CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209112Orig1s009

Trade Name:	**ASCOR**
Generic or Proper Name:	(ascorbic acid)
Sponsor:	MCGUFF PHARMACEUTICALS, INC.
Approval Date:	January 17, 2024
Indication:	**ASCOR** is vitamin C indicated for the 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

209112Orig1s009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209112Orig1s009

APPROVAL LETTER

NDA 209112/S-009

APPROVAL LETTER

McGuff Pharmaceuticals, Inc.
Attention: Jacqueline McKay
Regulatory Affairs Manager
4040 W. Carriage Drive
Suite 141
Santa Ana, CA 92704

Dear Ms. McKay:

Please refer to your Supplemental New Drug Application (sNDA) dated September 15, 2023, and received October 5, 2023, and your amendments, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ascor (ascorbic acid injection).

This "Changes Being Effected" supplemental new drug application provides for labeling changes as specified in the Agency's Supplement Request Letter dated August 01, 2023.

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

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 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 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).

CARTON AND CONTAINER LABELS

Submit final printed carton and container labels that are identical to enclosed carton and container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 209112/S-009.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Oluwafunmike (Funke) Ajomale, Regulatory Business Process Manager, at oluwafunmike.ajomale@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
Supervisor, Division of Product Quality Assessment IV
Office of Product Quality Assessment I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 1/17/2024 02:40:48PM
GUID: 502d0913000029f375128b0de8c50020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209112Orig1s009

LABELING

Top of Page

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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: 01/2024

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)]*.

Bottom of Page

Side One (Front)

Notes:

1. Fold in half starting at Fold #1. Repeat for Fold #2

   Fold insert such that the product name on Side One is face up and visible. Final fold size is 4.5” x 3.5”

Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: Package Insert, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial, Pharmacy Bulk Package		
Approved by / Date:	Size:	Document #: DRW-0037 Part #: M381-0073	Rev: 05
	Sheet: 1 of 2		

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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.

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 (7.5)]*.

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)]*.

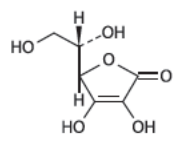
10 OVERDOSAGE

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), 130 mg of Sodium bicarbonate, and 0.25 mg of edetate disodium. Sodium hydroxide is added for pH adjustment (pH range 5.6-6.6). 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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Side Two (Back)

Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: Package Insert, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial, Pharmacy Bulk Package		
Approved by / Date:	Size:	Document #: DRW-0037 Part #: M381-0073	Rev: 05
	Sheet: 2 of 2		

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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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.

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

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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: 01/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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)]*.

Bottom of Page

Side One (Front)

Notes:

1. Fold in thirds starting at Fold #1. Repeat for Fold #2.
2. Fold in half starting at Fold #3.

   Fold insert such that the 2d barcode on Side One is face up and visible.
   Final fold size is 1.5” x 7”

Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: Package Insert, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial, Pharmacy Bulk Package		
Approved by / Date:	Size:	Document #: DRW-0037 Part #: M381-0073	Rev: 05
	Sheet: 1 of 2		

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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.

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 (7.5)]*.

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)]*.

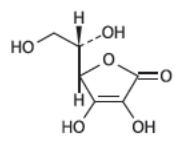
10 OVERDOSAGE

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), 130 mg of Sodium bicarbonate, and 0.25 mg of edetate disodium. Sodium hydroxide is added for pH adjustment (pH range 5.6-6.6). 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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Side Two (Back)

Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: Package Insert, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial, Pharmacy Bulk Package		
Approved by / Date:	Size:	Document #: DRW-0037 Part #: M381-0073	Rev: 05
	Sheet: 2 of 2		

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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: 01/2024

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.

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 (7.5)]*.

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Side One (Front)

Notes:

1. Fold insert such that the product name and 2d barcode on Side One is face up and visible. Final fold size is 1.416" x 6"
2. Glue dots are applied to the interior surface of the top flap of the insert

Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: Package Insert, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial, Pharmacy Bulk Package		
Approved by / Date:	Size:	Document #: DRW-0037 Part #: M381-0073	Rev: 05
	Sheet: 1 of 2		

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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)]*.

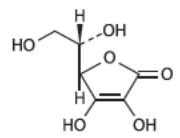
10 OVERDOSAGE

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), 130 mg of Sodium bicarbonate, and 0.25 mg of edetate disodium. Sodium hydroxide is added for pH adjustment (pH range 5.6-6.6). 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

Bottom of Page

Side Two (Back)

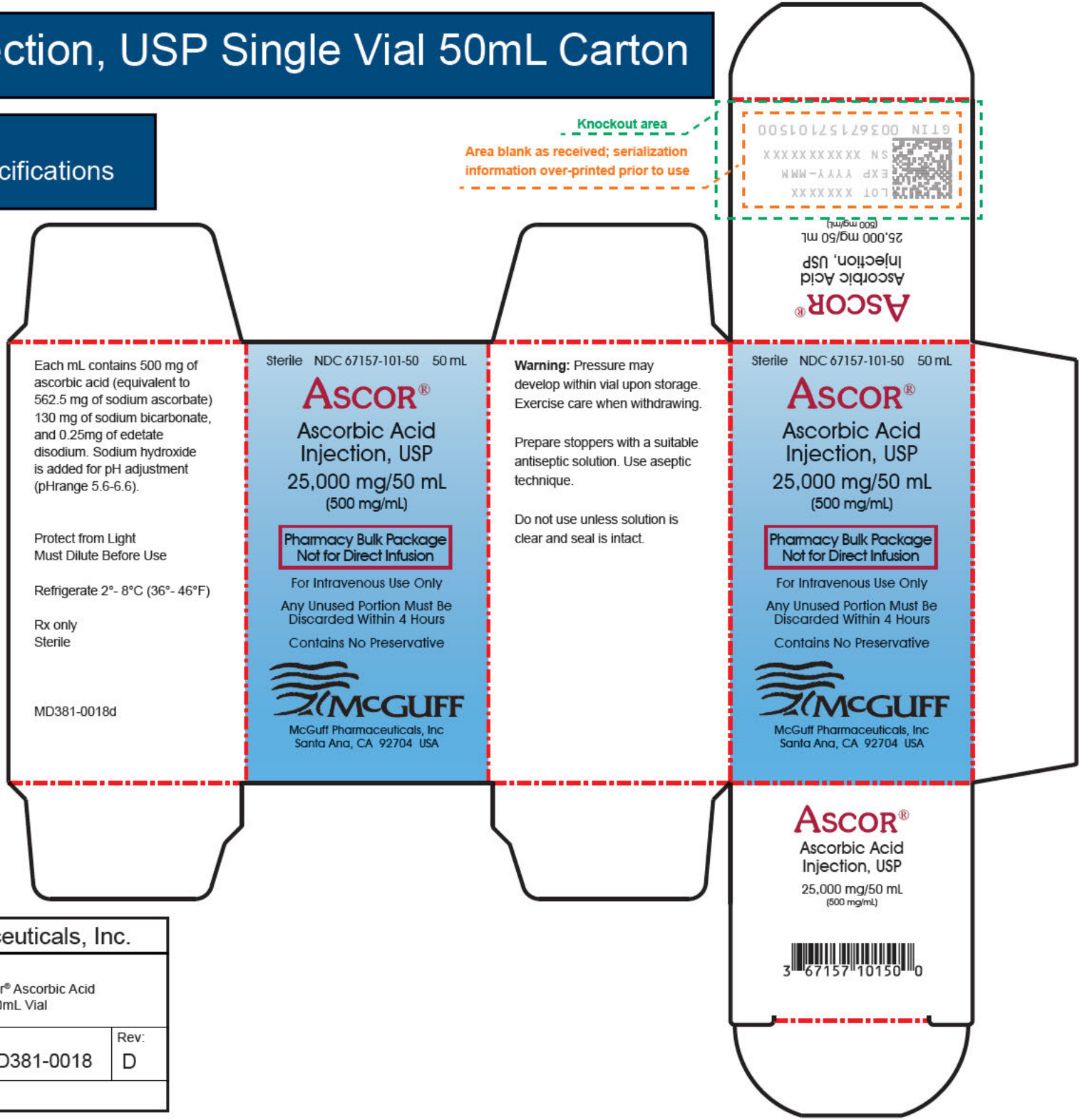
Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: Package Insert, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial, Pharmacy Bulk Package		
Approved by / Date:	Size:	Document #: DRW-0037 Part #: M381-0073	Rev: 05
	Sheet: 2 of 2		

Ascorbic Acid Injection, USP Single Vial 50mL Carton

Ascorbic Acid Injection, USP
Single Vial 50mL Carton Specifications

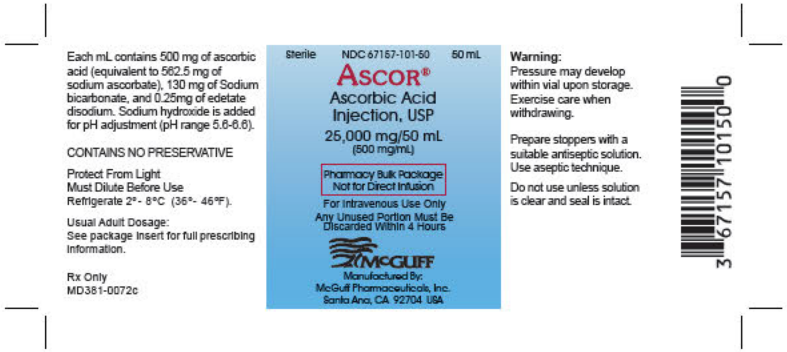
(b) (4)

Single Vial 50mL Carton:



Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: Single Vial 50mL Carton, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial		
Approved by / Date:	Size:	Document #: DRW-0041/ MD381-0018	Rev: D
	Sheet: 1 of 1		

Ascorbic Acid Injection, USP Vial Label



Ascorbic Acid Injection, USP Vial Label Specifications

(b) (4)

Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: Vial Label, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial		
Approved by / Date:	Size:	Document #: DRW-0036 / MD381-0072	Rev: C
	Sheet: 1 of 1		

Each mL contains 500 mg of ascorbic acid (equivalent to 562.5 mg of sodium ascorbate), 130 mg of Sodium bicarbonate, and 0.25mg of edetate disodium. Sodium hydroxide is added for pH adjustment (pH range 5.6-6.6).

CONTAINS NO PRESERVATIVE

Protect From Light
Must Dilute Before Use
Refrigerate 2°- 8°C (36°- 46°F).

Usual Adult Dosage:
See package insert for full prescr bing information.

Rx Only
MD381-0072c

Sterile NDC 67157-101-50 50 mL

ASCOR®

Ascorbic Acid Injection, USP

25,000 mg/50 mL
(500 mg/mL)

Pharmacy Bulk Package
Not for Direct Infusion

For Intravenous Use Only
Any Unused Portion Must Be Discarded Within 4 Hours

McGUFF

Manufactured By:
McGuff Pharmaceuticals, Inc.
Santa Ana, CA 92704 USA

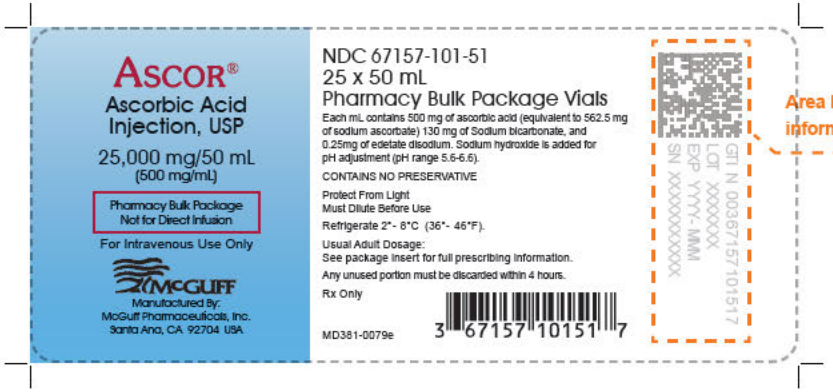
Warning:
Pressure may develop within vial upon storage. Exercise care when withdrawing.

Prepare stoppers with a suitable antiseptic solution. Use aseptic technique.

Do not use unless solution is clear and seal is intact.

3 67157 10150 0

Ascorbic Acid Injection, USP 25 Tray Pack Label



Area blank as received; serialization information over-printed prior to use

Ascorbic Acid Injection, USP 25 Tray Pack Label Specifications

(b) (4)

Created by / Date:	McGuff Pharmaceuticals, Inc.		
	Title: 25 Tray Pack Label, Ascor® Ascorbic Acid Injection, USP (500mg/mL), 50mL Vial		
Approved by / Date:	Size:	Document #: MD381-0079	Rev: E
	Sheet: 1 of 1		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209112Orig1s009

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-209112-SUPPL-009
   sNDA Recommendation: Approval
   sNDA Managed by: OPQ

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	CBE-0	10/05/2023	10/05/2023	10/10/2023	04/05/2024	01/16/2024
IR Response SD89		11/07/2023	11/07/2023			
IR Response SD90		12/19/2023	12/19/2023			

3. **Provides For:**
   - Labeling changes as requested in the Supplement Request Letter dated August 01, 2023.

4. **Review #**: 01

5. **Clinical Review Division**: OCHEN/DGE

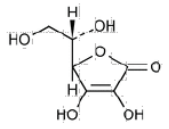
6. **Name and Address of Applicant**:
   McGuff Pharmaceuticals, Inc.
   29211 W. MacArthur Boulevard, Suite 141
   Santa Ana, CA, USA, 92704

   Contact: Jacqueline McKay
   Phone: 714-918-7277
   Email: jmckay@mcguff.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product	Orphan Designation
ASCOR (ascorbic acid injection)	Solution for injection	500 mg/mL	Intravenous	Rx	Yes	07-2437

8. **Chemical Name and Structure of Drug Substance**:

	**USAN:** Ascorbic Acid, USP **Chemical Name:** (2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one **Molecular Formula:** $C_6H_8O_6$ **MW**: 176.12 g/mol

9. **Indication**: 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.

10. **Supporting/Related Documents**:
    - Supplement Request Letter available on Panorama, 08/01/2023 (Funke Ajomale)
    - OLDP Response to OGD Labeling Consult available on Panorama, 07/31/2023 (Sarah Zimmermann)
    - OGD Labeling Consult available on Panorama, 06/15/2023 (Elizabeth Kim)

11. **Disciplines/Consults**:

Disciplines/Consults	Recommendation	Date	Reviewer
DMEPA	Adequate	12/12/2023	Peggy Rahbani

12. **Executive Summary**:

Supplement 009 was provided in response to the supplement request letter dated August 01, 2023 to provide revision to the labeling and (b) (4) to include (b) (4) and to list the quantity of sodium bicarbonate (b) (4) In S-009 submission SD86 submitted on October 05, 2023 the firm clarified that (b) (4) xecuted batch records for Batches 23F0041, 23F0071, and 23F0111 were provided to support the statement that (b) (4) The drug product (b) (4) was revised to list the amount of sodium bicarbonate as 130 mg, (b) (4) An IR was issued to the firm on October 31, 2023 to provide revised labeling to list sodium bicarbonate quantity pursuant to 21 CFR 201.100(b)(5)(iii). A second IR was issued to (b) (4) on November 17, 2023 to provide annotated labeling changes, revised expiration dating format, revised dosage form on the carton labels, and labeling in the SPL format. Labeling revisions were provided in SD89 submitted on November 07, 2023 as well as SD90 submitted on December 19, 2023.

DMEPA has found the provided labeling acceptable (12/12/2023, Peggy Rahbani).

The firm has adequately addressed the concerns issued in the Supplement Request Letter dated August 01, 2023 and the provided labeling is acceptable from a CMC perspective.

13. **Conclusions & Recommendations**: This supplement is recommended for approval.

14. **Comments/Deficiencies to be Conveyed to Applicant**: None

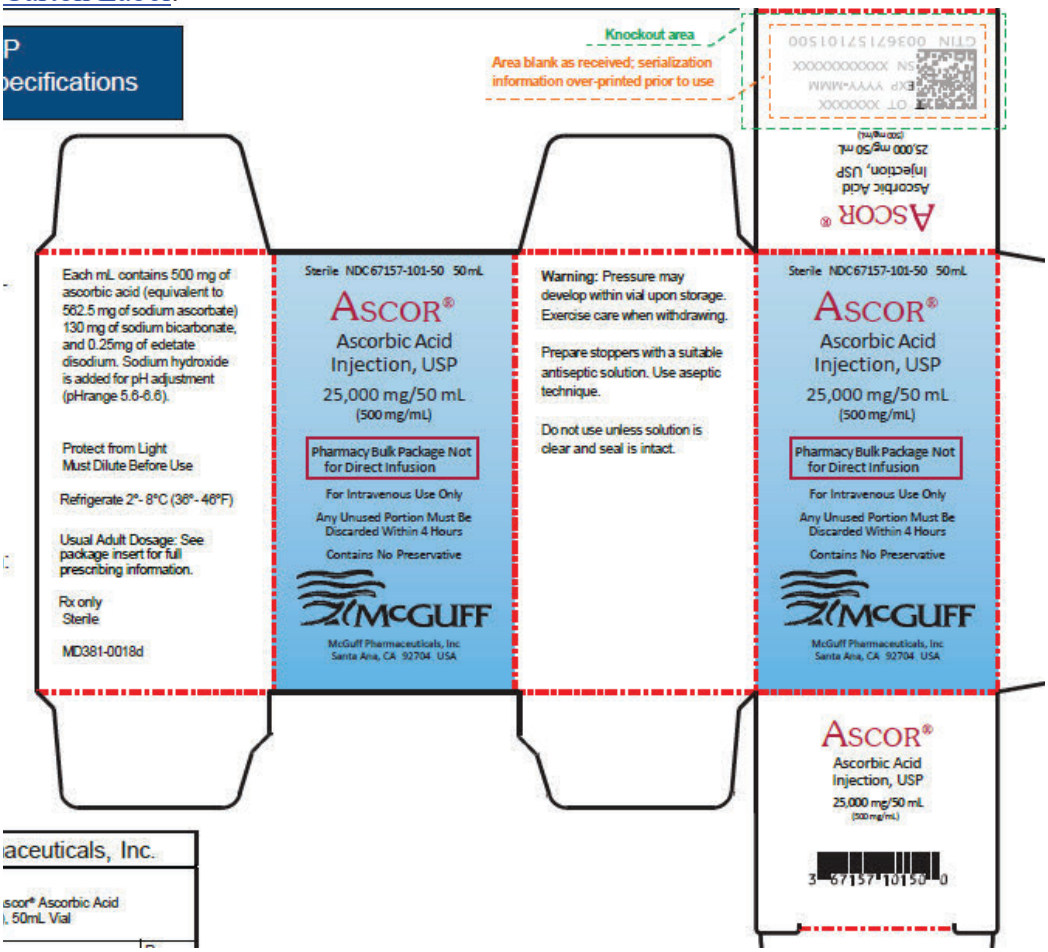
15. **Primary Reviewer**:
Sarah C. Zimmermann, Ph.D., CMC reviewer, Branch 1, DPMAI, OLDP, OPQ

16. **Secondary Reviewer**:
Rohit Kolhatkar, Ph.D., SPQA, Branch 1, DPMAI, OLDP, OPQ

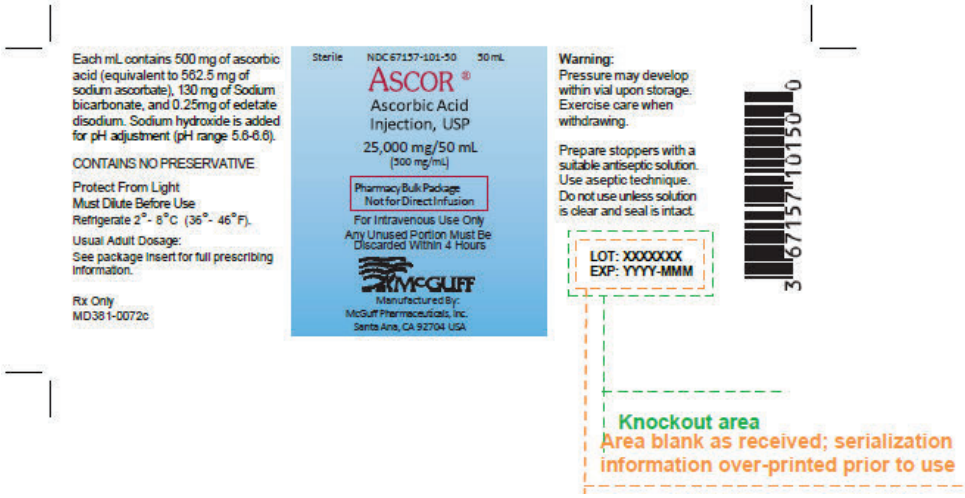
17. Labeling as provided in SD90 submitted on 12/19/2023: pack, carton, and vial labeling were revised to list the quantity of sodium bicarbonate as 130 mg.

25 x 50mL Pack Label:

Carton Label:



Vial Label:



USPI Sections 3, 11, and 16: There are no proposed changes to Sections 3 and 16. Section 11 was revised to list the amount of sodium bicarbonate as 130 mg and only list sodium hydroxide as a pH adjuster.

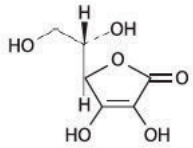
3 DOSAGE FORMS AND STRENGTHS

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

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), 130 mg of Sodium bicarbonate, and 0.25mg of edetate disodium. Sodium hydroxide is added for pH adjustment (pH range 5.6-6.6). It contains no bacteriostatic or antimicrobial agent.

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.

Sarah Zimmermann

Digitally signed by Sarah Zimmermann
Date: 1/17/2024 10:21:44AM
GUID: 59aeccce003cb2b7276f6582f89c37ee

Rohit Kolhatkar

Digitally signed by Rohit Kolhatkar
Date: 1/17/2024 10:23:42AM
GUID: 57bf531500b52a2eccd5395bec77ebc2
Comments: concur with the recommendation to approve from CMC standpoint

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209112Orig1s009

OTHER REVIEW(S)

REGULATORY BUSINESS PROCESS MANAGER LABELING REVIEW

Office of Program and Regulatory Operations

Application: NDA-209112-SUPPL-9 (CBE-0)

Name of Drug: Ascor (ascorbic acid injection)

Applicant: McGuff Pharmaceuticals, Inc.

Submission and amendment(s) receipt date:

Submission Dates:

NDA-209112-SUPPL-9
October 5, 2023

Amendment Dates:

NDA-209112-SUPPL-9
November 7, 2023
December 19, 2023

Material Reviewed (as applicable):

Material	Submit Date	Receipt Date	Compared to last approved labels/labeling
Package Insert	11-07-2023	11-07-2023	07-08-2022 NDA-209112-SUPPL-7
Vial Carton	11-07-2023	11-07-2023	NDA-209112-SUPPL-5 Approved April 01, 2022 (labels not included in Action Letter, but referenced in action letter and DMEPA review)
Vial Label	11-07-2023	11-07-2023	NDA-209112-SUPPL-5 Approved April 01, 2022 (labels not included in Action Letter, but referenced

			in action letter and DMEPA review)
25 Pack label	11-07-2023	11-07-2023	NDA-209112-SUPPL-5 Approved April 01, 2022 (labels not included in Action Letter, but referenced in action letter and DMEPA review)

Background and Summary Description:

Ascor (ascorbic acid injection) was approved on October 02, 2017, for the treatment of scurvy in adult and pediatric patients aged 5 months and older for whom oral administration is not possible, insufficient, or contraindicated for McGuff Pharmaceuticals, Inc.

(b) (4)

On October 5, 2023, McGuff Pharmaceuticals, Inc. submitted a CBE-0 Supplement (Supplement 009) to NDA 209112. The supplement provides for the Labeling Changes as requested in the Supplement Request Letter dated 01 August 2023.

As a result of a request for information sent on Oct 31, 2023, the applicant submitted draft vial, carton, and 25ct tray pack labels and the package insert.

Per email from OND RPM (Meghna Jairath) on November 15, 2023, there are no pending safety labeling updates or OND managed labeling supplements in house.

There were changes submitted outside of the CMC sections, on November 17, 2023, OND RPM (Meghna Jairath), indicated that the clinical division considers these typographical corrections, and no further comments are needed.

Labeling History

Application	Date	Approved Labeling
NDA-209112-SUPPL-7	July 08, 2022	• Content of Labeling ○ Prescribing Information
NDA-209112-SUPPL-5	April 01, 2022	• Content of Labeling ○ Prescribing Information

		• Carton and Container Labeling (labels not included in Action Letter, but referenced in action letter and DMEPA review) ○ Package Label (Pharmacy Bulk Package) ○ 25 Tray Pack Label (500 mg/ml) 50 ml single dose vials ○ Single Vial 50ml Box Label
NDA-209112-ORIG-1	October 02, 2017	• Content of Labeling ○ Prescribing Information • Carton and Container Labeling ○ Package Label (Pharmacy Bulk Package) ○ Single Vial 50ml Box Label ○ 25 Tray Pack Label (500 mg/ml) 50 ml single dose vials

Consult(s)
A DMEPA consult was submitted on October 31, 2023. On December 12, 2023, Peggy Rahbani, PharmD, BCPS and Madhuri R. Patel, PharmD from DMEPA completed a labeling review. The evaluation did not identify areas of vulnerability that may lead to medication errors. They have no recommendations at this time.

Information Request
An IR was sent on October 31, 2023, requesting the applicant amend the drug product labeling to list sodium bicarbonate in a manner consistent with its stated function in the Suppl-9 (b) (4) The applicant responded on November 7, 2023, providing the draft vial, carton, tray pack labels and package insert.

A second IR was sent on November 17, 2023, requesting the redlined/annotated labels and labeling, addition of the lot and expiration date to the vial label, addition of the dosage information to the carton label and the SPL format of the labeling. The applicant provided the redlined vial, carton, 25 pack labels and the package insert in addition to the SPL format.

CMC Review
CMC Review was performed and approval was recommended by Sarah C. Zimmermann,

Ph.D., CMC reviewer and Rohit Kolhatkar, Ph.D., SPQA, on January 17, 2024.

Review

This comparison was done by visually comparing the proposed to the last submitted or approved labeling on file.

The following are the assessments for each change identified:

Prescribing Information

1. **Revised year**

   Comments: Revised Year will be updated to an approved Month/Year upon taking action.

2. **Section 5, WARNINGS AND PRECAUTIONS**, subsection 5.3, **Laboratory Test Interference**,

   a. Last Approved Change (NDA-209112-SUPPL-7, 07-08-2022):

> **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 (7.5)]*.

   b. Proposed Change (submitted 12-19-2023):

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.~~5~~4)]*.

Comments: Adequate, typographical corrections per clinical division.

3. **Section 11, DESCRIPTION**: clarified that [redacted] (b) (4)

   a. Last Approved Change (NDA-209112-SUPPL-7, 07-08-2022):

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.

b. Proposed Change (submitted 12-19-2023):

(b) (4)

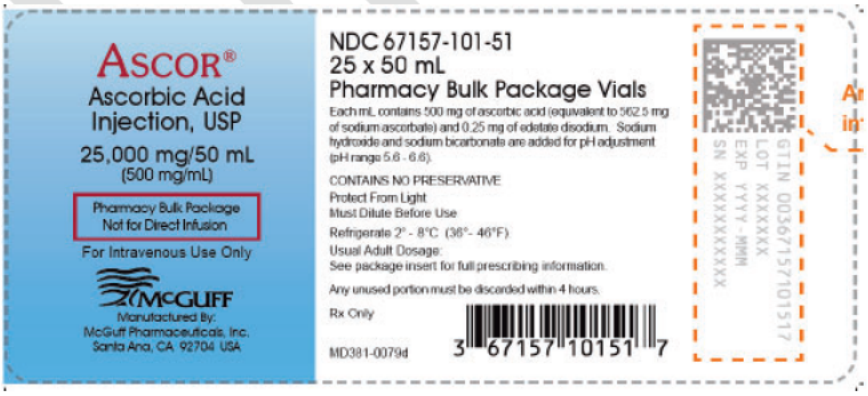
[redacted]

Comments: Adequate, Per CMC/DMEPA review and 21 CFR 201.100(b)(5)(iii)

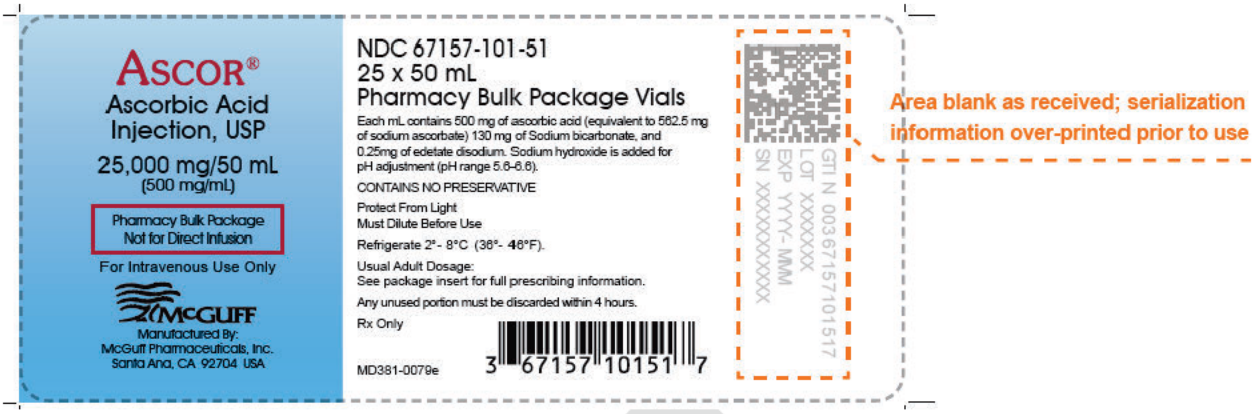
Carton Labeling and Container Label

1. **USP 25 Tray Pack Label**: the following changes are.
   i. Addition of Sodium bicarbonate (and amount) to list of ingredients.
   ii. Removal of Sodium bicarbonate as a pH adjuster.
   iii. Change in internal number from 'MD 381-0079d' to 'MD381-007in9e'.

b. Last Approved Label (NDA-209112-SUPPL-5, approved April 01, 2022, DMEPA Review): Attach last approved



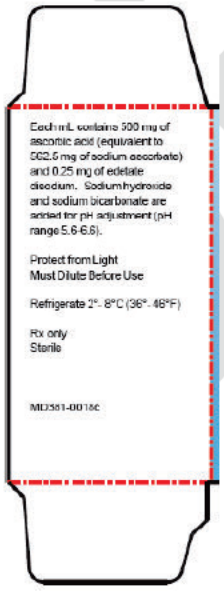
b. Proposed Change (SDN 90, submitted 12-19-2023): Attach proposed



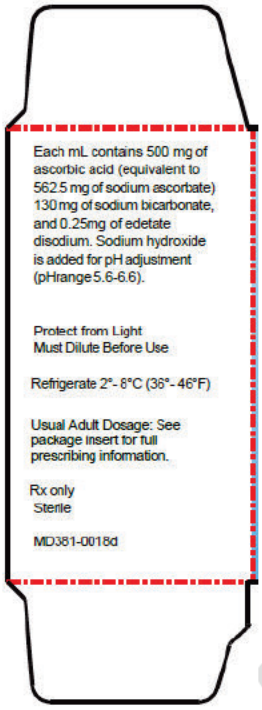
Comments: Adequate, Per CMC/DMEPA review, editorial changes, 21 CFR 201.100(b)(5)(iii).

2. **Single Vial 50ml Carton**, Right Side Panel, the following changes are proposed:
   i. Addition of Sodium bicarbonate (and amount) to list of ingredients.
   ii. Removal of Sodium bicarbonate as a pH adjuster.
   iii. Addition of "Usual Adult Dosage: See package insert for full prescribing information".
   iv. Change in internal number from 'MD 381-0018c' to 'MD381-0018d'

   a. Last Approved Label (NDA-209112-SUPPL-5, approved April 01, 2022, DMEPA Review):

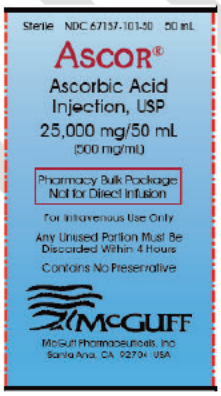


   b. Proposed Change (SDN 90, submitted 12-19-2023): Attach proposed

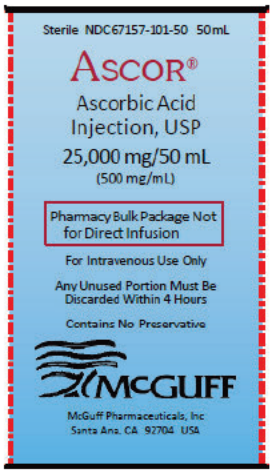


Comments: Adequate, Per CMC/DMEPA review, 21 CFR 201.55, editorial changes.

3. **Single Vial 50ml Carton**, Back Panel, Change in format/layout of the phrase, "Pharmacy Bulk Package Not for Direct Infusion".
   a. Last Approved Label (NDA-209112-SUPPL-5, approved April 01, 2022, DMEPA Review):



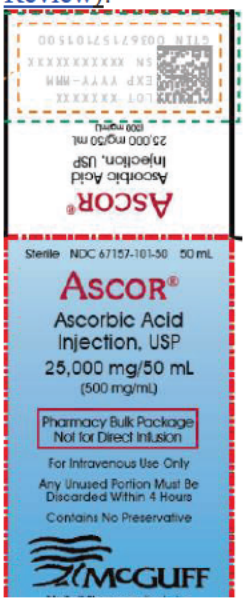
   b. Proposed Change (SDN 90, submitted 12-19-2023): Attach proposed



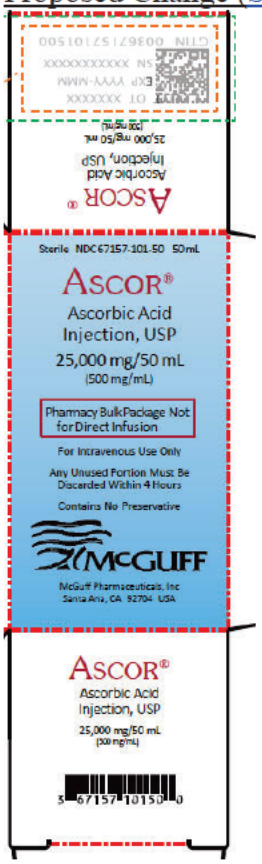
Comments: Adequate, Per CMC/DMEPA review, formatting changes

4. **Single Vial 50ml Carton**, Principal Display Panel, Change in format/layout of the phrase, "Pharmacy Bulk Package Not for Direct Infusion".

Last Approved Label (NDA-209112-SUPPL-5, approved April 01, 2022, DMEPA Review):



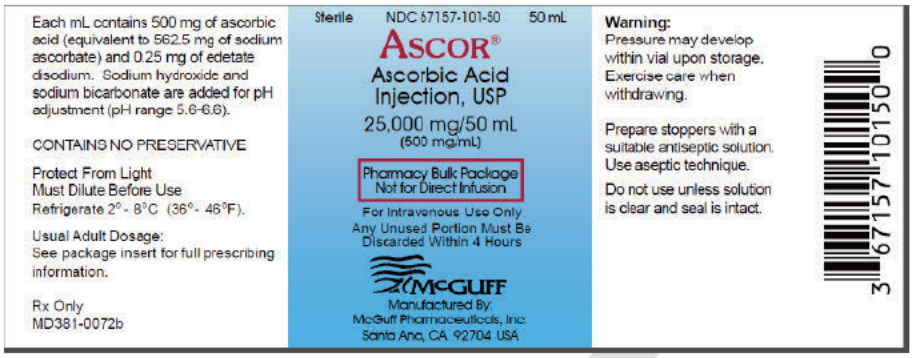
Proposed Change (SDN 90, submitted 12-19-2023):



Comments: Adequate, Per DMEPA review, formatting changes

5. **USP Vial Label.** The following changes are.
   i. Addition of Sodium bicarbonate (and amount) to list of ingredients.
   ii. Removal of Sodium bicarbonate as a pH adjuster.
   iii. Change in internal number from 'MD 381-0072b' to 'MD381-0072c'.
   iv. Change in format/layout of the phrase, "Pharmacy Bulk Package Not for Direct Infusion".
   v. Addition of Lot and Expiration date

   a. Last Approved Label (NDA-209112-SUPPL-5, approved April 01, 2022, DMEPA Review):



b. Proposed Change (SDN 90, submitted 12-19-2023): Attach proposed

Comments: Adequate, Per CMC/DMEPA review, 21 CFR 201.18, 21 CFR 201.17

Recommendations

The change to the labels/labeling is acceptable. The supplement is recommended for approval.

{See appended electronic signature page}

Oluwafunmike (Funke) Ajomale, MSPH, PMP Date
Regulatory Business Process Manager
Office of Programs and Regulatory Operations
Office of Pharmaceutical Quality

Key:

IFU – Instructions for Use
MG – Medication Guide
USPI – United States Prescribing Information
PLR – Physician Labeling Rule
PPI - Patient Package Insert
C+C – Carton and/or Container
CMC- Chemistry, Manufacturing, and Controls
LBL- Labeling supplement

Oluwafunmike (Funke) Ajomale

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Date: 1/17/2024 10:33:29AM
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 12, 2023
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 209112/S-009 (b) (4)
Product Name, Dosage Form, and Strength:	Ascor (ascorbic acid) injection, 500 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	McGuff Pharmaceuticals, Inc.
FDA Received Date:	October 5, 2023, October 10, 2023, and November 7, 2023
TTT ID #:	2023-7338 and 2023-7067
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 REASON FOR REVIEW

McGuff Pharmaceuticals, Inc. submitted a changes being effected (CBE-0) Chemistry Manufacturing and Controls (CMC) supplement (S-009) to provide for labeling revisions regarding sodium bicarbonate composition in drug product (b) (4) (b) (4) (b) (4) Subsequently, the Office of Pharmaceutical Quality (OPQ) roposed Ascor prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed Ascor prescribing information (PI), container label, and carton labeling did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ascor that McGuff Pharmaceuticals, Inc. submitted on October 10, 2023.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Ascor</th></tr>
<tr><td>Initial Approval Date</td><td>10/2/1017</td></tr>
<tr><td>Active Ingredient</td><td>ascorbic acid</td></tr>
<tr><td>Indication</td><td>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.</td></tr>
<tr><td>Route of Administration</td><td>intravenous infusion</td></tr>
<tr><td>Dosage Form</td><td>injection</td></tr>
<tr><td>Strength</td><td>25,000 mg /50 mL (500 mg/mL)</td></tr>
<tr><td>Dose and Frequency</td><td>Table 1: Recommended Dose of ASCOR and Infusion Rate of Diluted ASCOR Solution
<table><tr><th>Patient Population</th><th>ASCOR Once Daily Dose (mg)</th><th>Infusion Rate of Diluted ASCOR Solution (mg/minute)</th></tr><tr><td>Pediatric Patients age 5 months to less than 12 months</td><td>50</td><td>1.3</td></tr><tr><td>Pediatric Patients age 1 year to less than 11 years</td><td>100</td><td>3.3</td></tr><tr><td>Adults and Pediatric Patients 11 years and older</td><td>200</td><td>33</td></tr></table>ASCOR 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: recommended single dose is 200 mg.</td></tr>
<tr><td>How Supplied</td><td>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</td></tr>
<tr><td>Storage</td><td>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.</td></tr>
<tr><td>Container Closure</td><td>Vial</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 22, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Ascor'. Our search identified once previous reviews[a] since the date of our last search on February 25, 2021, and we confirmed that our previous recommendations were implemented.

[a] Fanari M. Label and Labeling Review for Ascor (NDA 209112/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 FEB 28. OSE RCM #: 2022-212

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error experiences with similar products, we reviewed the following Ascor labels and labeling submitted by McGuff Pharmaceuticals, Inc.

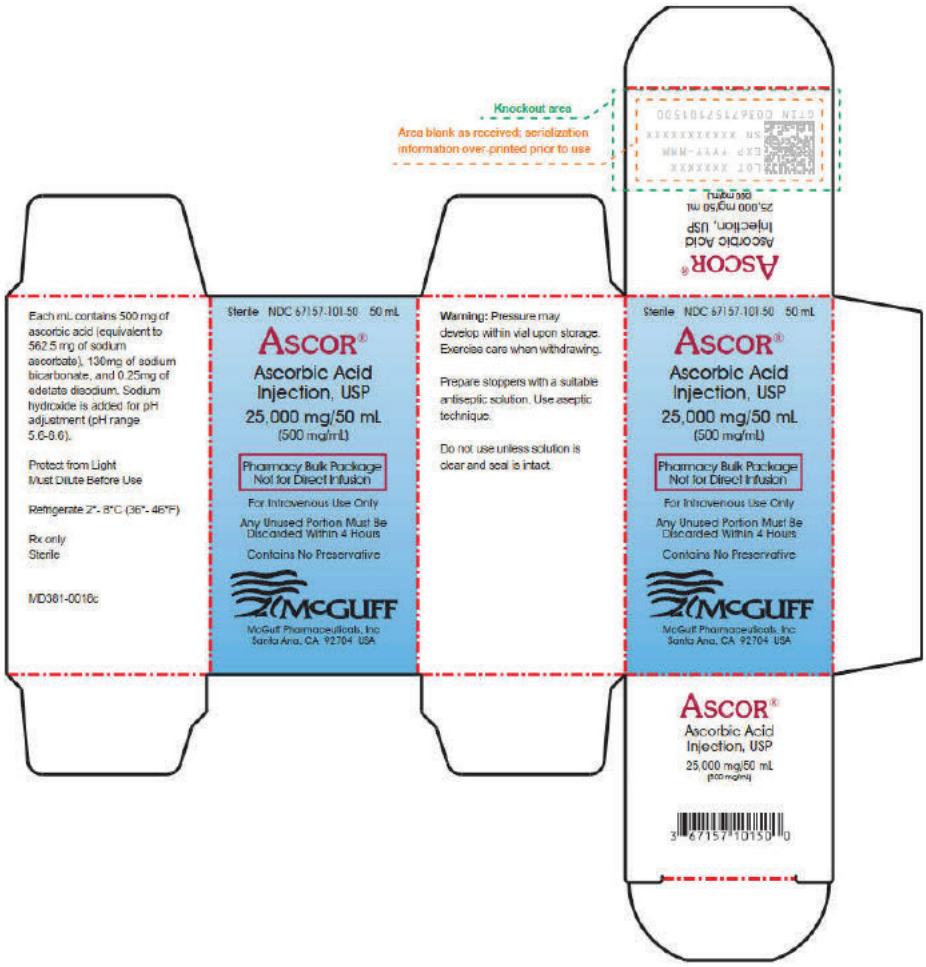
- Container label received on November 7, 2023
- Carton labeling received on November 7, 2023
- Prescribing Information (Image not shown) received on November 7, 2023, available from \\CDSESUB1\EVSPROD\nda209112\0091\m1\us\m1-14-labeling\pi.pdf

F.2 Label and Labeling Images

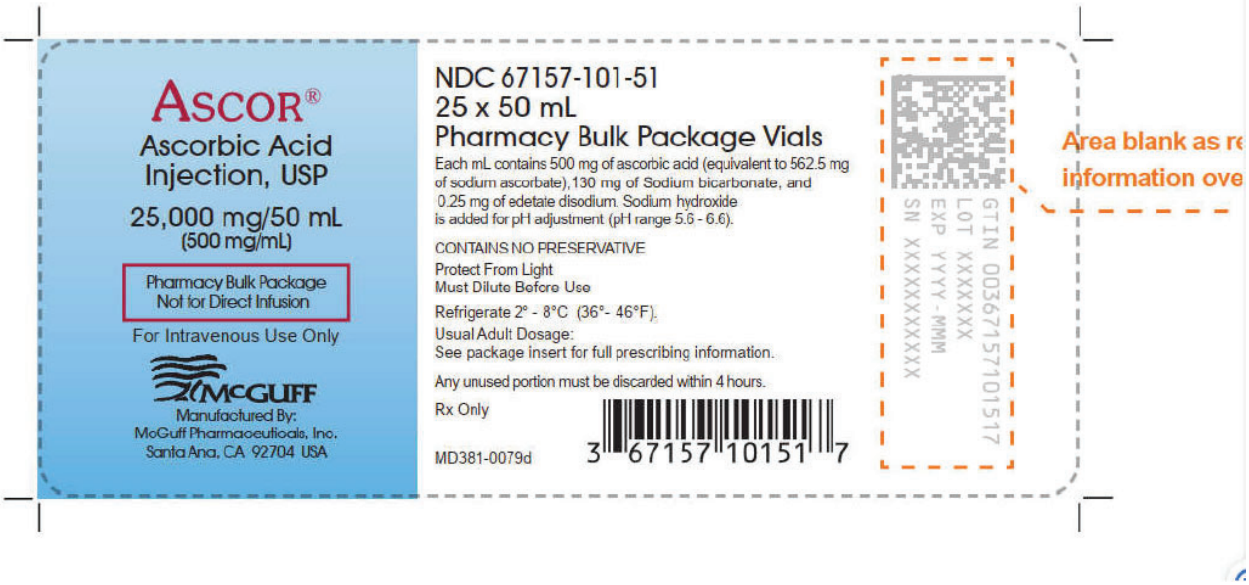
Container label

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton labeling



Tray Labeling



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/

PEGGY M RAHBANI
12/12/2023 11:51:08 AM

MADHURI R PATEL
12/12/2023 11:53:58 AM