

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

KRYSTEXXA 8 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 8 mg of pegloticase (8 mg/ml concentrate). The strength indicates the quantity of the uricase moiety of pegloticase without consideration of the PEGylation.

The active substance pegloticase is a covalent conjugate of uricase produced by a genetically modified strain of *Escherichia coli* and monomethoxypoly (ethylene glycol).

The potency of this product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class.

For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless solution at pH 7.3±0.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KRYSTEXXA is indicated for the treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalize serum uric acid with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated (see section 4.4).

The decision to treat with KRYSTEXXA should be based on an on-going assessment of the benefits and risks for the individual patient (see section 4.4).

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of severe refractory chronic gout.

The medicinal product should be administered in a healthcare setting and by healthcare professionals prepared to manage anaphylaxis and infusion reactions. Close monitoring is required during the infusion and for at least 2 hours after the end of the infusion. Availability of resuscitation equipment must be ensured. Delayed-type hypersensitivity reactions have also been reported.

Posology

The recommended dose is 8 mg pegloticase given as an intravenous infusion every two weeks.

Prior to infusion, patients should receive pre-medication to minimize the risk of infusion-related reactions, e.g. antihistamine the evening before, and again approximately 30 minutes before the infusion, as well as paracetamol and a corticosteroid immediately before each infusion (see section 4.4).

Monitoring of serum uric acid level is required prior to each infusion. KRYSTEXXA should not be administered if two consecutive levels above 6 mg/dl (360 µmol/L) have been measured (see section 4.4).

Before starting the treatment and especially before monitoring the serum uric acid levels, patients should discontinue oral urate-lowering medication and not institute therapy with oral urate-lowering medication while taking KRYSTEXXA (see section 4.4).

The optimal treatment duration has not been established (see section 4.4). The duration of treatment should be based upon maintenance of response (serum uric acid levels < 6 mg/dl) and clinical judgment.

Patients with renal impairment

Based on similar efficacy and safety profiles of pegloticase in patients with creatinine clearance below and above 50 ml/min, no dose adjustment is required for patients with renal impairment (see section 5.2).

Elderly patients

No dose adjustment is needed for patients 65 years of age and older (see section 5.2).

Paediatric population

The safety and efficacy of KRYSTEXXA in children and adolescents aged below 18 years has not been established. No data are available.

Method of administration

KRYSTEXXA, once diluted with 250 ml of sodium chloride solution, 4.5 mg/ml (0.45%) or 9 mg/ml (0.9%), is administered as an intravenous infusion over no less than 2 hours, at a flow rate of approximately 2 ml/minute.

For instructions on the preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Glucose-6-phosphate dehydrogenase (G6PD) deficiency and other cellular metabolic disorders known to cause haemolysis and methemoglobinemia. All patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) should be screened for G6PD deficiency before starting KRYSTEXXA.

4.4 Special warnings and precautions for use

The benefit/risk balance should be assessed for each individual patient on an on-going basis considering the effect on tophus resolution as well as the risk of infusion reactions, gout flares, and potentially increased cardiac risk. The long-term risk of prophylactic medications to prevent infusion reactions, such as glucocorticoids, should also be taken into consideration.

The data for long-term treatment from controlled clinical studies are limited. This should be considered when the decision is made for a therapy longer than 6 months.

Infusion-related reactions / Anaphylaxis

KRYSTEXXA can induce severe allergic responses, including anaphylactic shock with cardiac arrest. Special attention is recommended for patients with pre-existing cardiopulmonary disease.

Patients should be pre-treated with antihistamines, corticosteroids, and paracetamol, and closely monitored for the onset of adverse reactions suggesting severe hypersensitivity reactions including anaphylaxis for at least 1 hour after the end of the infusion (see section 4.8). If an infusion reaction

occurs during the administration, the infusion may be slowed, or stopped and restarted at a slower rate, at the discretion of the physician.

Most infusion-related reactions have been observed after loss of therapeutic response due to the development of anti-peglyticase antibodies, i.e. when serum uric acid values were above 6 mg/dl (360 µmol/L). Therefore, monitoring of serum uric acid level is required prior to each infusion. KRYSTEXXA should be discontinued if 2 consecutive levels above 6 mg/dl have been measured.

Since concomitant use of oral urate-lowering therapy may potentially mask the rise of serum uric acid associated with the loss of response, patients taking concomitant oral urate-lowering therapy may be at increased risk of infusion reactions and/or anaphylaxis. It is therefore recommended to discontinue oral urate-lowering medications before starting treatment and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Acute gouty attacks (gout flare)

An increase in gout flares is frequently observed upon treatment initiation, probably as a result of mobilization of urate from tissue deposits. To reduce the likelihood of gout flares after initiation of KRYSTEXXA prophylaxis with colchicine or a non-steroidal anti-inflammatory drug (NSAID) is recommended. It is recommended to start this treatment 1 week before initiation of KRYSTEXXA and continue for at least 6 months, unless medically contraindicated or not tolerated.

KRYSTEXXA does not need to be interrupted because of a gout flare, which should be managed concurrently as appropriate for the individual patient. Continuous treatment with peglyticase decreases frequency and intensity of gout flares.

Congestive heart failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but a small number of patients with pre-existing cardiovascular conditions who were treated with peglyticase in the clinical trials had exacerbations of their congestive heart failure. Caution should be exercised in patients who have congestive heart failure and patients should be monitored closely following infusion.

Haemolysis and/or Methemoglobinemia

If haemolysis and/or methemoglobinemia occur in patients receiving KRYSTEXXA, treatment should be immediately and permanently discontinued and appropriate measures initiated.

Patients over 100 kg body weight

Lower response rates were observed in patients over 100 kg BW; however, confounding factors in a small sample size make it unclear if in patients over 100 kg BW the dose was optimal to achieve an effect. Also, high titres of anti-peglyticase antibodies and infusion-related reactions showed a tendency to occur in a greater proportion of patients in this weight group (see section 4.8).

Retreatment with KRYSTEXXA

Very limited data are available about retreatment after interruption of therapy for more than 4 weeks. Because of the immunogenicity of KRYSTEXXA, patients receiving retreatment may be at increased risk of infusion-related reactions, including anaphylaxis. It is therefore recommended that patients given repeat infusions of KRYSTEXXA after a treatment interruption be monitored carefully.

Sodium intake

KRYSTEXXA contains 4.2 mg sodium (less than 1 mmol) per dose (essentially sodium free).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

As anti-peglyticase antibodies can bind to the PEG moiety of KRYSTEXXA, there may be potential for binding to other PEGylated products. It is unknown whether the development of anti-PEG antibodies may reduce the efficacy of other PEGylated medicinal products.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no data from the use in pregnant women. The embryofetal development study in rats does not indicate direct or indirect harmful effects with respect to reproductive toxicity. The results of the on-going reproductive toxicity studies are not available (see section 5.3). KRYSTEXXA is not recommended during pregnancy.

Breast-feeding

It is unknown whether peglyticase or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Therefore, KRYSTEXXA should not be used during breast-feeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Fertility

Effect on male and female fertility has not been studied.

4.7 Effects on ability to drive and use machines

KRYSTEXXA has no or negligible influence on the ability to drive and use machines. If patients experience treatment-related symptoms affecting their ability to concentrate and react (i.e. headache or dizziness), it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

Summary of safety profile

In controlled clinical trials, the most commonly reported serious adverse reactions were anaphylaxis, which occurred at a frequency of 6.5% (8/123) in patients treated with 8 mg every 2 weeks; infusion reactions, which occurred at a frequency of 26% and gout flares, which were more common during the first 3 months of treatment.

Tabulated list of adverse reactions

The following convention has been used for classification of the adverse reactions reported in the Phase 3 clinical trials (see Table 1 below): very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse Reactions

System Organ Class	Adverse Reaction
Metabolism and nutrition disorders	Common: Hyperglycaemia Uncommon: Hyperkalaemia
Cardiac disorders	Uncommon: Exacerbation of congestive heart failure
Gastrointestinal disorders	Very common: Nausea Common: Vomiting
Skin and subcutaneous disorders	Very common: Dermatitis, urticaria, pruritus, skin irritation, dry skin Uncommon: Cellulitis
Musculoskeletal and connective tissue disorders	Very common: Gout flare Common: Joint swelling
Blood and lymphatic disorders	Not known: Haemolysis
General disorders and administration site conditions	Very common: Infusion related reaction Common: Anaphylaxis, influenza like illness

Description of selected adverse reactionsInfusion-related reactions

Infusion-related reactions can occur after initiation of any infusion, in spite of patients being pre-medicated with oral antihistamine, intravenous corticosteroid and/or paracetamol, and generally during or within 1 hour after the infusion is completed. The first infusion reaction usually occurs after the 2nd to 4th infusion.

The most common signs and symptoms of local infusion reactions are: erythema, pruritus, and rash. The most common signs and symptoms of systemic infusion reactions are: urticaria, dyspnoea, flushing, hyperhidrosis, chest discomfort or pain, chills, and hypertension.

Anaphylaxis (characterized by stridor, wheezing, peri-oral/lingual oedema, or hemodynamic instability, with or without rash or urticaria) occurred in 14 (5.1%) of 273 total patients treated with KRYSTEXXA in clinical studies. One patient treated with KRYSTEXXA 8 mg every 4 weeks experienced a delayed type hypersensitivity reaction.

In clinical trials, 91% of patients who experienced an infusion-related reaction had a serum uric acid level above 6 mg/dl (360 µmol/L) due to the development of anti-pegloticase antibodies.

Infusion-related reactions showed a tendency to occur in a greater proportion of patients with over 100 kg bodyweight. They were reported in 54% of the patients in the 70 to ≤100 kg weight group, 70% of the patients in the >100 to ≤120 kg weight group, and 75% of patients in the >120 kg weight group, respectively.

Many infusion-related reactions resolved with slowing, or stopping the infusion, before restarting the infusion at a slower rate. Others resolved with supportive treatment with i.v. fluids, additional glucocorticoids or antihistamines, or following discontinuation of the infusion and with epinephrine for anaphylactic reactions.

In the post-marketing setting, severe anaphylactic reactions have been reported, including loss of consciousness, circulatory collapse, and cardiac arrest, which required transfer to hospital emergency department.

Gout flares

The frequency of gout flares may increase after initiation of treatment with KRYSTEXXA, despite gout prophylaxis with colchicine or NSAIDs, but the frequency and severity of gout flares diminishes after 3 months of KRYSTEXXA therapy.

In clinical trials, the percentage of patients that had flares in the first 3 months was 75% in patients treated with KRYSTEXXA 8 mg every 2 weeks compared with 54% in placebo-treated patients. This compared with flare rates of 41% and 67% in the same groups in the subsequent 3 months, and gout flares were infrequent in patients that received pegloticase 8 mg every 2 weeks for over one year.

Immunogenicity

In clinical trials, anti-pegloticase antibodies (IgM and IgG) developed in 89% of patients treated with KRYSTEXXA 8 mg every 2 weeks and 15% in the placebo group. Anti-PEG antibodies also developed in 41% of patients treated with KRYSTEXXA 8 mg every 2 weeks.

High anti-pegloticase antibody titres were associated with a failure to maintain normalisation of uric acid (<6 mg/dl).

There was also a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titres: 46% (18 of 39) in the KRYSTEXXA every 2 weeks group compared to 9% (4 of 46) in patients with low or no antibody titres.

4.9 Overdose

No case of overdose with KRYSTEXXA has been reported during clinical development. The maximum dose that has been administered as a single intravenous dose during clinical studies was 12 mg. A post-marketing report documented administration of the contents of 2 vials (16 mg) without any adverse reaction related to KRYSTEXXA administration.

It is recommended that patients suspected of receiving an overdose be monitored, and general supportive measures be initiated as no specific antidote has been identified.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-gout preparations, other anti-gout preparations, ATC code: M04AX02

Pegloticase is a uricase enzyme conjugated with mPEG at an average degree of substitution of 40.8 moles of mPEG/mole of protein (10.2 moles of mPEG/monomeric sub-unit of the mature homotetrameric uricase protein). The average molecular mass of pegloticase is approximately 545 kDa of which the protein moiety constitutes approximately 137 kDa.

Mechanism of action

Pegloticase catalyses the conversion of uric acid into the inert highly water-soluble metabolite allantoin, with hydrogen peroxide and carbon dioxide as oxidative by-products. Allantoin is eliminated by renal excretion, thereby lowering serum uric acid. This induces a concentration gradient between serum uric acid and tissue/joints deposits of monosodium urate resulting in the migration of urate from tissues/joints, which makes it accessible to conversion to allantoin.

Pharmacodynamic effects

In clinical trials, the mean plasma uric acid (PUA) levels fell to 0.7 mg/dl approximately 24 hours following the first dose of pegloticase in patients treated with KRYSTEXXA 8 mg every 2 weeks compared with a mean PUA of 8.2 mg/dl in the placebo-treated patients.

Plasma uric acid decreased with increasing pegloticase dose or concentration. Sustained decrease in plasma uric acid below the solubility concentration of 6 mg/dl was observed for more than 12 days with single doses of 8 mg and 12 mg.

Clinical efficacy and safety

The efficacy and safety of KRYSTEXXA was assessed in two replicate Phase III pivotal trials (GOUT 1 and GOUT 2) that were conducted in 212 adult patients with chronic gout refractory to allopurinol.

Patients were randomised in a 2:2:1 ratio to receive 8 mg every 2 weeks or every 4 weeks or placebo for 6 months. The mean PUA at baseline was 9.8 mg/dl. Seventy-one percent (71%) of patients had baseline tophi. The average number of gout flares per patient was 10 during the 18 months prior to study entry.

The primary endpoint in both trials was the proportion of responder patients that achieved plasma uric acid (PUA) less than 0.36 mmol/L (6 mg/dl) for at least 80% of the time during Month 3 and Month 6.

As shown in Table 2, a greater proportion of patients treated with KRYSTEXXA 8 mg every 2 weeks were responders as compared to patients receiving placebo. Responders maintained PUA values < 6 mg/dl throughout the 6-month treatment period. Although the 4-week regimen also demonstrated efficacy for the primary endpoint, this regimen was associated with increased frequency of infusion reactions.

Table 2. Plasma Uric Acid < 6 mg/dl for at Least 80% of the Time During Months 3 and 6

Treatment Group	N	Number (%) of Subjects Who Met Response Criteria	95% Confidence Interval ¹	p-Value ²
GOUT³ 1				
Pegloticase 8 mg every 2 weeks	43	20 (47%)	[32%, 61%]	<0.001
Pegloticase 8 mg every 4 weeks	41	8 (20%)	[7%, 32%]	0.044
Placebo	20	0 (0%)		
GOUT³ 2				
Pegloticase 8 mg every 2 weeks	42	16 (38%)	[23%, 53%]	<0.001
Pegloticase 8 mg every 4 weeks	43	21 (49%)	[34%, 64%]	<0.001
Placebo	23	0 (0%)		

¹95% confidence interval for differences in responder rate between pegloticase group vs. placebo

²P-value using Fisher's exact test to compare pegloticase group vs. placebo

³GOUT = Gout Outcomes and Urate-lowering Therapy

The effect of treatment on tophi was assessed using standardized digital photography and image analysis by a Central Reader blinded to treatment assignment. As shown in Table 3 at Month 6, the percentage of patients who achieved complete tophus response (defined as 100% resolution of at least one target tophus, without the appearance of any new tophi or any progression of existing tophi) was 29.0% in patients treated with 8 mg pegloticase every 2 weeks compared to 6.9% in placebo patients excluding patients with missing data, who were considered as a failure.

Table 3. Overall Complete Tophus Resolution (Pooled Analysis of GOUT 1 and GOUT 2)

Assessment Time point	8 mg Pegloticase Every 2 Weeks (N = 62)		Placebo (N = 29)		p-Value ³
	N ¹	Number of Patients with CR (%) ²	N ¹	Number of Patients with CR (%) ²	
Week 13	46	10 (16.1%)	25	0 (0.0%)	p≤0.05
Week 19	44	16 (25.8%)	26	2 (6.9%)	p≤0.05
Week 25	40	18 (29.0%)	25	2 (6.9%)	p≤0.05

¹Number of patients with available data

²Patients with missing data were considered as a failure

³p values based on Fisher's exact test to compare pegloticase versus placebo

The HAQ-PGA scores were 42.4 at baseline vs. 27.1 at Week 25 in patients treated with pegloticase 8 mg every 2 weeks compared to 51.6 vs. 53.4 in the placebo group ($p \leq 0.001$).

The HAQ-DI scores were 1.1 at baseline vs. 0.84 at Week 25 in patients treated with pegloticase 8 mg every 2 weeks compared to 1.2 vs. 1.3 in the placebo group ($p \leq 0.01$). The Pain scores using a visual analogue scale were 44.2 at baseline vs. 28.4 at Week 25 in patients treated with pegloticase 8 mg every 2 weeks compared to 53.9 vs. 57.2 in the placebo group ($p \leq 0.001$).

Among the other secondary endpoints, reduction from baseline in the number of tender and swollen joints were observed in patients treated with KRYSTEXXA every 2 weeks while there was little change in patients on placebo.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with KRYSTEXXA in one or more subset of the paediatric population in the treatment and/or prevention of hyperuricaemia related to Tumour Lysis Syndrome (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

KRYSTEXXA was administered by intravenous infusion with a T_{max} of 2.25 h (range: 1.92 – 4.25 h for initial dose). There was potential for some accumulation with the KRYSTEXXA 8 mg every two weeks dosing regimen due to the long half-life of pegloticase (214 h; range: 123 - 444 h for terminal half-life). The mean C_{max} calculated on the last infusion was 2.17 $\mu\text{g/ml}$ (range: 1.25 - 4.77). The mean area under the KRYSTEXXA plasma concentration versus time curve at steady-state (AUC_{0-t}) was 445 $\text{h} \cdot \mu\text{g/ml}$ (range: 223 – 1040 $\text{h} \cdot \mu\text{g/ml}$). From the nonclinical studies, the elimination of pegloticase is via renal/urinary excretion. For the PEG moiety, urinary excretion is likely to be the major route of elimination.

The population PK analyses showed that age, sex and weight did not influence the pharmacokinetics of pegloticase. Anti-pegloticase antibodies were associated with an increase in CL and V_c as determined by compartmental analysis. Clearance was 0.0145 L/h with a range of 0.00904 – 0.0229 for no increase in anti-pegloticase antibodies and 0.0193 L/h with a range of 0.00675 – 0.0340 for an increase in anti-pegloticase antibodies. The volume of distribution was 4.45 L with a range of 2.62 – 5.89 for no increase in anti-pegloticase antibodies and 5.77 L with a range of 2.77 – 10.6 for an increase in anti-pegloticase antibodies.

The Phase 1 pharmacokinetics showed proportionality within the dose interval (0.5 – 8 mg) as reflected in C_{max} values. However, due to variability in the AUC values, AUC proportionality was not seen which might be a reflection of antibody clearance for some of the subjects.

The PK/PD analysis showed that higher doses were associated with lower uric acid levels and a more rapid decrease in these levels than lower doses. Antibodies to pegloticase associated with clearance of pegloticase resulted in a small stimulation in the elimination of urate. Those subjects that did not have anti-pegloticase antibodies that cleared pegloticase had a significant effect on the stimulation in the elimination of urate. Neither body weight nor baseline creatinine clearance had a significant effect on the PD response.

Special populations

No formal studies were conducted to examine the effects of renal insufficiency on pegloticase pharmacokinetics. A total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤ 62.5 ml/min.

No formal studies were conducted to examine the effects of hepatic impairment.

In the clinical studies, 34% (29 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or efficacy were observed between older and younger patients, but greater

sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

The pharmacokinetics of KRYSTEXXA has not been studied in children and adolescents.

5.3 Preclinical safety data

In repeated dose toxicity studies with KRYSTEXXA in rats and dogs, the occurrence of pegloticase-containing vacuoles was observed in different tissues. The degree of vacuolization and the number of tissues affected appeared to be dependent both on the applied pegloticase dose and the duration of exposure. The potential clinical relevance of these findings is currently unknown; however no adverse effects were associated with the presence of vacuoles.

Non-clinical studies to evaluate the carcinogenic and mutagenic potential have not been performed.

In the pregnant rat study there was no evidence of embryotoxicity or teratogenicity at 46 times the clinical exposure (AUC). There were no effects on the fertility of male or female rats. Prenatal and postnatal development study in rats, as well as the embryofetal development study in rabbits are ongoing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

Physical and chemical stability of KRYSTEXXA diluted in 250 ml sodium chloride 4.5 mg/ml (0.45%) or 9 mg/ml (0.9%) has been demonstrated for 4 hours at 2°C to 8°C and at room temperature (20°C to 25°C), if the solution is prepared as described in section 6.6. From a microbiological point of view, the product should be used immediately. If the diluted solution is not used immediately, it can be stored refrigerated (2°C to 8°C). The solution should be used within 4 hours of dilution (see section 6.6).

6.4 Special precautions for storage

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

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml vial (Type I glass) with a Teflon coated bromobutyl rubber stopper and aluminium seal with polypropylene flip-off cap, containing 1 ml concentrate for solution for infusion.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Instructions for preparation:

- KRYSTEXXA vial should be visually inspected for particles and discolouration prior to dilution and administration. Only solutions which are clear to slightly opalescent, colourless and free of visible particles should be used.
- Appropriate aseptic technique should be used when preparing the infusion. The vial should not be shaken.
- 1 ml of KRYSTEXXA should be withdrawn from the vial into a sterile syringe.
- 1 ml of KRYSTEXXA should be injected into a single 250 ml bag of sodium chloride 4.5 mg/ml (0.45%) or 9 mg/ml (0.9%) solution for injection for infusion.
- The infusion bag containing the diluted KRYSTEXXA solution should be inverted a number of times gently to ensure thorough mixing. The infusion bag containing diluted KRYSTEXXA should not be shaken.
- Before administration, the diluted solution of KRYSTEXXA should be allowed to reach room temperature. KRYSTEXXA in a vial or in an intravenous infusion fluid must never be subjected to artificial heating (e.g., hot water, microwave).

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

7. MARKETING AUTHORISATION HOLDER

Crealta Pharmaceuticals Ireland Limited
Commercial House, Millbank Business Park, Lower Lucan Road, Lucan, Co. Dublin
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/810/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08/01/2013

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(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

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

Name and address of the manufacturer(s) of the biological active substance

Bio-Technology General (Israel) Ltd.
Be'er Tuvia Industrial Park
Kiryat Malachi 83104
Israel

Name and address of the manufacturer responsible for batch release

United Drug, plc
United Drug House
Magna Business Park
Magna Drive, Citywest Road
Dublin 24
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs

The PSUR cycle for the medicinal product should follow the standard requirements.

**• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE
USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
M0402: EU Pegloticase post-marketing Observational Study The applicant should conduct a long-term EU observational study to end December 2018 on safety of pegloticase use in adult hyperuricemic patients with severe debilitating chronic tophaceous gout and efficacy and safety data in re-exposed patients. The applicant should submit yearly interim reports.	Study protocol within 2 months after Commission Decision

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

KRYSTEXXA 8 mg concentrate for solution for infusion
pegloticase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 8 mg of pegloticase (8 mg/ml concentrate)

3. LIST OF EXCIPIENTS

Disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride,
water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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.
Keep the vial in the outer carton 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

Crealta Pharmaceuticals Ireland Limited
Commercial House, Millbank Business Park, Lower Lucan Road, Lucan, Co. Dublin
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/810/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

KRYSTEXXA 8 mg concentrate for solution for infusion
 pegloticase
 Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8 mg / 1 ml

6. OTHER

B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package Leaflet: Information for the user

KRYSTEXXA 8 mg concentrate for solution for infusion pegloticase

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.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

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

1. What KRYSTEXXA is and what it is used for

KRYSTEXXA contains the active substance pegloticase. Pegloticase belongs to the class anti-gout medicines.

Pegloticase is used to treat severe long-term gout in adult patients who also have one or more painful deposits of uric acid crystals under the skin that cause difficulty in carrying out daily activities and who do not respond or cannot take other anti-gout medicines.

How KRYSTEXXA works

People with gout have too much uric acid in their body. Uric acid deposits as crystals in joints, kidneys, and other organs which may cause profound pain, redness and swelling (inflammation). KRYSTEXXA contains an enzyme called uricase that transforms the uric acid into a substance called allantoin, which can be removed easily in the urine.

2. What you need to know before you receive KRYSTEXXA

Do not use KRYSTEXXA

- If you are allergic to pegloticase, or other uricases or any of the other ingredients of this medicine (listed in section 6).
- If you have a rare blood problem called glucose 6-phosphate dehydrogenase (G6PD) deficiency or favism. Your doctor may test you for G6PD before you start KRYSTEXXA.

Warnings and precautions

Talk to your doctor or nurse before using KRYSTEXXA:

- **if you are currently taking other medicines to lower your uric acid level**
- **if you have been told you have heart failure**
- **if you have ever been told you have an enzyme deficiency that causes anaemia**
- **if you weigh over 100 kg**
- **if you have been treated with KRYSTEXXA before**

Monitoring during treatment

Your doctor will test your blood to measure uric acid levels before each dose to make sure that you should continue receiving KRYSTEXXA.

Children and adolescents

KRYSTEXXA has not been studied in children or adolescents under 18 years of age. Therefore, this medicine is not recommended in this age group.

Other medicines and KRYSTEXXA

Tell your doctor if you are taking, have recently taken or might take any other medicines. It is especially important to tell your doctor if you are currently taking other urate-lowering medicines (such as allopurinol or Febuxostat) or medicines containing polyethylene glycol (PEG) (such as pegylated interferon or Doxorubicin). These medicines may put you at higher risk of infusion reaction.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Do not use KRYSTEXXA if you are pregnant or breast-feeding, since it is not known how it will affect you or your baby.

Driving and using machines

KRYSTEXXA has little or no effect on your ability to drive. If you do not feel well, experience symptoms such as dizziness or headache, or are tired after receiving KRYSTEXXA, you should not drive or operate any machines.

KRYSTEXXA contains sodium

KRYSTEXXA contains 4.2 mg sodium per dose which means it is essentially sodium free.

3. How to use KRYSTEXXA

KRYSTEXXA should be given to you by a doctor or nurse experienced in the treatment of severe chronic gout in a healthcare centre.

How much KRYSTEXXA is given

The recommended dose of KRYSTEXXA is 8 mg. This dose is not adjusted for weight, age or kidney disease.

Before you start treatment with KRYSTEXXA, your doctor may recommend that you take other medicines (such as an antihistamine, paracetamol and a corticosteroid) to help reduce the risk that you will get infusion-related reactions due to this treatment. Take these medicines as directed by your doctor.

How KRYSTEXXA is administered

KRYSTEXXA is injected slowly into a vein (i.v. infusion) and your treatment will take about 2 hours or sometimes longer. If you have a reaction during the infusion, your doctor may stop or adjust the treatment. Your doctor may also ask you to wait after your treatment to be sure that you do not have an infusion-related reaction.

You will receive KRYSTEXXA every 2 weeks.

If you stop taking KRYSTEXXA, and then are treated again, you may be at increased risk of infusion reactions, including severe acute allergic reactions (anaphylaxis) so your doctor will monitor you carefully when you restart treatment.

Your doctor will also test your blood to measure uric acid before your next dose to make sure that you should continue receiving KRYSTEXXA.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most commonly reported serious side effects are: severe acute allergic reactions (**common**), infusion reactions (**very common**), and gout flares (**very common**).

KRYSTEXXA will be administered by a doctor or nurse who will monitor you for side effects while you receive KRYSTEXXA and for some time afterwards.

Severe allergic reactions (**common**) include fainting, sudden drop in blood pressure, and cardiac arrest. Allergic reactions usually happen within 2 hours of the infusion, but may also happen at a later time.

If you suddenly notice:

- a swelling of the throat, tongue or other part of your body
- tightness of the throat, hoarse voice or trouble swallowing
- a shortness of breath, wheezing or breathing problems
- a rash, itching or hives

tell your doctor or nurse IMMEDIATELY, since any of these may be signs of a serious allergic reaction.

The most common signs and symptoms of local infusion reactions were: redness at the injection site, itching, and rash. The most common signs and symptoms of generalised infusion reactions were: hives, shortness of breath, redness in the face, sweating, chest discomfort or pain, chills, and high blood pressure.

Allergic reactions may be more likely to occur in patients who weigh more than 100 kg.

An increase in gout flares is frequently observed when starting KRYSTEXXA. Your doctor may prescribe medicines to reduce the likelihood of gout flares after starting KRYSTEXXA.

KRYSTEXXA does not need to be discontinued because of a gout flare.

Very common side effects (may affect more than 1 in 10 people): hives, skin rash, itchy, dry or irritated skin, nausea

Common side effects (may affect up to 1 in 10 people): high blood sugar levels, vomiting, joint swelling, flu-like symptoms

Uncommon side effects: (may affect up to 1 in 100 people): worsening of a type of heart disease called congestive heart failure, skin infection, elevated potassium levels in the blood

Frequency not known (cannot be estimated from available data): destruction of red blood cells

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store KRYSTEXXA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month.

This medicine will be stored in a healthcare facility where it is administered.

Store in a refrigerator (2°C to 8°C).

Keep the vial in the outer carton in order to protect from light.

From a bacteriological point of view, the product should be used immediately. If the diluted solution is not used immediately it can be stored refrigerated (2°C to 8°C). The solution should be used within 4 hours of dilution.

Do not use this medicine if you notice any particles or discolouration in the diluted solution.

6. Contents of the pack and other information

What KRYSTEXXA contains

- The active substance is pegloticase. Each vial contains 8 mg of pegloticase (8 mg/ml concentrate).
- The other ingredients are disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride and water for injections.

What KRYSTEXXA looks like and contents of the pack

KRYSTEXXA 8 mg concentrate for solution for infusion is supplied in 2 ml glass vials containing 1 ml concentrate. KRYSTEXXA is a clear to slightly opalescent colourless solution.

Pack size of 1 vial.

Marketing Authorisation Holder

Crealta Pharmaceuticals Ireland Limited
Commercial House, Millbank Business Park, Lower Lucan Road, Lucan, Co. Dublin
Ireland

Manufacturer

United Drug, plc
United Drug House
Magna Business Park
Magna Drive, Citywest Road
Dublin 24
Ireland

This leaflet was last revised in {MM/YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

KRYSTEXXA must be prepared as follows:

Instructions for preparation of the solution for infusion:

- KRYSTEXXA vial should be visually inspected for particles and discolouration prior to dilution and administration. Only solutions which are clear to slightly opalescent, colourless and free of visible particles should be used.

- Appropriate aseptic technique should be used when preparing the infusion. The vial should not be shaken.
- 1 ml of KRYSTEXXA should be withdrawn from the vial into a sterile syringe.
- 1 ml of KRYSTEXXA should be injected into a single 250 ml bag of sodium chloride 4.5 mg/ml (0.45%) or 9 mg/ml (0.9%) solution for injection or infusion.
- The infusion bag containing the diluted KRYSTEXXA solution should be inverted a number of times gently to ensure thorough mixing. The infusion bag containing diluted KRYSTEXXA should not be shaken.
- Before administration, the diluted solution of KRYSTEXXA should be allowed to reach room temperature. KRYSTEXXA in a vial or in an intravenous infusion fluid must never be subjected to artificial heating (e.g., hot water, microwave).

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

Medicinal product no longer authorised

Annex IV

Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisation

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for pegloticase, the scientific conclusions of CHMP are as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Reports of infusion related reactions or anaphylaxis coincident with concomitant use of oral urate lowering agents were submitted in this Periodic Safety Update Report, where infusion reactions in 28 cases and 9 cases with anaphylactic reactions were reported. As the development of these adverse events may have been prevented in at least some of these cases if the patients would not have been treated with concomitant urate lowering substances, an amendment of the summary of product characteristics focusing on the importance of stopping treatment with uric acid lowering agents with regard to masking the results of serum uric acid values (and therefore increasing the risk for infusion reactions and anaphylactic reactions) should be implemented. The revised order of the two corresponding paragraphs is to emphasize the correlation between concomitant medication with urate lowering products and serum uric acid measurement. In addition, a further amendment regarding the extension of the time of observation following the end of infusion from 1 hour to 2 hours as a precautionary measure has been included along with a statement that delayed-type hypersensitivity reactions have also been reported.

Therefore, in view of available data regarding anaphylaxis and infusion reactions, the Pharmacovigilance Risk Assessment Committee considered that changes to the product information were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for pegloticase the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing pegloticase is favourable subject to the proposed changes to the product information

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.