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U.S. FOOD & DRUG ADMINISTRATION

NDA 209112/S-007

SUPPLEMENT APPROVAL

McGuff Pharmaceuticals, Inc.
Attention: Damon P. Jones
Vice President and Director of Operations
2921 W. MacArthur Boulevard, Suite 141
Santa Ana, CA 92704

Dear Mr. Jones:

Please refer to your Supplemental New Drug Application (sNDA) dated January 12, 2022, and received January 19, 2022, and your amendment, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ascor (ascorbic acid injection).

This Prior Approval supplemental new drug application provides for labeling changes to allow ambient storage/shipping of Ascor for up to 30 days.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling and with minor editorial revisions listed below and reflected in the enclosed labeling.

The revision date listed at the end of the Highlights of Prescribing Information has been updated to “07/2022" and the grammatical error identified in the second sentence in Section 5.2 to add “deficiency”.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to, except with the revisions listed, the enclosed labeling (text for the perscribing 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.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at

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http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via 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 MS Word format, that includes the changes with the revisions listed above approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, 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).

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 Christopher LaFleur, Regulatory Business Process Manager, at (240) 402 - 4724.

Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
Chief, Branch 1
Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ASCOR (ascorbic acid injection), for intravenous use

Initial U.S. Approval: 1947

INDICATIONS AND USAGE

ASCOR is vitamin C indicated for the short term (up to 1 week) treatment of scurvy in adult and pediatric patients age 5 months and older for whom oral administration is not possible, insufficient or contraindicated.

Limitations of Use

ASCOR is not indicated for treatment of vitamin C deficiency that is not associated with signs and symptoms of scurvy.

DOSAGE AND ADMINISTRATION

- Supplied in a Pharmacy Bulk Package (PBP). Dispense single doses to multiple patients in a pharmacy admixture program; use within 4 hours of puncture (2.1)
- Must be diluted prior to use (2.1)
- Administer as a slow intravenous infusion (2.1)
- See Full Prescribing Information for important administration instructions (2.1)
- Maximum recommended duration is one week (2.2)

Population (2.2)	**Recommended Doses**
Pediatric patients age 5 months to less than 12 months	50 mg once daily
Pediatric patients age 1 year to less than 11 years	100 mg once daily
Adults and pediatric patients age 11 years and older	200 mg once daily
Specific Populations (2.3, 8.1, 8.2)	
Pregnant women, lactating women, patients with glucose-6-phosphate dehydrogenase deficiency	Should not exceed the U.S. Recommended Dietary Allowance (RDA)

DOSAGE FORMS AND STRENGTHS

Injection: 25,000 mg/50 mL (500 mg/mL) – Pharmacy Bulk Package

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Oxalate nephropathy and Nephrolithiasis: Ascorbic acid has been associated with development of acute or chronic oxalate nephropathy following prolonged use of high doses of ascorbic acid infusion. Patients with renal disease including renal impairment, history of oxalate kidney stones, geriatric patients, and pediatric patients less than 2 years old may be at increased risk (5.1).
- Hemolysis: Patients with glucose-6-phosphate dehydrogenase deficiency are at risk of severe hemolysis; a reduced dose is recommended (5.2).
- Laboratory Test Interference: Ascorbic acid may interfere with laboratory tests based on oxidation-reduction reactions, including blood and urine glucose testing (5.3).

ADVERSE REACTIONS

Most common adverse reactions are pain and swelling at the site of infusion (6)

To report SUSPECTED ADVERSE REACTIONS, contact McGuff Pharmaceuticals, Inc., toll free at 1-800-603-4795 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Antibiotics: Ascorbic acid may decrease the activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated *in vitro* by ascorbic acid (7.1).
- Amphetamine and Other Drugs Affected by Urine Acidification: Ascorbic acid may cause acidification of the urine and result in decreased amphetamine serum levels and affect excretion and plasma concentrations of other drugs sensitive to urine pH (7.2).
- Warfarin: Continue standard monitoring (7.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ASCOR® is indicated for the short term (up to 1 week) treatment of scurvy in adult and pediatric patients, age 5 months and older, for whom oral administration is not possible, insufficient or contraindicated.

Limitations of Use

ASCOR is not indicated for the treatment of vitamin C deficiency that is not associated with signs and symptoms of scurvy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Preparation and Administration Instructions

- ASCOR vials contain 25,000 mg of ascorbic acid and the largest recommended single dose is 200 mg. Do not give the entire contents of the vial to a single patient.
- Do not administer ASCOR as an undiluted intravenous injection.
- Minimize exposure to light because ASCOR is light sensitive.
- ASCOR is supplied as a **Pharmacy Bulk Package** (PBP) which is intended for dispensing of single doses to multiple patients in a pharmacy admixture program and is restricted to the preparation of admixtures for infusion:

a. Use only in a suitable ISO Class 5 work area such as a laminar flow hood (or an equivalent clean air compounding area).

b. Penetrate each PBP vial closure **only one time** with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents. Given that pressure may develop within the vial during storage, exercise caution when withdrawing contents from the vial.

c. Once the closure system has been penetrated, **complete all dispensing from the PBP vial within 4 hours**. Each dose **must be used immediately**. Discard unused portion.

d. **Prior to administration, ASCOR must be diluted in a suitable infusion solution and the final solution for infusion must be isotonic** (undiluted the osmolarity of ASCOR is approximately 5,900 mOsmol/L). Prior to preparing the admixture for infusion, calculate the osmolarity of the intended admixture for infusion. Add one daily dose of ASCOR directly to an appropriate volume of a suitable infusion solution (e.g., 5% Dextrose Injection, Sterile Water for Injection) and add appropriate solutes, as necessary, to make the final solution isotonic. **Sterile Water for Injection is highly hypotonic; adjust solute content, as necessary, to make the final infusion solution isotonic prior to injection**. Do not mix ASCOR with solutions containing elemental compounds that can be reduced (e.g., copper). The concentration of ascorbic acid in the final, admixture solution for infusion is to be in the range of 1 to 25 mg of ascorbic acid per mL. For example, for the largest recommended dose:

Add 200 mg of ascorbic acid (equivalent to 0.4 mL of ASCOR) to 7.5 mL of Sterile Water for Injection to produce an infusion solution having an approximate osmolarity of 290 mOsmol/L. In this specific example, addition of solute is NOT necessary because the solution is isotonic.

e. **Prepare the recommended dose based on the patient population *[see Dosage and Administration (2.2),(2.3)]*.**

f. Visually inspect for particulate matter and discoloration prior to administration (the diluted ASCOR solution should appear colorless to pale yellow).

g. Immediately administer the admixture for infusion as a slow intravenous infusion *[see Recommended Dosage (2.2)]*

2.2 Recommended Dosage

Table 1 provides recommended doses of ASCOR based on patient population and infusion rates of diluted ASCOR solution.

Table 1: Recommended Dose of ASCOR and Infusion Rate of Diluted ASCOR Solution

Patient Population	ASCOR Once Daily Dose (mg)	Infusion Rate of Diluted ASCOR Solution (mg/minute)
Pediatric Patients age 5 months to less than 12 months	50	1.3
Pediatric Patients age 1 year to less than 11 years	100	3.3
Adults and Pediatric Patients 11 years and older	200	33

The recommended maximum duration of daily treatment with ASCOR is seven days. If no improvement in scorbutic symptoms is observed after one week of treatment, retreat until resolution of scorbutic symptoms is observed.

Repeat dosing is not recommended in pediatric patients less than 11 years of age.

2.3 Dosage Reductions in Specific Populations

Women who are pregnant or lactating and patients with glucose-6-dehydrogenase deficiency should not exceed the U.S. Recommended Dietary Allowance (RDA) or daily Adequate Intake (AI) level for ascorbic acid for their age group and condition *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 25,000 mg /50 mL (500 mg/mL) supplied as a Pharmacy Bulk Package (clear, colorless to pale yellow solution)

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Oxalate Nephropathy and Nephrolithiasis

Acute and chronic oxalate nephropathy have been reported with prolonged administration of high doses of ascorbic acid. Acidification of the urine by ascorbic acid may cause precipitation of cysteine, urate or oxalate stones. Patients with renal disease including renal impairment, history of oxalate kidney stones, and geriatric patients may be at increased risk for oxalate nephropathy while receiving treatment with ascorbic acid. Pediatric patients less than 2 years of age may be at increased risk for oxalate nephropathy during treatment with ascorbic acid because their kidneys are immature *[see Use in Specific Populations (8.4, 8.5, 8.6)]*. Monitor renal function in patients at increased risk receiving ASCOR. Discontinue ASCOR in patients who develop oxalate nephropathy and treat any suspected oxalate nephropathy.

ASCOR is not indicated for prolonged administration (the maximum recommended duration is one week) *[see Dosage and Administration (2.1)]*.

5.2 Hemolysis in Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

Hemolysis has been reported with administration of ascorbic acid in patients with glucose-6-phosphate dehydrogenase deficiency. Patients with glucose-6-phosphate dehydrogenase deficiency may be at increased risk for severe hemolysis during treatment with ascorbic acid. Monitor hemoglobin and blood count and use a reduced dose of ASCOR in patients with glucose-6-phosphate dehydrogenase deficiency *[see Dosage and Administration (2.3)]*. Discontinue treatment with ASCOR if hemolysis is suspected and treat as needed.

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5.3 Laboratory Test Interference

Ascorbic acid may interfere with laboratory tests based on oxidation-reduction reactions, including blood and urine glucose testing, nitrite and bilirubin levels, and leucocyte count testing. If possible, laboratory tests based on oxidation-reduction reactions should be delayed until 24 hours after infusion of ASCOR *[see Drug Interactions (7.4)]*.

6 ADVERSE REACTIONS

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

- Oxalate nephropathy and Nephrolithiasis *[see Warnings and Precautions (5.1)]*.
- Hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency *[see Warnings and Precautions (5.2)]* .

The following adverse reactions associated with the use of ascorbic acid were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure:

Administration site reactions: pain and swelling.

ASCOR should not be rapidly administered. Rapid intravenous administration (>250 mg/minute) of ASCOR may cause temporary faintness or nausea, lethargy, flushing, dizziness, and headache (the recommended infusion rates of diluted ASCOR solution are 1.3 mg/minute (Pediatric Patients age 5 months to less than 12 months), 3.3 mg/minute (Pediatric Patients age 1 year to less than 11 years) and 33 mg/minute (Adults and Pediatric Patients 11 years and older) *[see Dosage and Administration (2.2)]*).

Acute and chronic oxalate nephropathy have occurred with prolonged administration of high doses of ascorbic acid *[see Warnings and Precautions (5.1)]*. In patients with glucose-6-phosphate dehydrogenase deficiency, severe hemolysis has occurred *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Antibiotics

Ascorbic acid may decrease activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated *in vitro* by ascorbic acid. If the antibiotic efficacy is suspected to be decreased by concomitant administration of ASCOR, discontinue ASCOR administration.

7.2 Amphetamine & Other Drugs Affected by Urine Acidification

Ascorbic acid may acidify the urine and lower serum concentrations of amphetamine by increasing renal excretion (as reflected by changes in amphetamine urine recovery rates). In case of decreased amphetamine efficacy, discontinue ASCOR administration. Standard monitoring of therapy is warranted.

In addition, acidification of urine by ascorbic acid will alter the excretion of certain drugs affected by the pH of the urine (e.g., fluphenazine) when administered concurrently. It has been reported that concurrent administration of ascorbic acid and fluphenazine has resulted in decreased fluphenazine plasma concentrations. Standard monitoring of therapy is warranted.

7.3 Warfarin

Limited case reports have suggested interference of ascorbic acid with the anticoagulation effects of warfarin; however, for patients on warfarin therapy treated with ascorbic acid doses up to 1000 mg/day (5 times the largest recommended single dose) for 2 weeks (twice the maximum recommended duration), no effect was observed. Standard monitoring for anti-coagulation therapy should continue during ascorbic acid treatment, as per standard of care.

7.4 Laboratory Test Interference

Because ascorbic acid is a strong reducing agent, it can interfere with numerous laboratory tests based on oxidation-reduction reactions (e.g., glucose, nitrite and bilirubin levels, leukocyte count, etc.). Chemical detecting methods based on colorimetric reactions are generally those tests affected. Ascorbic acid may lead to inaccurate results (false negatives) obtained for checking blood or urinary glucose levels, nitrite, bilirubin, and leukocytes if tested during or within 24 hours after infusion *[see Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on use of ASCOR in pregnant women to inform a drug-associated risk of adverse developmental outcomes; however, use of ascorbic acid (vitamin C) has been used during pregnancy for several decades and no adverse developmental outcomes are reported in the published literature *[see Data]*. There are dose adjustments for ascorbic acid (vitamin C) use during pregnancy *[see Clinical Considerations]*.

Animal reproduction studies have not been conducted with ASCOR.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Dose Adjustments During Pregnancy and Post-Partum Period

Follow the U.S. Recommended Dietary Allowances (RDA) for pregnant women when considering use of ASCOR for treatment of scurvy *[see Dosage and Administration (2.3)]*.

Data

Human Data

There are no available data on use of ASCOR or another ascorbic acid injection in pregnant women. However, a published meta–analysis of randomized studies evaluating a large number of pregnant women who took oral ascorbic acid (vitamin C) (through diet and supplementation) at doses ranging from 500 to 1000 mg/day (2.5 to 5 times the recommended daily intravenous dose, respectively) *[see Dosage and Administration (2.3)]* between the 9th and 16th weeks of pregnancy showed no increased risk of adverse pregnancy outcomes such as miscarriage, preterm premature rupture of membranes, preterm delivery or pregnancy induced hypertension when compared to placebo. These data cannot definitively establish or exclude the absence of a risk with ascorbic acid (vitamin C) during pregnancy.

8.2 Lactation

Risk Summary

There are no data on the presence of ascorbic acid (vitamin C) in human milk following intravenous dosing in lactating women. Ascorbic acid (vitamin C) is present in human milk after maternal oral intake. Maternal oral intake of ascorbic acid (vitamin C) exceeding the U.S. Recommended Dietary Allowances (RDA) for lactation does not influence the ascorbic acid (vitamin C) content in breast milk or the estimated daily amount received by breastfed infants. There are no data on the effect of ascorbic acid (vitamin C) on milk production or the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ASCOR and any potential adverse effects on the breastfed child from ASCOR or from the underlying maternal condition. Follow the U.S. Recommended Dietary Allowances (RDA) for lactating women when considering use of ASCOR for treatment of scurvy *[see Dosage and Administration (2.3)]*.

8.4 Pediatric Use

ASCOR is indicated for the short term (up to 1 week) treatment of scurvy in pediatric patients age 5 months and older for whom oral administration is not possible, insufficient or contraindicated. The safety profile of ascorbic acid in pediatric patients is similar to adults; however, pediatric patients less than 2 years of age may be at higher risk of oxalate nephropathy following ascorbic acid administration due to age-related decreased glomerular filtration *[see Warnings and Precautions (5.1)]*.

ASCOR is not indicated for use in pediatric patients less than 5 months of age.

8.5 Geriatric Use

Glomerular filtration rate is known to decrease with age and as such may increase risk for oxalate nephropathy following ascorbic acid administration in elderly population *[see Warnings and Precautions (5.1)]*.

8.6 Renal Impairment

ASCOR should be used with caution in scorbutic patients with a history of or risk of developing renal oxalate stones or evidence of renal impairment or other issues (e.g., patients on dialysis, patients with diabetic nephropathy, and renal transplant recipients). These patients may be at increased risk of developing acute or chronic oxalate nephropathy following high dose ascorbic acid administration *[see Warning and Precautions (5.1)]*.

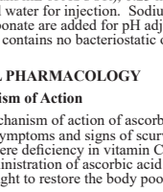
10 OVERDOSAGE

Overdose with ascorbic acid may cause nausea, vomiting, diarrhea, facial flushing, rash, headache, fatigue or disturbed sleep. If overdose of ASCOR occurs, immediately discontinue administration and treat symptoms and signs of overdose, avoiding additional intake of ascorbic acid.

11 DESCRIPTION

ASCOR (ascorbic acid injection) for intravenous use is a colorless to pale yellow, preservative-free, hypertonic, sterile, non-pyrogenic solution of ascorbic acid. ASCOR must be diluted with an appropriate infusion solution (e.g., 5% Dextrose Injection, USP; Sterile Water for Injection, USP) *[see Dosage and Administration (2.1)]*.

The chemical name of Ascorbic Acid is L-ascorbic acid. The molecular formula is $C_6H_8O_6$. It has the following structural formula:



Each ASCOR, 50 mL, Pharmacy Bulk Package vial contains 25,000 mg ascorbic acid, equivalent to 28,125 mg sodium ascorbate.

Each mL of ASCOR contains 500 mg of ascorbic acid (equivalent to 562.5 mg of sodium ascorbate which amounts to 65 mg sodium/mL of ASCOR), 0.25 mg of edetate disodium, and water for injection. Sodium hydroxide and sodium bicarbonate are added for pH adjustment (pH range 5.6 to 6.6). It contains no bacteriostatic or antimicrobial agent.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action of ascorbic acid for the treatment of symptoms and signs of scurvy (a disorder caused by severe deficiency in vitamin C) is unknown; however, administration of ascorbic acid in patients with scurvy is thought to restore the body pool of ascorbic acid.

12.3 Pharmacokinetics

In a single pharmacokinetic study, healthy male and female adults (n=8) were given a single intravenous dose of 1000 mg ascorbic acid (5 times the largest recommended single dose) infused over a 30 minute period. The mean peak exposure to ascorbic acid was 436.2 µM and occurred at the end of the 30 minute infusion.

Distribution

Ascorbic acid is distributed widely in the body, with large concentrations found in the liver, leukocytes, platelets, glandular tissues, and lens of the eye. Based on data from oral exposure, ascorbic acid is known to be distributed into breast milk and crosses the placental barrier.

Elimination

When the body is saturated with ascorbic acid, the plasma concentration will be about the same as that of the renal threshold; if further amounts are then administered, most of it is excreted in the urine. When body tissues are not saturated and plasma concentration is low, administration of ascorbic acid results in little or no renal excretion. The mean±SD (N=3) half-life observed in the single dose PK study, as described above, was 7.4±1.4 h.

Metabolism

A major route of metabolism of ascorbic acid involves its conversion to urinary oxalate, presumably through intermediate formation of its oxidized product, dehydroascorbic acid.

Excretion

There is a renal threshold for ascorbic acid (vitamin C); the vitamin is excreted by the kidney in large amounts only when the plasma concentration exceeds this threshold, which is approximately 1.4 mg/100 mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies have not been performed with ASCOR.

16 HOW SUPPLIED/STORAGE AND HANDLING

ASCOR for intravenous use is a colorless to pale yellow solution supplied as:

- NDC 67157-101-50 One 25,000 mg/50 mL (500 mg/mL) Pharmacy Bulk Package vial
- NDC 67157-101-51 Tray pack of twenty five 25,000 mg/50 mL (500 mg/mL) Pharmacy Bulk Package vials

Store in a refrigerator at 2° to 8°C (36° to 46°F).

Protect from light. This product contains no preservative. See Dosage and Administration (2.1) for detailed instructions on preparation, dilution, and administration of ASCOR. Excursions to ambient conditions for up to 30 days during storage or shipping are acceptable.

17 PATIENT COUNSELING INFORMATION

- Inform patients that treatment with ASCOR may increase their risk of oxalate nephropathy *[see Warnings and Precautions (5.1)]*.
- Inform patients that treatment with ASCOR may impact laboratory results, including blood and urine glucose tests, up to 24 hours after infusion *[see Warnings and Precautions (5.3)]*.
- Inform patients with glucose-6-phosphate dehydrogenase deficiency that treatment with ASCOR may increase their risk of hemolysis *[see Warnings and Precautions (5.2)]*.

Manufactured By:

McGuff Pharmaceuticals, Inc., Santa Ana, CA 92704

M381-0073

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Ramesh Raghavachari

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