KRYSTEXXA Infusion Guide

HOW TO USE THIS GUIDE:

This guide is designed to help you discuss and educate your patients on uncontrolled gout and the benefits of KRYSTEXXA treatment. The guide is broken up into 4 sections:

① Uncontrolled Gout Overview

The nature of uncontrolled gout and the consequences of not addressing it

② KRYSTEXXA Overview

The efficacy and safety profile of KRYSTEXXA

③ Infusion Process

Information on the infusion process from preinfusion to postinfusion, as well as a tear-off infusion checklist

④ Explaining KRYSTEXXA to Patients

Resources on how to communicate the role of KRYSTEXXA to your patients

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INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

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

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

Please see additional Important Safety Information throughout and on pages 14-15 and see Full Prescribing Information, including Boxed Warning.

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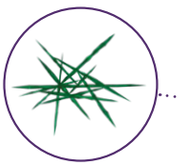
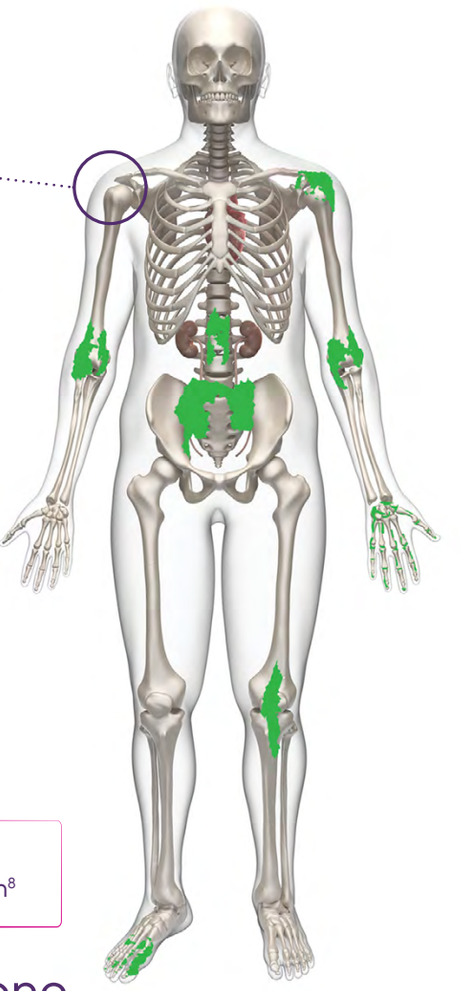
Gout is a chronic and systemic inflammatory disease[1,2]

Gout is a type of arthritis associated with high amounts of urate, also known as hyperuricemia.[3,4]

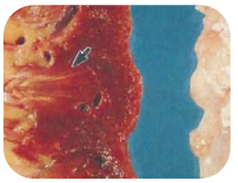
When urate builds up, it can turn into crystals. These crystals cause painful flares and tophi.[1]



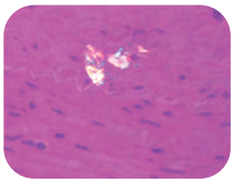


Urate crystals can deposit almost anywhere in the body, in organs like the kidneys and heart, and in the joints and bones[1,2]

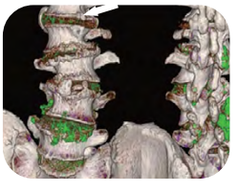
KIDNEY[5]



HEART[6]



SPINE[7]



KRYSTEXXA has not been studied to reverse damage to the kidneys, heart, spine, or any of the body's organs.

Adapted from Nickeleit V, et al. *Nephrol Dial Transplant*. 1997;12:1832-1838. Adapted from Park JJ, et al. *BMJ Open*. 2014;4:e005308. Adapted from Lu H, et al. *Medicine (Baltimore)*. 2017;96:e7670.

Urate crystal buildup isn't always visible from the outside.
Up to 75% of the urate burden may not be detected upon physical examination[8]

While it can help manage flares, diet alone won't treat the underlying cause of gout[9,10]

Only one-third of urate in the body comes from what patients eat.[9]

For many patients, urate crystal buildup is primarily due to:

GENETICS[11]
Some people are naturally prone to retaining higher levels of uric acid

RENAL ISSUES[1,12]
Chronic kidney disease (CKD) can make it harder for the body to remove uric acid

Diet is not a substitute for treatment as dietary restrictions may reduce uric acid levels by only ~1 mg/dL[13]

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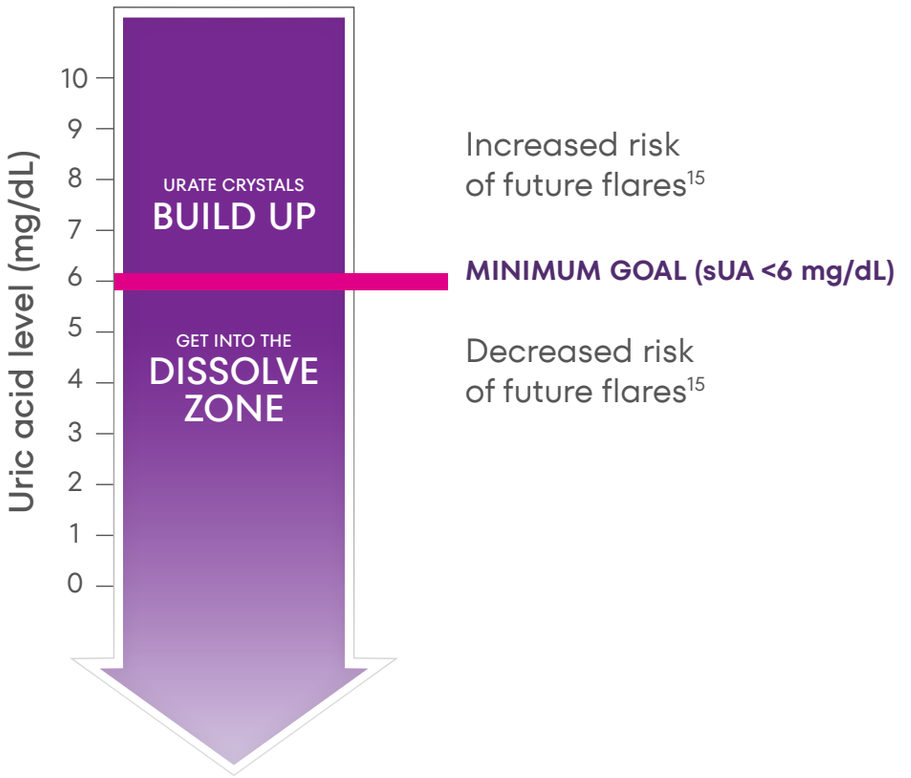
Help patients understand the impact of reducing their uric acid levels

To reduce urate crystal buildup, a patient's sUA must be low enough for crystals to dissolve.

- Guidelines recommend lowering the sUA level to a target of <6 mg/dL[14]
- Lowering the sUA level to <5 mg/dL may be needed to more rapidly dissolve urate crystals and reduce flare frequency[15]
  - Lower sUA levels have been shown to increase the speed of tophus resolution suggesting that a lower sUA target may be preferred for patients with more severe gout[15,16]



The lower the sUA level, the faster crystal buildup can dissolve[14,15]

sUA, serum uric acid.

Does your patient have uncontrolled gout?

Use our STOP chart to evaluate your patient. If they have any of the symptoms listed below, you should talk to them about uncontrolled gout.

sUA >6	TOPHI	ORAL ULT FAILURE	PAINFUL FLARES
Is their uric acid level >6 mg/dL?	Do they have nonresolving tophi?	Have they been taking the maximum medically appropriate dose of ULTs?	Have they had 2 or more painful flares in the past year?

STOP is based on the **2020 ACR Guidelines:** Pegloticase is the ONLY UNCONTROLLED GOUT TREATMENT **RECOMMENDED by the 2020 ACR Guidelines**[14]

IF THEIR GOUT IS UNCONTROLLED

It's time for KRYSTEXXA[17]

Uncontrolled gout is defined as having sUA >6 mg/dL along with 2 or more flares per year and/or 1 or more nonresolving tophi while receiving the maximum medically appropriate dose of oral ULT.[14,17,18]

KRYSTEXXA is not indicated for the treatment of pain.

ACR, American College of Rheumatology; ULT, urate-lowering therapy.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial of KRYSTEXXA co-administered with methotrexate (MTX) compared to KRYSTEXXA alone, one patient treated with KRYSTEXXA co-administered with MTX (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis treated with KRYSTEXXA alone. Patients were pre-treated with infusion reaction prophylaxis and KRYSTEXXA was discontinued following 2 consecutive serum uric acid levels above 6 mg/dL to reduce the risk of anaphylaxis and infusion reactions. These risks are higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

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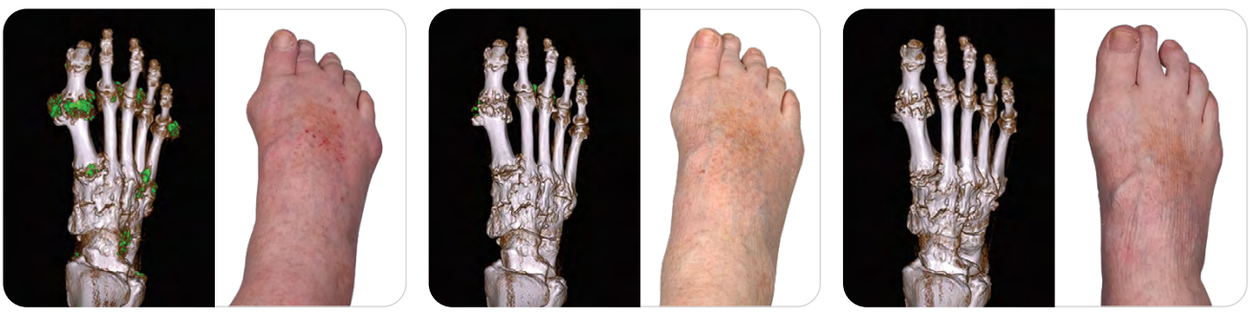
KRYSTEXXA can change the course of uncontrolled gout by **dissolving years of systemic urate deposition in as little as 6-12 months**[17]

71% **of patients** receiving KRYSTEXXA with methotrexate (71/100) met the primary endpoint and reduced their sUA to <6 mg/dL for at least 80% of the time during Month 6 vs 39% of patients receiving KRYSTEXXA alone (20/52) (*P*<0.0001)[17]

60% **of patients** receiving KRYSTEXXA with methotrexate (60/100) met the secondary endpoint and reduced their sUA to <6 mg/dL for at least 80% of the time during Month 12 vs 31% of patients receiving KRYSTEXXA alone (16/52) (*P*=0.0003)[17]

54% **of patients** (28/52) met the secondary endpoint and had complete resolution of at least 1 target tophus, with no new or progressive tophi, within the first-year vs 31% (9/29) receiving KRYSTEXXA alone (*P*=0.048)[17,19]

6-12 months of KRYSTEXXA may reverse years of urate deposition[17]



Baseline[20] **6 months[20]** **12 months[20]**

Photos and DECT images from a patient in MIRROR trial.[20]
DECT is a dual-energy computed tomography. It can reveal urate deposits (in green) throughout the body, including soft tissue deposits, like tendons and ligaments.

Best results were seen at 6-12 months.[17] Optimal treatment duration has not been established.[17] Individual results may vary.

The MIRROR RCT was a 52-week, randomized, double-blind, placebo-controlled trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA (8 mg Q2W) co-administered with 15 mg/week oral methotrexate and 1 mg/day oral folic acid (n=100) vs KRYSTEXXA with placebo (n=52).[17,18]

Q2W, once every two weeks; RCT, randomized controlled trial.

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WARNINGS AND PRECAUTIONS

Anaphylaxis

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Anaphylaxis was reported with 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.

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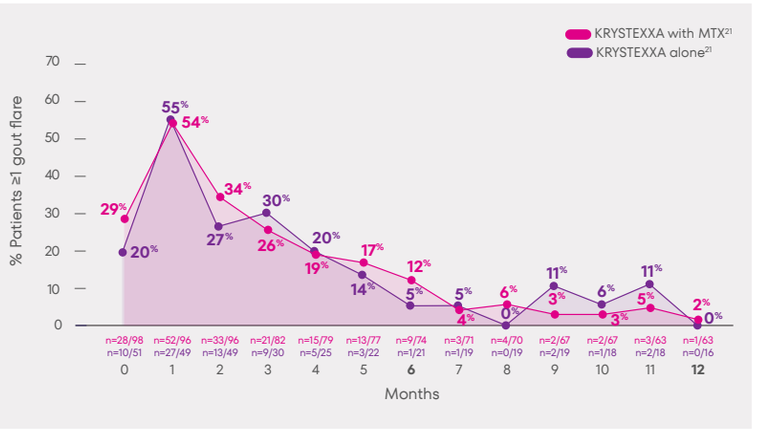
ADVERSE REACTIONS: GOUT FLARES

Gout flares decreased over time[18]

KRYSTEXXA leads to dissolving of urate crystals, which can cause them to break off, resulting in mobilization flares.[17]

- Gout flares in the first 3 months can be a sign that KRYSTEXXA is working to mobilize urate from tissue deposits[17]
- It is important to educate patients on mobilization flares, which are common with the use of all ULTs[17]



sUA level can help identify patients at risk for infusion reactions[22]

KRYSTEXXA Monitoring Protocol: close monitoring of sUA levels within 48 hours prior to the infusion can significantly reduce infusion reactions.[17,22]

sUA can help identify patients at risk for infusion reactions[17,22]

For use after first infusion

Take a preinfusion sUA measurement, preferably within 48 hours prior to each infusion

Continue treatment if the preinfusion sUA level is ≤6 mg/dL

Discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed

The Monitoring Protocol was established after a post-hoc analysis revealed that sUA is a useful biomarker for identifying risk of infusion reactions.[17,22]

MTX, methotrexate.

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WARNINGS AND PRECAUTIONS

Gout Flares

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 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.

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KRYSTEXXA step-by-step

KRYSTEXXA is a short-term treatment[17]

- It's not a medication patients will take for the rest of their lives
- Optimal treatment duration has not been established; best results were seen at 6-12 months

Recommended dosing is KRYSTEXXA co-administered with methotrexate[17,18,*]

- 4 weeks prior to treatment initiate 15 mg oral methotrexate weekly with 1 mg folic acid daily
- Administer 8 mg of KRYSTEXXA as an intravenous infusion every 2 weeks
- Continue 15 mg methotrexate weekly with 1 mg folic acid daily throughout treatment with KRYSTEXXA

Preinfusion lab work is required[17]

- Confirm the patient has normal G6PD activity[†] and has discontinued other urate-lowering therapies
- Perform sUA test prior to each infusion to ensure sUA <6 mg/dL

Before each infusion[17,22]

- Confirm sUA level was tested, preferably in the last 48 hours
- Administer pretreatment medications per prescribing orders of the doctor

Infusion length[17]

- No less than 120 minutes
- Reminder: Infusion pumps may vary. Always verify actual run time and adjust to ensure the infusion lasts no less than 120 minutes

After each infusion[17,18]

- Observe patients for approximately an hour postinfusion
- Remind patients of their next sUA test, upcoming infusion appointments, and any premedications they should continue taking, including corticosteroids, antihistamines, 15 mg oral methotrexate weekly with 1 mg folic acid daily

Therapy duration[17]

- Best results for KRYSTEXXA with methotrexate were seen at 6-12 months of treatment
- Optimal treatment duration has not been established

Possible side effects seen with KRYSTEXXA with methotrexate[17]

- In the MIRROR clinical trial, common side effects seen in ≥5% of patients were
  - — Gout flares
  - — Arthralgia
  - — COVID-19
  - — Nausea
  - — Fatigue

For full treatment protocol, see the **Infusion Checklist** at the back of this guide and under resources at **KRYSTEXXAhcp.com**

*KRYSTEXXA alone may be used in patients for whom methotrexate is contraindicated or not clinically appropriate.[17]

[†]G6PD deficiency is an abnormally low level of glucose-6-phosphate dehydrogenase. Patients of African, Mediterranean, and Southern Asian ancestry have a higher risk of G6PD deficiency.[17,23,24]

G6PD, glucose-6-phosphate dehydrogenase.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Anaphylaxis

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, nausea or vomiting. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen, which may have resulted in an underestimate of anaphylaxis frequency reported.

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Amgen By Your Side

A Patient Support Program

Amgen By Your Side is a support program for patients prescribed KRYSTEXXA. After your patient has enrolled, they will be paired with a dedicated support partner, called a Patient Access Liaison (PAL). Their PAL can be a partner, providing nonmedical education to help them navigate their unique treatment experience—including information on insurance, financial assistance options, important appointment-related information, and other patient support services.

After your patient has enrolled in the program by completing the Patient Enrollment Form (PEF), their PAL will educate them on the following:

Financial Support Options‡

Patient Support

Infusion Logistics

Insurance Benefits Investigation

Has your patient signed up for Amgen By Your Side? It's not too late!

Here are three steps to initiate the patient enrollment process:

1. Fill out all required fields on pages 1 and 2 as indicated by the asterisks, including the prescriber signature and date within the Prescriber section.
2. Obtain the patient consent ("I Consent" check box), patient signature and date within the Patient Consent and Authorization section at the top of page 2, if possible.
3. Send both the front and back of the patient's insurance card(s) along with all 4 pages of the PEF.

Initiate your patient's enrollment by submitting the Patient Enrollment Form.
Options available at AmgenByYourSideEnrollment.com

‡For eligible patients.
Reminder: Your patient must sign the form to complete enrollment.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Anaphylaxis

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.

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.

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AMGEN BY your side

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Ready-to-Use (RTU) vial—with the same KRYSTEXXA you've come to rely on[17]

The RTU vial—no IV bags, no saline dilution, and it's ready for infusion via an infusion pump.[17]

1. **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration**, whenever solution and container permit. Do not use vial if either is present.
2. Allow the RTU vial to **reach room temperature** at 20°C to 25°C (68°F to 77°F). KRYSTEXXA in a vial should never be subjected to artificial heating (eg, hot water, microwave). Unopened vial may be stored for up to 4 hours at room temperature.
3. Use appropriate aseptic technique. Insert a vented intravenous set through the septum of the vial. **Once the stopper is punctured, use immediately.**
4. To administer, **invert and hang the vial** utilizing the built-in hanger label affixed to the bottom of the vial.
5. **Administer as an intravenous infusion over no less than 120 minutes using an infusion pump.** After the entire contents of the vial have been administered, flush the intravenous line with sodium chloride injection to ensure delivery of the required dose.
   - To administer the RTU vial over 120 minutes, the appropriate infusion rate is 25 mL per hour

Reminder: Account for infusion pump variance. Check settings and confirm infusion completes in no less than 120 minutes.

NDC: 75987-058-01[17]
Not actual size.

REMINDERS FOR STORAGE AND PREPARATION[17]

- ✓ Before the preparation for use, **KRYSTEXXA must be stored in the carton** and maintained at all times under refrigeration **between 2°C to 8°C (36°F to 46°F). Protect from light. Do not shake or freeze.**
- ✓ **Do not use beyond the expiration date stamped.**
- ✓ Allow the **RTU vial to reach room temperature. KRYSTEXXA in a vial should never be subjected to artificial heating (eg, hot water, microwave). It may be stored for up to 4 hours at ambient room temperature.**

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion Reactions
In the 52-week trial, infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with MTX group compared to 31% of patients treated with KRYSTEXXA alone. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion.

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Infusion reaction prophylaxis in the clinical trials[17,25]

Individual prescriber orders may vary.

PREINFUSION MEDICATIONS[17,25]			
Class	**Drug(s)**	**Dosing**	**Time in relation to infusion**
IV corticosteroids	Methylprednisolone, hydrocortisone, other	Dose determined by healthcare provider	Immediately prior to each infusion
Antihistamines	Allegra® (fexofenadine) Benadryl® (diphenhydramine)		Night before infusion and/or can administer prior to each infusion
Oral analgesic	Tylenol® (acetaminophen)		Prior to each infusion

Gout flare prophylaxis[17]

While individual results may vary, since patients receiving KRYSTEXXA typically experience an initial drop in serum uric acid, it is recommended to take steps to proactively manage mobilization flares.

Class	Drug(s)	Dosing	Time in relation to infusion
Anti-gout flare agent	Colcrys® (colchicine)	Dose determined by healthcare provider	Daily, treatment initiated 1 week prior to initiation of KRYSTEXXA and lasting at least 6 months, unless medically contraindicated or not tolerated
Oral NSAIDs	Advil® (ibuprofen) Aleve® (naproxen sodium)		

The drop in uric acid causes mobilization of urate crystals from stores in the body.
Gout flares can be a sign that KRYSTEXXA is working to lower the uric acid in the blood[17]

After the infusion

Observation of patients for approximately 1 hour postinfusion should be considered[17]

Remind the patient of their next sUA test, upcoming infusion appointments, and the importance of taking any premedications, including methotrexate and folic acid[17]

KRYSTEXXA should be given every 2 weeks. It is recommended to provide a standing order to the lab to check the patient's sUA level prior to each infusion.[17]

NSAIDs, nonsteroidal anti-inflammatory drugs.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion Reactions
During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, 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, which may have resulted in an underestimate of infusion reaction frequency reported.

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Letting your patients know what to expect during treatment

An everyday analogy may be a helpful way to explain to your patients how KRYSTEXXA dissolves crystal buildup within the body.

IMAGINE A SNOWY DAY...

Urate crystals build up over time in your body, similar to how snow collects on the sidewalk[1,26]

KRYSTEXXA is an enzyme that helps urate crystals dissolve, similar to how salt melts snow[17,27]

Dissolved urate crystals leave the body through the urine, similar to how melted snow flows down a drain[17,27]

This is a visual illustration of how KRYSTEXXA works over multiple treatments. Results may vary.

Explaining the role of methotrexate to your patients

KRYSTEXXA is recommended to be co-administered with methotrexate.[17] Methotrexate is an additional medication that is a type of immunomodulator that helps reduce the risk of having an allergic reaction, allowing gout patients to stay on KRYSTEXXA treatment as long as their doctor recommends, and may improve patient response.[28]

Immunomodulators are commonly used along with biologic treatments to reduce immunogenicity. KRYSTEXXA alone may be used in patients for whom methotrexate is contraindicated or not clinically appropriate.

Antidrug antibody (ADA) development can be common with biologic therapies[28]

Reducing ADAs may slow clearance of the biologic[28]

Reducing ADAs can lead to reduced risk of infusion reactions and improve patient response[17,19,28]

KRYSTEXXA with methotrexate can be an effective treatment and has an established safety profile[17]

- KRYSTEXXA with methotrexate reduced the rate of infusion reactions to 4% (4/96) vs 31% (15/49) with KRYSTEXXA alone[17]
- Most common adverse reactions when KRYSTEXXA was co-administered with methotrexate were gout flares, arthralgia, COVID-19, nausea, and fatigue[17]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion Reactions

Manifestations of these reactions included urticaria (10.6%), dyspnea (7.1%), chest discomfort (9.5%), chest pain (9.5%), erythema (9.5%), and pruritus (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 occurred at any time during a course of treatment with ~3% occurring with the first infusion, and ~91% occurred during the time of infusion.

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.

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Answers to common patient questions

Can I take KRYSTEXXA if I have chronic kidney disease (CKD)?
KRYSTEXXA was studied in patients with CKD. Your doctor doesn't have to change the way KRYSTEXXA is prescribed to you based on your CKD.[17]

Will my CKD make KRYSTEXXA less effective?
People with kidney disease saw similar reductions in their uric acid levels compared to people without kidney disease.[17,29]

How does KRYSTEXXA work?
KRYSTEXXA works to change uric acid into a water-soluble substance that can be more easily eliminated by the kidneys through urine.[17]

Why can't I take KRYSTEXXA as a pill?
KRYSTEXXA is an intravenous infusion medicine given to you every 2 weeks. It may be co-administered with 15 mg of oral methotrexate weekly and 1 mg of oral folic acid daily. If methotrexate is not appropriate for you, KRYSTEXXA may also be given alone.[17,18]

Do I have to get KRYSTEXXA infused every 2 weeks?
Yes. The recommended dosing schedule is KRYSTEXXA every 2 weeks in combination with oral methotrexate (15 mg) weekly and folic acid (1 mg) daily throughout treatment.[17,18]

KRYSTEXXA can also be taken without methotrexate if your doctor does not think it's right for you.

What happens if I miss an infusion?
Making time for your infusions can be challenging, but in order to see the best results with KRYSTEXXA, it's important to receive your infusion every 2 weeks. If you are going to miss an appointment, contact your doctor or infusion center as soon as possible to reschedule.[17]

When will I start seeing results with KRYSTEXXA?
KRYSTEXXA starts working within 24 hours. In clinical studies, best results were seen at 6-12 months of treatment. Optimal treatment duration has not been established.[17,30]

What happens after I finish taking KRYSTEXXA?
You and your doctor will decide on a plan to keep urate crystals from building up again.[17]

Could I still have flares after starting KRYSTEXXA?
Yes, gout flares are common even when the treatment is working. KRYSTEXXA rapidly reduces the uric acid level in the blood, allowing urate crystals to dissolve. As these crystal deposits break down, flares can occur including in areas where patients haven't previously had a flare. You may be able to prevent or alleviate this by taking anti-inflammatory medication.[17]

Your gout flares may increase in the first 3 months when you start taking KRYSTEXXA. It's important to continue taking KRYSTEXXA even if you have a flare, because the amount of flares will decrease after 3 months of treatment. Your doctor may give you other medicines to help reduce your gout flares for the first few months after starting KRYSTEXXA. Other patients have reported experiencing fewer flares by the end of treatment after an initial increase.[17]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Congestive Heart Failure (CHF)
KRYSTEXXA has not been formally studied in patients with CHF, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Two cases of CHF 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 CHF while receiving KRYSTEXXA 8 mg every 2 weeks during the OLE study. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

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Answers to common patient questions (cont'd)

Do I still take my other gout medicine(s) with KRYSTEXXA?
While taking KRYSTEXXA, do not take any other uric acid-lowering drugs, such as allopurinol or febuxostat. Your doctor may give you medicine (colchicine and/or NSAIDs) to help with gout flares you may have while on KRYSTEXXA. In preparation for your KRYSTEXXA infusion, your doctor may also give you antihistamines and corticosteroids to help reduce the likelihood of an infusion reaction.[17]

What are the most common side effects?
In the clinical trial, the most common side effects in people taking KRYSTEXXA with methotrexate (≥5% of patients) were gout flares, joint pain, coronavirus disease 2019 (COVID-19), nausea, and fatigue. The most common side effects in people taking KRYSTEXXA alone were gout flares, allergic reactions (including infusion reactions), nausea, bruising, sore throat, constipation, chest pain, COVID-19, and vomiting. This is not a complete list of all possible side effects. Tell your doctor or treatment team if you have any side effect that bothers you or that does not go away.[17]

What happens if I have an allergic reaction?
You'll receive KRYSTEXXA in a healthcare setting where a doctor or nurse will watch you for any side effects or allergic reactions. If you have any side effects, your doctor may stop or slow the infusion and may give you medicine. You should seek medical care immediately if you experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA.[17]

Can I continue taking KRYSTEXXA if I have an infusion reaction?
It depends. Based on the doctor's assessment, the infusion may be slowed or stopped and restarted when the reaction is resolved. It is also possible that treatment may not be restarted.[17]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Re-treatment with KRYSTEXXA
No controlled trial data are available on re-treatment 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.

Please see additional Important Safety Information throughout and on pages 14-15 and see Full Prescribing Information, including Boxed Warning.

KRYSTEXXA® pegloticase

INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

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

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial of KRYSTEXXA co-administered with methotrexate (MTX) compared to KRYSTEXXA alone, one patient treated with KRYSTEXXA co-administered with MTX (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis treated with KRYSTEXXA alone. Patients were pre-treated with infusion reaction prophylaxis and KRYSTEXXA was discontinued following 2 consecutive serum uric acid levels above 6 mg/dL to reduce the risk of anaphylaxis and infusion reactions. These risks are higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Anaphylaxis was reported with 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, nausea or vomiting. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen, which may have resulted in an underestimate of anaphylaxis frequency reported. 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.

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.

Infusion Reactions

In the 52-week trial, infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with MTX group compared to 31% of patients treated with KRYSTEXXA alone. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion.

Please see Important Safety Information continued on next page and see Full Prescribing Information, including Boxed Warning.

KRYSTEXXA® pegloticase

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, 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, which may have resulted in an underestimate of infusion reaction frequency reported.

Manifestations of these reactions included urticaria (10.6%), dyspnea (7.1%), chest discomfort (9.5%), chest pain (9.5%), erythema (9.5%), and pruritus (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 occurred at any time during a course of treatment with ~3% occurring with the first infusion, and ~91% occurred during the time of infusion.

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.

Gout Flares

In the 52-week trial of KRYSTEXXA co-administered with MTX vs KRYSTEXXA alone, patients were administered gout flare prophylaxis, resulting in 66% and 69% of patients with any flare for the first 3 months, respectively. In the KRYSTEXXA co-administered with MTX group, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27%, 8%, and 9% during Months 6, 9, and 12, respectively; in the group treated with KRYSTEXXA alone, 14%, 9%, and 21% during Months 6, 9, and 12, respectively.

During the 24-week pre-marketing, controlled trials, with KRYSTEXXA alone the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months, and decreased in the subsequent 3 months. 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 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 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.

Congestive Heart Failure (CHF)

KRYSTEXXA has not been formally studied in patients with CHF, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Two cases of CHF 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 CHF while receiving KRYSTEXXA 8 mg every 2 weeks during the OLE study. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on re-treatment 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.

ADVERSE REACTIONS

The most common adverse reactions (≥5%) are:

Co-administration with MTX:

Gout flares, arthralgia, COVID-19, nausea, and fatigue.

KRYSTEXXA alone:

Gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

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KRYSTEXXA® pegloticase

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References: 1. Doghramji PP, et al. *Postgrad Med*. 2012;124:98-109. **2.** Khanna PP, et al. *J Clin Med*. 2020;9:3204. **3.** Roddy E, et al. *Arthritis Res Ther*. 2010;12:223. **4.** Edwards NL. *Arthritis Rheum*. 2008;58:2587-2590. **5.** Nickeleit V, et al. *Nephrol Dial Transplant*. 1997;12:1832-1838. **6.** Park JJ, et al. *BMJ Open*. 2014;4:e005308. **7.** Lu H, et al. *Medicine (Baltimore)*. 2017;96:e7670. **8.** Choi HK, et al. *Ann Rheum Dis*. 2009;68:1609-1612. **9.** Kang DH, et al. *Electrolyte Blood Press*. 2014;12:1-6. **10.** Major TJ, et al. *BMJ*. 2018;363:k3951. **11.** Doherty M. *Rheumatology (Oxford)*. 2009;48(suppl 2):ii2-ii8. **12.** Krishnan E. *PLoS One*. 2012;7:e50046. **13.** Burns CM, et al. *Ther Adv Chronic Dis*. 2012;3:271-286. **14.** FitzGerald JD, et al. *Arthritis Care Res (Hoboken)*. 2020;72:744-760. **15.** Perez-Ruiz F. *Rheumatology (Oxford)*. 2009;48(suppl 2):ii9-ii14. **16.** Araujo EG, et al. *RMD Open*. 2015;1:e000075. **17.** KRYSTEXXA (pegloticase) [prescribing information] Amgen. **18.** Botson JK, et al. *Arthritis Rheumatol*. 2023;75:293-304. **19.** Botson JK, et al. *ACR Open Rheumatol*. 2023;5:407-418. **20.** Dalbeth N, et al. *Joint Bone Spine*. 2024;105715. **21.** Data on File. Amgen, October 2021. **22.** Keenan RT, et al. *Rheumatol Ther*. 2019;6:299-304. **23.** Minucci A, et al. *IUBMB Life*. 2009;61:27-34. **24.** Frank JE. *Am Fam Physician*. 2005;72:1277-1282. **25.** Baraf HSB, et al. *J Clin Rheumatol*. 2014;20:427-432. **26.** Schett G, et al. *RMD Open*. 2015;1(suppl 1):e000046. **27.** McDonagh EM, et al. *Pharmacogenet Genomics*. 2014;24:464-476. **28.** Keenan RT, et al. *Semin Arthritis Rheum*. 2021;51:347-352. **29.** Yood RA, et al. *BMC Res Notes*. 2014;7:54. **30.** Sundy JS, et al. *JAMA*. 2011;306:711-720.

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