CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

016084Orig1s051

016084Orig1s052

Trade Name:	**ZYLOPRIM**
Generic or Proper Name:	allopurinol
Sponsor:	Casper Pharma, LLC
Approval Date:	September 21, 2023

Indication:

ZYLOPRIM is a xanthine oxidase inhibitor indicated for the management of:

- Adult patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
- Adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels
- Adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despise lifestyle changes

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APPROVAL LETTER

NDA 016084/S-048
NDA 016084/S-051
NDA 016084/S-052

SUPPLEMENT APPROVAL

Casper Pharma LLC
2 Tower Center Blvd, Suite 1401C
East Brunswick, NJ 08816

Attention: Ravi Vatchavai
Senior Director, Regulatory Affairs

Dear Ravi Vatchavai:

Please refer to your supplemental new drug applications (sNDA) dated and received March 19, 2020, April 19 and June 23, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zyloprim (allopurinol) tablets.

These Prior Approval supplemental NDAs provide for adding HLA-B*58:01 allele and allopurinol induced severe cutaneous adverse reaction (SCAR), updates to the Warnings section to further describe SCAR, and Physician Labeling Rule (PLR) conversion (including compliance to the Pregnancy and Lactation Labeling Rule (PLLR)), respectively.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Javonna Stevens, Regulatory Project Manager, at (301) 796-4240.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

OZLEM A BELEN
09/21/2023 08:19:35 AM

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LABELING

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYLOPRIM safely and effectively. See full prescribing information for ZYLOPRIM.

ZYLOPRIM® (allopurinol) tablets, for oral use
Initial U.S. Approval:1966

----------INDICATIONS AND USAGE----------

ZYLOPRIM is a xanthine oxidase inhibitor indicated for the management of:

- Adult patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy) (1)
- Adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels (1)
- Adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despite lifestyle changes (1)

Limitations of Use

ZYLOPRIM is not recommended for the treatment of asymptomatic hyperuricemia. (1)

----------DOSAGE AND ADMINISTRATION----------

- Gout: Prior to initiating treatment assess serum uric acid level, complete blood count, chemistry panel, liver and kidney function tests. Prophylactic treatment for gout flares is recommended. (2.1, 2.2)
  - Patients with normal kidney function: Initial dosage is 100 mg orally daily. Increase by 100 mg weekly increments until serum uric acid of 6 mg/dl or less is reached (maximum 800 mg daily). (2.3)
  - Patients with impaired kidney function: The initial dosage is 50 mg orally daily. Follow recommendations for titration in patients with renal impairment until target serum uric acid level is reached. (2.6)
  - See complete information in the Full Prescribing Information (FPI).
- Hyperuricemia Associated with Cancer Therapy: The recommended dosage is:
  - Adults: 300 mg to 800 mg orally daily.
  - Pediatric patients: 100 mg/m^2 orally every 8 hours to 12 hours (10 mg/kg/day, maximum 800 mg/day)
  - See complete information in the FPI. (2.4, 2.6)
- Recurrent Calcium Oxalate Calculi: The recommended initial dosage in patients with normal kidney function is 200 mg to 300 mg orally daily. (2.5)
- Dosage in Patients with Renal Impairment: See FPI for dosage modifications in patients with renal impairment. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 100 mg, 200 mg, and 300 mg, functionally scored

----------CONTRAINDICATIONS----------

Known hypersensitivity to allopurinol or to any of the ingredients of ZYLOPRIM.

----------WARNINGS AND PRECAUTIONS----------

- Skin Rash and Hypersensitivity: Allopurinol has been associated with serious and sometimes fatal dermatological reactions. Discontinue ZYLOPRIM at the first appearance of skin rash or other signs of hypersensitivity reaction. (5.1)
- Gout Flares: May occur during initiation of treatment. Concurrent prophylactic treatment with colchicine or anti-inflammatory agents is recommended. (5.2)
- Nephrotoxicity: Allopurinol may affect kidney function. Patients with decreased kidney function require lower doses of ZYLOPRIM. (5.3)
- Hepatoxicity: Cases of reversible hepatotoxicity have occurred. If signs and symptoms of hepatotoxicity develop, evaluate liver function. (5.4)
- Myelosuppression: Bone marrow suppression has been reported with allopurinol. (5.5)
- Potential Effect on Driving and Use of Machinery: Drowsiness, somnolence and dizziness have been reported in patients taking ZYLOPRIM. (5.6)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence > 1%) are nausea, diarrhea, and increase in liver function tests. (6)

To report SUSPECTED ADVERSE REACTIONS, Casper Pharma LLC at 1-844-5-CASPER (1-844-522-7737) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- The following drugs may increase the risk of serious skin reactions: bendamustine, thiazide diuretics, ampicillin and amoxicillin. (7.1)
- Capecitabine: Avoid concomitant use. (7.2)
- Mercaptopurine or Azathioprine: Reduce mercaptopurine or azathioprine dose as recommended in the respective prescribing information. (7.2)
- Pegloticase: Discontinue and refrain from initiating treatment with ZYLOPRIM. (7.2)
- See FPI for complete list of significant drug interactions. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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For current labeling information, please visit https://www.fda.gov/drugsatfda

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYLOPRIM is indicated for:

- The management of adults with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
- The management of adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels
- The management of adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despite lifestyle changes (such as reduction of dietary sodium, non-dairy animal protein, oxylate rich foods, refined sugars and increases in oral fluids and fruits and vegetables)

Limitations of Use

ZYLOPRIM is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Testing Prior to Treatment Initiation

Prior to initiating treatment with ZYLOPRIM in patients with gout, assess the following baseline tests: serum uric acid level, complete blood count, chemistry panel, liver function tests (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin), kidney function tests (serum creatinine and eGFR).

2.2 Recommended Prophylaxis for Gout Flares

Gout flares may occur after initiation of ZYLOPRIM due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with colchicine or an anti-inflammatory agent according to practice guidelines is recommended upon initiation of ZYLOPRIM. While adjusting the dosage of ZYLOPRIM in patients who are being treated with colchicine and/or anti-inflammatory agents, continue flare prophylaxis drugs until serum uric acid has been normalized and the patient has been free of gout flares for several months. If a gout flare occurs during ZYLOPRIM treatment, ZYLOPRIM need not be discontinued. Manage the gout flare concurrently, as appropriate for the individual patient *[see Warnings and Precautions (5.2)]*.

2.3 Recommended Dosage for Gout

The initial recommended dosage for the management of gout is 100 mg orally daily, with weekly increments of 100 mg, until a serum uric acid level of 6 mg/dL or less is reached. Initiating treatment with lower dosages of ZYLOPRIM and titrating slowly, decreases the risk of gout flares and drug induced serious adverse reactions.

In patients with renal impairment the initial dosage is 50 mg orally daily with lower dose increases until serum uric acid level of 6 mg/dL or less is reached. For complete dosage recommendations for patients with renal impairment see Table 1 *[see Dosage and Administration (2.6)]*.

The minimal effective dosage is 100 mg to 200 mg daily and the maximal recommended dosage is 800 mg daily. The appropriate dosage may be administered in divided doses or as a single

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equivalent dose with the 300 mg tablet. Doses in excess of 300 mg should be administered in divided doses. Monitor patients' kidney function during the early stages of administration of ZYLOPRIM and decrease the dosage or withdraw the drug if persistent abnormalities in kidney function occur *[see Dosage and Administration (2.6), Warnings and Precautions (5.3), Use in Specific Populations (8.6)]*.

The dosage of ZYLOPRIM to achieve control of gout varies with the severity of the disease. In general, gout control is achieved with 200 mg to 300 mg daily in patients with mild gout, and with 400 mg to 600 mg daily in patients with moderate to severe tophaceous gout. Gout attacks usually become shorter and less severe after several months of therapy.

If a dose of ZYLOPRIM is missed, there is no need to double the dose at the next scheduled time. ZYLOPRIM is generally better tolerated if taken following meals. A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or preferably, slightly alkaline urine are desirable.

Inform patients of the possibility of gout flares *[see Warnings and Precautions (5.2)]*. Instruct them to remain on ZYLOPRIM if this occurs and to increase fluid intake during therapy to prevent kidney stones.

Concurrent Use of Uricosuric Agents

Some patients, may benefit using uricosuric agents concurrently, to reduce serum uric acid to target levels.

When transferring a patient from a uricosuric agent to ZYLOPRIM, reduce the dose of the uricosuric agent over a period of several weeks and increase the dose of ZYLOPRIM gradually to the required dose needed to maintain target serum uric acid level.

2.4 Recommended Dosage for Hyperuricemia Associated with Cancer Therapy

Initiate therapy with ZYLOPRIM 24 hours to 48 hours before the start of chemotherapy known to cause tumor cell lysis. Administer fluids sufficient to yield a daily urinary output of at least 2 liters in adults (at least 100 mL/m^2/hour in pediatric patients) with a neutral or, preferably, slightly alkaline urine.

The recommended dosage of ZYLOPRIM is:

- Adult patients – 300 mg to 800 mg orally daily
- Pediatric patients - 100 mg/m^2 orally every 8 hours to 12 hours (10 mg/kg/day, maximum 800 mg/day). In patients with body surface area < 0.5 m^2, consider using an alternative allopurinol formulation.

The dosage of ZYLOPRIM to maintain normal or near-normal serum uric acid varies with the severity of the disease. Monitor serum uric acid levels at least daily and administer ZYLOPRIM at a dose and frequency to maintain the serum uric acid within the normal range. Discontinue ZYLOPRIM when the risk of tumor lysis has abated (2 days to 3 days from start of chemotherapy). For complete dosage recommendations for patients with renal impairment, see Table 2 *[see Dosage and Administration (2.6)]*.

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2.5 Recommended Dosage for Management of Recurrent Calcium Oxalate Calculi in Hyperuricosuric Patients

The recommended dosage for the management of recurrent calcium oxalate stones in hyperuricosuric patients is 200 mg to 300 mg orally daily in divided doses or as the single equivalent. This dose may be adjusted depending upon the resultant control of the hyperuricosuria based upon subsequent 24-hour urinary urate determinations.

2.6 Recommended Dosage in Patients with Renal Impairment

The recommended initial dosages of ZYLOPRIM in adult patients with renal impairment are shown in Tables 1 and 2 *[see Use in Specific Populations (8.6)]*.

Patients with Gout

The recommended initial dosages in adult patients with gout with impaired kidney function are shown in Table 1 *[see Use in Specific Populations (8.6)]*.

Initiate treatment with a lower dose of ZYLOPRIM and increase the dose gradually in 50 mg/day increments every 2 weeks to 4 weeks in patients with renal impairment to decrease the risk of drug induced serious adverse reactions. Use the lowest dose possible to achieve the desired effect on serum and/or urine uric acid. Monitor kidney function in gout patients with chronic kidney disease closely when initiating treatment with ZYLOPRIM and decrease or withdraw the drug if increased abnormalities in kidney function appear and persist.

Table 1. Recommended Initial Dosage in Adult Patients with Gout

eGFR	Initial Dosage
> 60 mL/minute	No dosage modification
> 30 to 60 mL/minute	50 mg daily
> 15 to 30 mL/minute	50 mg every other day
5 to 15 mL/minute	50 mg twice weekly
< 5 mL/minute	50 mg once weekly

The maximum dosage that should be used in patients with various levels of renal impairment is not defined at different eGFR levels.

Patients with Recurrent Calcium Oxalate Calculi

Data are insufficient to provide dosage recommendations for the treatment of recurrent calcium oxalate calculi in patients with renal impairment. Allopurinol and its metabolites are excreted by the kidney, and accumulation of the drug can occur in renal failure *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

Hyperuricemia Associated with Cancer Therapy

The recommended dosage of ZYLOPRIM for the management of hyperuricemia associated with cancer therapy in adult patients with renal impairment is shown in Table 2 *[see Use in Specific Populations (8.6)]*.

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Table 2. Recommended Dosage of ZYLOPRIM in Adult Patients for Management of Hyperuricemia Associated with Cancer Therapy with Renal Impairment

eGFR	Recommended Dosage
> 20 mL/min to 60 mL/min	No dosage modification
10 mL/min to 20 mL/min	200 mg/day
< 10 mL/min	100 mg/day
On dialysis	50 mg every 12 hours, or 100 mg every 24 hours

Treatment with ZYLOPRIM has not been studied in pediatric patients with severe renal impairment (eGFR < 20 mL/min) or on dialysis. There is insufficient information to establish dosing for ZYLOPRIM in pediatric patients with renal impairment. In these patients, consider the risks and potential benefits before initiating treatment with ZYLOPRIM *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

ZYLOPRIM tablets have functional scoring and are available in the following strengths:

- 100 mg: A flat-faced raised hexagon, beveled edge, white to off-white tablet, one side engraved "ZYLOPRIM 100" with a score bar and the other side plain.
- 200 mg: White to off-white, biconvex, round, scored tablets, imprinted "ZYLOPRIM" about the upper periphery, and 200 on the lower half, below the score and plain on the other side.
- 300 mg: A flat-faced raised hexagon, beveled edge, peach tablet, one side engraved "ZYLOPRIM 300" with a score bar and the other side plain.

4 CONTRAINDICATIONS

ZYLOPRIM is contraindicated in patients with a history of hypersensitivity reaction to allopurinol or to any of the ingredients of ZYLOPRIM.

5 WARNINGS AND PRECAUTIONS

5.1 Skin Rash and Hypersensitivity

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking allopurinol *[see Adverse Reactions (6)]*. These reactions occur in approximately 5 in 10,000 (0.05%) patients taking allopurinol. Other serious hypersensitivity reactions that have been reported include exfoliative, urticarial and purpuric lesions, generalized vasculitis, and irreversible hepatotoxicity. Discontinue ZYLOPRIM permanently at the first appearance of skin rash or other signs which may indicate a hypersensitivity reaction.

The HLA-B*58:01 allele is a genetic marker for severe skin reactions indicative of hypersensitivity to allopurinol. Patients who carry the HLA-B*58:01 allele are at a higher risk of allopurinol hypersensitivity syndrome (AHS), but hypersensitivity reactions have been reported in patients

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who do not carry this allele. The frequency of this allele is higher in individuals of African, Asian (e.g., Han Chinese, Korean, Thai), and Native Hawaiian/Pacific Islander ancestry *[see Clinical Pharmacology (12.5)]*. The use of ZYLOPRIM is not recommended in HLA- B*58:01 positive patients unless the benefits clearly outweigh the risks.

Consider screening for HLA-B*5801 before starting treatment with ZYLOPRIM in patients from populations in which the prevalence of this HLA-B*5801 allele is known to be high. Screening is generally not recommended in patients from populations in which the prevalence of HLA-B*58:01 is low, or in current allopurinol users, as the risk of SJS/TEN/DRESS is largely confined to the first few months of therapy, regardless of HLA- B*58:01 status.

Hypersensitivity reactions to ZYLOPRIM may be increased in patients with decreased kidney function receiving thiazide diuretics and ZYLOPRIM concurrently. Concomitant use of the following drugs may also increase the risk of skin rash, which may be severe: bendamustine, ampicillin and amoxicillin *[see Drug Interactions (7.1)]*.

Discontinue ZYLOPRIM immediately if a skin rash develops. Instruct patients to stop taking ZYLOPRIM immediately and seek medical attention promptly if they develop a rash.

5.2 Gout Flares

Gout flares have been reported during initiation of treatment with ZYLOPRIM, even when normal or subnormal serum uric acid levels have been attained due to the mobilization of urates from tissue deposits. Even with adequate therapy with ZYLOPRIM, it may require several months to deplete the uric acid pool sufficiently to achieve control of the flares. The flares typically become shorter and less severe after several months of therapy.

In order to prevent gout flares when treatment with ZYLOPRIM is initiated, concurrent prophylactic treatment with colchicine or an anti-inflammatory agent is recommended *[see Dosage and Administration (2.2)]*. Advise patients to continue ZYLOPRIM and prophylactic treatment even if gout flares occur, as it may take months to achieve control of gout flares.

5.3 Nephrotoxicity

Treatment with ZYLOPRIM may result in acute kidney injury due to formation of xanthine calculi or due to precipitation of urates in patients receiving concomitant uricosuric agents. Patients with pre-existing kidney disease, including chronic kidney disease or history of kidney stones, may be at increased risk for worsening of kidney function or acute kidney injury due to xanthine calculi while receiving treatment with ZYLOPRIM.

In patients receiving ZYLOPRIM for the management of gout or the management of recurrent calcium oxalate calculi, monitor kidney function frequently during the early stages of allopurinol administration. Maintain fluid intake sufficient to yield a urinary output of at least 2 liters per day of neutral or, preferably, slightly alkaline urine to avoid the possibility of formation of xanthine calculi and help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

In patients receiving ZYLOPRIM for the management of tumor lysis syndrome, monitor kidney function at least daily during the early stages of allopurinol administration. Maintain fluid intake sufficient to yield a urinary output of at least 2 liters per day in adults and at least 2 liters/m^2/day (or at least 100 mL/m^2/hour) in pediatric patients *[see Dosage and Administration (2.4)]*.

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5.4 Hepatotoxicity

Cases of reversible clinical hepatotoxicity have occurred in patients taking ZYLOPRIM, and in some patients, asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss, or pruritus develop in patients on ZYLOPRIM, evaluate liver enzymes. In patients with pre-existing liver disease, monitor liver enzymes periodically. Discontinue ZYLOPRIM in patients with elevated liver enzymes.

5.5 Myelosuppression

Myelosuppression, manifested by anemia, leukopenia or thrombocytopenia, has been reported in patients receiving ZYLOPRIM. The cytopenias have occurred as early as 6 weeks up to 6 years after the initiation of therapy of ZYLOPRIM. Concomitant use of ZYLOPRIM with cytotoxic drugs associated with myelosuppression may increase the risk of myelosuppression. Monitor blood counts more frequently when cytotoxic drugs are used concomitantly *[see Drug Interactions (7.2)]*.

Concomitant use with allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of myelosuppression. Reduce the dosage of mercaptopurine or azathioprine as recommended in their respective prescribing information when used concomitantly with ZYLOPRIM *[see Drug Interactions (7.2)]*.

5.6 Potential Effect on Driving and Use of Machinery

Drowsiness, somnolence and dizziness have been reported in patients taking ZYLOPRIM *[see Adverse Reactions (6)]*. Inform patients also that the central nervous system depressant effects of ZYLOPRIM may be additive to those of alcohol and other CNS depressants.

Advise patients to avoid operation of automobiles or other dangerous machinery and activities made hazardous by decreased alertness when starting ZYLOPRIM or increasing the dose, until they know how the drug affects them.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Skin Rash and Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Nephrotoxicity *[see Warnings and Precautions (5.3)]*
- Hepatoxicity *[see Warnings and Precautions (5.4)]*
- Myelosuppression *[see Warnings and Precautions (5.5)]*
- Potential Effect on Driving and Use of Machinery *[see Warnings and Precautions (5.6)]*

The following adverse reactions associated with the use of ZYLOPRIM were identified in literature, unpublished clinical trials or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most frequent adverse reaction to ZYLOPRIM is skin rash.

Most Common Adverse Reactions (≥ 1%)

Gastrointestinal: Diarrhea, nausea, alkaline phosphatase increase, AST/ALT increase.

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Metabolic and Nutritional: Acute attacks of gout.

Skin and Appendages: Rash, maculopapular rash.

Less Common Adverse Reactions (< 1%)

Body As a Whole: Ecchymosis, fever, headache, malaise.

Cardiovascular: Necrotizing angiitis, vasculitis, pericarditis, peripheral vascular disease, thrombophlebitis, bradycardia, vasodilation.

Gastrointestinal: Hepatic necrosis, granulomatous hepatitis, hepatomegaly, hyperbilirubinemia, cholestatic jaundice, vomiting, intermittent abdominal pain, gastritis, dyspepsia, hemorrhagic pancreatitis, gastrointestinal bleeding, stomatitis, salivary gland swelling, hyperlipidemia, tongue edema, anorexia.

Hemic and Lymphatic: Thrombocytopenia, eosinophilia, leukocytosis, leukopenia, aplastic anemia, agranulocytosis, eosinophilic fibrohistiocytic lesion of bone marrow, pancytopenia, prothrombin decrease, anemia, hemolytic anemia, reticulocytosis, lymphadenopathy, lymphocytosis.

Musculoskeletal: Myopathy, arthralgias, myalgia.

Nervous: Peripheral neuropathy, neuritis, paresthesia, somnolence, optic neuritis, confusion, dizziness, vertigo, foot drop, decrease in libido, depression, amnesia, tinnitus, asthenia, insomnia.

Respiratory: Epistaxis, bronchospasm, asthma, pharyngitis, rhinitis.

Skin and Appendages: Erythema multiforme exudativum (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), hypersensitivity vasculitis, purpura, vesicular bullous dermatitis, exfoliative dermatitis, eczematoid dermatitis, pruritus, urticaria, alopecia, onycholysis, lichen planus, furunculosis, facial edema, sweating, skin edema.

Special Senses: Taste loss/perversion, cataracts, macular retinitis, iritis, conjunctivitis, amblyopia.

Urogenital: Renal failure, uremia, nephritis, impotence, primary hematuria, albuminuria.

Endocrine: Infertility (male), hypercalcemia, gynecomastia (male).

7 DRUG INTERACTIONS

7.1 Drugs Known to Affect the Occurrence of Skin Rash and Hypersensitivity

Concomitant use of the following drugs may increase the risk of skin rash, which may be severe: bendamustine, thiazide diuretics, ampicillin and amoxicillin. Renal impairment may further increase risk with concomitant use of thiazide diuretics *[see Warnings and Precautions (5.1, 5.2) and Clinical Pharmacology (12.2)]*.

Monitor kidney function and reduce the dose of ZYLOPRIM in patients with concomitant thiazide diuretic use and impaired renal function *[see Dosage and Administration (2.6), Warnings and Precautions (5.1)]*.

Discontinue ZYLOPRIM at the first appearance of skin rash or other signs which may indicate a hypersensitivity reaction when use concomitantly with these drugs *[see Warnings and Precautions (5.1)]*.

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7.2 Drugs Known to Have Clinically Important Drug Interactions with ZYLOPRIM

Table 3: Interventions for Clinically Important Drug Interactions with ZYLOPRIM

Capecitabine	
Clinical Impact	Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites, which may decrease capecitabine efficacy.
Intervention	Avoid the use of ZYLOPRIM during treatment with capecitabine
Chlorpropamide	
Clinical Impact	ZYLOPRIM prolongs the half-life of chlorpropamide as both compete for renal tubular excretion. In patients with renal insufficiency, the risk of hypoglycemia may be increased due to this mechanism.
Intervention	Monitor patients with renal insufficiency for hypoglycemia when administering chlorpropamide and ZYLOPRIM concomitantly.
Cyclosporine	
Clinical Impact	Concomitant use of allopurinol increases cyclosporine concentrations, which may increase the risk of adverse reactions.
Intervention	Increase frequency of monitoring cyclosporine concentrations as reflected in its prescribing information and modify the dosage of cyclosporine as appropriate when used concomitantly with ZYLOPRIM.
Cyclophosphamide and Other Cytotoxic Agents	
Clinical Impact	Concomitant use of allopurinol with cyclophosphamide and other cytotoxic agents (doxorubicin, bleomycin, procarbazine, mechloroethamine) increases bone marrow suppression among patients with neoplastic disease, except leukemia.
Intervention	Blood count monitoring and regular physician follow-up are recommended.
Dicumarol	
Clinical Impact	ZYLOPRIM prolongs the half-life of the anticoagulant, dicumarol. The mechanism of this drug interaction has not been established but should be noted when ZYLOPRIM is given to patients already on dicumarol therapy.
Intervention	Monitor prothrombin time. Adjust the dosage of dicumarol accordingly when ZYLOPRIM is added to anticoagulant therapy.
Fluorouracil	
Clinical Impact	Based on non-clinical data, allopurinol may decrease anti-tumor activity due to suppression of phosphorylation of 5-fluorouracil.
Intervention	Concomitant administration with fluorouracil should be avoided.
Mercaptopurine or Azathioprine	
Clinical Impact	Allopurinol inhibits xanthine oxidase mediated metabolism of mercaptopurine and azathioprine. Concomitant use of allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of their adverse reactions, including myelosuppression *[see Warnings and Precautions 5.5]*.
Intervention	In patients receiving mercaptopurine or azathioprine, the concomitant administration of 300 mg to 600 mg of ZYLOPRIM per day will require a reduction in dose to approximately one third to one fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of

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	mercaptopurine or azathioprine should be made on the basis of therapeutic response and the appearance of toxic effects.
Pegloticase	
Clinical Impact	Concomitant use of ZYLOPRIM and pegloticase may potentially blunt the rise of serum uric acid levels and increase the risk of pegloticase related anaphylaxis in patients whose uric acid level increase to above 6 mg/dL.
Intervention	Discontinue and do not institute ZYLOPRIM therapy during treatment with pegloticase.
Theophylline	
Clinical Impact	Concomitant use of allopurinol doses greater than or equal to 600 mg/day may decrease the clearance of theophylline
Intervention	Monitor and adjust theophylline doses as reflected in the prescribing information.
Uricosuric Drugs	
Clinical Impact	Uricosuric agents increase the excretion of the active allopurinol metabolite oxypurinol. Concomitant use with uricosuric agents decreases oxypurinol exposure which may reduce the inhibition of xanthine oxidase by oxypurinol and increases the urinary excretion of uric acid. The net effect of such combined therapy may be useful in some patients in achieving minimum serum uric acid levels provided the total urinary uric acid load does not exceed the competence of the patient's kidney function.
Intervention	Monitor uric acid levels due to the increased chance of hypouricemic effects.
Warfarin	
Clinical Impact	Allopurinol may inhibit the metabolism of warfarin, possibly enhancing its anticoagulant effect.
Intervention	Monitor patients on concomitant therapy for excessive anticoagulation. Assess INR frequently and adjust warfarin dosage accordingly when allopurinol is added to warfarin therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, ZYLOPRIM may cause fetal harm when administered to a pregnant woman. Adverse developmental outcomes have been described in exposed animals *(see Data)*. Allopurinol and its metabolite oxypurinol have been shown to cross the placenta following administration of maternal allopurinol.

Available limited published data on allopurinol use in pregnant women do not demonstrate a clear pattern or increase in frequency of adverse developmental outcomes. Among approximately 50 pregnancies described in published literature, 2 infants with major congenital malformations have been reported with following maternal allopurinol exposure. Advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown.

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In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Experience with ZYLOPRIM during human pregnancy has been limited partly because women of reproductive age rarely require treatment with ZYLOPRIM. A case report published in 2011 described the outcome of a full-term pregnancy in a 35-year-old woman who had recurrent kidney stones since age 18 who took allopurinol throughout the pregnancy. The child had multiple complex birth defects and died at 8 days of life. A second report in 2013 provided data on 31 prospectively ascertained pregnancies involving mothers exposed to allopurinol for varying durations during the first trimester. The overall rate of major fetal malformations and spontaneous abortions was reported to be within the normal expected range; however, one child had severe malformations similar to those described in the cited earlier case report.

Animal Data

There was no evidence of fetotoxicity or teratogenicity in rats or rabbits treated during the period of organogenesis with oral allopurinol at doses up to 200 mg/kg/day and up to 100 mg/kg/day, respectively (about 2.4 times the human dose on a mg/m^2 basis). However, there is a published report in pregnant mice that single intraperitoneal doses of 50 mg/kg or 100 mg/kg (about 0.3 or 0.6 times the human dose on a mg/m^2 basis) of allopurinol on gestation days 10 or 13 produced significant increases in fetal deaths and teratogenic effects (cleft palate, harelip, and digital defects). It is uncertain whether these findings represented a fetal effect or an effect secondary to maternal toxicity.

8.2 Lactation

Risk Summary

Allopurinol and oxypurinol are present in human milk. Based on information from a single case report, allopurinol and its active metabolite, oxypurinol, were detected in the milk of a mother receiving 300 mg of allopurinol daily at 5 weeks postpartum. The estimated relative infant dose were 0.14 mg/kg and 0.2 mg/kg of allopurinol and between 7.2 mg/kg to 8 mg/kg of oxypurinol daily. There was no report of effects of allopurinol on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatments with ZYLOPRIM and for one week after the last dose.

8.4 Pediatric Use

Hyperuricemia Associated with Cancer Therapy

The safety and effectiveness of allopurinol for the management of pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels have been established in approximately 200 pediatric patients. The efficacy and safety profile observed in this patient population were similar to that observed in adults.

Primary or Secondary Gout

The safety and effectiveness of ZYLOPRIM have not been established for the treatment of signs and symptoms of primary or secondary gout in pediatric patients.

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Recurrent Calcium Oxalate Calculi

The safety and effectiveness of ZYLOPRIM have not been established for the management of pediatric patients with recurrent calcium oxalate calculi.

Inborn Errors of Metabolism

The safety and effectiveness of ZYLOPRIM have not been established in pediatric patients with rare inborn errors of purine metabolism.

8.6 Renal Impairment

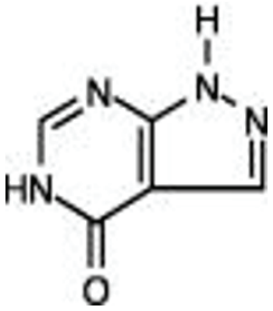
ZYLOPRIM and its primary active metabolite, oxipurinol, are eliminated by the kidneys; therefore, changes in renal function have a profound effect on exposure. In patients with decreased renal function or who have concurrent illnesses which can affect renal function, perform periodic laboratory parameters of renal function and reassess the patient's dosage of ZYLOPRIM *[see Dosage and Administration (2.6), Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

In the management of overdosage there is no specific antidote for ZYLOPRIM. Both ZYLOPRIM and oxipurinol are dialyzable; however, the usefulness of hemodialysis or peritoneal dialysis in the management of an overdose of ZYLOPRIM is unknown.

11 DESCRIPTION

ZYLOPRIM (allopurinol) is a xanthine oxidase inhibitor. It has the following structural formula:



ZYLOPRIM is known chemically as 1, 5-dihydro-4*H*-pyrazolo [3, 4-*d*]pyrimidin-4-one and it has a molecular weight of 136.11 g/mol. Its solubility in water at 37°C is 80.0 mg/dL and is greater in an alkaline solution. It is a xanthine oxidase inhibitor which is administered orally.

Each scored white hexagon-shaped tablet contains 100 mg allopurinol and the inactive ingredients lactose monohydrate, magnesium stearate, potato starch, and povidone.

Each scored white round tablet contains 200 mg allopurinol and the inactive ingredients lactose monohydrate, magnesium stearate, corn starch, and povidone.

Each scored peach tablet contains 300 mg allopurinol and the inactive ingredients corn starch, FD&C Yellow No. 6 Lake, lactose monohydrate, magnesium stearate, and povidone.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZYLOPRIM (allopurinol) is a structural analogue of the natural purine base, hypoxanthine.

Allopurinol acts on purine catabolism, without disrupting the biosynthesis of purines. It reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation. It is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in humans. Allopurinol is metabolized to the corresponding xanthine analogue, oxypurinol (alloxanthine), which also is an inhibitor of xanthine oxidase.

12.2 Pharmacodynamics

ZYLOPRIM reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation in a dose dependent manner. The pharmacological action of allopurinol is generally believed to be mediated by its oxypurinol metabolite.

Effect on Hypoxanthine and Xanthine

Reutilization of both hypoxanthine and xanthine for nucleotide and nucleic acid synthesis is markedly enhanced when their oxidations are inhibited by ZYLOPRIM and oxipurinol. This reutilization does not disrupt normal nucleic acid anabolism, however, because feedback inhibition is an integral part of purine biosynthesis. As a result of xanthine oxidase inhibition, the serum concentration of hypoxanthine plus xanthine in patients receiving ZYLOPRIM for treatment of hyperuricemia is usually in the range of 0.3 mg/dL to 0.4 mg/dL compared to a normal level of approximately 0.15 mg/dL. A maximum of 0.9 mg/dL of these oxypurines has been reported when the serum urate was lowered to less than 2 mg/dL by high doses of ZYLOPRIM. These values are far below the saturation levels at which point their precipitation would be expected to occur (above 7 mg/dL). The increased xanthine and hypoxanthine in the urine in patients who were treated with oral allopurinol have not been accompanied by problems of nephrolithiasis; however, there are isolated case reports of xanthine crystalluria.

Drug Interaction Studies

Fluorouracil: Based on non-clinical data, allopurinol may decrease anti-tumor activity due to suppression of phosphorylation of 5-fluorouracil.

Pegloticase: Concomitant use of ZYLOPRIM and pegloticase may potentially blunt the rise of serum uric acid levels required for monitoring the safe use of pegloticase.

Cytotoxic Agents: Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease, except leukemia, in the presence of ZYLOPRIM.

Thiazide Diuretics: Reports that the concomitant administration of allopurinol and thiazide diuretics contributed to increased allopurinol toxicity were reviewed; however, a causal mechanism or cause-and-effect relationship was not found.

12.3 Pharmacokinetics

Absorption

ZYLOPRIM is approximately 90% absorbed from the gastrointestinal tract. Peak plasma levels

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generally occur at 1.5 hours and 4.5 hours for ZYLOPRIM and oxipurinol respectively. After a single oral dose of 300 mg ZYLOPRIM, maximum plasma levels of about 3 mcg/mL of ZYLOPRIM and 6.5 mcg/mL of oxipurinol are produced.

Elimination

The half-life of allopurinol and oxipurinol are approximately 1 hour to 2 hours and 15 hours following oral dose of ZYLOPRIM, respectively.

Metabolism

Allopurinol is metabolized to the corresponding xanthine analogue, oxypurinol (alloxanthine), which also is an inhibitor of xanthine oxidase.

Excretion

ZYLOPRIM and its primary active metabolite, oxipurinol, are eliminated by the kidneys. Approximately 20% of the ingested ZYLOPRIM is excreted in the feces. Oxipurinol is primarily eliminated unchanged in urine by glomerular filtration and tubular reabsorption.

Drug Interaction Studies

Capecitabine: Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites, which may decrease capecitabine efficacy.

Cyclosporine: Concomitant use of allopurinol increases cyclosporine concentrations which may increase the risk of adverse reactions.

Mercaptopurine or Azathioprine: Allopurinol inhibits xanthine oxidase mediated metabolism of mercaptopurine and azathioprine. Concomitant use of allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of their adverse reactions including myelosuppression.

Theophylline: Concomitant use of allopurinol doses greater than or equal to 600 mg/day may decrease the clearance of theophylline.

Uricosuric Agents: Uricosuric agents increase the excretion of the active allopurinol metabolite oxypurinol. Concomitant use with uricosuric agents decreases oxypurinol exposure which may reduce the inhibition of xanthine oxidase by oxypurinol and increases the urinary excretion of uric acid.

Warfarin: Allopurinol may inhibit the metabolism of warfarin, possibly enhancing its anticoagulant effect.

12.5 Pharmacogenomics

HLA-B*5801 allele

The HLA-B*5801 allele is a genetic marker that has shown to be associated with risk of developing ZYLOPRIM related hypersensitivity syndrome (DRESS) and SJS/TEN. The frequency of the HLA- B*58:01 allele ranges from 8 to 10% in Han Chinese populations, about 8% in Thai populations, and about 6% in Korean populations based upon published literature and available databases. The frequency of the HLA-B*58:01 allele is about 4% in Blacks, about 1 % to 2 % in indigenous peoples of the Americas and Hispanic populations, and < 1% in people from European descent and Japanese.

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Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) can still occur in patients who are found to be negative for HLA-B*5801 irrespective of ethnic origin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in male or female mice or rats that received oral allopurinol for the majority of their life spans (greater than 88 weeks) at doses up to 20 mg/kg/day (0.1 and 0.2 times the MRHD on a mg/m^2 basis in mice and rats, respectively).

Allopurinol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay. Allopurinol administered intravenously to rats (50 mg/kg) was not incorporated into rapidly replicating intestinal DNA. No evidence of clastogenicity was observed in lymphocytes taken from patients treated with allopurinol (mean duration of treatment 40 months), or in an in vitro assay with human lymphocytes.

Allopurinol oral doses of 20 mg/kg/day had no effect on male or female fertility in rats or rabbits (approximately 0.2 or 0.5 times the MRHD on a mg/m^2 basis, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ZYLOPRIM (allopurinol) is available in multiple tablet strengths with functional scoring and package sizes (bottles with child-resistant caps) as listed in Table 4.

TABLE 4: ZYLOPRIM Presentations

Tablet Strength	Tablet Description	Package Sizes (NDC)
100 mg	Flat-faced raised hexagon, beveled edge, white tablet, one side engraved “ZYLOPRIM 100” with a score bar, and plain on the other side	Bottles of: • 90 tablets (NDC 70199-031-90) • 100 tablets (NDC 70199-031-01) • 500 tablets (NDC 70199-031-05) • 1,000 tablets (NDC 70199-031-99)
200 mg	Biconvex, round, white scored tablets, imprinted ZYLOPRIM about the upper periphery, and 200 on the lower half, below the score, and plain on the other side	Bottles of: • 90 tablets (NDC 70199-032-90) • 100 tablets (NDC 70199-032-01) • 500 tablets (NDC 70199-032-05) • 1,000 tablets (NDC 70199-032-99)
300 mg	Flat-faced raised hexagon, beveled edge, peach tablet, one side engraved “ZYLOPRIM 300” with a score bar, and plain on the other side	Bottles of: • 90 tablets (NDC 70199-033-90) • 100 tablets (NDC 70199-033-01) • 500 tablets (NDC 70199-033-05) • 1,000 tablets (NDC 70199-033-99)

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Storage and Handling

Store at 20°C to 25°C (USP Controlled Room Temperature) (68°F to 77°F) in a dry place. Dispense in a tight container as defined in the USP.

17 PATIENT COUNSELING INFORMATION

Administration

Advise patients to take ZYLOPRIM after meals to minimize gastric irritation. If a single dose of ZYLOPRIM is occasionally forgotten, there is no need to double the dose at the next scheduled time.

Skin Rash and Hypersensitivity

Inform patients that ZYLOPRIM may increase the risk of serious and sometimes fatal dermatologic reactions. Instruct patients to discontinue ZYLOPRIM and to seek medical attention immediately, at the first sign of a skin rash, blisters, fever, painful urination, blood in the urine, irritation of the eyes, swelling of the lips or mouth, or other signs and symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Gout Flares During Treatment With ZYLOPRIM

Inform patients that gout flares may occur during initiation of treatment with ZYLOPRIM, even when their serum uric acid is normal. Concurrent use of additional medications such as colchicine or other anti-inflammatory agents can prevent gout flares. Advise patients to continue treatment with both, ZYLOPRIM and the prophylactic therapy as prescribed, even if gout flares occur. Reassure them that it may take months to achieve control of the flares but the flares typically become shorter and less severe after several months of therapy *[see Warnings and Precautions (5.2)]*.

Nephrotoxicity

Inform patients that ZYLOPRIM may affect kidney function. Advise them to increase fluid intake during therapy (i.e., for adults, at least 2 liters of liquids per day) and to stay well hydrated to prevent kidney stones *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

Inform patients of the risk of hepatotoxicity and to report to their healthcare provider any signs and symptoms of liver failure, including jaundice, pruritus, bleeding, bruising, or anorexia *[see Warnings and Precautions (5.4)]*.

Myelosuppression

Advise patients of the risk of myelosuppression and to report any signs and symptoms of infection, fever, bleeding, shortness of breath, or significant fatigue to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Potential Effect on Driving and Use of Machinery

Inform patients that drowsiness, somnolence and dizziness have been reported in patients taking ZYLOPRIM. Inform also that the central nervous system depressant effects of ZYLOPRIM may be additive to those of alcohol and other CNS depressants. Advise patients to avoid operation of automobiles or other dangerous machinery and activities made hazardous by decreased alertness

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when starting ZYLOPRIM or increasing the dose, until they know how the drug affects them *[see Warnings and Precautions (5.6)]*.

Risks Associated with Use of Concomitant Medications

Inform patients that there are risks of adverse effects when ZYLOPRIM is used with the following drugs: dicumarol, warfarin, sulfinpyrazone, mercaptopurine, azathioprine, ampicillin, amoxicillin, pegloticase, theophylline, and thiazide diuretics. Advise patients to disclose all medications in use and they should follow the instructions of their physician *[see Drug Interactions (7.2)]*.

Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with ZYLOPRIM *[see Use in Specific Populations (8.1)]*.

Lactation

Advise women not to breastfeed during treatment with ZYLOPRIM and for one week after the last dose *[see Use in Specific Populations (8.2)]*.

Casper Pharma LLC

Manufactured by:
Casper Pharma Private Limited
Telangana-500108, India

M.L No.: TS/RR/2020-58622

Manufactured for:
Casper Pharma LLC
East Brunswick, NJ 08816

PIB03399-07

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

016084Orig1s051
016084Orig1s052

OTHER REVIEW(S)

Division of Rheumatology and Transplant Medicine
Associate Director for Labeling Review

Product Title	Zyloprim (allopurinol) 100 mg, 200 mg, 300 mg tablets
Applicant	Casper Pharma LLC
Application Number/ Supplement	NDA 016084/ S048, S051 and S52
Approved Indications	• Management of adult patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy) • Management of adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels • Management of adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despite lifestyle changes
Review Date	August 24, 2023

INTRODUCTION

This review addresses the applicant's Prior Approval Supplements (PAS) S048, S051 and S052 requesting the inclusion of additional information regarding the risk of serious dermatological adverse reactions associated with the presence of the HLA-B*58:01 allele. During the review of S048 and S052, Division of Rheumatology and Transplant Medicine (DRTM) seized the opportunity to propose to the applicant the conversion of the Prescribing Information (PI) of ZYLOPRIM (allopurinol) from the current format to an updated version in compliance with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR). The conversion of the labeling to the Physician Labeling Rule (PLR format) was conducted under S052.

LABELING HISTORY

NDA 016084 ZYLOPRIM (allopurinol) was originally approved on August 19, 1966. The most recent labeling was approved on August 4, 2022 (Labeling Supplement 49) which added the 200 mg strength to the U.S. market, added higher tablet count bottle presentations for all the three tablet strengths, and added an alternate drug product manufacturing, packaging, and testing facility for the 100 mg, 200 mg, and 300 mg tablets (see Approval Letter dated 08/04/2022). Prior to S049, labeling supplement S-044 submitted on October 30, 2013, revised the labeling to update the section PRECAUTIONS, subsection "Pregnancy: Teratogenic Effects" by removing the pregnancy category in compliance with the Pregnancy and Lactation Labeling Rule. In addition, the section "Warnings" was updated to inform the occurrence of

reports of Drug Rash with Eosinophilia and Systemic Symptoms associated with the use of allopurinol. At that time, the association of the HLA-B*5801 and the occurrence of serious skin reactions was unclear and no specific information regarding such association was approved for labeling (see clinical review by Dr. Sarah Yim, dated 08/20/2015).

(b) (4) the Agency requested that the application holder update the labeling of ZYLOPRIM, to include cautionary language regarding the association between the presence of the HLA-B*58:01 allele and allopurinol-induced severe cutaneous adverse reactions based on evidence from published literature. The following is the statement recommended by FDA: "The HLA-B*5801 allele is a genetic marker for severe skin reactions indicative of hypersensitivity to allopurinol." (b) (4) (b) (4)

On (b) (4) (b) (4) (b) (4) Such association is now recognized and its inclusion in labeling is appropriate and warranted for allopurinol products.

The application holder (b) (4) supplement S051 on April 19, 2023, by FDA's request with proposal for additional cautionary language with supporting information for the warning. Because the labeling was not in the format established by the Physician Labeling Rule (PLR) (b) (4) (b) (4) DRTM seized the opportunity to request again the conversion of the labeling to the PLR format and FDA issued a Prior Approval Supplement Request Letter (DARRTS 05/25/2023) requesting the PLR conversion along with a draft of PLR labeling created by FDA. On June 23, 2023, the application holder submitted labeling supplement S052 (b) (4)

The labeling approved by S052 follows largely the recently approved labeling for another allopurinol product, ALOPRIM (NDA 020298), approved on February 17, 2022, by the Division of Hematologic Malignancies 1 and the labeling of other drugs approved for the treatment of gout namely, DUZALLO (NDA 209203) and ULORIC (NDA 021856), in order to maintain consistency across the drug class, as well as for consistency across the indications,

whenever possible. Outdated and redundant information were removed, and updated information was included to conform with current guidelines and practice.

This review describes the updates implemented to the Prescribing Information (PI) to help ensure that it:

- Complies with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1].
- Is consistent with labeling guidance recommendations[2] and with CDER OND best labeling practices and policies.
- Conveys the essential scientific information needed for safe and effective use of the product.
- Is clinically meaningful and scientifically accurate.
- Is a useful communication tool for health care providers.
- Is consistent with other PI with the same active moiety, drug class, or similar indication.

LABELING FORMATTING AND CONTENT

The conversion of the current ZYLOPRIM labeling to PLR format provided an opportunity to:

- Place information from the old labeling within the sections and subsections established by the PLR.
- Remove information that is considered redundant or outdated, whenever possible.

The following groups provided assistance in the conversion of the labeling to the format according to the PLR:

- Division of Hematological Malignancies 1: Donna Przepiorka, MD, Elizabeth Everhart, ACNP
- Division of Cardiology and Nephrology: Aliza Thompson, MD, Evan Fisher, MD, Michael Monteleone, MS
- Division of Pediatrics and Maternal Health: Dina Zand, MD, Mona Khurana, MD, Tamara Johnson, MD, Christos Mastroyannis, MD
- Division of Translational and Personalized Medicine: Dr. Jeffrey Kraft, Ph.D.
- Division of Rheumatology and Transplant Medicine: Rosemarie Neuner, MD (Clinical), Timothy Robison, PhD (Nonclinical), Ping Ji, PhD, Sanjida Mahjabeen, PhD (Clinical Pharmacology), Craig Bertha, PhD (Product Quality)

HIGHLIGHTS OF PRESCRIBING INFORMATION

[1] See January 2006 Physician Labeling Rule available at https://www.federalregister.gov/documents/2006/01/24/06-545/requirements-on-content-and-format-of-labeling-for-human-prescription-drug-and-biological-products ; 21 CFR 201.56 and 201.57; and December 2014 Pregnancy and Lactation Labeling Rule available at https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

[2] See PLR Requirements for PI website for PLR labeling guidances.

Reference ID: 5244304

The subsections of the Highlights of Prescribing Information ("Highlights") follow the recommendations of content and formatting, to the extent possible, of the final guidance for industry "Labeling for Human Prescription Drug and Biological Products- Implementing the PLR Content and Format Requirements"[3], unless noted otherwise. The sections are described below:

- **Highlights Statement, Product Title and Initial US Approval**: The format and contents of Product Title and Initial US Approval follow recommendations proposed by the draft guidance for industry, "Product Title and Initial US Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products- Content and Format"[4]. It will read as follows:

  ZYLOPRIM® (allopurinol) tablets, for oral use
  Initial U.S. Approval:1966

- **Boxed Warning**: ZYLOPRIM does not have a boxed warning.

- **Indication and Usage**: This section includes three indications[5]. The established pharmacological class term "xanthine oxidase inhibitor" was added based on the FDA established pharmacologic class list (2022)[6]. This section will read as follows:

  ----------**INDICATIONS AND USAGE**----------
  ZYLOPRIM is a xanthine oxidase inhibitor indicated for the management of:
  - Adult patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy) (1)
  - Adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels (1)
  - Adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despite lifestyle changes (1)

[3] See final guidance for industry "Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements | FDA"

[4] See the draft guidance for industry "Product Title and Initial US Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products- Content and Format" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-title-and-initial-us-approval-highlights-prescribing-information-human-prescription-drug-and

[5] See draft guidance for industry Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry | FDA

[6] See the final guidance for industry "Labeling for Human Prescription Drug and Biological Products- Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information" available at Prescribing Information Resources | FDA

- **Dosage and Administration**: This section will provide the recommended dosages for each indication, and will refer the reader to the Full Prescribing Information (FPI) for the recommended dosages for patients with renal impairment as follows:

> ----------**DOSAGE AND ADMINISTRATION**----------
> - Gout: Prior to initiating treatment assess serum uric acid level, complete blood count, chemistry panel, liver and kidney function tests. Prophylactic treatment for gout flares is recommended. (2.1, 2.2)
>   - Patients with normal kidney function: Initial dosage is 100 mg orally daily. Increase by 100 mg weekly increments until serum uric acid of 6 mg/dl or less is reached (maximum 800 mg daily). (2.3)
>   - Patients with impaired kidney function: The initial dosage is 50 mg orally daily. Follow recommendations for titration in patients with renal impairment until target serum uric acid level is reached. (2.6)
>   - See complete information in the Full Prescribing Information (FPI).
> - Hyperuricemia Associated with Cancer Therapy: The recommended dosage is:
>   - Adults: 300 mg to 800 mg orally daily.
>   - Pediatric patients: 100 mg/m^2 orally every 8 hours to 12 hours (10 mg/kg/day, maximum 800 mg/day)
>   - See complete information in the FPI. (2.4, 2.6)
> - Recurrent Calcium Oxalate Calculi: The recommended initial dosage in patients with normal kidney function is 200 mg to 300 mg orally daily. (2.5)
> - Dosage in Patients with Renal Impairment: See FPI for dosage modifications in patients with renal impairment. (2.6)

- **Dosage Forms and Strengths**: The labeling will be updated to include information that ZYLOPRIM tablets are functionally scored. The application holder submitted split tablet studies in supporting documents 173, 177, 181, and 184, associated with manufacturing supplements 49 and 50, as noted in the reviews by Richard Matsuoka, PhD and Joyce Crich, PhD (PANORAMA, 08/02/2022 and 12/19/2022, respectively). The studies meet the criteria of the guidance for industry "Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation" and this information will be reflected in this section and sections 3 and 14 of the Full Prescribing Information. This section will provide the information as follows:

> ----------**DOSAGE FORMS AND STRENGTHS**----------
> Tablets: 100 mg, 200 mg, and 300 mg, functionally scored

- **Contraindications:** The contraindication has been edited to be clearer and more objective, according to the guidance for industry "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format"[7], as follows:

[7] See FDA guidance for industry "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format" available at Prescribing Information Resources | FDA.

----------CONTRAINDICATIONS----------

Known hypersensitivity to allopurinol or to any of the ingredients of ZYLOPRIM.

- **Warnings and Precautions**: This subsection summarizes the warnings and precautions that are listed in the FPI according to the guidance for industry "Labeling for Human Prescription Drug and Biological Products- Implementing the PLR Content and Format Requirements" as follows:

----------WARNINGS AND PRECAUTIONS----------

- Skin Rash and Hypersensitivity: Allopurinol has been associated with serious and sometimes fatal dermatological reactions. Discontinue ZYLOPRIM at the first appearance of skin rash or other signs of hypersensitivity reaction. (5.1)
- Gout Flares: May occur during initiation of treatment. Concurrent prophylactic treatment with colchicine or anti-inflammatory agents is recommended. (5.2)
- Nephrotoxicity: Allopurinol may affect kidney function. Patients with decreased kidney function require lower doses of ZYLOPRIM. (5.3)
- Hepatoxicity: Cases of reversible hepatotoxicity have occurred. If signs and symptoms of hepatotoxicity develop, evaluate liver function. (5.4)
- Myelosuppression: Bone marrow suppression has been reported with allopurinol. (5.5)
- Potential Effect on Driving and Use of Machinery: Drowsiness, somnolence and dizziness have been reported in patients taking ZYLOPRIM. (5.6)

- **Adverse Reactions**: This section provides a summary of the common adverse reactions. and this section will read as follows:

----------ADVERSE REACTIONS----------

(b) (4)

- **Drug Interactions**: Due to the limited space in the Highlights of Prescribing Information, this section of Highlights mentions the most clinically significant drug interaction and refers the reader to the full list of drug interactions in section **7 DRUG INTERACTIONS** of the FPI:

----------DRUG INTERACTIONS----------

- The following drugs may increase the risk of serious skin reactions: bendamustine, thiazide diuretics, ampicillin and amoxicillin. (7.1)
- Capecitabine: Avoid concomitant use. (7.2)
- Mercaptopurine or Azathioprine: Reduce mercaptopurine or azathioprine dose as recommended in the respective prescribing information. (7.2)
- Pegloticase: Discontinue and refrain from initiating treatment with ZYLOPRIM. (7.2)
- See FPI for complete list of significant drug interactions. (7.2)

- **Use in Specific Populations**: This section provides safety related information that pertains to pregnancy and lactation as follows:

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION

- **BOXED WARNING**: The original labeling of this drug product does not have a boxed warning.

- **1 INDICATIONS AND USAGE**: This section provides the currently approved indications, and it will include a "Limitations of Use" as follows:

1 INDICATIONS AND USAGE

ZYLOPRIM is indicated for:

- The management of adults with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
- The management of adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels
- The management of adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despite lifestyle changes (such as reduction of dietary sodium, non-dairy animal protein, oxylate rich foods, refined sugars and increases in oral fluids and fruits and vegetables)

Limitations of Use

ZYLOPRIM is not recommended for the treatment of asymptomatic hyperuricemia.

- **2 DOSAGE AND ADMINISTRATION:** This section was drafted to convey the dosage and administration information for each indication and population for which it is intended

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with input from DRTM, DCN and DHM1. Given the length and complexity of the information in this section please refer to the final labeling in APPENDIX 3.

Subsections **2.1 Recommended Treatment Prior to Treatment Initiation** and **2.2 Recommended Prophylaxis for Gout Flares**, convey critical information that healthcare providers need to know beforehand when initiating treatment in patients with gout and the information aligns with the labeling of other drugs for the treatment of gout.

In subsections **2.3 Recommended Dosage for Gout**, **2.4 Recommended Dosage for Hyperuricemia Associated with Cancer Therapy** and **2.5 Recommended Dosage for Management of Recurrent Calcium Oxalate Calculi in Hyperuricosuric Patients**, the dosage recommendations are clearly displayed under dedicated subsections for each indication and the respective populations.

In subsection **2.4 Recommended Dosage for Hyperuricemia Associated with Cancer Therapy** the dosage recommendations for the management of hyperuricemia associated with cancer therapy in adult and pediatric patients.

The dosage recommendations to manage hyperuricemia associated with cancer in pediatric patients are provided based on body surface area (BSA) and on body weight, supported by information provided by DHM1 (see internal communication in APPENDIX 1 and the excerpt from the approval package for ALOPRIM (b) (4) (b) (4) APPENDIX 2). Dosage for pediatric patients was updated to the current standard of care. DPMH noted that the lowest dose obtained with the 100 mg scored tablet is 50 mg, which allows dosing to pediatric patients with a BSA as low as 0.5 m^2 (see review by Dr. Dina Zand, DARRTS 7/20/2023). The labeling will now include the statement "Consider using an alternative allopurinol formulation in patients with body surface < 0.5 m^2".

In subsection **2.5 Recommended Dosage for Management of Recurrent Calcium Oxalate Calculi in Hyperuricosuric Patients** the dosage recommendations are from the non-PLR labeling with minor editorial changes.

Subsection **2.6 Recommended Dosage in Patients with Renal Impairment** conveys dosage recommendations for the treatment of patients with renal impairment for each indication according to the draft guidance for industry "Dosage and Administration Section of Labeling for Human and Prescription Drug and Biological Products- Content and Format", under separate headings within the subsection.

The dosage recommendations for the treatment of gout in adults with renal impairment was updated with clearer instructions and current recommendations supported by published

[8] Coiffier, B, Altman, A, Pui, C-H, et al. Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An Evidence-Based Review. Journal of Clinical Oncology, 26:2767-2778, 2008.

literature and guidelines. [9,10,11] For example, the laboratory parameters for assessment of renal function were updated to reflect the current practice, by using eGFR values, rather than the clearance of creatinine as the latter is typically no longer used to report renal function. The recommendations are provided in a tabular format using eGFR cut-off values, which is more reflective of current practice[12].

Because there were no data to inform dosage recommendations for this indication. A statement suggested by DCN was included for clarity and completeness.

The dosage recommendations for the management of hyperuricemia associated with cancer therapy in patients with renal impairment align with the recently approved labeling for ALOPRIM, with minor modifications for clarity.

- **3 DOSAGE FORMS AND STRENGTHS:** This section of the FPI will describe the dosage forms as follows:

> **3 DOSAGE FORMS AND STRENGTHS**
>
> ZYLOPRIM tablets have functional scoring and are available in the following strengths:
>
> - 100 mg: A flat-faced raised hexagon, beveled edge, white to off-white tablet, one side engraved "ZYLOPRIM 100" with a score bar and the other side plain.
> - 200 mg: White to off-white, biconvex, round, scored tablets, imprinted "ZYLOPRIM" about the upper periphery, and 200 on the lower half, below the score and plain on the other side.
> - 300 mg: A flat-faced raised hexagon, beveled edge, peach tablet, one side engraved "ZYLOPRIM 300" with a score bar and the other side plain.

- **4 CONTRAINDICATIONS:** The contraindication has been edited to be clearer and more objective, according to the guidance for industry "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format", as follows:

> **4 CONTRAINDICATIONS**
>
> ZYLOPRIM is contraindicated in patients with a history of hypersensitivity reaction to allopurinol or to any of the ingredients of ZYLOPRIM.

---

[9] Fitzgerald, JD, Dalbeth, N, Mikuls, T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care & Research*, 72 (6): 744-760, 2020.

[10] Stamp, LK, Taylor, WJ, Jones, PB, et al. Starting Dose Is a Risk Factor for Allopurinol Hypersensitivity Syndrome- A Proposed Safe Starting Dose of Allopurinol. *Arthritis & Rheumatism*, 64 (8): 2529-2536, 2012

[11] Day, RO, Kannangara, DRW, Stocker, SL, et al. Allopurinol: insights from studies of dose-response relationships. *Expert Opinion on Drug Metabolism & Toxicology*, 13 (4): 449-462, 2017.

[12] See FDA draft guidance for industry "Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products- Content and Format", p. 18.

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- **5 WARNINGS AND PRECAUTIONS:** This section was revised to align with the recommendations from the final guidance for industry "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format."[13] Subsections were created following the general format of the labeling of ALOPRIM, with the addition of a subsection specific to the gout indication warning about regarding the possibility occurrence of gout flares during treatment.

  - **5.1 Skin Rash and Hypersensitivity:** This warning was the reason for the submission of the Prior Approval Supplement S 048 and S051, and it is being addressed with this labeling conversion. (b) (4) (b) (4) (b) (4) The frequency of this allele is higher in individuals of African, Asian (e.g., Han Chinese, Korean, Thai), and Native Hawaiian/Pacific Islander ancestry. The serious and sometimes fatal dermatologic reactions included toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms. The request was supported by published literature that was included in the submission. This adverse reaction is now recognized in the scientific community and has been included in the recently approved labeling of ALOPRIM. The inclusion of this information is warranted in section 5 and is the first listed in the section given its seriousness.

    For this subsection, Dr Jeffrey Kraft provided guidance regarding appropriate language for this subsection and for section **12.5 Pharmacogenomics** based on available literature and reports described in his review dated August 8, 2020, for ALOPRIM**.**

    This subsection also alerts the healthcare provider of the potential increase of hypersensitivity reactions when ZYLOPRIM is used concomitantly with thiazide diuretics, ampicillin, and amoxicillin (as listed in the currently approved labeling), as well as bendamustine (this information is in the labeling of bendamustine products and ALOPRIM). Subsection 5.1 will read as follows:

[13] See the final guidance for industry "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format" available at https://www.fda.gov/media/71866/download

5.1 Skin Rash and Hypersensitivity

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking allopurinol *[see Adverse Reactions (6)]*. These reactions occur in approximately 5 in 10,000 (0.05%) patients taking allopurinol. Other serious hypersensitivity reactions that have been reported include exfoliative, urticarial and purpuric lesions, generalized vasculitis, and irreversible hepatotoxicity. Discontinue ZYLOPRIM permanently at the first appearance of skin rash or other signs which may indicate a hypersensitivity reaction.

The HLA-B*58:01 allele is a genetic marker for severe skin reactions indicative of hypersensitivity to allopurinol. Patients who carry the HLA-B*58:01 allele are at a higher risk of allopurinol hypersensitivity syndrome (AHS), but hypersensitivity reactions have been reported in patients who do not carry this allele. The frequency of this allele is higher in individuals of African, Asian (e.g., Han Chinese, Korean, Thai), and Native Hawaiian/Pacific Islander ancestry *[see Clinical Pharmacology (12.5)]*. The use of ZYLOPRIM is not recommended in HLA- B*58:01 positive patients unless the benefits clearly outweigh the risks.

Consider screening for HLA-B*5801 before starting treatment with ZYLOPRIM in patients from populations in which the prevalence of this HLA-B*5801 allele is known to be high. Screening is generally not recommended in patients from populations in which the prevalence of HLA-B*58:01 is low, or in current allopurinol users, as the risk of SJS/TEN/DRESS is largely confined to the first few months of therapy, regardless of HLA- B*58:01 status.

Hypersensitivity reactions to ZYLOPRIM may be increased in patients with decreased kidney function receiving thiazide diuretics and ZYLOPRIM concurrently. Concomitant use of the following drugs may also increase the risk of skin rash, which may be severe: bendamustine, ampicillin and amoxicillin *[see Drug Interactions (7.1)]*.

Discontinue ZYLOPRIM immediately if a skin rash develops. Instruct patients to stop taking ZYLOPRIM immediately and seek medical attention promptly if they develop a rash.

- **5.2 Gout Flares**: This is a new warning, and it aligns with the labeling of another drug for the treatment of gout (ULORIC, NDA 021856). It is important to warn healthcare providers and patients of this effect because gout flares may occur during treatment initiation, even when normal or subnormal serum uric acid levels have been attained and patients may be inclined to stop therapy. Gout flares may be prevented with concomitant prophylactic therapy, which cross-references subsection **2.2 Recommended Prophylaxis for Gout Flares**. This subsection also alerts healthcare providers to advise patients to continue treatment despite the occurrence of gout flares. This section will read as follows:

5.2 Gout Flares

Gout flares have been reported during initiation of treatment with ZYLOPRIM, even when normal or subnormal serum uric acid levels have been attained due to the mobilization of urates from tissue deposits. Even with adequate therapy with ZYLOPRIM, it may require several months to deplete the uric acid pool sufficiently to achieve control of the flares. The flares typically become shorter and less severe after several months of therapy.

In order to prevent gout flares when treatment with ZYLOPRIM is initiated, concurrent prophylactic treatment with colchicine or an anti-inflammatory agent is recommended *[see Dosage and Administration (2.2)]*. Advise patients to continue ZYLOPRIM and prophylactic treatment even if gout flares occur, as it may take months to achieve control of gout flares.

- **5.3 Nephrotoxicity**, **5.4 Hepatotoxicity**, and **5.5 Myelosuppression:** The messages in these three warnings are from the non-PLR labeling which were reorganized and edited for completeness and clarity, following the general organization of the labeling of another allopurinol product (ALOPRIM, NDA 020298) with the distinction that section **5.3 Nephrotoxicity** contains specific hydration recommendations for each patient population.

- **5.6 Potential Effect on Driving and Use of Machinery:** This message was in section **Information for Patients** of the non-PLR labeling. Given the importance of this effect of ZYLOPRIM, this message merits placement in section **5 Warnings and Precautions,** as well as in section **17 Patient Counseling Information** as follows:

5.6 Potential Effect on Driving and Use of Machinery

Drowsiness, somnolence and dizziness have been reported in patients taking ZYLOPRIM *[see Adverse Reactions (6)]*. Inform patients also that the central nervous system depressant effects of ZYLOPRIM may be additive to those of alcohol and other CNS depressants.

Advise patients to avoid operation of automobiles or other dangerous machinery and activities made hazardous by decreased alertness when starting ZYLOPRIM or increasing the dose, until they know how the drug affects them.

- **6 ADVERSE REACTIONS**: This section was updated to conform with the content and formatting requirements of the guidance for industry "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products- Content and Format", to the extent possible. The adverse reactions described in the non-PLR labeling were identified in literature, unpublished clinical trials and postmarketing reports. The adverse reactions remained in the labeling and were listed by frequency more than 1% and less than 1%.

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- **7 DRUG INTERACTIONS:** This section retained all the information from the current approved labeling and information on additional drugs that may interact with allopurinol such as capecitabine, fluoracil, pegloticase, theophylline, and warfarin was added for the following reasons: safety; drug interactions with allopurinol are mentioned in the labelings of the mentioned drugs; some interactions are included in the European product labeling; other approved allopurinol labelings contain information on these drug interactions. The subsection headings follow the same organization of the labeling for ALOPRIM, and the list of drug interactions are shown in a tabular format for improved accessibility and readability.

- **8 USE IN SPECIFIC POPULATIONS:** This section was updated in compliance with the PLLR and the draft guidance for industry "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products- Content and Format."[14] For further detail please refer to the memorandum from DPMH by Dr. Dina Zand and Dr. Mona Khurana (DARRTS, 07/20/2023), and by Dr. Christos Mastroyannis and Dr. Tamara Johnson, (cross-reference consult for NDA 020298, DARRTS, 01/28/2021) and the review by the nonclinical reviewer Dr. Timothy Robison (DARRTS, 08/11/2023).

    - **8.1 Pregnancy:** We provided recommendations for sections 8.1 consistent with the labeling of ALOPRIM, based on the currently approved labeling, the systematic review of available evidence provided by the DPMH and the nonclinical reviewer. For further details please refer to the reviews noted above. This subsection will differ from the labeling of ALOPRIM as it will include human data and animal data has been revised as noted in the review from Dr. Robison. It will read as follows:

> **8.1 Pregnancy**
>
> Risk Summary
>
> Based on findings in animals, ZYLOPRIM may cause fetal harm when administered to a pregnant woman. Adverse developmental outcomes have been described in exposed animals *(see Data)*. Allopurinol and its metabolite oxypurinol have been shown to cross the placenta following administration of maternal allopurinol.
>
> Available limited published data on allopurinol use in pregnant women do not demonstrate a clear pattern or increase in frequency of adverse developmental outcomes. Among approximately 50 pregnancies described in published literature, 2 infants with major congenital malformations have been reported with following maternal allopurinol exposure. Advise pregnant women of the potential risk to a fetus.
>
> All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown.

[14] See the draft guidance for industry "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products- Content and Format" available at https://www.fda.gov/media/90160/download

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In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Experience with ZYLOPRIM during human pregnancy has been limited partly because women of reproductive age rarely require treatment with ZYLOPRIM. A case report published in 2011 described the outcome of a full-term pregnancy in a 35-year-old woman who had recurrent kidney stones since age 18 who took allopurinol throughout the pregnancy. The child had multiple complex birth defects and died at 8 days of life. A second report in 2013 provided data on 31 prospectively ascertained pregnancies involving mothers exposed to allopurinol for varying durations during the first trimester. The overall rate of major fetal malformations and spontaneous abortions was reported to be within the normal expected range; however, one child had severe malformations similar to those described in the cited earlier case report.

Animal Data

There was no evidence of fetotoxicity or teratogenicity in rats or rabbits treated during the period of organogenesis with oral allopurinol at doses up to 200 mg/kg/day and up to 100 mg/kg/day, respectively (about 2.4 times the human dose on a mg/m^2 basis). However, there is a published report in pregnant mice that single intraperitoneal doses of 50 mg/kg or 100 mg/kg (about 0.3 or 0.6 times the human dose on a mg/m^2 basis) of allopurinol on gestation days 10 or 13 produced significant increases in fetal deaths and teratogenic effects (cleft palate, harelip, and digital defects). It is uncertain whether these findings represented a fetal effect or an effect secondary to maternal toxicity.

- **8.2 Lactation**: We provided recommendations for section 8.2 and as a conservative approach this section will be consistent with the labeling of ALOPRIM, based on the currently approved labeling, the systematic review of available evidence provided by DPMH and by the nonclinical reviewer. This subsection will read as follows:

8.2 Lactation

Risk Summary

Allopurinol and oxypurinol are present in human milk. Based on information from a single case report, allopurinol and its active metabolite, oxypurinol, were detected in the milk of a mother at five weeks postpartum at an estimated relative infant dose of 0.14 and 0.2 mg/kg of allopurinol and between 7.2 to 8 mg/kg of oxypurinol daily. There was no report of effects of allopurinol on the breastfed infant or on milk production. (b) (4)

(b) (4)

- (b) (4)

- **8.4 Pediatric Use:** Consistent with the requirement of 21 CFR 201.56(a)(2) and the FDA guidance for industry "Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling", we provided recommendations regarding inclusion and placement of pediatric information so that it is updated, clear, and accessible to health care providers.

  The only pediatric indication of Zyloprim is the management of pediatric patients diagnosed with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels. The labeling of ALOPRIM for the same pediatric indication served as the basis for the PLR labeling of ZYLOPRIM to maintain consistency across these labelings.

  Of note, the current approved labeling for ZYLOPRIM alludes to the use of allopurinol in patients with inborn errors of metabolism. The non-PLR labeling for ZYLOPRIM section states, "Zyloprim is rarely indicated for use in children with the exception of those with hyperuricemia secondary to malignancy or to certain rare inborn errors of metabolism." No dosage recommendations were described for the treatment of inborn errors of metabolism. DPMH noted that historically, diagnoses of aberrant purine metabolism such as Lesch-Nyhan syndrome, an X-linked disorder caused by a deficiency in the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT), (b) (4) (b) (4) For this reason, and because the literature varies as to the recommended dosage for effectiveness for each diagnosis and safety concerns, DPMH agreed that the Pediatric Use subsection of the PLR formatted labeling should be updated to state the following:

  > Inborn Errors of Metabolism
  >
  > The safety and effectiveness of ZYLOPRIM have not been established in pediatric patients with rare inborn errors of purine metabolism.

- **8.6 Renal Impairment:** This section will present this information as follows:

  > **8.6 Renal Impairment**
  >
  > ZYLOPRIM and its primary active metabolite, oxipurinol, are eliminated by the kidneys; therefore, changes in renal function have a profound effect on exposure. In patients with decreased renal function or who have concurrent illnesses which can affect renal function, perform periodic laboratory parameters of renal function and reassess the patient's dosage of ZYLOPRIM *[see Dosage and Administration (2.6), Warnings and Precautions (5.3)].*

- **10 OVERDOSAGE:** This section was edited according to 21 CFR 201.57 (11) and current labeling practices. The animal data described in the currently approved labeling is uninformative for healthcare providers. Therefore, this section was omitted as any

subsection, or specific information that is clearly inapplicable must be omitted from labeling[15].

- **11 DESCRIPTION:** This section contains the same information as the currently approved labeling. It was edited according to 21 CFR 201.57 (c) and current labeling practices. The established pharmacologic class was added according to 21 CFR 201.57(c)(12)(i)(E).

- **12 CLINICAL PHARMACOLOGY:** Subsections **12.1 Mechanism of Action**, **12.2 Pharmacodynamics**, and **12.3 Pharmacodynamics** and **12.5 Pharmacogenomics** were revised to provide the information in compliance with current labeling practices and clinical pharmacology guidances.

  Under the guidance of DRTM Clinical Pharmacology Review Team, the information from the currently approved labeling was distributed under the headings and subheadings established by regulation [21 CFR 201.57 (c)(13)] and the final guidance for industry "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products- Content and Format."[16]

  Section **12.5 Pharmacogenomics** was edited under the guidance of Dr. Jeffrey Kraft based on updated information regarding the association of serious skin hypersensitivity reactions, and estimated frequency of the HLA-B*58:01 in the population. The labeling is consistent with the FDA guidance for industry "Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling". Please also refer to the review by Dr. Kraft review dated August 8, 2020, for NDA 020298. This subsection will read as follows:

> **12.5 Pharmacogenomics**
>
> HLA-B*5801 allele
>
> The HLA-B*5801 allele is a genetic marker that has shown to be associated with risk of developing ZYLOPRIM related hypersensitivity syndrome (DRESS) and SJS/TEN. The frequency of the HLA- B*58:01 allele ranges from 8 to 10% in Han Chinese populations, about 8% in Thai populations, and about 6% in Korean populations based upon published literature and available databases. The frequency of the HLA-B*58:01 allele is about 4% in Blacks, about 1 % to 2 % in indigenous peoples of the Americas and Hispanic populations, and < 1% in people from European descent and Japanese.
>
> Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) can still occur in patients who are found to be negative for HLA-B*5801 irrespective of ethnic origin.

- **13 NONCLINICAL TOXICOLOGY:** The current labeling for ZYLOPRIM does not include information from carcinogenesis, genotoxicity, and fertility and reproductive

[15] See the final guidance for industry "Labeling for Human Prescription Drug and Biological Products- Implementing the PLR Content and Format Requirements", p. 18.
[16] See the final guidance for industry "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products- Content and Format" available at https://www.fda.gov/media/74346/download

performance that is typically found in **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.**

Information that was added to the PLR labeling included description of lifetime carcinogenicity studies in mice and rats, descriptions of the standard battery of genetic toxicity studies with allopurinol, description of two non-standard genetic toxicity studies, and description of a fertility and reproductive performance study in male and female rats. This information was obtained by consulting the labelings for NDAs 18832, 18877, 20298, and 209203, which should be acceptable through the 505(b)(2) path as all labels are old and no longer covered by patent protection. The information under the section was proposed to the application holder as shown below with the guidance of Dr. T. Robison. For further detail please refer to Dr. Robison's review (DARRTS 08/11/2023). Below is the recommended labeling.

> **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
>
> No evidence of tumorigenicity was observed in male or female mice or rats that received oral allopurinol for the majority of their life spans (greater than 88 weeks) at doses up to 20 mg/kg/day (0.1 and 0.2 times the MRHD on a mg/m^2 basis in mice and rats, respectively).
>
> Allopurinol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay. Allopurinol administered intravenously to rats (50 mg/kg) was not incorporated into rapidly replicating intestinal DNA. No evidence of clastogenicity was observed in lymphocytes taken from patients treated with allopurinol (mean duration of treatment 40 months), or in an in vitro assay with human lymphocytes.
>
> Allopurinol oral doses of 20 mg/kg/day had no effect on male or female fertility in rats or rabbits (approximately 0.2 or 0.5 times the MRHD on a mg/m^2 basis, respectively).

- **14 CLINICAL STUDIES:** This section was omitted as there are no clinical studies described in the currently approved non-PLR labeling for ZYLOPRIM.

- **16 HOW SUPPLIED/STORAGE AND HANDLING:** This section contains information according to 21 CFR 201.57 (c)(17). It will inform that the tablets are functionally scored. A tabular form was chosen to present the information to facilitate readability.

- **17 PATIENT COUNSELING INFORMATION:** This section was created to include all the important messages that are to be conveyed to patients by the physician, so patients can be educated and advised on risks associated with the use of ZYLOPRIM, according to 21 CFR 201.57 (c)(18).

FINAL LABELING

See APPENDIX 3 for the final agreed upon labeling submitted by the application holder on August 30, 2023.

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APPENDIX 1

Filie, Jane

From: Przepiorka, Donna
Sent: Friday, May 19, 2023 11:32 AM
To: Filie, Jane
Cc: Belen, Ozlem; Thompson, Aliza; Neuner, Rosemarie; Karanes, Chatchada
Subject: RE: ZYLOPRIM labeling- dosing for tumor lysis syndrome
Attachments: Allopurinol IV vs Oral.pdf; jco.2007.15.0177.pdf

Categories: Purple Category, Red Category, Yellow Category

For the prevention of uric acid nephropathy during the vigorous therapy of neoplastic disease, treatment with 600 to 800 mg daily for 2 or 3 days is advisable together with a high fluid intake. Otherwise similar considerations to the above recommendations for treating patients with gout govern the regulation of dosage for maintenance purposes in secondary hyperuricemia.

The dose of ZYLOPRIM recommended for management of recurrent calcium oxalate stones in hyperuricosuric patients is 200 to 300 mg/day in divided doses or as the single equivalent. This dose may be adjusted up or down depending upon the resultant control of the hyperuricosuria based upon subsequent 24 hour urinary urate determinations. Clinical experience suggests that patients with recurrent calcium oxalate stones may also benefit from dietary changes such as the reduction of animal protein, sodium, refined sugars, oxalate-rich foods, and excessive calcium intake, as well as an increase in oral fluids and dietary fiber.

Children, 6 to 10 years of age, with secondary hyperuricemia associated with malignancies may be given 300 mg ZYLOPRIM daily while those under 6 years are generally given 150 mg daily. The response is evaluated after approximately 48 hours of therapy and a dosage adjustment is made if necessary.

Hey, Jane -

Below is the original and our current recommended revised text as cleared by the DHM1 Division Director.

(b) (4) confirmed 100% bioavailability for the active moiety oxypurinol (attached). We cite a range to allow dose titration by uric acid level. The proposed dose is consistent with a guideline (attached), and the same dose is used in the Harriet Lane Manual and in the Children's Oncology Group (COG trials).

The text below has been added to the USPI in SharePoint with a comment to the applicant. We noted the renal function caveat that was added and think that might not be necessary for this label.

Thanks.

Donna Przepiorka, MD, PhD
CDER/OOD/DHM1
Phone 301 796 5358

Original Zyloprim D&A

Recommended text:

2.4 Recommended Dosage for Hyperuricemia Associated with Cancer Therapy

Reference ID: 5244304

Initiate therapy with ZYLOPRIM 24 to 48 hours before the start of chemotherapy known to cause tumor cell lysis. Administer fluids sufficient to yield a daily urinary output of at least two liters in adults with a neutral or, preferably, slightly alkaline urine.

The recommended dosage of ZYLOPRIM is:

- Adult patients - 300 to 800 mg orally daily
- Pediatric patients - 100 mg/m^2 orally every 8-12 hours (10 mg/kg/day, maximum 800 mg/day)

The dosage of ZYLOPRIM to maintain normal or near-normal serum uric acid varies with the severity of the disease. Monitor serum uric acid levels at least daily and administer ZYLOPRIM at a dose and frequency to maintain the serum uric acid within the normal range. Discontinue ZYLOPRIM when the risk of tumor lysis has abated (2-3 days from start of chemotherapy).

APPEARS THIS WAY ON ORIGINAL

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX 3- ZYLOPRIM LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYLOPRIM safely and effectively. See full prescribing information for ZYLOPRIM.

ZYLOPRIM® (allopurinol) tablets, for oral use
Initial U.S. Approval:1966

----------**INDICATIONS AND USAGE**----------

ZYLOPRIM is a xanthine oxidase inhibitor indicated for the management of:

- Adult patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy) (1)
- Adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels (1)
- Adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despite lifestyle changes (1)

Limitations of Use

ZYLOPRIM is not recommended for the treatment of asymptomatic hyperuricemia. (1)

----------**DOSAGE AND ADMINISTRATION**----------

- Gout: Prior to initiating treatment assess serum uric acid level, complete blood count, chemistry panel, liver and kidney function tests. Prophylactic treatment for gout flares is recommended. (2.1, 2.2)
  - Patients with normal kidney function: Initial dosage is 100 mg orally daily. Increase by 100 mg weekly increments until serum uric acid of 6 mg/dl or less is reached (maximum 800 mg daily). (2.3)
  - Patients with impaired kidney function: The initial dosage is 50 mg orally daily. Follow recommendations for titration in patients with renal impairment until target serum uric acid level is reached. (2.6)
  - See complete information in the Full Prescribing Information (FPI).
- Hyperuricemia Associated with Cancer Therapy: The recommended dosage is:
  - Adults: 300 mg to 800 mg orally daily.
  - Pediatric patients: 100 mg/m^2 orally every 8 hours to 12 hours (10 mg/kg/day, maximum 800 mg/day)
  - See complete information in the FPI. (2.4, 2.6)
- Recurrent Calcium Oxalate Calculi: The recommended initial dosage in patients with normal kidney function is 200 mg to 300 mg orally daily. (2.5)
- Dosage in Patients with Renal Impairment: See FPI for dosage modifications in patients with renal impairment. (2.6)

----------**DOSAGE FORMS AND STRENGTHS**----------

Tablets: 100 mg, 200 mg, and 300 mg, functionally scored

----------**CONTRAINDICATIONS**----------

Known hypersensitivity to allopurinol or to any of the ingredients of ZYLOPRIM.

----------**WARNINGS AND PRECAUTIONS**----------

- Skin Rash and Hypersensitivity: Allopurinol has been associated with serious and sometimes fatal dermatological reactions. Discontinue ZYLOPRIM at the first appearance of skin rash or other signs of hypersensitivity reaction. (5.1)
- Gout Flares: May occur during initiation of treatment. Concurrent prophylactic treatment with colchicine or anti-inflammatory agents is recommended. (5.2)
- Nephrotoxicity: Allopurinol may affect kidney function. Patients with decreased kidney function require lower doses of ZYLOPRIM. (5.3)
- Hepatoxicity: Cases of reversible hepatotoxicity have occurred. If signs and symptoms of hepatotoxicity develop, evaluate liver function. (5.4)
- Myelosuppression: Bone marrow suppression has been reported with allopurinol. (5.5)
- Potential Effect on Driving and Use of Machinery: Drowsiness, somnolence and dizziness have been reported in patients taking ZYLOPRIM. (5.6)

----------**ADVERSE REACTIONS**----------

Most common adverse reactions (incidence > 1%) are nausea, diarrhea, and increase in liver function tests. (6)

To report SUSPECTED ADVERSE REACTIONS, Casper Pharma LLC at 1-844-5-CASPER (1-844-522-7737) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------**DRUG INTERACTIONS**----------

- The following drugs may increase the risk of serious skin reactions: bendamustine, thiazide diuretics, ampicillin and amoxicillin. (7.1)
- Capecitabine: Avoid concomitant use. (7.2)
- Mercaptopurine or Azathioprine: Reduce mercaptopurine or azathioprine dose as recommended in the respective prescribing information. (7.2)
- Pegloticase: Discontinue and refrain from initiating treatment with ZYLOPRIM. (7.2)
- See FPI for complete list of significant drug interactions. (7.2)

----------**USE IN SPECIFIC POPULATIONS**----------

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYLOPRIM is indicated for:

- The management of adults with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
- The management of adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels
- The management of adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despite lifestyle changes (such as reduction of dietary sodium, non-dairy animal protein, oxylate rich foods, refined sugars and increases in oral fluids and fruits and vegetables)

Limitations of Use

ZYLOPRIM is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Testing Prior to Treatment Initiation

Prior to initiating treatment with ZYLOPRIM in patients with gout, assess the following baseline tests: serum uric acid level, complete blood count, chemistry panel, liver function tests (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin), kidney function tests (serum creatinine and eGFR).

2.2 Recommended Prophylaxis for Gout Flares

Gout flares may occur after initiation of ZYLOPRIM due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with colchicine or an anti-inflammatory agent according to practice guidelines is recommended upon initiation of ZYLOPRIM. While adjusting the dosage of ZYLOPRIM in patients who are being treated with colchicine and/or anti-inflammatory agents, continue flare prophylaxis drugs until serum uric acid has been normalized and the patient has been free of gout flares for several months. If a gout flare occurs during ZYLOPRIM treatment, ZYLOPRIM need not be discontinued. Manage the gout flare concurrently, as appropriate for the individual patient *[see Warnings and Precautions (5.2)]*.

2.3 Recommended Dosage for Gout

The initial recommended dosage for the management of gout is 100 mg orally daily, with weekly increments of 100 mg, until a serum uric acid level of 6 mg/dL or less is reached. Initiating treatment with lower dosages of ZYLOPRIM and titrating slowly, decreases the risk of gout flares and drug induced serious adverse reactions.

In patients with renal impairment the initial dosage is 50 mg orally daily with lower dose increases until serum uric acid level of 6 mg/dL or less is reached. For complete dosage recommendations for patients with renal impairment see Table 1 *[see Dosage and Administration (2.6)]*.

The minimal effective dosage is 100 mg to 200 mg daily and the maximal recommended dosage is 800 mg daily. The appropriate dosage may be administered in divided doses or as a single

equivalent dose with the 300 mg tablet. Doses in excess of 300 mg should be administered in divided doses. Monitor patients' kidney function during the early stages of administration of ZYLOPRIM and decrease the dosage or withdraw the drug if persistent abnormalities in kidney function occur *[see Dosage and Administration (2.6), Warnings and Precautions (5.3), Use in Specific Populations (8.6)].*

The dosage of ZYLOPRIM to achieve control of gout varies with the severity of the disease. In general, gout control is achieved with 200 mg to 300 mg daily in patients with mild gout, and with 400 mg to 600 mg daily in patients with moderate to severe tophaceous gout. Gout attacks usually become shorter and less severe after several months of therapy.

If a dose of ZYLOPRIM is missed, there is no need to double the dose at the next scheduled time. ZYLOPRIM is generally better tolerated if taken following meals. A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or preferably, slightly alkaline urine are desirable.

Inform patients of the possibility of gout flares *[see Warnings and Precautions (5.2)].* Instruct them to remain on ZYLOPRIM if this occurs and to increase fluid intake during therapy to prevent kidney stones.

Concurrent Use of Uricosuric Agents

Some patients, may benefit using uricosuric agents concurrently, to reduce serum uric acid to target levels.

When transferring a patient from a uricosuric agent to ZYLOPRIM, reduce the dose of the uricosuric agent over a period of several weeks and increase the dose of ZYLOPRIM gradually to the required dose needed to maintain target serum uric acid level.

2.4 Recommended Dosage for Hyperuricemia Associated with Cancer Therapy

Initiate therapy with ZYLOPRIM 24 hours to 48 hours before the start of chemotherapy known to cause tumor cell lysis. Administer fluids sufficient to yield a daily urinary output of at least 2 liters in adults (at least 100 mL/m^2/hour in pediatric patients) with a neutral or, preferably, slightly alkaline urine.

The recommended dosage of ZYLOPRIM is:

- Adult patients – 300 mg to 800 mg orally daily
- Pediatric patients - 100 mg/m^2 orally every 8 hours to 12 hours (10 mg/kg/day, maximum 800 mg/day). In patients with body surface area < 0.5 m^2, consider using an alternative allopurinol formulation.

The dosage of ZYLOPRIM to maintain normal or near-normal serum uric acid varies with the severity of the disease. Monitor serum uric acid levels at least daily and administer ZYLOPRIM at a dose and frequency to maintain the serum uric acid within the normal range. Discontinue ZYLOPRIM when the risk of tumor lysis has abated (2 days to 3 days from start of chemotherapy). For complete dosage recommendations for patients with renal impairment, see Table 2 *[see Dosage and Administration (2.6)]*.

2.5 Recommended Dosage for Management of Recurrent Calcium Oxalate Calculi in Hyperuricosuric Patients

The recommended dosage for the management of recurrent calcium oxalate stones in hyperuricosuric patients is 200 mg to 300 mg orally daily in divided doses or as the single equivalent. This dose may be adjusted depending upon the resultant control of the hyperuricosuria based upon subsequent 24-hour urinary urate determinations.

2.6 Recommended Dosage in Patients with Renal Impairment

The recommended initial dosages of ZYLOPRIM in adult patients with renal impairment are shown in Tables 1 and 2 *[see Use in Specific Populations (8.6)]*.

Patients with Gout

The recommended initial dosages in adult patients with gout with impaired kidney function are shown in Table 1 *[see Use in Specific Populations (8.6)]*.

Initiate treatment with a lower dose of ZYLOPRIM and increase the dose gradually in 50 mg/day increments every 2 weeks to 4 weeks in patients with renal impairment to decrease the risk of drug induced serious adverse reactions. Use the lowest dose possible to achieve the desired effect on serum and/or urine uric acid. Monitor kidney function in gout patients with chronic kidney disease closely when initiating treatment with ZYLOPRIM and decrease or withdraw the drug if increased abnormalities in kidney function appear and persist.

Table 1. Recommended Initial Dosage in Adult Patients with Gout

eGFR	Initial Dosage
> 60 mL/minute	No dosage modification
> 30 to 60 mL/minute	50 mg daily
> 15 to 30 mL/minute	50 mg every other day
5 to 15 mL/minute	50 mg twice weekly
< 5 mL/minute	50 mg once weekly

The maximum dosage that should be used in patients with various levels of renal impairment is not defined at different eGFR levels.

Patients with Recurrent Calcium Oxalate Calculi

Data are insufficient to provide dosage recommendations for the treatment of recurrent calcium oxalate calculi in patients with renal impairment. Allopurinol and its metabolites are excreted by the kidney, and accumulation of the drug can occur in renal failure *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

Hyperuricemia Associated with Cancer Therapy

The recommended dosage of ZYLOPRIM for the management of hyperuricemia associated with cancer therapy in adult patients with renal impairment is shown in Table 2 *[see Use in Specific Populations (8.6)]*.

Table 2. Recommended Dosage of ZYLOPRIM in Adult Patients for Management of Hyperuricemia Associated with Cancer Therapy with Renal Impairment

eGFR	Recommended Dosage
> 20 mL/min to 60 mL/min	No dosage modification
10 mL/min to 20 mL/min	200 mg/day
< 10 mL/min	100 mg/day
On dialysis	50 mg every 12 hours, or 100 mg every 24 hours

Treatment with ZYLOPRIM has not been studied in pediatric patients with severe renal impairment (eGFR < 20 mL/min) or on dialysis. There is insufficient information to establish dosing for ZYLOPRIM in pediatric patients with renal impairment. In these patients, consider the risks and potential benefits before initiating treatment with ZYLOPRIM *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

ZYLOPRIM tablets have functional scoring and are available in the following strengths:

- 100 mg: A flat-faced raised hexagon, beveled edge, white to off-white tablet, one side engraved "ZYLOPRIM 100" with a score bar and the other side plain.
- 200 mg: White to off-white, biconvex, round, scored tablets, imprinted "ZYLOPRIM" about the upper periphery, and 200 on the lower half, below the score and plain on the other side.
- 300 mg: A flat-faced raised hexagon, beveled edge, peach tablet, one side engraved "ZYLOPRIM 300" with a score bar and the other side plain.

4 CONTRAINDICATIONS

ZYLOPRIM is contraindicated in patients with a history of hypersensitivity reaction to allopurinol or to any of the ingredients of ZYLOPRIM.

5 WARNINGS AND PRECAUTIONS

5.1 Skin Rash and Hypersensitivity

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking allopurinol *[see Adverse Reactions (6)]*. These reactions occur in approximately 5 in 10,000 (0.05%) patients taking allopurinol. Other serious hypersensitivity reactions that have been reported include exfoliative, urticarial and purpuric lesions, generalized vasculitis, and irreversible hepatotoxicity. Discontinue ZYLOPRIM permanently at the first appearance of skin rash or other signs which may indicate a hypersensitivity reaction.

The HLA-B*58:01 allele is a genetic marker for severe skin reactions indicative of hypersensitivity to allopurinol. Patients who carry the HLA-B*58:01 allele are at a higher risk of allopurinol hypersensitivity syndrome (AHS), but hypersensitivity reactions have been reported in patients

who do not carry this allele. The frequency of this allele is higher in individuals of African, Asian (e.g., Han Chinese, Korean, Thai), and Native Hawaiian/Pacific Islander ancestry *[see Clinical Pharmacology (12.5)]*. The use of ZYLOPRIM is not recommended in HLA- B*58:01 positive patients unless the benefits clearly outweigh the risks.

Consider screening for HLA-B*5801 before starting treatment with ZYLOPRIM in patients from populations in which the prevalence of this HLA-B*5801 allele is known to be high. Screening is generally not recommended in patients from populations in which the prevalence of HLA-B*58:01 is low, or in current allopurinol users, as the risk of SJS/TEN/DRESS is largely confined to the first few months of therapy, regardless of HLA- B*58:01 status.

Hypersensitivity reactions to ZYLOPRIM may be increased in patients with decreased kidney function receiving thiazide diuretics and ZYLOPRIM concurrently. Concomitant use of the following drugs may also increase the risk of skin rash, which may be severe: bendamustine, ampicillin and amoxicillin *[see Drug Interactions (7.1)]*.

Discontinue ZYLOPRIM immediately if a skin rash develops. Instruct patients to stop taking ZYLOPRIM immediately and seek medical attention promptly if they develop a rash.

5.2 Gout Flares

Gout flares have been reported during initiation of treatment with ZYLOPRIM, even when normal or subnormal serum uric acid levels have been attained due to the mobilization of urates from tissue deposits. Even with adequate therapy with ZYLOPRIM, it may require several months to deplete the uric acid pool sufficiently to achieve control of the flares. The flares typically become shorter and less severe after several months of therapy.

In order to prevent gout flares when treatment with ZYLOPRIM is initiated, concurrent prophylactic treatment with colchicine or an anti-inflammatory agent is recommended *[see Dosage and Administration (2.2)]*. Advise patients to continue ZYLOPRIM and prophylactic treatment even if gout flares occur, as it may take months to achieve control of gout flares.

5.3 Nephrotoxicity

Treatment with ZYLOPRIM may result in acute kidney injury due to formation of xanthine calculi or due to precipitation of urates in patients receiving concomitant uricosuric agents. Patients with pre-existing kidney disease, including chronic kidney disease or history of kidney stones, may be at increased risk for worsening of kidney function or acute kidney injury due to xanthine calculi while receiving treatment with ZYLOPRIM.

In patients receiving ZYLOPRIM for the management of gout or the management of recurrent calcium oxalate calculi, monitor kidney function frequently during the early stages of allopurinol administration. Maintain fluid intake sufficient to yield a urinary output of at least 2 liters per day of neutral or, preferably, slightly alkaline urine to avoid the possibility of formation of xanthine calculi and help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

In patients receiving ZYLOPRIM for the management of tumor lysis syndrome, monitor kidney function at least daily during the early stages of allopurinol administration. Maintain fluid intake sufficient to yield a urinary output of at least 2 liters per day in adults and at least 2 liters/m^2/day (or at least 100 mL/m^2/hour) in pediatric patients *[see Dosage and Administration (2.4)]*.

5.4 Hepatotoxicity

Cases of reversible clinical hepatotoxicity have occurred in patients taking ZYLOPRIM, and in some patients, asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss, or pruritus develop in patients on ZYLOPRIM, evaluate liver enzymes. In patients with pre-existing liver disease, monitor liver enzymes periodically. Discontinue ZYLOPRIM in patients with elevated liver enzymes.

5.5 Myelosuppression

Myelosuppression, manifested by anemia, leukopenia or thrombocytopenia, has been reported in patients receiving ZYLOPRIM. The cytopenias have occurred as early as 6 weeks up to 6 years after the initiation of therapy of ZYLOPRIM. Concomitant use of ZYLOPRIM with cytotoxic drugs associated with myelosuppression may increase the risk of myelosuppression. Monitor blood counts more frequently when cytotoxic drugs are used concomitantly *[see Drug Interactions (7.2)]*.

Concomitant use with allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of myelosuppression. Reduce the dosage of mercaptopurine or azathioprine as recommended in their respective prescribing information when used concomitantly with ZYLOPRIM *[see Drug Interactions (7.2)]*.

5.6 Potential Effect on Driving and Use of Machinery

Drowsiness, somnolence and dizziness have been reported in patients taking ZYLOPRIM *[see Adverse Reactions (6)]*. Inform patients also that the central nervous system depressant effects of ZYLOPRIM may be additive to those of alcohol and other CNS depressants.

Advise patients to avoid operation of automobiles or other dangerous machinery and activities made hazardous by decreased alertness when starting ZYLOPRIM or increasing the dose, until they know how the drug affects them.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Skin Rash and Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Nephrotoxicity *[see Warnings and Precautions (5.3)]*
- Hepatoxicity *[see Warnings and Precautions (5.4)]*
- Myelosuppression *[see Warnings and Precautions (5.5)]*
- Potential Effect on Driving and Use of Machinery *[see Warnings and Precautions (5.6)]*

The following adverse reactions associated with the use of ZYLOPRIM were identified in literature, unpublished clinical trials or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most frequent adverse reaction to ZYLOPRIM is skin rash.

Most Common Adverse Reactions (≥ 1%)

Gastrointestinal: Diarrhea, nausea, alkaline phosphatase increase, AST/ALT increase.

Metabolic and Nutritional: Acute attacks of gout.

Skin and Appendages: Rash, maculopapular rash.

Less Common Adverse Reactions (< 1%)

Body As a Whole: Ecchymosis, fever, headache, malaise.

Cardiovascular: Necrotizing angiitis, vasculitis, pericarditis, peripheral vascular disease, thrombophlebitis, bradycardia, vasodilation.

Gastrointestinal: Hepatic necrosis, granulomatous hepatitis, hepatomegaly, hyperbilirubinemia, cholestatic jaundice, vomiting, intermittent abdominal pain, gastritis, dyspepsia, hemorrhagic pancreatitis, gastrointestinal bleeding, stomatitis, salivary gland swelling, hyperlipidemia, tongue edema, anorexia.

Hemic and Lymphatic: Thrombocytopenia, eosinophilia, leukocytosis, leukopenia, aplastic anemia, agranulocytosis, eosinophilic fibrohistiocytic lesion of bone marrow, pancytopenia, prothrombin decrease, anemia, hemolytic anemia, reticulocytosis, lymphadenopathy, lymphocytosis.

Musculoskeletal: Myopathy, arthralgias, myalgia.

Nervous: Peripheral neuropathy, neuritis, paresthesia, somnolence, optic neuritis, confusion, dizziness, vertigo, foot drop, decrease in libido, depression, amnesia, tinnitus, asthenia, insomnia.

Respiratory: Epistaxis, bronchospasm, asthma, pharyngitis, rhinitis.

Skin and Appendages: Erythema multiforme exudativum (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), hypersensitivity vasculitis, purpura, vesicular bullous dermatitis, exfoliative dermatitis, eczematoid dermatitis, pruritus, urticaria, alopecia, onycholysis, lichen planus, furunculosis, facial edema, sweating, skin edema.

Special Senses: Taste loss/perversion, cataracts, macular retinitis, iritis, conjunctivitis, amblyopia.

Urogenital: Renal failure, uremia, nephritis, impotence, primary hematuria, albuminuria.

Endocrine: Infertility (male), hypercalcemia, gynecomastia (male).

7 DRUG INTERACTIONS

7.1 Drugs Known to Affect the Occurrence of Skin Rash and Hypersensitivity

Concomitant use of the following drugs may increase the risk of skin rash, which may be severe: bendamustine, thiazide diuretics, ampicillin and amoxicillin. Renal impairment may further increase risk with concomitant use of thiazide diuretics *[see Warnings and Precautions (5.1, 5.2) and Clinical Pharmacology (12.2)]*.

Monitor kidney function and reduce the dose of ZYLOPRIM in patients with concomitant thiazide diuretic use and impaired renal function *[see Dosage and Administration (2.6), Warnings and Precautions (5.1)]*.

Discontinue ZYLOPRIM at the first appearance of skin rash or other signs which may indicate a hypersensitivity reaction when use concomitantly with these drugs *[see Warnings and Precautions (5.1)]*.

7.2 Drugs Known to Have Clinically Important Drug Interactions with ZYLOPRIM

Table 3: Interventions for Clinically Important Drug Interactions with ZYLOPRIM

Capecitabine	
Clinical Impact	Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites, which may decrease capecitabine efficacy.
Intervention	Avoid the use of ZYLOPRIM during treatment with capecitabine
Chlorpropamide	
Clinical Impact	ZYLOPRIM prolongs the half-life of chlorpropamide as both compete for renal tubular excretion. In patients with renal insufficiency, the risk of hypoglycemia may be increased due to this mechanism.
Intervention	Monitor patients with renal insufficiency for hypoglycemia when administering chlorpropamide and ZYLOPRIM concomitantly.
Cyclosporine	
Clinical Impact	Concomitant use of allopurinol increases cyclosporine concentrations, which may increase the risk of adverse reactions.
Intervention	Increase frequency of monitoring cyclosporine concentrations as reflected in its prescribing information and modify the dosage of cyclosporine as appropriate when used concomitantly with ZYLOPRIM.
Cyclophosphamide and Other Cytotoxic Agents	
Clinical Impact	Concomitant use of allopurinol with cyclophosphamide and other cytotoxic agents (doxorubicin, bleomycin, procarbazine, mechloroethamine) increases bone marrow suppression among patients with neoplastic disease, except leukemia.
Intervention	Blood count monitoring and regular physician follow-up are recommended.
Dicumarol	
Clinical Impact	ZYLOPRIM prolongs the half-life of the anticoagulant, dicumarol. The mechanism of this drug interaction has not been established but should be noted when ZYLOPRIM is given to patients already on dicumarol therapy.
Intervention	Monitor prothrombin time. Adjust the dosage of dicumarol accordingly when ZYLOPRIM is added to anticoagulant therapy.
Fluorouracil	
Clinical Impact	Based on non-clinical data, allopurinol may decrease anti-tumor activity due to suppression of phosphorylation of 5-fluorouracil.
Intervention	Concomitant administration with fluorouracil should be avoided.
Mercaptopurine or Azathioprine	
Clinical Impact	Allopurinol inhibits xanthine oxidase mediated metabolism of mercaptopurine and azathioprine. Concomitant use of allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of their adverse reactions, including myelosuppression *[see Warnings and Precautions 5.5]*.
Intervention	In patients receiving mercaptopurine or azathioprine, the concomitant administration of 300 mg to 600 mg of ZYLOPRIM per day will require a reduction in dose to approximately one third to one fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of

	mercaptopurine or azathioprine should be made on the basis of therapeutic response and the appearance of toxic effects.
Pegloticase	
Clinical Impact	Concomitant use of ZYLOPRIM and pegloticase may potentially blunt the rise of serum uric acid levels and increase the risk of pegloticase related anaphylaxis in patients whose uric acid level increase to above 6 mg/dL.
Intervention	Discontinue and do not institute ZYLOPRIM therapy during treatment with pegloticase.
Theophylline	
Clinical Impact	Concomitant use of allopurinol doses greater than or equal to 600 mg/day may decrease the clearance of theophylline
Intervention	Monitor and adjust theophylline doses as reflected in the prescribing information.
Uricosuric Drugs	
Clinical Impact	Uricosuric agents increase the excretion of the active allopurinol metabolite oxypurinol. Concomitant use with uricosuric agents decreases oxypurinol exposure which may reduce the inhibition of xanthine oxidase by oxypurinol and increases the urinary excretion of uric acid. The net effect of such combined therapy may be useful in some patients in achieving minimum serum uric acid levels provided the total urinary uric acid load does not exceed the competence of the patient's kidney function.
Intervention	Monitor uric acid levels due to the increased chance of hypouricemic effects.
Warfarin	
Clinical Impact	Allopurinol may inhibit the metabolism of warfarin, possibly enhancing its anticoagulant effect.
Intervention	Monitor patients on concomitant therapy for excessive anticoagulation. Assess INR frequently and adjust warfarin dosage accordingly when allopurinol is added to warfarin therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, ZYLOPRIM may cause fetal harm when administered to a pregnant woman. Adverse developmental outcomes have been described in exposed animals *(see Data)*. Allopurinol and its metabolite oxypurinol have been shown to cross the placenta following administration of maternal allopurinol.

Available limited published data on allopurinol use in pregnant women do not demonstrate a clear pattern or increase in frequency of adverse developmental outcomes. Among approximately 50 pregnancies described in published literature, 2 infants with major congenital malformations have been reported with following maternal allopurinol exposure. Advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Experience with ZYLOPRIM during human pregnancy has been limited partly because women of reproductive age rarely require treatment with ZYLOPRIM. A case report published in 2011 described the outcome of a full-term pregnancy in a 35-year-old woman who had recurrent kidney stones since age 18 who took allopurinol throughout the pregnancy. The child had multiple complex birth defects and died at 8 days of life. A second report in 2013 provided data on 31 prospectively ascertained pregnancies involving mothers exposed to allopurinol for varying durations during the first trimester. The overall rate of major fetal malformations and spontaneous abortions was reported to be within the normal expected range; however, one child had severe malformations similar to those described in the cited earlier case report.

Animal Data

There was no evidence of fetotoxicity or teratogenicity in rats or rabbits treated during the period of organogenesis with oral allopurinol at doses up to 200 mg/kg/day and up to 100 mg/kg/day, respectively (about 2.4 times the human dose on a mg/m^2 basis). However, there is a published report in pregnant mice that single intraperitoneal doses of 50 mg/kg or 100 mg/kg (about 0.3 or 0.6 times the human dose on a mg/m^2 basis) of allopurinol on gestation days 10 or 13 produced significant increases in fetal deaths and teratogenic effects (cleft palate, harelip, and digital defects). It is uncertain whether these findings represented a fetal effect or an effect secondary to maternal toxicity.

8.2 Lactation

Risk Summary

Allopurinol and oxypurinol are present in human milk. Based on information from a single case report, allopurinol and its active metabolite, oxypurinol, were detected in the milk of a mother receiving 300 mg of allopurinol daily at 5 weeks postpartum. The estimated relative infant dose were 0.14 mg/kg and 0.2 mg/kg of allopurinol and between 7.2 mg/kg to 8 mg/kg of oxypurinol daily. There was no report of effects of allopurinol on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatments with ZYLOPRIM and for one week after the last dose.

8.4 Pediatric Use

Hyperuricemia Associated with Cancer Therapy

The safety and effectiveness of allopurinol for the management of pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels have been established in approximately 200 pediatric patients. The efficacy and safety profile observed in this patient population were similar to that observed in adults.

Primary or Secondary Gout

The safety and effectiveness of ZYLOPRIM have not been established for the treatment of signs and symptoms of primary or secondary gout in pediatric patients.

Recurrent Calcium Oxalate Calculi

The safety and effectiveness of ZYLOPRIM have not been established for the management of pediatric patients with recurrent calcium oxalate calculi.

Inborn Errors of Metabolism

The safety and effectiveness of ZYLOPRIM have not been established in pediatric patients with rare inborn errors of purine metabolism.

8.6 Renal Impairment

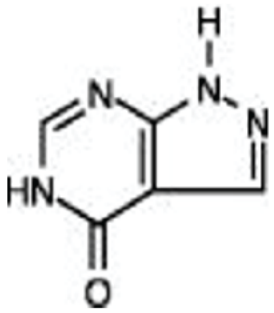
ZYLOPRIM and its primary active metabolite, oxipurinol, are eliminated by the kidneys; therefore, changes in renal function have a profound effect on exposure. In patients with decreased renal function or who have concurrent illnesses which can affect renal function, perform periodic laboratory parameters of renal function and reassess the patient's dosage of ZYLOPRIM *[see Dosage and Administration (2.6), Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

In the management of overdosage there is no specific antidote for ZYLOPRIM. Both ZYLOPRIM and oxipurinol are dialyzable; however, the usefulness of hemodialysis or peritoneal dialysis in the management of an overdose of ZYLOPRIM is unknown.

11 DESCRIPTION

ZYLOPRIM (allopurinol) is a xanthine oxidase inhibitor. It has the following structural formula:



ZYLOPRIM is known chemically as 1, 5-dihydro-4*H*-pyrazolo [3, 4-*d*]pyrimidin-4-one and it has a molecular weight of 136.11 g/mol. Its solubility in water at 37°C is 80.0 mg/dL and is greater in an alkaline solution. It is a xanthine oxidase inhibitor which is administered orally.

Each scored white hexagon-shaped tablet contains 100 mg allopurinol and the inactive ingredients lactose monohydrate, magnesium stearate, potato starch, and povidone.

Each scored white round tablet contains 200 mg allopurinol and the inactive ingredients lactose monohydrate, magnesium stearate, corn starch, and povidone.

Each scored peach tablet contains 300 mg allopurinol and the inactive ingredients corn starch, FD&C Yellow No. 6 Lake, lactose monohydrate, magnesium stearate, and povidone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZYLOPRIM (allopurinol) is a structural analogue of the natural purine base, hypoxanthine.

Allopurinol acts on purine catabolism, without disrupting the biosynthesis of purines. It reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation. It is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in humans. Allopurinol is metabolized to the corresponding xanthine analogue, oxypurinol (alloxanthine), which also is an inhibitor of xanthine oxidase.

12.2 Pharmacodynamics

ZYLOPRIM reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation in a dose dependent manner. The pharmacological action of allopurinol is generally believed to be mediated by its oxypurinol metabolite.

Effect on Hypoxanthine and Xanthine

Reutilization of both hypoxanthine and xanthine for nucleotide and nucleic acid synthesis is markedly enhanced when their oxidations are inhibited by ZYLOPRIM and oxipurinol. This reutilization does not disrupt normal nucleic acid anabolism, however, because feedback inhibition is an integral part of purine biosynthesis. As a result of xanthine oxidase inhibition, the serum concentration of hypoxanthine plus xanthine in patients receiving ZYLOPRIM for treatment of hyperuricemia is usually in the range of 0.3 mg/dL to 0.4 mg/dL compared to a normal level of approximately 0.15 mg/dL. A maximum of 0.9 mg/dL of these oxypurines has been reported when the serum urate was lowered to less than 2 mg/dL by high doses of ZYLOPRIM. These values are far below the saturation levels at which point their precipitation would be expected to occur (above 7 mg/dL). The increased xanthine and hypoxanthine in the urine in patients who were treated with oral allopurinol have not been accompanied by problems of nephrolithiasis; however, there are isolated case reports of xanthine crystalluria.

Drug Interaction Studies

Fluorouracil: Based on non-clinical data, allopurinol may decrease anti-tumor activity due to suppression of phosphorylation of 5-fluorouracil.

Pegloticase: Concomitant use of ZYLOPRIM and pegloticase may potentially blunt the rise of serum uric acid levels required for monitoring the safe use of pegloticase.

Cytotoxic Agents: Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease, except leukemia, in the presence of ZYLOPRIM.

Thiazide Diuretics: Reports that the concomitant administration of allopurinol and thiazide diuretics contributed to increased allopurinol toxicity were reviewed; however, a causal mechanism or cause-and-effect relationship was not found.

12.3 Pharmacokinetics

Absorption

ZYLOPRIM is approximately 90% absorbed from the gastrointestinal tract. Peak plasma levels

generally occur at 1.5 hours and 4.5 hours for ZYLOPRIM and oxipurinol respectively. After a single oral dose of 300 mg ZYLOPRIM, maximum plasma levels of about 3 mcg/mL of ZYLOPRIM and 6.5 mcg/mL of oxipurinol are produced.

Elimination

The half-life of allopurinol and oxipurinol are approximately 1 hour to 2 hours and 15 hours following oral dose of ZYLOPRIM, respectively.

Metabolism

Allopurinol is metabolized to the corresponding xanthine analogue, oxypurinol (alloxanthine), which also is an inhibitor of xanthine oxidase.

Excretion

ZYLOPRIM and its primary active metabolite, oxipurinol, are eliminated by the kidneys. Approximately 20% of the ingested ZYLOPRIM is excreted in the feces. Oxipurinol is primarily eliminated unchanged in urine by glomerular filtration and tubular reabsorption.

Drug Interaction Studies

Capecitabine: Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites, which may decrease capecitabine efficacy.

Cyclosporine: Concomitant use of allopurinol increases cyclosporine concentrations which may increase the risk of adverse reactions.

Mercaptopurine or Azathioprine: Allopurinol inhibits xanthine oxidase mediated metabolism of mercaptopurine and azathioprine. Concomitant use of allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of their adverse reactions including myelosuppression.

Theophylline: Concomitant use of allopurinol doses greater than or equal to 600 mg/day may decrease the clearance of theophylline.

Uricosuric Agents: Uricosuric agents increase the excretion of the active allopurinol metabolite oxypurinol. Concomitant use with uricosuric agents decreases oxypurinol exposure which may reduce the inhibition of xanthine oxidase by oxypurinol and increases the urinary excretion of uric acid.

Warfarin: Allopurinol may inhibit the metabolism of warfarin, possibly enhancing its anticoagulant effect.

12.5 Pharmacogenomics

HLA-B*5801 allele

The HLA-B*5801 allele is a genetic marker that has shown to be associated with risk of developing ZYLOPRIM related hypersensitivity syndrome (DRESS) and SJS/TEN. The frequency of the HLA- B*58:01 allele ranges from 8 to 10% in Han Chinese populations, about 8% in Thai populations, and about 6% in Korean populations based upon published literature and available databases. The frequency of the HLA-B*58:01 allele is about 4% in Blacks, about 1 % to 2 % in indigenous peoples of the Americas and Hispanic populations, and < 1% in people from European descent and Japanese.

Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) can still occur in patients who are found to be negative for HLA-B*5801 irrespective of ethnic origin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in male or female mice or rats that received oral allopurinol for the majority of their life spans (greater than 88 weeks) at doses up to 20 mg/kg/day (0.1 and 0.2 times the MRHD on a mg/m^2 basis in mice and rats, respectively).

Allopurinol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay. Allopurinol administered intravenously to rats (50 mg/kg) was not incorporated into rapidly replicating intestinal DNA. No evidence of clastogenicity was observed in lymphocytes taken from patients treated with allopurinol (mean duration of treatment 40 months), or in an in vitro assay with human lymphocytes.

Allopurinol oral doses of 20 mg/kg/day had no effect on male or female fertility in rats or rabbits (approximately 0.2 or 0.5 times the MRHD on a mg/m^2 basis, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ZYLOPRIM (allopurinol) is available in multiple tablet strengths with functional scoring and package sizes (bottles with child-resistant caps) as listed in Table 4.

TABLE 4: ZYLOPRIM Presentations

Tablet Strength	Tablet Description	Package Sizes (NDC)
100 mg	Flat-faced raised hexagon, beveled edge, white tablet, one side engraved “ZYLOPRIM 100” with a score bar, and plain on the other side	Bottles of: • 90 tablets (NDC 70199-031-90) • 100 tablets (NDC 70199-031-01) • 500 tablets (NDC 70199-031-05) • 1,000 tablets (NDC 70199-031-99)
200 mg	Biconvex, round, white scored tablets, imprinted ZYLOPRIM about the upper periphery, and 200 on the lower half, below the score, and plain on the other side	Bottles of: • 90 tablets (NDC 70199-032-90) • 100 tablets (NDC 70199-032-01) • 500 tablets (NDC 70199-032-05) • 1,000 tablets (NDC 70199-032-99)
300 mg	Flat-faced raised hexagon, beveled edge, peach tablet, one side engraved “ZYLOPRIM 300” with a score bar, and plain on the other side	Bottles of: • 90 tablets (NDC 70199-033-90) • 100 tablets (NDC 70199-033-01) • 500 tablets (NDC 70199-033-05) • 1,000 tablets (NDC 70199-033-99)

Storage and Handling

Store at 20°C to 25°C (USP Controlled Room Temperature) (68°F to 77°F) in a dry place. Dispense in a tight container as defined in the USP.

17 PATIENT COUNSELING INFORMATION

Administration

Advise patients to take ZYLOPRIM after meals to minimize gastric irritation. If a single dose of ZYLOPRIM is occasionally forgotten, there is no need to double the dose at the next scheduled time.

Skin Rash and Hypersensitivity

Inform patients that ZYLOPRIM may increase the risk of serious and sometimes fatal dermatologic reactions. Instruct patients to discontinue ZYLOPRIM and to seek medical attention immediately, at the first sign of a skin rash, blisters, fever, painful urination, blood in the urine, irritation of the eyes, swelling of the lips or mouth, or other signs and symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Gout Flares During Treatment With ZYLOPRIM

Inform patients that gout flares may occur during initiation of treatment with ZYLOPRIM, even when their serum uric acid is normal. Concurrent use of additional medications such as colchicine or other anti-inflammatory agents can prevent gout flares. Advise patients to continue treatment with both, ZYLOPRIM and the prophylactic therapy as prescribed, even if gout flares occur. Reassure them that it may take months to achieve control of the flares but the flares typically become shorter and less severe after several months of therapy *[see Warnings and Precautions (5.2)]*.

Nephrotoxicity

Inform patients that ZYLOPRIM may affect kidney function. Advise them to increase fluid intake during therapy (i.e., for adults, at least 2 liters of liquids per day) and to stay well hydrated to prevent kidney stones *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

Inform patients of the risk of hepatotoxicity and to report to their healthcare provider any signs and symptoms of liver failure, including jaundice, pruritus, bleeding, bruising, or anorexia *[see Warnings and Precautions (5.4)]*.

Myelosuppression

Advise patients of the risk of myelosuppression and to report any signs and symptoms of infection, fever, bleeding, shortness of breath, or significant fatigue to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Potential Effect on Driving and Use of Machinery

Inform patients that drowsiness, somnolence and dizziness have been reported in patients taking ZYLOPRIM. Inform also that the central nervous system depressant effects of ZYLOPRIM may be additive to those of alcohol and other CNS depressants. Advise patients to avoid operation of automobiles or other dangerous machinery and activities made hazardous by decreased alertness

when starting ZYLOPRIM or increasing the dose, until they know how the drug affects them *[see Warnings and Precautions (5.6)]*.

Risks Associated with Use of Concomitant Medications

Inform patients that there are risks of adverse effects when ZYLOPRIM is used with the following drugs: dicumarol, warfarin, sulfinpyrazone, mercaptopurine, azathioprine, ampicillin, amoxicillin, pegloticase, theophylline, and thiazide diuretics. Advise patients to disclose all medications in use and they should follow the instructions of their physician *[see Drug Interactions (7.2)]*.

Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with ZYLOPRIM *[see Use in Specific Populations (8.1)].*

Lactation

Advise women not to breastfeed during treatment with ZYLOPRIM and for one week after the last dose *[see Use in Specific Populations (8.2)].*

Casper Pharma LLC

Manufactured by:
Casper Pharma Private Limited
Telangana-500108, India

M.L No.: TS/RR/2020-58622

Manufactured for:
Casper Pharma LLC
East Brunswick, NJ 08816

PIB03399-07

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANE FILIE
09/14/2023 03:15:07 PM

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 016084/S- 052

Application Type: PLR Conversion Labeling Supplement

Drug Name(s)/Dosage Form(s): Zyloprim (allopurinol) tablets

Applicant: Casper Pharma LLC

Receipt Date: June 23, 2023

Goal Date: December 23, 2023

1. Regulatory History and Applicant's Main Proposals

Casper Pharma LLC submitted a Prior Approval Supplement (Proposed PLR Labeling) to NDA 016084 for Zyloprim (allopurinol) 100mg, 200mg, and 300mg tablets.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Reference ID: 5232537

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment: *Full Prescribing Information on separate page no horizontal line*

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Reference ID: 5232537

Selected Requirements of Prescribing Information

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Reference ID: 5232537

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 5232537

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]."*

Comment:

Reference ID: 5232537

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

N/A 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). 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 to drug exposure."

Comment:

Reference ID: 5232537

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Missing*

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Reference ID: 5232537

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 5232537

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/s/

JAVONNA STEVENS
08/24/2023 05:01:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

016084Orig1s051
016084Orig1s052

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ADVICE / INFORMATION REQUEST

DATE: August 29, 2023

To: Ravi Vatchavai Senior Director, Regulatory Affairs	**From:** Javonna Stevens, PharmD, BCPS Regulatory Management Officer
Company: Casper Pharma LLC	Division of Rheumatology and Transplant Medicine
Email: rvatchavai@casperpharma.com	**Email:** javonna.stevens@fda.hhs.gov

Subject: Zyloprim (allopurinol) NDA 016084/S-048, S-051, S-052
FDA Labeling Comments

Comments:

Please confirm receipt.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-4240 or email at javonna.stevens@fda.hhs.gov. Thank you.

We are reviewing Zyloprim S-048/S-051/S-052 and have the following comments provided in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. Be advised that these labeling recommendations are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

FDA edits were made as tracked changes to the USPI submitted on August 7, 2023.

Any additional revisions should be made using a clean Word version of the labeling being sent and edit using tracked changes.

Submit revised labeling incorporating the changes to the supplemental NDAs no later than 2 days after receipt of this request.

If you have any questions, please contact Javonna Stevens, Regulatory Project Manager, at javonna.stevens@fda.hhs.gov or at (301) 796-4240.

Drafted by: JStevens 08.28.2023
Initialed by: CFord 08.28.2023
JFilie 08.29.2023
CBertha 08.29.2023
Finalized by: JStevens 08.29.2023

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/s/

JAVONNA STEVENS
08/29/2023 10:45:55 AM

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ADVICE / INFORMATION REQUEST

DATE: August 2, 2023

To: Ravi Vatchavai Senior Director, Regulatory Affairs	**From:** Javonna Stevens, PharmD, BCPS Regulatory Management Officer
Company: Casper Pharma LLC	Division of Rheumatology and Transplant Medicine
Email: rvatchavai@casperpharma.com	**Email:** javonna.stevens@fda.hhs.gov
Subject: NDA 016084 Zyloprim (allopurinol) FDA Labeling Comments	

Comments:

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Zyloprim labeling supplements submitted March 19, 2020, April 19 and June 23, 2023, are under review, and we have the following comments provided in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. Be advised that these labeling recommendations are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

FDA edits were made as tracked changes to the USPI submitted on June 23, 2023.

Any additional revisions should be made using a clean Word version of the labeling being sent and edit using tracked changes.

Submit revised labeling incorporating the changes no later than 1 week after receipt of this request, to the supplemental NDAs.

If you have any questions, please contact Javonna Stevens, Regulatory Project Manager, at javonna.stevens@fda.hhs.gov or at (301) 796-4240.

Drafted by: JStevens 08.01.2023
Initialed by: CFord 08.02.2023
Finalized by: JStevens 08.02.2023

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/s/

JAVONNA STEVENS
08/02/2023 05:10:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urology, and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

MEMORANDUM TO FILE

From:	Dina Zand, MD Division of Pediatrics and Maternal Health (DPMH) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) Office of New Drugs (OND)
Through:	Mona Khurana, MD, Pediatric Team Leader DPMH, ORPURM, OND John J. Alexander, MD, MPH, Deputy Director DPMH, ORPURM, OND
To:	Javonna Stevens Division of Regulatory Operations for Immunology and Inflammation (DROII) Office of Regulatory Operations (ORO), CDER
Drug:	Allopurinol tablets
Drug Class:	Xanthine oxidase inhibitor
NDA:	016084
Applicant:	Casper Pharma, LLC
Approved Indications:	Adult patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)

Reference ID: 5211971

	Adult and pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels Adult patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients, despite lifestyle changes
Dosage Form:	Tablet (100, 200, and 300 mg)
Approved Dosage:	Gout (adults): 100 mg/day with increase in 100 mg increments weekly until serum uric acid of 6 mg/dl (800 mg/day maximum) Hyperuricemia associated with cancer therapy Adults: 300 mg to 800 mg daily Pediatrics: ≥ 6 years 300 mg daily < 6 years 150 mg daily Recurrent calcium oxalate calculi (adults): 200-300 mg daily initial dosing

Consult Request:
The Division of Rheumatology and Transplant Medicine (DRTM) in DROII requested that DPMH provide input into a prior labeling supplement initiated to update the Warnings section of Zyloprim labeling. In addition, the Division was proceeding with updating the labeling into Physician Labeling Rule (PLR) format and sought specific assistance from DPMH regarding pediatric use information throughout labeling that would be in accordance with the PLR.

Regulatory History

Zyloprim
FDA initially approved Zyloprim (allopurinol 100 mg, 200 mg, and 300 mg scored tablets for oral use), a xanthine oxidase inhibitor, in 1966 for the treatment of gout. Zyloprim labeling remains in non-PLR format with the most recent labeling for the tablet dosage form dated December 31, 2018.[1]

Casper Pharma, LLC submitted labeling supplements on March 19, 2020, and April 19, 2023, to update section 5 of Zyloprim labeling (Warnings & Precautions) to include information regarding association of the presence of the HLA-B*58:01 allele and severe cutaneous adverse reactions. Because the prescribing information (PI) was not in PLR format in accordance with 21 CFR 201.57, DRTM decided to update the labeling into PLR format during this supplemental

[1] Drugs@FDA

Reference ID: 5211971

review cycle to ensure labeling was accurate and in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).[2] The recently updated PLR labeling completed by the Division of Hematologic Malignancies 1 (DHM1) for Aloprim (allopurinol sodium solution for intravenous injection) was relied upon by DRTM in this PLR labeling update, with the intention to provide consistent information between Zyloprim and Aloprim labeling. DHM1 and DPMH were both consulted to aid in the updated labeling of Zyloprim.

DPMH Discussion of Zyloprim Labeling

Per the most recently available approved labeling in non-PLR format, Zyloprim appears to be approved for three indications, one of which is approved for Aloprim in the pediatric population. The prior non-PLR labeling for Zyloprim stated the following indications:

- the management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy).

- the management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels. Treatment with ZYLOPRIM should be discontinued when the potential for overproduction of uric acid is no longer present.

- the management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients. Therapy in such patients should be carefully assessed initially and reassessed periodically to determine in each case that treatment is beneficial and that the benefits outweigh the risks.

DPMH reviewed the non-PLR formatted Zyloprim labeling to determine the currently approved indications and approved populations and noted the following:

- The Indications and Usage section did not distinguish between adults and pediatric patients as the approved populations for each of the three indications.

- The Pediatric Use section states, “Zyloprim is rarely indicated for use in children with the exception of those with hyperuricemia secondary to malignancy or to certain rare inborn errors of metabolism.”

- The Dosage and Administration section provides no pediatric dosing information for certain rare inborn errors of metabolism but does state, “Children 6 to 10 years of age with secondary hyperuricemia associated with malignancies may be given 300 mg Zyloprim daily while those under 6 years are generally given 150 mg daily.”

[2] DARRTS NDA 016084 Prior Approval Supplement Request – PLR conversion dated May 25, 2023. Reference ID 5180299

Reference ID: 5211971

Based on the pediatric dosing information specified in the non-PLR labeling, DPMH discussed and confirmed with DROII that Zyloprim is labeled for pediatric use only for treatment of secondary hyperuricemia. As a result, DPMH's labeling recommendations for subsequent labeling sections focused on pediatric use information relevant to the secondary hyperuricemia indication.

Aloprim

Labeling for Aloprim (allopurinol sodium for intravenous injection) was updated into PLR format on February 17, 2022.[3] On the revised labeling, Aloprim is indicated for

"… the management of adult and pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels and who cannot tolerate oral therapy."

The approved dosage for Aloprim labeling is the following:

Adult Patients	*200 mg/m^2/day to 400 mg/m^2/day* *Maximum 600 mg/day*
Pediatric Patients	*Starting Dose 100 mg/m^2/day* *Maximum 400 mg/day*

Both Zyloprim and Aloprim are indicated for the management of pediatric patients diagnosed with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy. In the PLR conversion for Zyloprim Section 2 (**Dosing**) was modified for consistency of labeling with Aloprim.

DPMH's labeling review focused on section 1 (**Indications and Usage**), subsection 2.4 (**Recommended Dosage for Hyperuricemia Associated with Cancer Therapy**), subsection 2.6, (**Recommended Dosage in Patients with Renal Impairment**), subsection 5.3 (**Nephrotoxicity**), and Section 8.4 (**Pediatric Use**)

Subsection 2.4 (Recommended Dosage for Hyperuricemia Associated with Cancer Therapy)

Dosing for pediatric patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy in the most recent non-PLR labeling for Zyloprim is age based[4]:

Pediatrics: ≥ 6 years 300 mg daily
< 6 years 150 mg daily

[3] Drugs@FDA; Aloprim label dated February 2022
[4] Drugs@FDA; Section 2, Zyloprim label dated February 2022

Reference ID: 5211971

In the PLR update, DRTM included the following language:

The recommended dosage of ZYLOPRIM is:

- Adult patients - 300 to 800 mg orally daily
- Pediatric patients - 100 mg/m^2 orally every 8 hours to -12 hours (10 mg/kg/day, maximum 800 mg/day)

DRTM deferred to DHM1 regarding the recommended pediatric dose. DHM1 recommended a pediatric dosage of 100 mg/m^2, but DHM1's rationale for recommending this initial dosing of Zyloprim tablets in pediatric patients of all ages is unclear for the following reasons:

- The pharmacokinetic (PK) study described in Aloprim labeling appears to have compared the PK profile of Aloprim when given orally versus when given by injection. This study did not appear to use a solid oral dosage form of allopurinol as a comparator. Therefore, it is unclear how Zyloprim dosing can be derived from the PK study conducted with Aloprim unless there is clear evidence that Zyloprim tablets are 100% bioavailable.

- Treatment guidelines for tumor lysis syndrome (Coiffier et al. 2008) recommend oral allopurinol dosing of 50-100 mg/m^2/dose.

Based on our calculations of the expected dose that would be needed across a range of BSAs in the target pediatric population (see **Appendix**; **Table 1**), the existing dosage strength of Zyloprim tablets could only be delivered to patients with BSA $\geq$ 1 m^2 if given whole. DPMH is unaware of data supporting the stability and bioequivalence of manipulating the tablets that would support their use in this manner. Without data supporting the stability and bioequivalence of crushing Zyloprim tablets, avoid tablet manipulation and convey the following to prescribers:

- *Do not crush, cut, or chew tablets. Swallow tablets whole.*

DPMH also recommended the Division add the following statement to inform prescribers to consider an alternative allopurinol formulation to dose patients with BSA < 1 m^2 as the existing strengths of Zyloprim tablets will not allow direct administration of the recommended dose to this BSA group.

DPMH noted that the working version of Zyloprim labeling contained both body surface area (BSA) and weight-based dosing and recommended that DHM1 select one approach rather than include both because the recommended dose differs depending on whether the dose was calculated as mg/m^2 versus mg/kg. This difference could contribute to prescriber confusion. See Appendix; Table 1.

Reference ID: 5211971

DHM1 acknowledged the historical use of allopurinol in both adult and pediatric cancer patients to inform the acceptability of a wide range of dosing by BSA or mg/kg. An allopurinol dose that may fall in the low end of the dosing is preferred over no treatment of elevated uric acid due to chemotherapy. DHM1 also explained the longstanding gap in scientific evidence to support the bioequivalence of allopurinol tablets to the injectable solution. Recommending not to manipulate (crush or cut) tablets could result in no treatment of pediatric patients if the injectable dose form is not available. DPMH deferred to DHM1 as to whether these benefit:risk considerations and the long-term experience with dosing in the pediatric population justified retention of both weight- and BSA-based pediatric dosing in section 2 of Zyloprim labeling.

The DRTM ADL stated that Zyloprim tablets are functionally scored and, therefore, each half of a split tablet is expected to contain equally dispersed amounts of the active ingredient. Based on this explanation, DPMH agreed that the lowest available dosage strength of 100 mg could be cut in half to provide a 50 mg dose to patients with a BSA as low as 0.5 m^2. In order to clarify to pediatric prescribers that patients with lower BSAs would not be able to receive the recommended dose with the existing tablet strengths, DHM1 and DPMH agreed to include the following language in subsection 2.4:

- *In patients with body surface area < 0.5 m^2, consider using an alternative allopurinol formulation.*

Subsection 2.6 (Recommended Dosage in Patients with Renal Impairment)

DPMH noted that renal dosing recommendations for both adults and pediatric patients was based on outdated language which was not appropriate for the pediatric population. See Table 2.

Table 2. Recommended Dosage of ZYLOPRIM in Adult Patients for Management of Hyperuricemia Associated with Cancer Therapy

eGFR	Recommended Dosage
10 mL/min to 20 mL/min	200 mg/day
< 10 mL/min	100 mg/day
On dialysis	50 mg every 12 hours, or 100 mg every 24 hours or 100 mg every 24 hours)

Source: Subsection 2.6 of working version of Zyloprim labeling

DPMH proposed Table 2 be revised as follows in accordance with the draft Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format | FDA.

Reference ID: 5211971

Estimated GFR (eGFR)	Maximum Daily Dose	Frequency
> 20 mL/minute	800 mg	Daily
10 to 20 mL/minute	200 mg	Daily
< 10 mL/minute	100 mg	≥ 24 hours

Source: Adapted by this reviewer from Table 2 in subsection 2.6 of working version of Zyloprim labeling

DPMH also recommended to add the following statement to Zyloprim labeling:

- *There is insufficient information to establish dosing for ZYLOPRIM in pediatric patients with renal impairment.*

Subsection 5.3 (Nephrotoxicity)

DPMH met with DRTM and DCN on July 19, 2023, to discuss revisions to this subsection of labeling. Key aspects of this discussion included the following:

- Potential replacement of the title of the subsection from "Nephrotoxicity" to "Acute Kidney Injury" or "Drug-Induced Kidney Injury" or "Renal Impairment". DPMH and DCN agreed that the term "Acute Kidney Injury" is currently defined in the clinical community as increases in serum creatinine that occur within a specified period of time and that use of this term in Section 5 of Zyloprim labeling may not accurately reflect the risk of calculi formation that is associated with uricosuric agents such as Zyloprim. DPMH and DCN noted that the corresponding warning subsection in approved Aloprim labeling is entitled, "Renal Function Impairment". DCN acknowledged that the term "Nephrotoxicity" is a dated term but is generally well-accepted to denote drug-induced kidney injury and is consistent with terminology in section 5 of Zyloprim labeling regarding liver injury that is entitled, "Hepatotoxicity". For these reasons, DPMH, DRTM, and DCN agreed that the title of this subsection should remain as "Nephrotoxicity".

- DPMH and DCN agreed that language in (b) (4) proposed by the Applicant that (b) (4) from Zyloprim use should be deleted.

- DPMH and DCN agreed that language about the importance of adequate hydration was relevant for all three approved indications and could be consolidated to avoid redundancy. DPMH recommended adding language about maintaining fluid intake of at least 2 liters/m^2/day in pediatric patients with normal kidney function who receive Zyloprim.

Reference ID: 5211971

- DPMH, DRTM, and DCN agreed that kidney function should be monitored in patients receiving Zyloprim for all three approved indications but that the frequency of monitoring may vary across indications and should be specified in this subsection.

Based on the discussion, DPMH, DRTM, and DCN agreed that the language proposed by the Applicant in this subsection should be removed and replaced with language approved in (b) (4) of approved Aloprim labeling with some slight modification to provide consistency.

Subsection 8.4 (Pediatric Use)

DPMH noted that, per the Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice | FDA, this subsection should start with any pediatric-specific contraindications if relevant followed then by statements about indications for which safety and effectiveness have been established in some or all of the pediatric population. As such, DPMH recommended that subsection 8.4 be revised to list the indications in the following order:

- Hyperuricemia Associated with Cancer therapy
- Primary or Secondary Gout
- Recurrent Calcium Oxalate Calculi
- Inborn Errors of Metabolism

The Division stated the original order was intended to mirror the order the indications were listed in section 1. DPMH acknowledged the Division's intent to be consistent with the format in section 1 and subsection 8.4 but noted that DPMH generally recommends placement of indications for which safety and effectiveness have not been established in pediatric patients at the end of the subsection so that the indication approved in pediatrics is placed prominently at the beginning. This approach is consistent with Section 3 of the Pediatric Labeling Guidance.

Given the language in the Pediatric Use section of non-PLR Zyloprim labeling that states Zyloprim is rarely indicated for use in children with the exception of those with certain rare inborn errors of metabolism, DPMH discussed with DROII whether Zyloprim is considered approved for pediatric use for the management of certain inborn errors of metabolism. DPMH noted the lack of pediatric dosing information for this indication elsewhere in Zyloprim labeling.

In discussions with DOII, DPMH noted that, historically, diagnoses of aberrant purine metabolism such as Lesch-Nyhan syndrome, an X-linked disorder caused by a deficiency in the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT), (b) (4) (b) (4) (b) (4) Previous language used in the subsection entitled "Pediatric Use" of the non-PLR format Zyloprim labeling stated "Zyloprim is rarely indicated for use in

Reference ID: 5211971

children with the exception of those with hyperuricemia secondary to malignancy or to certain rare inborn errors of purine metabolism. The PLR Aloprim labeling does not mention patients with inborn errors of metabolism.

Small size case reports [5,6,7,8] of patients receiving allopurinol noted improvement in systemic uric acid levels but no improvement in the behavioral or cognitive decline associated with the diagnosis. A case series of patients with HPRT deficiency from Spain[9] also suggests that long term use of allopurinol (mean follow-up of 7.6 years) can reduce systemic uric acid levels but does not impact behavioral or cognitive decline. The current literature[10] recommends use of allopurinol as standard of care in both pediatric and adult patients with HPRT, adenine phosphoribosyl transferase (APRT) deficiency, and inherited diagnoses of uric acid transport.[11]

Because data from these studies have not been submitted to the Agency and the literature varies as to the recommended dosage for effectiveness for each diagnosis and safety concerns, DPMH agreed that the Pediatric Use subsection of the PLR formatted labeling should be updated to state the following:

- *The safety and effectiveness of ZYLOPRIM have not been established in pediatric patients with rare inborn errors of purine metabolism.*

DPMH recommends that the Applicant submit a literature-based supplement to support an indication for use in adult and pediatric patients with inborn errors of purine metabolism as off label use is considered the standard of care to reduce systemic uric acid levels.

[5] Bradmore et al. Effect of allopurinol on pyrimidine metabolism in the Lesch-Nyhan syndrome. Lancet (1970) pages 830-831
[6] Marks et al. Lesch-Nyhan syndrome treated from the early neonatal period. Pediatrics 1968;42:357-359
[7] Rosenbloom et al. Inherited disorder of purine metabolism: correlation between central nervous system dysfunction and biochemical defects. JAMA 1967;1202:103-105
[8] Crawhall et al. Diagnosis and treatment of Lesch-Nyhan syndrome. Pediatr Res 1972;6:504-513.
[9] Torres et al. Efficacy and safety of allopurinol in patients with hypoxanthine-guanine phosphoribosyl transferase deficiency. Metabolism Clinical and experimental 2007;56:1179-1186
[10] Medical Officer search of PubMed on July 5, 2023.
[11] Balasubramaniam et al. Inborn errors of purine metabolism: clinical updates and therapies. J Inherit Metab Dis. 2014;37:669-686.

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JOHN J ALEXANDER
07/20/2023 01:44:30 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Division of Hematologic Malignancies 1 Attn: Amy Baird	Javonna Stevens, Division of Rheumatology and Transplant Medicine (DRTM), 301.796.4240

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/1/2023		016084	PAS labeling supplement	04/19/2023

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zyloprim (allopurinol)		Xanthine Oxidase Inhibitor	6/1/2023

NAME OF FIRM: Casper

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Casper submitted a prior approval supplement – labeling supplement to update prescribing information to include updates to the Warnings section. In updating the labeling for Zyloprim we are converting the labeling to PLLR format.

View EDR: View submission in docuBridge

Cover Letter: \\CDSESUB1\evsprod\NDA016084\0036\m1\us\cover-letter.pdf

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Javonna Stevens	☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAVONNA STEVENS
05/01/2023 04:51:45 PM