KRYSTEXXA®
pegloticase 32 mg/ ml
32 mg pegloticase correspond to 8 mg of uricase protein conjugated to 24 mg of 10 kDa mPEG.
Concentrate for solution for infusion

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS;
G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. (5.1, 5.2)**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. (5.1)**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. (5.1, 5.2)**
- **Patients should be premedicated with antihistamines and corticosteroids. (5.1, 5.2)**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. (5.1)**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. (5.2)**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency. (4, 5.3)**

1 THERAPEUTIC INDICATION

KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Important Limitations of Use:

KRYSTEXXA® is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended dose and regimen of KRYSTEXXA® for adult patients is 8 mg (uricase protein) given as an intravenous infusion every two weeks.
The optimal treatment duration with KRYSTEXXA® has not been established.

2.2 Preparation

Visually inspect KRYSTEXXA® for particulate matter and discoloration before administration, whenever solution and container permit. Do not use vials if either is present *[see Dosage Forms and Strengths (3)]*. Use appropriate aseptic technique. Withdraw 1 mL of KRYSTEXXA® from the vial into a sterile syringe. Discard any unused portion of product remaining in the 2 mL vial. Inject into a single 250 mL bag of 0.9% Sodium Chloride Injection, USP or 0.45% Sodium Chloride Injection, USP for intravenous infusion. Do not mix or dilute with other drugs.

Invert the infusion bag containing the dilute KRYSTEXXA® solution a number of times to ensure thorough mixing. Do not shake.
KRYSTEXXA® diluted in infusion bags is stable for 4 hours at 2º to 8ºC and at room temperature (20º to 25ºC). However it is recommended that diluted solutions be stored under refrigeration, not frozen, protected from light, and used within 4 hours of dilution *[see How Supplied/Storage and Handling (16)]*.

Before administration, allow the diluted solution of KRYSTEXXA® to reach room temperature. KRYSTEXXA® in a vial or in an intravenous infusion fluid should never be subjected to artificial heating (e.g., hot water, microwave).

2.3 Administration

Do not administer as an intravenous push or bolus.

It is recommended that before starting KRYSTEXXA® patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while patients are on KRYSTEXXA® therapy.

Monitoring Therapy: The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed *[see Warnings and Precautions (5.1, 5.2)]*.

The KRYSTEXXA® admixture should only be administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump.

Patients should receive pre-infusion medications (e.g., antihistamines, corticosteroids), to minimize the risk of anaphylaxis and infusion reactions. Administer KRYSTEXXA® in a healthcare setting and by healthcare providers prepared to manage anaphylaxis and infusion reactions, and observe patients for an appropriate period of time after administration *[see Warnings and Precautions (5.1, 5.2)]*.

If an infusion reaction occurs during the administration of KRYSTEXXA, the infusion may be slowed, or stopped and restarted at a slower rate, at the discretion of the physician. Since infusion reactions can occur after completion of infusion, observation of patients for approximately an hour post-infusion should be considered *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*.

3 DOSAGE FORMS AND STRENGTHS

KRYSTEXXA® is a clear, colorless, sterile 8 mg/mL solution of pegloticase in a 2 mL single-dose vial, expressed as amounts of uricase protein. KRYSTEXXA® must be diluted prior to use.

4 CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions (5.3)]*

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

During pre-marketing clinical trials, anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA® every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen.

There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA® or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA® should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA®. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA® may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA® patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA®.

5.2 Infusion Reactions

During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with KRYSTEXXA® 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA® 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA® should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids.

KRYSTEXXA® should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA® may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA® patients discontinue oral urate-lowering medications and

not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

5.3 G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA® in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA® to patients with G6PD deficiency *[see Contraindications (4)]*. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA®.
For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

5.4 Gout Flares

During the controlled treatment period with KRYSTEXXA® or placebo, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA® treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA® 8 mg every 2 weeks, KRYSTEXXA® 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA® 8 mg every 2 weeks, KRYSTEXXA® 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA®.

Gout flares may occur after initiation of KRYSTEXXA®. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA® therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA® does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient *[see Dosage and Administration (2)]*.

5.5 Congestive Heart Failure

KRYSTEXXA® has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA® 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA® 8 mg every 2 weeks during the open-label extension study.

Exercise caution when using KRYSTEXXA® in patients who have congestive heart failure and monitor patients closely following infusion.

5.6 Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA® after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA®, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis *[see Warnings and Precautions (5.1)]*
- Infusion Reactions *[see Warnings and Precautions (5.2)]*
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia *[see Warnings and Precautions (5.3)]*
- Gout Flares *[see Warnings and Precautions (5.4)]*
- Congestive Heart Failure *[see Warnings and Precautions (5.5)]*

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il.

6.1 Clinical Trials Experience

The data described below reflect exposure to KRYSTEXXA® in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 6-month clinical trials: 85 patients were treated with KRYSTEXXA® 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA® 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

The most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA® 8 mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA® Compared to Placebo

Adverse Reaction (Preferred Term)	**KRYSTEXXA 8 mg every 2 weeks (N=85)** N[a] (%)	**Placebo (N=43)** N (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

6.2 Immunogenicity

Anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA® every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA® every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KRYSTEXXA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling.

7 DRUG INTERACTIONS

No studies of interactions of KRYSTEXXA® with other drugs have been conducted.

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA® in pregnant women.
Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively *[see Data]*.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m^2 basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m^2 basis at maternal doses up to 40 and 30 mg/kg every other day, in

rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m^2 basis at maternal doses up to 10 mg/kg twice weekly in both species).

8.2 Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA® should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

8.4 Pediatric Use

The safety and effectiveness of KRYSTEXXA® in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the total number of patients treated with KRYSTEXXA® 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) 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 effectiveness 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.

8.6 Renal Impairment

No dose adjustment is required for patients with renal impairment. 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 overall differences in efficacy were observed.

10 OVERDOSAGE

No reports of overdosage with KRYSTEXXA® have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein.

Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

11 DESCRIPTION

KRYSTEXXA® (pegloticase) is a uric acid specific enzyme which is a PEGylated product that consists of recombinant modified mammalian urate oxidase (uricase) produced by a genetically modified strain of Escherichia coli. Uricase is covalently conjugated to monomethoxypoly (ethylene glycol) [mPEG] (10 kDa molecular weight). The cDNA coding for uricase is based on mammalian sequences.
Each uricase subunit has a molecular weight of approximately 34 kDa per subunit.
The average molecular weight of pegloticase (tetrameric enzyme conjugated to mPEG) is approximately 540 kDa.

KRYSTEXXA® is intended for intravenous infusion.

KRYSTEXXA® is a sterile, clear, colorless solution containing 8 mg/mL pegloticase in phosphate-buffered saline.

KRYSTEXXA® (pegloticase) concentrations are expressed as concentrations of uricase protein.
Each mL of KRYSTEXXA® contains 8 mg of uricase protein (conjugated to 24 mg of 10 kDa mPEG), 8.77 mg Sodium Chloride, 2.18 mg Disodium Hydrogen Phosphate Dihydrate, 0.43 mg Sodium Dihydrogen Phosphate Dihydrate and Water for Injection to deliver 8 mg of pegloticase (as uricase protein).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KRYSTEXXA® is a uric acid specific enzyme which is a recombinant uricase and achieves its therapeutic effect by catalyzing the oxidation of uric acid to allantoin, thereby lowering serum uric acid. Allantoin is an inert and water soluble purine metabolite; it is readily eliminated, primarily by renal excretion.

12.2 Pharmacodynamics

Approximately 24 hours following the first dose of KRYSTEXXA®, mean plasma uric acid levels for subjects in the KRYSTEXXA® groups were 0.7 mg/dL for the KRYSTEXXA® 8 mg every 2 weeks group.
In comparison, the mean plasma uric acid level for the placebo group was 8.2 mg/dL.

In a single-dose, dose-ranging trial, following 1-hour intravenous infusions of 0.5, 1, 2, 4, 8 or 12 mg of pegloticase in 24 patients with symptomatic gout (n=4 subjects/dose group), plasma uric acid decreased with increasing pegloticase dose or concentrations. The duration of suppression of plasma uric acid appeared to be positively associated with pegloticase dose. Sustained decrease in plasma uric acid below the solubility concentration of 6 mg/dL for more than 300 hours was observed with doses of 8 mg and 12 mg.

12.3 Pharmacokinetics

Pegloticase levels were determined in serum based on measurements of uricase enzyme activity.

Absorption
Following single intravenous infusions of 0.5 mg to 12 mg pegloticase in 23 patients with symptomatic gout, maximum serum concentrations of pegloticase increased in proportion to the dose administered.
The population pharmacokinetic analysis showed that age, sex, weight, and creatinine clearance did not influence the pharmacokinetics of pegloticase.

Distribution
Significant covariates included in the model for determining clearance and volume of distribution were found to be body surface area and anti-pegloticase antibodies.

Special Populations
Pediatric Populations
The pharmacokinetics of pegloticase has not been studied in children and adolescents.

Patients with Renal or Hepatic Impairment
No formal studies were conducted to examine the effects of either renal or hepatic impairment on pegloticase pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of pegloticase.

The genotoxic potential of pegloticase has not been evaluated.

There was no evidence of impairment on fertility at pegloticase doses up to 40 mg/kg (approximately 50 times the MRHD on mg/m2 basis) every other day in rats.

13.2 Animal Toxicology and/or Pharmacology

Pegloticase at similar to and higher than the maximum recommended human dose (MRHD) on a plasma AUC basis [at intravenous (IV) doses of ≥ 0.4 mg/kg in dogs] caused cytoplasmic vacuoles in multiple organs, and

edema and histiocyte infiltration in the aortic outflow tract in dogs. Organs with cytoplasmic vacuoles included the spleen, adrenal gland, liver, heart, duodenum, and jejunum. Vacuoles in the spleen, adrenal glands, and heart persisted after a 1-year recovery period at pegloticase doses (≥ 1.5 mg/kg in dogs) approximately 5 times the MRHD, but were absent at a dose similar to the MRHD. Vacuoles in the liver, duodenum, and jejunum persisted after a 3-month recovery period at a pegloticase dose (10 mg/kg in dogs) approximately 30 times the MRHD, but were absent at doses (≤ 1.5 mg/kg) approximately 5 times and similar to the MRHD. The edema and histiocyte infiltration in the aortic outflow tract was absent after recovery periods of 6 and 12 months, respectively.

Vacuoles in the spleen, liver, duodenum, and jejunum were within macrophages and most likely represented phagocytic removal of pegloticase from the circulation. However, the vacuolated cells in the heart and adrenal gland did not stain as macrophages. In the aortic outflow tract of the heart, vacuoles were in the cytoplasm of endothelial cells in the intimal lining of the aorta. In the adrenal gland, vacuoles were located within cortical cells in the zona reticularis and zona fasciculata. The clinical significance of these findings and the functional consequences are unknown.

14 CLINICAL STUDIES

The efficacy of KRYSTEXXA® was studied in adult patients with chronic gout refractory to conventional therapy in two replicate, multicenter, randomized, double-blind, placebo-controlled studies of six months duration: Trial 1 and Trial 2. Patients were randomized to receive KRYSTEXXA® 8 mg every 2 weeks or every 4 weeks or placebo in a 2:2:1 ratio.
Studies were stratified for the presence of tophi. Seventy-one percent (71%) of patients had baseline tophi. All patients were prophylaxed with an oral antihistamine, intravenous corticosteroid and acetaminophen. Patients also received prophylaxis for gout flares with non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine, or both, beginning at least one week before KRYSTEXXA® treatment unless medically contraindicated or not tolerated. Patients who completed the randomized clinical trials were eligible to enroll in a 2-year open label extension study.

Entry criteria for patients to be eligible for the trials were: baseline serum uric acid (SUA) of at least 8 mg/dL; had symptomatic gout with at least 3 gout flares in the previous 18 months or at least 1 gout tophus or gouty arthritis; and had a self-reported medical contraindication to allopurinol or medical history of failure to normalize uric acid (to less than 6 mg/dL) with at least 3 months of allopurinol treatment at the maximum medically appropriate dose.

The mean age of study subjects was 55 years (23-89); 82% were male, mean body mass index (BMI) was 33 kg/m2, mean duration of gout was 15 years, and mean baseline SUA was 10 mg/dL.

To assess the efficacy of KRYSTEXXA® in lowering uric acid, the primary endpoint in both trials was the proportion of patients who achieved plasma uric acid (PUA) less than 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® every 2 weeks achieved urate lowering to below 6 mg/dL than patients receiving placebo. Although the 4 week regimen also demonstrated efficacy for the primary endpoint, this regimen was associated with increased frequency of anaphylaxis and infusion reactions and less efficacy with respect to tophi.

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]
Trial 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%)		
Trial 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%)		

[1] 95% confidence interval for differences in responder rate between pegloticase group vs. placebo

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

Note: Based on post-hoc analyses of the clinical trial data, if KRYSTEXXA® had been stopped when a patient's uric acid level rose to greater than 6 mg/dL on a single occasion, the incidence of infusion reactions would have been reduced by approximately 67%, but the success rates for the primary efficacy endpoint would have been reduced by approximately 20%. If KRYSTEXXA® had been stopped after 2 consecutive uric acid levels greater than 6 mg/dL, the incidence of infusion reactions would have been half, and there would have been little change in the efficacy outcome.

The effect of treatment on tophi was a secondary efficacy endpoint and was assessed using standardized digital photography, image analysis, and a Central Reader blinded to treatment assignment. Approximately 70% of patients had tophi at baseline. A pooled analysis of data from Trial 1 and Trial 2 was performed as pre-specified in the protocols. At Month 6, the percentage of patients who achieved a complete response (defined as 100% resolution of at least one target tophus, no new tophi appear and no single tophus showing progression) was 45%, 26%, and 8%, with KRYSTEXXA® 8 mg every 2 weeks, KRYSTEXXA® 8 mg every 4 weeks, and placebo, respectively. The difference between KRYSTEXXA® and placebo was statistically significant for the every 2 week dosing regimen, but not for the every 4 week dosing regimen.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KRYSTEXXA® is supplied as a clear, colorless, sterile solution in phosphate buffered saline intended for intravenous infusion after dilution. KRYSTEXXA® is supplied in a single-dose 2 mL glass vial with a Teflon® coated (latex-free) rubber injection stopper to deliver KRYSTEXXA® as 8 mg of uricase protein in 1 mL volume.

Storage and Handling

Before the preparation for use, KRYSTEXXA® must be stored in the carton and maintained at all times under refrigeration between 2° to 8°C. **Protect from light. Do not shake or freeze.**
After dilution, store under refrigeration between 2° to 8°C or between 20°-25°C and use within 4 hours.
Protect from light. Do not freeze.
The expiry date of the product is indicated on the packaging materials. Do not use beyond the expiration date stamped.

Registration number: 161-93-35304-00

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