patients with TIO
If you are a patient with TIO who requires treatment of the underlying tumour (i.e. radiation therapy or surgical removal), treatment with CRYSVITA will be stopped by your doctor. After treatment of the tumour is completed, your doctor will perform checks of your phosphate levels and restart treatment with CRYSVITA if serum phosphate levels are low.

If you have been given more CRYSVITA than you should
If you think that you have been given too much CRYSVITA, tell your doctor straight away.

If you miss a dose of CRYSVITA
If a dose is missed, talk to your doctor straight away. The missed dose should be given as soon as possible and your doctor will re-arrange future doses accordingly.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects in children and adolescents with XLH
Very common (may affect more than 1 in 10 children and adolescents)
- Tooth abscess (infection)
- Cough
- Headache
- Dizziness
- Vomiting
- Nausea
- Diarrhoea
- Constipation
- Tooth decay or cavities
- Rash
- Pain in muscles (myalgia) and hands and feet
- Reactions where the injection was given, which may include:
    - redness or rash
    - pain or itching
    - swelling
    - bleeding or bruising

  These injection site reactions are usually mild and occur within a day after the injection and usually get better in around 1 to 3 days.
- Fever
- Low vitamin D in your blood

Common (may affect up to 1 in 10 children and adolescents)
- Hives
- Increased parathyroid hormone in your blood

Uncommon (may affect up to 1 in 100 children and adolescents)
- High levels of calcium in your blood

Not known (frequency cannot be estimated from the available data)
- High levels of calcium in your urine
- Increased phosphate or high levels of parathyroid hormone in your blood

Side effects in children and adolescents with TIO
Side effects in children and adolescents are not known, as no clinical studies have been carried out.

Side effects in adults with XLH and TIO
Very common (may affect more than 1 in 10 adults)
- Tooth abscess (infection)
- Headache
- Dizziness
- 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)
- Constipation
- Pain in back
- Muscle spasm
- Reactions where the injection was given, which may include pain or swelling.
- Low vitamin D in your blood

Common (may affect up to 1 in 10 adults)
- Increased or high levels of parathyroid hormone in your blood
- High levels of calcium in your blood or urine
- Rash

- Hives
- Increased phosphate in your blood

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CRYSVITA

Keep CRYSVITA out of the sight and reach of children.
Do not use CRYSVITA after the expiry date which is stated on the carton and label after ''EXP''.
The expiry date refers to the last day of that month.
Store in a refrigerator (2°C to 8°C). Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Do not use CRYSVITA if it contains visible particles.
Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.
If self-injecting, see step 4 of the 'Instructions for Use' in the end of the Package Leaflet for instructions on disposal of unused medicines and supplies. If you have questions on how to throw away medicines you no longer use, ask your healthcare provider or pharmacist.

6. Contents of the pack and other information

What CRYSVITA contains
The active substance is burosumab.

10 mg pre-filled syringe:
Each pre-filled syringe contains 10 mg of burosumab in 0.33 ml solution.

20 mg pre-filled syringe:
Each pre-filled syringe contains 20 mg of burosumab in 0.67 ml solution.

30 mg pre-filled syringe:
Each pre-filled syringe contains 30 mg of burosumab in 1 ml solution.

The other ingredients are L-histidine, D-sorbitol (E 420), polysorbate 80 (E 433), L-methionine, 10%, hydrochloric acid, and water for injections. (See "CRYSVITA contains sorbitol" in section 2 for more information).

What CRYSVITA looks like and contents of the pack
CRYSVITA comes as a clear to slightly opalescent, colourless to pale yellow/brown solution for injection in a pre-filled syringe. Each pack contains 1 pre-filled syringe.

The different strengths of the medicinal product can be identified by a different coloured plunger rod: 10 mg (blue), 20 mg (red), and 30 mg (green).

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medinfo@kyowakirin.com

Manufacturer
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Kyowa Kirin Holdings B.V.
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

INSTRUCTIONS FOR USE

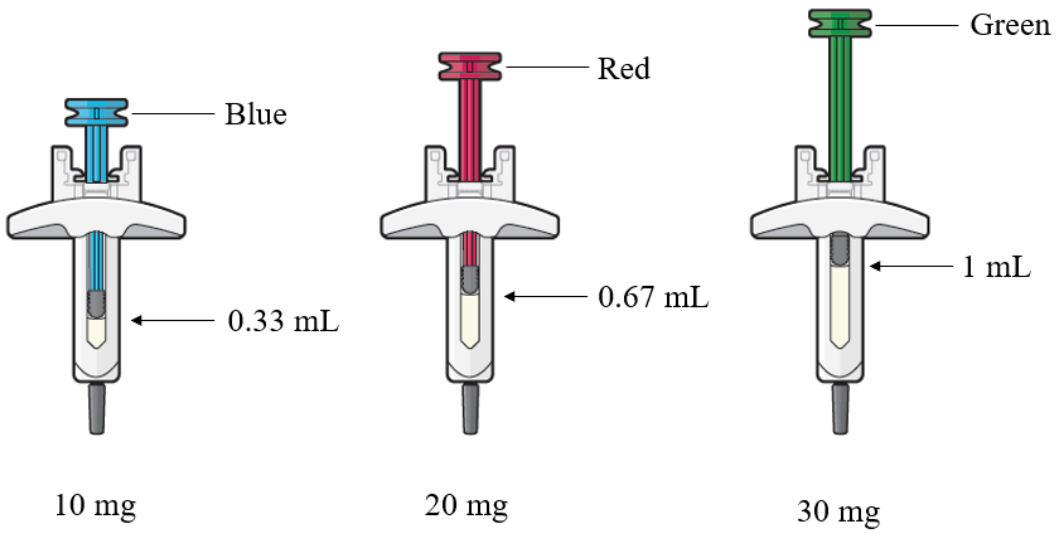
The following Instructions for Use are intended for:
- **self-administration**
- **administration by a caregiver or healthcare professional**

Read these Instructions for Use carefully before you use CRYSVITA:

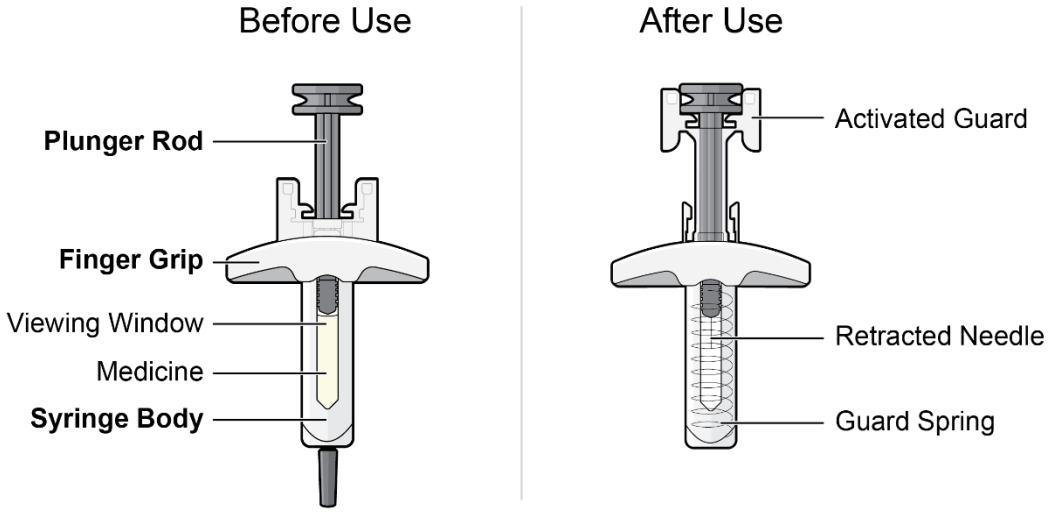
- Only give this medicine to yourself or someone else if you have been told to do so by your doctor.
- You should only give this medicine to yourself or someone else after you have been trained in injection technique. The first self-injection after start of treatment or after any dose change should be carried out in front of a doctor, pharmacist, or nurse (healthcare provider).
- Always use this medicine exactly as your healthcare provider has told you. Check with your healthcare provider if you are not sure.
- Your doctor will prescribe your correct dose. Your dose is measured in milligrams (mg).
- Your healthcare provider will tell you how much CRYSVITA to give yourself or someone else. You may need more than one pre-filled syringe to get the correct dose.
- If your healthcare provider tells you that more than one injection is needed to give your required dose, you must repeat the following Steps 2-4 for each injection.
- Use new supplies for each injection.
- Each pre-filled syringe is for single use only. Always use a new CRYSVITA pre-filled syringe for each injection, see step 4 on how to dispose used syringes and other supplies.
- When possible, use a different site on the body for each injection.
- When giving CRYSVITA to a young child, it may be helpful to have another person present to provide support.
- Do not use CRYSVITA if allergic to any ingredients of this medicine. Stop using CRYSVITA if you have any allergic reaction during or after the injection and contact your healthcare provider straightaway. See section 2 of the package leaflet for more information.

CRYSVITA is available in three different strengths of pre-filled syringe: 10 mg (blue), 20 mg (red), and 30 mg (green). The amount of liquid in the pre-filled syringes varies per strength. The syringes you will be given will depend upon your prescribed dose.

These instructions are used for all three strengths.



The parts of the CRYSVITA pre-filled syringe are shown below:



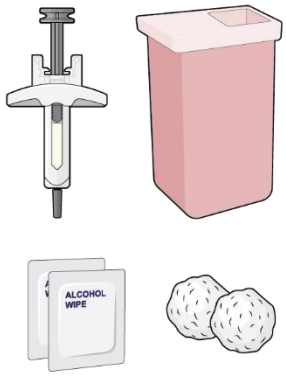
Step 1. Gather and Inspect Supplies

CRYSVITA should be stored in a refrigerator before use. When you need to give CRYSVITA to yourself or someone else, take CRYSVITA out of the refrigerator, but keep it in the carton. Place the carton on a clean, flat surface.
Look at the CRYSVITA cartons to check the strength of each pre-filled syringe you have been given. Make sure that you have the correct number of syringes, and correct strengths of each pre-filled syringes to match the dose in mg as advised by your healthcare provider.
If you are not sure, ask your healthcare provider for advice.

Let the pre-filled syringe carton warm to room temperature **for 45 minutes**. **Do not** warm the pre-filled syringe in any other way, such as with hot water or a microwave oven. **Do not** put the pre-filled syringe in direct sunlight.

After 45 minutes, open the carton and remove the plastic tray. Gently grasp the pre-filled syringe by the syringe body and remove from the tray.

Do not lift the syringe by the plunger rod or needle cap.
Do not touch the plunger rod or remove the needle cap until you are ready to use them.



Place all the items you will need on a clean, flat surface. For each injection you will need:

- CRYSVITA pre-filled syringe
- Alcohol wipes
- Sharps container
- Gauze pad or cotton wool

Contact your healthcare provider if you do not have these supplies.

Do not use the pre-filled syringe if the needle cap is missing or not securely attached.
Do not use the pre-filled syringe if it is cracked or broken in any way.

Note down the date of administration, name of the medicine and batch number (which is on the packaging after Lot) and keep this information in a safe place.

Check the strength on the label of each pre-filled syringe.
Check the expiry date (shown after EXP) on the label of each pre-filled syringe.
Do not use the pre-filled syringe if it is past the expiry date.

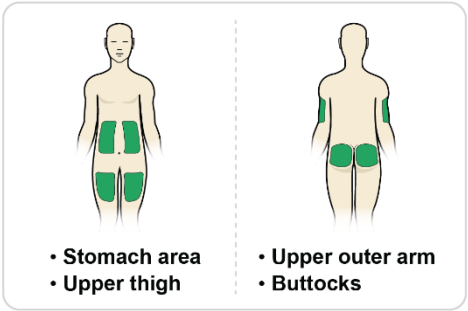
Inspect the liquid in the pre-filled syringe. Do not shake.
CRYSVITA liquid should be clear to slightly opalescent, colourless to pale brown-yellow.

Note: It is normal for the medicine to have air bubbles. Air bubbles will not harm you or affect your dose.

Do not use the pre-filled syringe if the liquid is discoloured, cloudy or contains any particles.

Wash your hands thoroughly with soap and water before going to Step 2.

Step 2. Prepare the Injection Site



The injection must be given into the fatty layer just below the skin. You will need to choose an injection site. If you are giving the injection to yourself, suitable areas are:

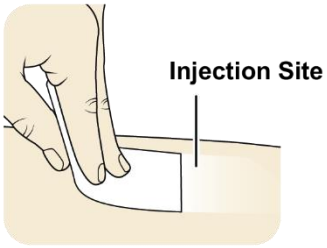
- stomach area, upper thighs

If you are giving the injection to someone else, suitable areas are:

- stomach area, upper thighs, outer area of upper arms, buttocks

Do not inject:

- an area that is sore, red, bruised or where the skin is broken
- an area that has stretch marks or scars (including burns)
- directly into a mole, or an area around a mole



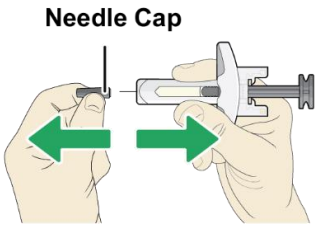
Clean the injection site with an alcohol wipe and let it air dry.

Do not touch or blow on the clean injection site.

If you are giving more than one injection, use a **different site** for each injection. Clean each injection site with a new alcohol wipe and leave the skin to air dry.

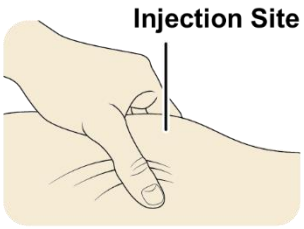
CRYSVITA should be injected into clean dry skin.

Step 3. Inject CRYSVITA

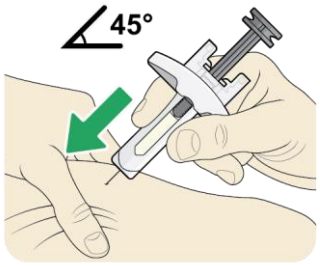


Hold by the **syringe body** with one hand and with the **needle cap pointed away from you**.
Pull the **needle cap straight off** with your other hand.
Do not twist the needle cap.
Throw the needle cap away in an approved sharps container.

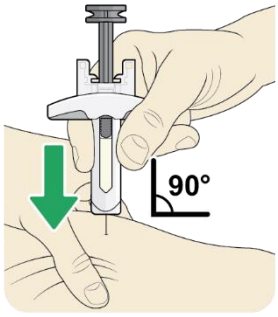
- **Do not** touch the needle or plunger rod.
- **Do not** allow the needle to touch any surface once the cap has been removed.
- **Do not** use the syringe if you drop it after removing the cap or if the needle appears damaged.



Without touching the clean injection site, pinch the surrounding skin firmly between your thumb and fingers, creating an area about 5 cm wide.

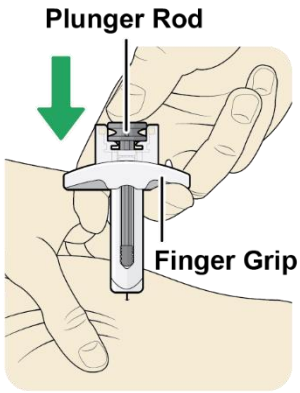


OR



Hold the syringe between the thumb and index finger of your dominant hand.
The needle should be inserted into the skin at **a 45° angle or 90° angle.**
Your healthcare provider will tell you which angle you should use.

Use a quick 'dart-like' motion to insert the needle into the pinched skin.
Do not push the plunger when inserting the needle.



When the needle is inserted do not move it around.

Keep pinching the skin.
Grasp the **finger grip** with one hand and **slowly and steadily push** the **plunger rod** all the way down until the syringe is empty.

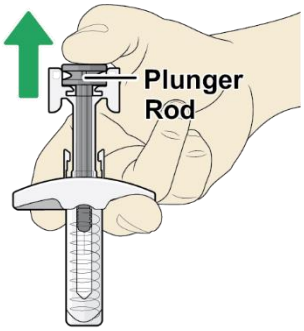
Do not remove the needle yet.

After you have given the full dose, **keep the syringe at the same injection angle** and remove by gently pulling the syringe straight out.

Do not tilt the syringe while removing it.

Do not rub the injection site.

Release the pinched skin.



Release the plunger rod. The guard will activate and cover the needle.

To avoid any injury, **do not** put the cap back on the needle.

Do not touch any exposed needle.

If there is any bleeding, press the injection site with a cotton ball or gauze pad for a few seconds.

Step 4. After each injection

Put your used caps and syringes in the sharps disposal container.
Do not throw away syringes in your household waste.

When your sharps container is almost full, you will need to follow your local guidelines to request another container and to dispose of it correctly.

Reminder: If you are giving more than one injection, repeat steps 2-4 for each injection.
Use new supplies for each injection.

Note the date of the injection and note all the areas where you have injected so that where possible you can use different sites for the next injection.