▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION - CRYSVITA (BUROSUMAB) SOLUTION FOR INJECTION

1. NAME OF THE MEDICINE

Burosumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CRYSVITA 10 mg/mL solution for injection contains 10 mg burosumab in a single use vial
CRYSVITA 20 mg/mL solution for injection contains 20 mg burosumab in a single use vial
CRYSVITA 30 mg/mL solution for injection contains 30 mg burosumab in a single use vial

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

Excipient with known effect
Each vial contains 45.91 mg sorbitol.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

Sterile, single-use, preservative-free, clear to slightly opalescent, colourless to pale brownish-yellowish solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CRYSVITA (burosumab) is indicated for the treatment of X-linked hypophosphataemia (XLH) in adults, adolescents and children 1 year of age or older.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated and monitored by specialist medical practitioners experienced in the management of patients with metabolic bone disease.

Important dosage and administration information

Discontinue oral phosphate and active vitamin D analogues (e.g. calcitriol, paricalcitol, doxercalciferol, calcifediol) 1 week prior to initiation of treatment (see Section 4.3 Contraindications). Vitamin D replacement or supplementation with inactive forms of vitamin D may be continued as per local guidelines (see 25-Hydroxy Vitamin D Supplementation below**)**.

Fasting serum phosphate concentration should be below the reference range for age prior to initiation of treatment (see Section 4.3 Contraindications).

Burosumab is administered by subcutaneous injection and should be administered by a healthcare provider.

The maximum volume of burosumab per injection site is 1.5 mL. If multiple injections are required, administer at different injection sites.

Paediatric Patients with X-linked hypophosphataemia (children aged 1-11 years and adolescents aged 12-17 years of age)

The recommended starting dose regimen is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, every 2 weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. All doses should be rounded to the nearest 10 mg.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 4 weeks for the first 3 months of treatment, and thereafter as appropriate. If serum phosphate is within the reference range for age, continue with the same dose. Follow dose adjustment schedule below to maintain serum phosphate within the reference range for age.

Dose adjustment
Reassess fasting serum phosphate level 4 weeks after dose adjustment.
Do not adjust burosumab more frequently than every 4 weeks.

Dose increase
If serum phosphate is below the reference range for age, the dose may be increased stepwise up to a maximum of 2.0 mg/kg, rounded to the nearest 10 mg, administered every 2 weeks (maximum dose of 90 mg).

Table 1: XLH Paediatric Dose Schedule for Stepwise Dose Increase

Body Weight (kg)	Starting Dose (mg)	First Dose Increase to (mg)	Second Dose Increase to (mg)
10 – 14	10	15*	20
15 – 18	10	20	30
19 – 31	20	30	40
32 – 43	30	40	60
44 – 56	40	60	80
57 – 68	50	70	90
69 – 80	60	90	90
81 – 93	70	90	90
94 – 105	80	90	90
106 and greater	90	90	90

*This dose increase is an exception to rounding to the nearest 10 mg

Dose decrease
If serum phosphate is above the reference range for age, withhold the next dose and reassess the serum phosphate level within 4 weeks. The patient must have serum phosphate below the reference range for age to restart burosumab. Once serum phosphate is below the reference range for age, treatment may be restarted as per Table 2 below. Reassess serum phosphate level 4 weeks after dose adjustment. If serum phosphate is below the reference range for age 4 weeks after dose adjustment, the dose can be restarted at 0.8 mg/kg every 2 weeks.

Table 2: XLH Paediatric Dose Schedule for Re-Initiation of Therapy

Previous Dose (mg)	Re-Initiation Dose (mg)
10	5
15	10
20	10
30	10
40	20
50	20
60	30
70	30
80	40
90	40

Adult patients with X-linked hypophosphataemia (18 years of age and older)

The recommended dose regimen in adults is 1 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered every 4 weeks.

After initiation of treatment with burosumab, measure fasting serum phosphate every 4 weeks, measured 2 weeks post-dose, for the first 3 months of treatment, and thereafter as appropriate. If serum phosphate is within the normal range, continue with the same dose.

Dose decrease
Reassess fasting serum phosphate level 2 weeks after dose adjustment.
Do not adjust burosumab more frequently than every 4 weeks.

If serum phosphate is above the normal range, withhold the next dose and reassess the serum phosphate level within 4 weeks. The patient must have serum phosphate below the normal range to be able to restart 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 according to the dose schedule shown in Table 3 below. Reassess serum phosphate 2 weeks after any change in dose.

Table 3: XLH Adult Dose Schedule for Re-Initiation of Therapy

Previous Dose (mg)	Re-Initiation Dose (mg)
40	20
50	20
60	30
70	30
80 and greater	40

All Patients

Missed or late dosing
If a patient misses a dose, resume burosumab as soon as possible at prescribed dose. To avoid missed doses, treatments may be administered 3 days either side of the scheduled treatment date.

25-Hydroxy Vitamin D Supplementation
Monitor 25-hydroxy vitamin D levels. Supplement with cholecalciferol or ergocalciferol to maintain 25-hydroxy vitamin D levels in the normal range for age. Do not administer active Vitamin D analogues during burosumab treatment (see Section 4.3 Contraindications).

Special Populations

Renal impairment
Burosumab has not been studied in patients with renal impairment. Burosumab must not be given to patients with severe or end stage renal disease (see Section 5.2 Pharmacokinetic Properties).

Method of administration

For subcutaneous use.

Burosumab should be injected in the upper arm, abdomen, buttock or thigh. Injection sites should be rotated with each injection administered at a different anatomic location than the previous injection. Do not inject into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact. 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 should be split and should be administered at different injection sites. Injection sites should be rotated and carefully monitored for signs of potential reactions (see Section 4.4 Special warnings and precautions for use).

4.3 CONTRAINDICATIONS

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

Concurrent administration with oral phosphate and / or active vitamin D analogues.

Serum phosphate level within or above the normal range for age at initiation of treatment.

Severe renal impairment or end stage renal disease (see Section 5.2 Pharmacokinetic Properties).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Traceability
In order to improve the traceability of biological medicinal products, the name and batch number of administered product should be clearly recorded with 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 does not exceed the upper limit 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.

Serum parathyroid hormone
Increases in serum parathyroid hormone have been observed in some XLH patients during treatment with burosumab. Periodic measurement of serum parathyroid hormone is advised.

Injection site reactions
Administration may result in local injection site reactions. Administration should be interrupted in any patient experiencing severe injection site reactions.

Hypersensitivity
Discontinue burosumab if serious hypersensitivity reactions occur.

Use in the elderly
No conclusion can be made regarding any differences in safety or efficacy between patients over 65 years of age and those under 65 years of age.

Paediatric use
The safety and efficacy of burosumab in children with XLH under 1 year of age has not been established in clinical studies.

Effects on laboratory tests
No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No pharmacokinetic interaction studies have been performed for burosumab.

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 and could potentially exacerbate hypocalcaemia.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no clinical data available on the effect of burosumab on human fertility. The healthcare provider should discuss the use of appropriate contraception with sexually active women and adolescent girls taking burosumab to assist in weighing up the individual risks and benefits. No specific fertility studies in animals with burosumab were conducted, but relevant surrogate endpoints were examined in a general toxicity study in cynomolgus monkeys. Animals were treated with burosumab at doses up to 30 mg/kg every 2 weeks (yielding up to 56 times the exposure in adults at the maximum recommended clinical dose of 1 mg/kg every 4 weeks). Male monkeys showed mineralisation of the rete testis and seminiferous tubules (associated with hyperphosphataemia), but no changes in semen analysis. No adverse effects on reproductive organs to suggest impairment of fertility were observed in female monkeys.

Use in pregnancy – Category B3
There are no available data on burosumab use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Adverse effects on embryofetal development were observed with burosumab in animals. Burosumab is not recommended for use during pregnancy. Fetal loss and pre-term births were increased and the gestation period was shortened in pregnant cynomolgus monkeys given burosumab at 30 mg/kg once every 2 weeks (yielding 64 times the exposure in adults as the maximum

recommended clinical dose of 1 mg/kg every 4 weeks). This occurred in conjunction with maternal hyperphosphataemia and placental mineralisation. Burosumab was shown to cross the placenta. Ectopic mineralisation was not observed in fetuses or offspring, and treatment did not produce malformations, or affect growth, development or survival of the offspring.

Use in lactation

There are no data on the use of burosumab in breastfeeding women. It is unknown whether burosumab is excreted in human milk, although the presence of the maternal IgG in milk is recognised. A decision must be made whether to discontinue breast feeding or to discontinue / abstain from burosumab therapy taking into account the benefit of breast feeding for the child, the benefit of the therapy for the woman and the potential risk to the child from exposure to burosumab.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Burosumab may cause dizziness and, as a result, may influence the ability to drive or operate machinery. Patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that burosumab does not affect them adversely.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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, adverse reactions are presented in order of decreasing seriousness.

Adverse Reactions Reported in Paediatric Patients with XLH ≥1 year of age

The most common adverse reactions (>10%) reported in paediatric patients ≥1 year of age during clinical trials were injection site reactions (56%), cough (56%), headache (50%), pyrexia (43%), pain in extremity (40%), vomiting (39%), tooth abscess (35%), vitamin D decreased (32%), diarrhoea (25%), rash (24%), nausea (15%), constipation (11%), dental caries (11%) and myalgia (11%). This data is based the integrated safety assessment of 94 subjects who received at least one dose of burosumab and were included in studies UX023-CL201, UX023-CL205 and UX023-CL301.

An overview of adverse reactions observed from burosumab clinical trials and post marketing sources in paediatrics is presented in Table 4.

Table 4: Adverse Reactions Reported in Paediatric Patients with XLH ≥1 year of age

MedDRA System Organ Class	Frequency Category	Adverse Reaction
Infections and infestations	Very common	Tooth abscess[1]
Respiratory, thoracic and mediastinal disorders	Very common	Cough[2]
Nervous system disorder	Very common	Headache
	Common	Dizziness[3]
Gastrointestinal Disorders	Very common	Vomiting Nausea Diarrhoea Constipation Dental caries
Skin and subcutaneous tissue disorder	Very common	Rash[4]

Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Very common	Pain in extremity
General disorders and administration site conditions	Very common	Injection site reaction[5] Pyrexia
Investigations	Very common	Vitamin D decreased[6]
	Not known	Blood phosphorus increased[7]

[1]Tooth abscess includes: Tooth abscess, Tooth infection and Toothache.
[2]Cough includes: Cough and Productive cough.
[3]Dizziness includes: Dizziness and Dizziness exertional.
[4]Rash includes: Rash, Rash erythematous, Rash generalised, Rash pruritic, Rash maculo-papular and Rash pustular.
[5]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.
[6]Vitamin D decreased includes: Vitamin D deficiency, Blood 25-hydroxycholecalciferol decreased and Vitamin D decreased.
[7]Blood phosphorus increased includes: Blood phosphorus increased and Hyperphosphataemia.

Description of selected adverse reactions in children with XLH ≥1 year of age

Injection site reactions
Approximately 56% of the patients had an injection site reaction. The injection site reactions were generally mild in severity, occurred within 1 day of medicinal product injection, lasted approximately 1 to 3 days, required no treatment, and resolved in almost all instances.

Hypersensitivity reactions
The most frequent potential hypersensitivity reaction was rash (18%). The events were mild or moderate in severity.

Adverse Events Reported in Paediatric Patients with XLH ≥1 year of age in Study UX023-CL301

The most common adverse events in paediatric patients ≥ 1 year of age (reported in ≥ 5% of patients and having a higher incidence with burosumab than with active control) in Study UX023-CL301 are listed in Table 5.

Table 5: Common Adverse Events in Paediatric Patients ≥ 1 year of age (reported in ≥ 5% patients) with a Higher Incidence in the Burosumab Group (Study UX023-CL301)

Adverse Events by Body System	**Burosumab (N=29)**	**Active Control (N=32)**
General disorders		
Pyrexia	55.2%	21.9%
Injection site erythema	31.0%	0.0%
Injection site reaction	24.1%	0.0%
Injection site pruritus	10.3%	0.0%
Injection site swelling	10.3%	0.0%
Injection site rash	10.3%	0.0%
Pain	6.9%	0.0%
Injection site erosion	6.9%	0.0%
Injection site urticaria	6.9%	0.0%
Gastrointestinal disorders		
Vomiting	41.4%	25.0%
Dental caries	31.0%	6.3%
Diarrhoea	24.1%	6.3%
Constipation	17.2%	0.0%
Toothache	13.8%	3.1%
Abdominal pain upper	10.3%	9.4%
Nausea	10.3%	3.1%

Adverse Events by Body System	**Burosumab (N=29)**	**Active Control (N=32)**
Abdominal discomfort	6.9%	6.3%
Abdominal pain	6.9%	3.1%
Teething	6.9%	0.0%
Infections and infestations		
Tooth abscess	27.6%	9.4%
Upper respiratory tract infection	10.3%	9.4%
Rhinitis	6.9%	6.3%
Varicella	6.9%	0.0%
Pneumonia	6.9%	0.0%
Viral infection	6.9%	3.1%
Respiratory, thoracic and mediastinal disorders		
Cough	51.7%	18.8%
Rhinorrhea	24.1%	6.3%
Nasal congestion	17.2%	3.1%
Oropharyngeal pain	17.2%	3.1%
Asthma	13.8%	3.1%
Rhinitis allergic	6.9%	0.0%
Musculoskeletal and connective tissue disorders		
Arthralgia	44.8%	31.3%
Pain in extremity	37.9%	31.3%
Nervous system disorders		
Headache	34.5%	18.8%
Skin and subcutaneous tissue disorders		
Rash	10.3%	6.3%
Erythema	6.9%	0.0%
Injury, poisoning and procedural complications		
Contusion	13.8%	0.0%
Fall	10.3%	0.0%
Procedural pain	6.9%	0.0%
Ear and labyrinth disorders		
Ear pain	13.8%	3.1%
Investigations		
Vitamin D decreased	20.7%	3.1%
Metabolism and nutrition disorders		
Vitamin D deficiency	17.2%	3.1%
Immune system disorders		
Seasonal allergy	13.8%	6.3%
Congenital, familial and genetic disorders		
Tooth hypoplasia	6.9%	0.0%
Renal and urinary disorders		
Dysuria	6.9%	0.0%

Adverse Reactions Reported in Adult Patients with XLH

The most common adverse reactions reported in adult patients during clinical trials were back pain (23%), headache (21%), tooth infection (19%), restless legs syndrome (13%), muscle spasms (12%), vitamin D decrease (15%) and dizziness (11%). This data is based on the integrated safety assessment of 176 subjects who received at least 1 dose of burosumab and were included in studies UX023-CL203, UX023-CL303, UX023-CL304, KRN23-INT-001 and KRN23-INT-002.

An overview of adverse reactions observed from burosumab clinical trials in adults is presented in Table 6.

Table 6: Adverse Reactions Reported in Adult Patients with XLH

MedDRA System Organ Class	Frequency Category	Adverse Reaction
Infections and infestations	Very common	Tooth infection[1]
Nervous system disorders	Very common	Headache[2]
	Very common	Dizziness
	Very common	Restless legs syndrome
Gastrointestinal disorders	Common	Constipation
Musculoskeletal and connective tissue disorders	Very common	Back pain
	Very common	Muscle spasms
Investigations	Very common	Vitamin D decreased[3]
	Common	Blood phosphorus increased[4]

[1] Tooth infection includes: Tooth abscess and Tooth infection.

[2] Headache includes: Headache and Head discomfort.

[3] Vitamin D decreased includes: Vitamin D deficiency, Blood 25-hydroxycholecalciferol decreased and Vitamin D decreased.

[4] Blood phosphorus increased includes: Blood phosphorus increased and Hyperphosphataemia.

Description of selected adverse reactions in adults with XLH

Injection site reactions
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). The injection site reactions were generally mild in severity, occurred within 1 day of medicinal product injection, lasted approximately 1 to 3 days, required no treatment, and resolved in almost all instances.

Hypersensitivity reactions
The frequency of hypersensitivity reactions was 6% in both the burosumab and placebo groups. The hypersensitivity reactions were mild to moderate in severity.

Hyperphosphataemia
In the double-blind period of Study UX023-CL303, 9 of 134 (7%) patients in the burosumab treatment group experienced hyperphosphataemia meeting the protocol-specified criteria for dose reduction. The hyperphosphataemia was managed with dose reduction.

Restless legs syndrome
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.

Adverse Events Reported in Adult Patients with XLH in Study UX023-CL303

The most common adverse events in adult patients (reported in ≥5% of patients and having a higher incidence with burosumab than with placebo) in Study UX023-CL303 are listed in Table 7.

Table 7: Common Adverse Events in Adult Patients (reported in ≥ 5% of patients) with a Higher Incidence in the Burosumab Group During the Placebo-controlled Treatment Period (Study UX023-CL303)

Adverse Events by Body System	Burosumab (N=68)	Placebo (N=66)
Infections and infestations		
Nasopharyngitis	16.2%	9.1%
Tooth abscess	13.2%	9.1%
Influenza	5.9%	4.5%
Musculoskeletal and connective tissue disorders		
Back pain	14.7%	9.1%
Muscle spasms	7.4%	3.0%
Nervous system disorders		
Headache	13.2%	7.6%
Dizziness	11.8%	6.1%
Restless legs syndrome	11.8%	7.6%
Gastrointestinal disorders		
Nausea	10.3%	9.1%
Constipation	8.8%	0.0%
Injury, poisoning and procedural complications		
Procedural pain	5.9%	0.0%
Metabolism and nutrition disorders		
Vitamin D deficiency	7.4%	4.5%
Respiratory, thoracic and mediastinal disorders		
Cough	5.9%	4.5%
Rhinorrhoea	5.9%	4.5%

Immunogenicity

Overall, the incidence of anti-drug antibodies (ADA) to burosumab was <10% in adults and paediatric subjects administered burosumab. The incidence of neutralising ADA was 3.2% and neutralising ADA were only found in paediatric subjects. No adverse events, loss of efficacy, or changes in pharmacokinetics profile were associated with these findings.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems

4.9 OVERDOSE

There is no experience with overdose of burosumab. In case of overdose, it is recommended to stop burosumab and to monitor biochemical response. For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Burosumab is a recombinant human monoclonal IgG1 antibody that binds to and inhibits the biological activity of fibroblast growth factor 23 (FGF23), present in excess in X-linked hypophosphataemia. Neutralisation of FGF23 by burosumab increases renal tubular reabsorption of phosphate and the serum concentration of 1, 25 dihydroxy-Vitamin D.

Clinical trials

Paediatric X-Linked Hypophosphataemia

Burosumab has been evaluated in 3 studies enrolling a total of 126 paediatric patients with XLH.

Study UX023-CL301

Paediatric Study UX023-CL301 is a randomised, open-label study in 61 paediatric XLH patients, 1 to 12 years old, that compared treatment with burosumab to active control (oral phosphate and active vitamin D therapy). All patients had radiographic evidence of rickets at baseline, with an RSS score of ≥2 and had received oral phosphate and active vitamin D analogues for a mean (SD) duration of 3.8 (3.1) years. Oral phosphate and active vitamin D analogues were discontinued prior to study enrolment for a 7-day washout period and then restarted for patients in the active control group. Patients were randomised to receive either burosumab at a starting dose of 0.8 mg/kg every 2 weeks or oral phosphate and active vitamin D. Patients randomised to active control received a mean oral phosphate dose of approximately 41 mg/kg/day (18 to 110 mg/kg/day) at Week 40 and approximately 46 mg/kg/day (18 to 166 mg/kg/day) at Week 64. They also received either a mean oral calcitriol dose of 26 ng/kg/day at Week 40 and 27 ng/kg/day at Week 64 or a therapeutically equivalent amount of alfacalcidol. Eight patients in the burosumab group titrated up to 1.2 mg/kg based on serum phosphate measurements.

Study UX023-CL201

Paediatric Study UX023-CL201, is a randomised, open-label study in 52 prepubescent XLH patients, 5 to 12 years old, which compared treatment with burosumab administered every 2 weeks versus every 4 weeks. Following an initial 16-week dose titration phase, patients completed 48 weeks of treatment with burosumab every 2 weeks or every 4 weeks. Burosumab dose was adjusted to target a fasting serum phosphate concentration of 1.13 to 1.62 mmol/L [3.5 to 5.0 mg/dL] based on the fasting phosphate level on the day of dosing.

Twenty-six of 52 patients received burosumab every 2 weeks up to a maximum dose of 2 mg/kg. The average dose was 0.73 mg/kg (range: 0.3, 1.5) at Week 16, 0.98 mg/kg (range: 0.4, 2.0) at Week 40 and 1.04 mg/kg (range: 0.4, 2.0) at Week 60. The remaining 26 patients received burosumab every 4 weeks. At study entry, the mean age of patients was 8.5 years and 46% were male. Ninety-six percent had received oral phosphate and active vitamin D analogues for a mean (SD) duration of 6.9 (2.4) years. Oral phosphate and active vitamin D analogues were discontinued prior to study enrolment. Ninety-four percent of patients had radiographic evidence of rickets at baseline.

Study UX023-CL205

Paediatric Study UX023-CL205 is a randomised, open-label study in 13 paediatric XLH patients, aged 1 to 4 years. Patients received burosumab at a dose of 0.8 mg/kg every 2 weeks with 5 patients titrating up to 1.2 mg/kg based on serum phosphate measurements. All patients completed at least 40 weeks on study; no patients discontinued. At study entry, the mean age of patients was 2.9 years and 69% were male. All patients had radiographic evidence of rickets at baseline and had received oral phosphate and active vitamin D analogues for a mean (SD) duration of 16.4 (13.8) months. Oral phosphate and active vitamin D analogues were discontinued prior to study enrolment.

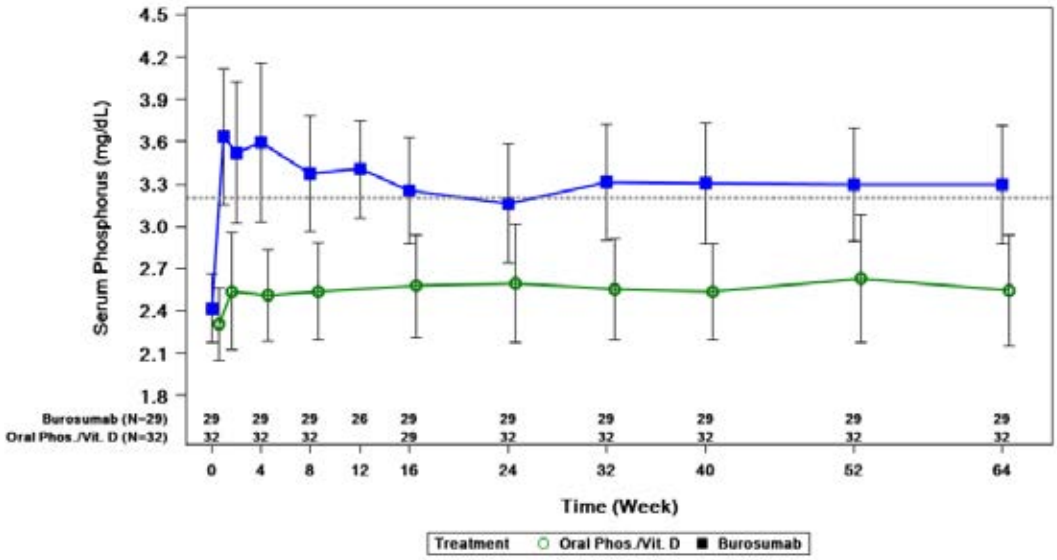
Serum Phosphate

In Study UX023-CL301, burosumab increased mean (SD) serum phosphate levels from 2.4 (0.24) mg/dL at baseline to 3.3 (0.43) mg/dL at Week 40. In the active control group, mean (SD) serum phosphate concentrations increased from 2.3 (0.26) mg/dL at baseline to 2.5 (0.34) mg/dL at Week 40 (Figure 1). The renal phosphate reabsorption assessed by TmP/GFR increased in the burosumab treated patients from a mean (SD) of 2.2 (0.37) at baseline to 3.4 (0.67) mg/dL at Week 40. In the active control group, mean (SD) TmP/GFR decreased from 2.0 (0.33) mg/dL at baseline to 1.8 (0.35) mg/dL at Week 40.

In Study UX023-CL201, burosumab increased serum phosphate levels 2.4 (0.41) mg/dL at baseline to 3.3 (0.40) mg/dL and 3.4 (0.45) mg/dL at Week 40 and Week 64 in the patients who received burosumab every 2 weeks. The ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) increased in these patients from mean (SD) of 2.2 (0.49) at baseline to 3.3 (0.60) and 3.4 (0.53) mg/dL at Week 40 and Week 64.

In Study UX023-CL205, mean (SD) fasting serum phosphate levels increased from 2.5 (0.28) mg/dL at baseline to 3.5 (0.49) mg/dL at Week 40.

Figure 1: Mean (± SD) Serum Phosphate Concentration (mg/dL) over Time in the Phase 3 UX023-CL301 Paediatric Study by Treatment Group in Paediatric subjects 1-12 years Receiving Burosumab Every 2 Weeks (Q2W) or Active Control



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

Radiographic Evaluation of Rickets

Radiographs were examined to assess XLH-related rickets using the 10-point Thacher Rickets Severity Score (RSS) and the 7-point Radiographic Global Impression of Change (RGI-C). The RSS score is assigned based on images of the wrist and knee from a single time point, with higher scores indicating greater rickets severity. The RGI-C score is assigned based on side-by side comparisons of wrist and knee radiographs from 2 time points, with higher scores indicating greater improvement in radiographic evidence of rickets. An RGI-C score of +2.0 was defined as radiographic evidence of substantial healing.

In study UX023-CL301, burosumab healed and reduced the severity of rickets to a greater extent than active control after 40 weeks of treatment, as assessed by decreasing RSS total scores and increasing RGI-C global score, shown in Table 8.

Table 8: Rickets Response in Paediatric Subjects 1-12 Years Receiving Burosumab Every 2 Weeks in Study UX023-CL301

Endpoint Timepoint	**Burosumab Every 2 Weeks (N=29)**	**Active Control (N=32)**
RSS Total Score		
Baseline Mean (SD)	3.2 (0.98)	3.2 (1.14)
LS Mean change from baseline in total score[a] (reduction indicates improvement) with 95% CI		
Week 40	-2.1 (-2.28, -1.87)	-0.7 (-1.03, -0.40)
RGI-C Global Score[b]		
LS Mean score[c] (positive indicates healing) with 95% CI		
Week 40	+1.92 (+1.76, +2.07)	+0.78 (+0.53, +1.03)

[a] The estimates of LS mean and 95% CI for Week 40 are from a GEE model accounting for treatment, visit, treatment by visit interaction and baseline age stratification factor as factors, baseline RSS score as a continuous covariate. The GEE model included data up to Week 64.
[b] RGI-C at Week 40 is the primary endpoint of Study UX023-CL301
[c] The estimates of LS mean and 95% CI for Week 40 are from a GEE model accounting for RGI-C as the dependent variable, treatment, visit, treatment by visit interaction and baseline age stratification factor as factors, baseline RSS score as a continuous covariate, with exchangeable covariate structure. The GEE model included data up to Week 64.

In Study UX023-CL201 and study UX023-CL205, RSS total score decreased, and RGI-C global score demonstrated healing after 40 weeks of treatment with burosumab every 2 weeks as shown in Table 9.

Table 9: Rickets Response in Paediatric Subjects aged 1-12 Years Receiving Burosumab Every 2 Weeks in Study UX023-CL201 and Study UX023-CL205

Endpoint Timepoint	**Burosumab Every 2 Weeks**	
	UX023-CL201[a] (N=26)	**UX023-CL205[b] (N=13)**
RSS Total Score		
Baseline Mean (SD)	1.9 (1.17)	2.9 (1.37)
LS Mean change from baseline in total score (reduction indicates improvement) with 95% CI		
Week 40	-1.1 (-1.28, -0.85)	-1.7 (-2.03, -1.44)
RGI-C Global Score		
LS Mean score (positive indicates healing) with 95% CI		
Week 40	+1.7 (+1.48, +1.84)	+2.3 (+2.16, +2.51)

[a] The estimates of LS mean and 95% CI are from a generalised estimating equation (GEE) model accounting for regimen, visit, regimen by visit interaction, baseline RSS for Study UX023-CL201.
[b] The estimates of LS mean and 95% CI are from an ANCOVA model accounting for age and baseline RSS for Study UX023-CL205.

Lower Extremity Skeletal Abnormality

In Study UX023-CL301, lower extremity skeletal abnormalities were assessed by RGI-C in standing long leg radiographs. At Week 64, the burosumab group maintained greater improvement compared with the active control group (LS mean [SE]: +1.25 [0.17] versus +0.29 [0.12]; difference of +0.97 [95% CI: +0.57, +1.37, GEE model]).

Serum Alkaline Phosphatase Activity

In Study UX023-CL301, mean (SD) serum alkaline phosphatase (ALP) activity decreased from 511 (125) U/L at baseline to 337 (86) U/L in the burosumab group (mean change: -33%), and from 523 (154) U/L at baseline to 495 (182) U/L in the active control group (mean change: -5%) at Week 64.

In Study UX023-CL201, mean (SD) serum total ALP activity decreased from 462 (110) U/L at baseline to 354 (73) U/L at Week 64 (mean change: -23%) in patients who received burosumab every 2 weeks.

In Study UX023-CL205, mean (SD) serum total ALP activity decreased from 549 (194) U/L at baseline to 335 (88) U/L at Week 40 (mean change: -36%).

Growth

In Study UX023-CL301, burosumab treatment for 64 weeks increased standing mean (SD) height Z score from -2.32 (1.17) at baseline to -2.11 (1.11) at Week 64 (LS mean change [SE] of +0.17 [0.07]). In the active control group, the mean (SD) height Z score increased from -2.05 (0.87) at baseline to -2.03 (0.83) at Week 64 (LS mean change [SE] of +0.02 [0.04]).

In Study UX023-CL201, burosumab treatment for 64 weeks increased standing mean (SD) height Z score from -1.72 (1.03) at baseline to -1.54 (1.13) in the patients who received burosumab every 2 weeks (LS mean change of +0.19 [95% CI: 0.09 to 0.29]).

Adult X-Linked Hypophosphataemia

Study UX023-CL303 is a randomised, double-blind, placebo-controlled study in 134 adult XLH patients. The study comprises a 24-week, double-blind, placebo-controlled treatment phase followed by a 24-week open-label treatment period in which all patients received burosumab. Subjects then continued burosumab treatment for an additional 48 weeks in a Treatment Extension Period I (until Week 96) and Treatment Extension Period II (End of Treatment). Burosumab was administered at a dose of 1 mg/kg every 4 weeks. At study entry, the mean age of patients was 40 years (range 19 to 66 years) and 35% were male. All patients had skeletal pain associated with XLH/osteomalacia at baseline. The baseline mean (SE) serum phosphate concentration was below the lower limit of normal at 0.64 (0.10) mmol/L [1.98 (0.314) mg/dL]. Oral phosphate and active vitamin D analogues were not allowed during the study. Of the 134 subjects who enrolled in the study, one patient in the burosumab group discontinued treatment during the 24-week placebo-controlled treatment period, and 7 patients discontinued Burosumab during the open-label treatment period. During Treatment Extension Period I, 7 patients discontinued treatment, and during Treatment Extension Period II, 1 patient discontinued treatment.

Study UX023-CL304 is an open-label, single-arm study in 14 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. At study entry, the mean age of patients was 40 years (range 25 to 52 years) and 43% were male. Oral phosphate and active vitamin D analogues were not allowed during the study.

Serum Phosphate

In Study UX023-CL303 at baseline, mean (SD) serum phosphate was 1.9 (0.32) mg/dL and 2.0 (0.30) mg/dL in the placebo and burosumab groups, respectively. During the initial 24-weekdouble-blind, placebo-controlled period, mean (SD) serum phosphate across the midpoints of dose intervals (2 weeks post dose) was 2.1 (0.30) mg/dL and 3.2 (0.53) mg/dL in the placebo and burosumab groups, and mean (SD) serum phosphate across the ends of dose intervals was 2.1(0.30) mg/dL and 2.7 (0.45) mg/dL in the placebo and burosumab groups.

A total of 93% of patients treated with burosumab achieved a serum phosphate level above the lower limit of normal (LLN) compared to 8% in the placebo group through Week 24 (Table 10).

Table 10: 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)

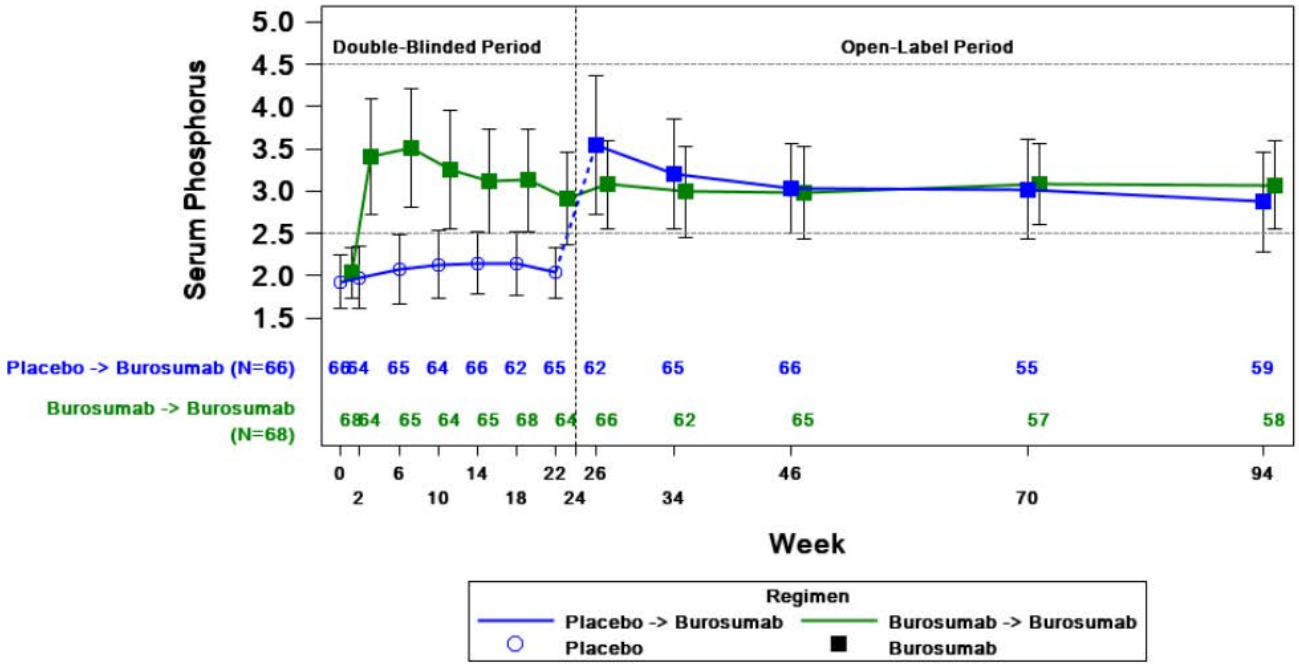
	Placebo (N=66)	Burosumab (N=68)
Achieved Mean Serum Phosphate > LLN Across Midpoints of Dose Intervals Through Week 24 - n (%)	5 (7.6%)	63 (92.6%)
95% CI	(3.3, 16.5)	(83.9, 96.8)
p-value[a]		<0.0001

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 the actual randomisation stratification of BPI Average Pain and region.

During the open-label treatment period, serum phosphate was maintained during continued burosumab therapy (Figure 2), with no evidence of loss of effect through Week 48. Similar results were seen during Treatment Extension Period I and Extension Treatment Period II.

Figure 2: Mean (± SD) Serum Phosphate Peak Concentrations (mg/dL) in Study UX023-CL303[a]



[a] Placebo subjects cross over to receive open-label Burosumab treatment at Week 24.
Note: Dashed lines in figure indicate the upper limit of the serum phosphate reference range, 4.5 mg/dL, and the lower limit of the serum phosphate reference range, 2.5 mg/dL

At baseline, the mean (SD) ratio of TmP/GFR was 1.60 (0.37) and 1.68 (0.40) mg/dL in the placebo and burosumab groups, respectively. At Week 22 (midpoint of a dose interval), mean (SD) TmP/GFR was 1.69 (0.37) and 2.73 (0.75) mg/dL in the placebo and burosumab groups. At Week 24 (end of a dose interval), mean (SD) TmP/GFR was 1.73 (0.42) and 2.22 (0.49) mg/dL in the placebo and burosumab groups. During the open-label treatment period, TmP/GFR remained stable during continued burosumab therapy through Week 48. Similar results were seen during Treatment Extension Period I and Treatment Extension Period II.

Bone Histomorphometry

In Study UX023-CL304, after 48 weeks of treatment, healing of osteomalacia was observed in 10 patients

as demonstrated by decreases in osteoid volume/bone volume (OV/BV) from a mean (SD) score of 26% (12.4) at baseline to 12% (6.6). Osteoid thickness (O.Th) declined in 11 patients from a mean (SD) of 17 (4.1) micrometres to 12 (3.1) micrometres.

Patient Reported Outcomes

Study UX023-CL303 evaluated stiffness and physical function using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index and pain using the Brief Pain Inventory (BPI).
WOMAC Index

The WOMAC Index comprises three domains: stiffness, pain and physical function; each domain ranges from 0 (best health) to 100 (worst health). Changes from baseline in WOMAC stiffness and physical function domain scores were key secondary endpoints. Burosumab treatment for 24 weeks resulted in a statistically significant favourable change relative to placebo in WOMAC Stiffness and trends favouring burosumab treatment in WOMAC Physical Function as shown in Table 11.

Table 11: WOMAC stiffness and physical function domain score changes from baseline to Week 24 and analysis of difference at Week 24

	Placebo	**Burosumab**
	N=66	N=68
WOMAC Index		
Stiffness		
LS Mean (SE) change from Baseline [95% CIs]	+0.25 (3.1) [-5.89, 6.39]	-7.87 (3.0) [-13.82, -1.91]
LS Mean (SE) Difference (Burosumab-Placebo)	-8.12 (3.2)	
p-value	0.0122	
Physical function		
LS Mean (SE) change from Baseline [95% CIs]	+1.79 (2.7) [-3.54, 7.13]	-3.11 (2.6) [-8.12, 1.89]
LS Mean (SE) Difference	-4.9 (2.5)	

5.2 PHARMACOKINETIC PROPERTIES

The following pharmacokinetic parameters were observed in patients with XLH administered the approved recommended starting dosage based on a 70 kg patient, unless otherwise specified.

Burosumab exhibited linear pharmacokinetics following subcutaneous injections within the dose range of 0.1 to 1 mg/kg (0.08 to 0.8 times the maximum approved recommended dosage based on a 70 kg patient). The steady-state trough mean (±SD) concentration of burosumab was 5.8 (±3.4) mcg/mL in adult patients, 15.8 (± 9.4) mcg/mL in patients aged 5 to 12 years, and 14.2 (± 4.0) mcg/mL in patients aged 1 to 4 years.

Absorption
The burosumab mean T_{max} values ranged from 8 to 11 days. The median time to reach maximum serum concentrations (T_{max}) of burosumab is approximately 7 to 13 days.

Distribution
The apparent volume of distribution of burosumab is 7.35 L.

Biotransformation
The exact pathway for burosumab metabolism has not been characterised. Burosumab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination
The clearance of burosumab is dependent on body weight and estimated to be 0.278 l/day in a typical adult (70kg) XLH patient with corresponding disposition half-life ($t_{1/2}$) in the serum of approximately 18 days.

Linearity/non-linearity
Burosumab displays pharmacokinetics that are linear to dose over the subcutaneous dose range of 0.1 to 1.0 mg/kg.

Paediatric Pharmacokinetics/Pharmacodynamics
No significant difference has been observed in the Pharmacokinetics (PK) and Pharmacodynamics of the paediatric XLH population as compared with the adult XLH population. Burosumab clearance and volume of distribution are body weight dependent.

Special Populations
Population PK analyses using data from paediatric and adult subjects who have XLH 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. The effect of renal impairment on the pharmacokinetics of burosumab is unknown. However, renal impairment can induce abnormal mineral metabolism which could increase phosphate concentrations greater than expected with burosumab alone. This increase may result in hyperphosphatemia which can induce nephrocalcinosis

Burosumab must not be given to patients with severe renal impairment, defined as:

- Paediatric patients with an estimated glomerular filtration rate (eGFR) of 15 mL/min/1.73m^3 to 29 mL/min/1.73m^3 or end stage renal disease (eGFR < 15 mL/min/1.73m^3
- Adult patients with a calculated eGFR of 15 mL/min/1.73m^3 to 29 mL/min/1.73m^3 or end stage renal disease (eGFR < 15 mL/min/1.73m^3

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Genotoxicity studies have not been conducted with burosumab. As a large protein molecule, burosumab is not expected to interact with DNA or other chromosomal material.

Carcinogenicity
The carcinogenic potential of burosumab has not been investigated in long-term animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

L-histidine
D-sorbitol
Polysorbate 80
L-methionine
Hydrochloric acid, 10% (for pH adjustment)
Water for injection

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Store in original package to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pack contains 1 mL solution in a clear glass vial with butyl rubber stopper, and aluminium seal.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

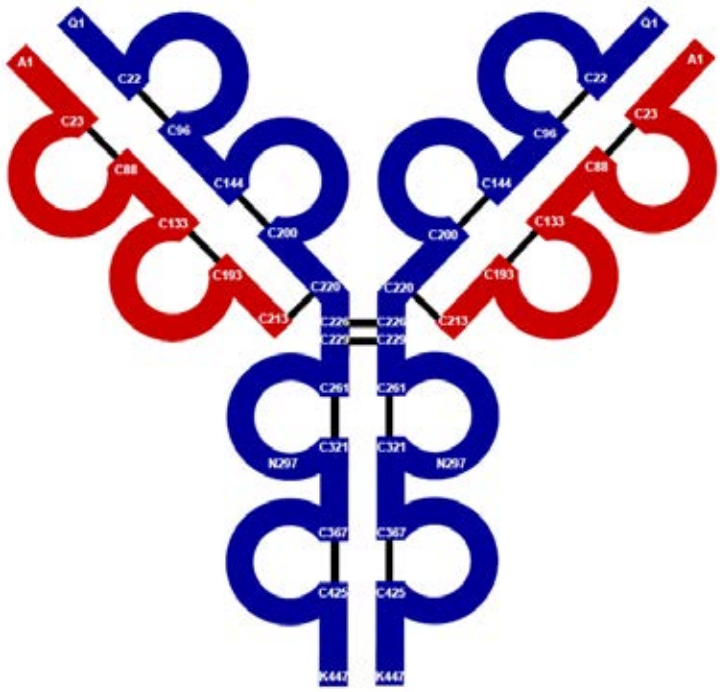
Product is for single use in one patient only. Discard any residue.

Do not shake the vial before use.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Heavy chains (HC) are shown in blue and Light chains are shown in red.

Black lines show the location of disulfide bonds.

N297 of HC: glycosylation site

CAS number

CAS registry number: 1610833-03-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Kyowa Kirin Australia Pty Ltd
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Sydney, NSW 2000

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9. DATE OF FIRST APPROVAL

10 September 2021

10. DATE OF REVISION

No revisions since date of first approval.

Section changed	Summary of new information