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RESEARCH**

APPLICATION NUMBER:

209112Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	9/28/2016
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 209112
Supplement#	
Applicant	McGuff Pharmaceuticals
Date of Submission	9/2/2016
PDUFA Goal Date	10/2/2017
Proprietary Name / Established (USAN) names	Ascorbic Acid Injection/ Sodium ascorbate
Dosage forms / Strength	Ascorbic Acid Injection, 25,000 mg/50 ml (500 mg/ml) solution in a single dose vial
Proposed Indication(s)	Treatment of scurvy
Recommended:	Approval

1. Introduction

On September 2, 2016 McGuff Pharmaceuticals submitted a New Drug Application (NDA) for Ascorbic Acid Injection under Section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act.

The applicant proposed the following indication: *Ascorbic acid injection is indicated for the treatment of scurvy.*

This NDA relies on data derived from published literature to support the claim that intravenous administration of ascorbic acid is safe and effective for the treatment of scurvy; the only study conducted by the Sponsor and included in this NDA is a single-dose PK study to characterize the PK of ascorbic acid after i.v. administration.

The product has been granted orphan designation for the treatment of scurvy.

2. Background

Ascorbic acid (vitamin C) is a water-soluble vitamin present in many plant-based foods such as citrus fruits. Ascorbic acid plays an important role in numerous cellular functions and acts as a reducing agent and as an antioxidant/oxidant. Ascorbic acid is an essential cofactor for enzymes involved in the biosynthesis of blood clotting factors, neurotransmitters, and collagen. Collagen is an essential component of connective tissue. Ascorbic acid has also been shown to play a role in immune function and absorption of iron.

Humans are not able to synthesize ascorbic acid, making it an essential dietary requirement. Thus, vitamin C deficiency may occur in those who does not consume sufficient amount of food containing ascorbic acid for prolonged periods of time (i.e., 2-4 months). Overall, vitamin C deficiency is rare in developed countries, but those with poor dietary intake, including elderly residents of nursing homes, patients with chronic illnesses (e.g., cancer, alcoholism), psychiatric patients that restrict themselves to certain foods, people on restrictive diets, homeless people, etc. are at risk for vitamin C deficiency. Scurvy is less common in the pediatric population, but case reports still appear. Groups at risk include infants who are fed cow or boiled milk, as ascorbic acid is destroyed by heat, and children with dietary restrictions due to psychiatric and developmental disorders.

Vitamin C deficiency can present either as an asymptomatic laboratory finding or as a severe, life-threatening medical condition, scurvy. Tissues such as skin, gums, mucous membranes and bones containing greater concentrations of collagen are more susceptible to vitamin C deficiencies. Thus, the most typical manifestations of scurvy are widespread skin changes (hyperkeratosis, xerosis), coiled hair, capillary fragility, bleeding (e.g., bleeding gums, petechiae, hemarthrosis, subperiosteal hemorrhage), poor wound healing etc. In its most severe presentation, scurvy may result in jaundice, petechiae, joint effusion, oliguria, dyspnea, edema, neuropathy and sudden death if left untreated. The severity of clinical manifestations depends on multiple factors including duration of vitamin C deficiency, degree of depletion of vitamin C stores, pre-existing medical conditions, etc.

Vitamin C deficiency cannot remit spontaneously and an improvement in signs and symptoms of severe vitamin C deficiency requires exogenous repletion of ascorbic acid stores and, to prevent recurrence, correction of the underlying condition that led to the deficiency. In general, supplementation with oral ascorbic acid is sufficient to treat scurvy. However, administration of vitamin C orally might not be always possible in patients who are unable to take drugs/food orally (e.g., patient with intestinal obstruction, inflammatory bowel disease, gastrointestinal bleeding, preparation for surgery, stroke, etc.) In such cases, injectable ascorbic acid is the preferred replacement option. In addition, the absorption of ascorbic acid is decreased in a dose-dependent fashion when administered orally (i.e., to about 50% with single dose > 1 g¹). When ascorbic acid is administered i.v high plasma levels can be attained rapidly, circumventing problems of bioavailability.

Availability of intravenous and oral ascorbic acid formulations:

- Ascorbic acid, oral, is generally recognized as safe (GRAS) and is included as an excipient in multiple FDA approved drug products, as a chemical preservative in foods, and alone or as a combination of marketed dietary supplement ingredients. As per the Food and Nutrition Board of the Institute of Medicine (IOM), National Academies report (2000), the recommended tolerable upper intake levels ULs for ascorbic oral dosing is 2000 mg/day for adults and 400-1800 mg/day for children¹.
- Ascorbic acid injection, USP, 500 mg/ml (Ascor-L 500, McGuff Pharmaceutical) was marketed in the US as an unapproved drug from 2002 through 2010 when it was voluntarily withdrawn to comply with the FDA's Unapproved Drug Initiative. The Ascor L 500 was

¹ Institute of Medicine-Food and Nutritional Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids. Washington, DC: National Academy Press, 2000.

used in doses up to 12 g/day in cancer and critically ill patients, for dietary supplementations, for urinary acidification, for treatment of vitamin C deficiency, etc.

Currently, ascorbic acid is approved and marketed in Canada (Ascor L 500) , Germany (Pascorbin) and New Zealand at doses 100 to 6000 mg daily for the treatment of various conditions including scurvy, “wound healing following extensive surgical procedures”, “when any doubt exists regarding previous nutrition with vitamin in patients with extensive injuries”, “before operations in gastrectomy patients”, etc.

There are five unapproved injectable formulations of ascorbic acid on the US market²; all of them are recommended for the treatment of scurvy. They are also widely used in hospital settings in patients with conditions that “increases need for ascorbic acid”² (e.g., cancer patients, patients with delayed wound healing and burns, patients with critical illness); however, these uses are outside the scope of this application and will not be further discussed.

- Ascorbic acid is a component in FDA approved multivitamin injectable products (Infuvite Adult and Pediatric: NDAs 021163, 021559, 021646, and M.V.I Adult and Pediatric: NDAs 021625, 021643, 018920, 08809). The approved indication for all injectable multivitamin formulations is: “prevention of vitamin deficiency in [patients] receiving parenteral nutrition “. Pediatric formulations are approved in children < 11 years old (daily dose for children contains 52 -80 mg of ascorbic acid) and adult formulations are approved in adults and children > 11 years old (daily dose contains 200 mg of ascorbic acid). The first ascorbic acid drug product approved by the FDA dates back to 1947 per our DARRTs record search.

Regulatory History

The following are the major regulatory interactions that took place between DMEP and the Sponsor regarding the Ascorbic Acid Injection development program for the treatment of scurvy:

Type B meeting (12/13/ 2007)

The Agency indicated that Ascorbic Acid Injection USP was not entitled to grandfather status and provided the overall recommendations regarding the requirements for submission of a literature based NDA for ascorbic acid under section 505(b) (2) of the FDCA. The Agency emphasized that if the Sponsor plans to pursue the indication of scurvy, the Sponsor must provide clinical data supporting the efficacy and safety of the proposed drug regimen; this data may be extracted from published literature. The Agency also agreed that a drug substance DMF is not required in support of the NDA, provided that required CMC information is submitted in the NDA itself. The Agency also reminded the Sponsor that the product will be regulated as a drug when submitted in the NDA and that compliance with cGMP will be required for all manufacturing and testing facilities of the drug substance and drug product.

² <https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=ascorbic+acid>

Type B PNDA meeting (9/22/2011)

- The Agency indicated that some of the planned [REDACTED] (b) (4)
- The Agency disagreed with the Sponsor's plan to [REDACTED] (b) (4)
- Because two published studies were performed in prisoners, the Agency indicated that the consultation with medical ethicists will be requested after the NDA submission in order to determine if these studies will be acceptable as support for approval of the product given the controversies surrounding the issue of whether prisoners can truly give informed consent for medical research.
- The Agency agreed that published literature supporting nonclinical data is acceptable for the NDA submission and nonclinical studies are not required, provided the submitted CMC data provides adequate characterization of Ascorbic Acid Injection.
- The Agency indicated that submission of evidence of in vivo bioavailability or demonstrating the in vivo bioequivalence of the ascorbic acid will be required. The Sponsor may select to characterize the bioavailability of the Ascorbic Acid Injection, USP or to determine the relative bioavailability of the Ascorbic Acid Injection, USP to another oral ascorbic acid formulation.
- The Sponsor planned to [REDACTED] (b) (4)

[REDACTED] The Agency emphasized that the Ascorbic Acid, USP will be API in a prescription drug and, thus, manufacturers of this API will be subject to FDA pre-approval inspections.

The Agency's recommendations on how to characterize the bioavailability of the Ascorbic Acid Injection, USP (email communication from 10/3/2011)

The Sponsor requested further clarification on how to characterize the bioavailability of the Ascorbic Acid Injection, USP. The agency clarified that a PK study will be required to characterize the new formulation the Sponsor intends to market. The Agency also indicated that this study will provide "information related to the intended dosage regimen not potentially resulting in subtherapeutic or toxic levels" and "information to compare your formulation performance to the database containing evidence of safety and efficacy".

Type C meeting (10/23/2014)

During this meeting, a further development program for Ascorbic Acid Injection was discussed between the Agency and the Sponsor:

- The indication for Ascorbic Acid Injection was clarified during this meeting. Agency indicated that treatment of scurvy is a separate indication [REDACTED] (b) (4) and that the application for scurvy can be accepted since "treatment of scurvy results in clearly observable clinical benefit".
- The Agency and the Sponsor discussed that a single-dose PK study with 1000 mg i.v. infusion will be reasonable to characterize PK after i.v. administration, since there is no other product similar to the proposed product on the market.
- The Agency emphasized that the Sponsor will need to provide a direct "bridge" between their product and the products referenced from the literature and "...should take into account differences in formulations, dose and patient population". Lastly, the Agency indicated that

“particular attention [in the NDA] should be paid to dose selection and safety. In addition, the NDA should include clear information about the diagnosis of scurvy, the proposed treatment dose or (b) (4), the duration of treatment...”

IND (b) (4) (submitted on 1/30/2014)

IND (b) (4) was opened with a protocol for a Phase 1 clinical study (MGP-101) to evaluate PK characteristics of a single dose of Ascorbic Acid Injection in healthy volunteers. The Sponsor was allowed to proceed with this study.

Ascorbic Acid Injection was granted Orphan Drug designation for “the treatment of scurvy” on August 31, 2007 by the Office of Orphan Products Development.

NDA submission (11/1/2016)

Ethical Consultation (10/27/2016)

The submitted NDA included data from two published studies evaluating the use of ascorbic acid in prisoners with low-vitamin C diet induced scurvy³ ⁴ and from one study in pacifists/contentious objectors⁵ who were relieved of the required military service obligations in WWII by volunteering for a similar study. Thus, OGCP ethical consultation was requested (as discussed during Type B PNDA meeting on 9/22/201; see above) to evaluate the ethical acceptability of using data derived from these research studies to support this NDA. OGCP reviewers, Kevin Prohaska and Joanne Less, reviewed the submitted trials and historical context in which the trials were conducted and confirmed that all three studies “were designed and conducted in a manner consistent with the ethical standards for human subjects protections that existed at the time the trials were conducted...participation in the Sheffield and Hodges studies was voluntary, informed consent was obtained, subjects were informed of the risks, and subjects were permitted to withdraw...subjects were closely followed to assure safety..” Thus, the reviewers concluded, that “although, these trials would not meet the standards for human subject protections expected of clinical investigations conducted today ... it is ethically acceptable to use the data from these trials in the evaluation of a new drug application”.

User fee goal is extended to 10/2/2017 (Division’s Letter from 6/19/2017)

The Division extended the user fee goal date to 10/2/2017 due to the submission of a major amendment to the application addressing the CMC issues.

Tele-conference (9/26/2017)

The Sponsor and the Agency discussed the excess amount in the product vial containing 50 ml compared to the proposed recommended 0.1-0.4 ml single dose.

The Agency asked the Sponsor to clarify how many patients with scurvy might require treatment with injectable ascorbic acid at the same time at a single hospital in US. The Sponsor

³ Hodges RE, Baker EM, Hood J, Sauberlich HE, March SC. Experimental scurvy in man. Am J Clin Nutr. 1969 May;22(5):535-48.

⁴ Hodges, RE., Hood, J., Canham, JE., Sauberlich, H E., Baker, EM. Clinical manifestations of ascorbic acid deficiency in man. Am J Clin Nutr, 1971, 24(4), 432-443

⁵ Krebs, H. A.. The Sheffield experiment on the vitamin C requirement of human adults. Proceedings of the Nutrition Society, 1953, 12(03), 237-246

clarified that the laboratory tests are not always reliable in the diagnosis of scurvy and the early symptoms and signs of scurvy are nonspecific making a . Thus, due to the difficulty in the diagnosis, more high risk patients (e.g., ICU patients, patients with poor oral intake) might require early treatment with vitamin C. The Sponsor also indicated that ascorbic acid Injection has been on the market for a long time as an unapproved drug and always has been packed in the similar large volume vial (Ascorbic Acid Injection, USP, 500 mg/ml, McGuff Pharmaceutical) and that the repackaging of the drug will require extensive validation of new manufacturing process associated with additional resources and time.

3. CMC/Device

The CMC reviewers recommend approval of this application (refer to Dr. Tran's executive summary). There are no outstanding issues that preclude approval. All facilities inspections have been completed and the Office of Pharmaceutical Quality and Office of Compliance has determined these facilities are acceptable (refer to review in Panorama dated 8/18/2017).

The drug substance is ascorbic acid. The CMC review indicates that the Sponsor refers to DMF (b) (4) for all the CMC information on the API and that DMF (b) (4) is currently adequate. The specification is based on the USP monograph with the (b) (4). The two degradants with limits higher than the applicable ICH qualification threshold (b) (4) (limit of (b) (4)%) and (b) (4) (limit of (b) (4)%) are (b) (4) and are found to be acceptable (confirmed by the Pharmacology Toxicology reviewers).

The drug product, Ascorbic Acid Injection, is a sterile, preservative-free solution to be diluted with 5% Dextrose Injection or (b) (4) Sterile Water for Injection (b) (4); adequate compatibility data are provided). Excipients (per ml) are 0.025 mg of edetate disodium, sodium bicarbonate, sodium hydroxide for pH adjustment (5.6 to 6.6), and sterile water for injection.

The presentation is 50 ml vial. Each 1 mL provides 562.5 mg of sodium ascorbate equivalent to 500 mg of ascorbic acid. The drug product is formulated to have a target concentration of 500 mg/mL. However, ascorbic acid has a solubility limit of 333 mg/mL. Therefore, (b) (4)

CMC and OPQ microbiology reviewers recommend to label the product as a Pharmacy Bulk Package (refer to Addendum to Review #1 in Panorama dated 9/19/2017). As per reviewers, "single dose" [as was requested initially by the Agency] is not appropriate for the product because, the (b) (4) daily dose is 200 mg or 0.4 mL, and the excess amount in the product vial containing 50 mL is not acceptable". However, the reviewers recommend to include additional language in the label stating "that the unused portion of the vial should be discarded within 4 hours and the diluted product should be used immediately" due to the lack of antimicrobial preservatives.

The product manufacturing process consists of (b) (4)

During the manufacturing process (b) (4)

(b) (4) Thus, CMC reviewers recommend to include the following caution statement in the label: “Warning: Pressure may develop within vial upon storage. Exercise care when withdrawing.”

The container closure system, a (b) (4) amber glass vial/bottle, with (b) (4) rubber stopper and (b) (4) cap, was found to be adequate.

An expiry of 12 months was granted when stored at 5 °C temperature. The product lacks an antimicrobial preservative; therefore, the in-use period of the to-be-administered diluted product is limited to 4 hours.

4. Nonclinical Pharmacology/Toxicology

The Sponsor did not conduct nonclinical studies with Ascorbic Acid Injection. Instead, the nonclinical data presented in this application summarizes information from published literature. There are no pharmacology/toxicology approvability issues for this application (refer to the review in DARRTS from 8/29/2017, for details of the nonclinical program).

Drs. Parvaneh Espandari and C. Lee Elmore concluded that data from published nonclinical studies using ascorbic acid up to 2 years in doses up to 2500 mg/kg administered by different routes, including i.v. route, “suggest no safety concerns for the proposed (b) (4) recommended clinical doses in adults, children and infants and safety margins support the proposed doses”.

There is a risk of hyperoxaluria with a potential for an acute oxalate nephropathy and renal stone formation with chronic administration of high doses of ascorbic acid. However, Dr. Espandari indicated that no safety issues were reported with i.v ascorbic acid administration and that the risk of the oxalate nephrocalcinosis and calcium oxalate stones is very low at the proposed doses (published studies demonstrated that infusion of ascorbic acid in doses up to 1.5 g/kg was well tolerated).

Ascorbic Acid Injection has not been evaluated in animal carcinogenicity studies. However, the concerns for tumorigenicity for ascorbic acid is very low because the API in Ascorbic Acid Injection is chemically identical to vitamin C obtained through diet and that published carcinogenicity studies in rodents at high oral doses were negative. Overall, the reviewer concluded that the proposed short-term clinical use of Ascorbic Acid Injection is not considered to carry a genotoxic and carcinogenic risks.

No animal reproduction studies were conducted with Ascorbic Acid Injection. However, reviewers indicated that the reproductive toxicity potential for Ascorbic Acid Injection is low, based on the published literature data. No adverse effects were observed in animals administered supraphysiologic doses of ascorbic acid during the embryo-fetal development and lactation periods.

Ascorbic Acid Injection contains an inactive ingredients, edetate disodium, sodium bicarbonate, water for injection, (b) (4) and sodium hydroxide. The reviewer indicated that all inactive ingredients are within USP/NF standards and below the FDA Inactive Ingredient Database drugs for IV infusion.

No extractables/leachables above the threshold of toxicological concern were identified in the drug product.

The impurities for the final drug product are (b) (4) (b) (4). The total concentration of impurities is higher than acceptable limits based on ICH Q3A and Q3B qualification thresholds. Thus, Dr. Espandiari performed risk analysis for these impurities. The reviewer indicated that there are no safety concerns with (b) (4) and (b) (4) that are (b) (4). There is a concern that (b) (4). However, the reviewers concluded that the proposed levels of (b) (4) (NMT (b) (4) % or (b) (4) mg) for the (b) (4) of proposed Ascorbic Acid Injection is acceptable⁴ and unlikely will be associated with (b) (4). The levels of (b) (4) are within acceptable thresholds for (b) (4) of proposed Ascorbic Acid Injection.

5. Clinical Pharmacology/Biopharmaceutics

Drs. Dipak S. Pisal and Jayabharathi Vaidyanathan note that there are no clinical pharmacology approvability issues for this application. For a detailed discussion, please refer to their Clinical Pharmacology review in DARRTS (8/29/2017).

The majority of clinical pharmacology information is based on the published literature; the only study conducted by the Sponsor with Ascorbic Acid Injection was a Phase 1 single dose study in healthy volunteers to evaluate the PK of i.v. formulation (study MGP-101).

The reviewers confirmed that although the applicant has not conducted any biopharmaceutic studies (comparative BA, or bioequivalence (BE)) to bridge the proposed drug product to the products used in the published literature, the submitted data supports bridging between the proposed drug product and the products used in the published literature. The reviewers concluded that “absolute and relative bioavailability data for ascorbic acid referenced from other studies provided information that can be used from the oral dosage forms used in efficacy trials and bridge to the Pharmacokinetic (PK) study conducted using the MPI Ascorbic Acid Injection, USP IV drug product formulation”.

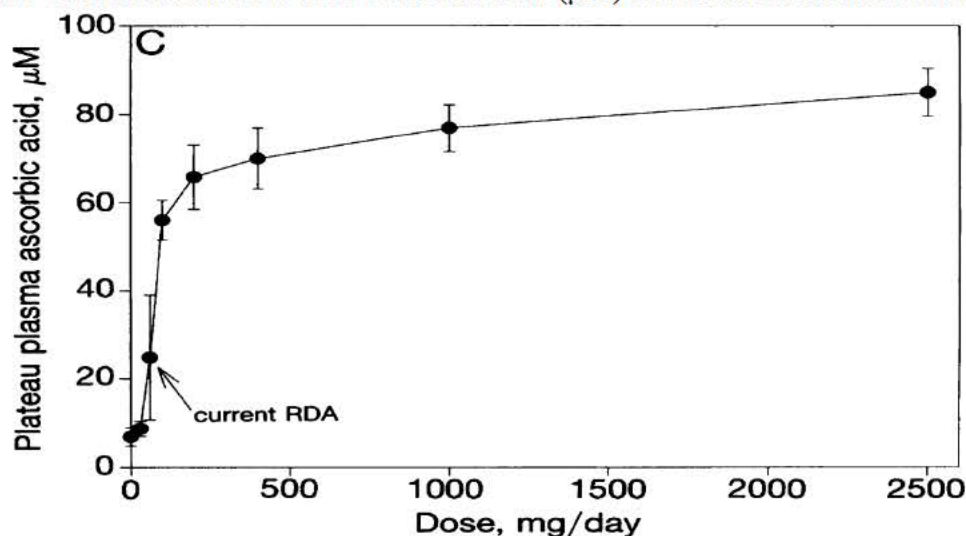
Dr. Pisal concluded that the PK profile of intravenous ascorbic acid has been established in several studies over a wide range of the doses. Overall, data obtained from multiple published studies demonstrated that following oral and intravenous administrations, ascorbic acid kinetics are nonlinear at low doses (<200 mg) and linear at doses > 200 mg. The PK findings are briefly summarized below (refer to Clin. Pharm review for detailed discussion).

- Results from Levine’s study (1996) investigating the PK of multiple i.v. and oral doses (200-250 mg daily) of ascorbic acid administered to vitamin C-depleted subjects demonstrated that serum levels of ascorbic acid reached a maximum plateau at around 75 to 85 µM with

(b) (4)

doses of 200 to 500 mg/day; no further increase in serum concentrations was observed with higher doses (Figure 1).

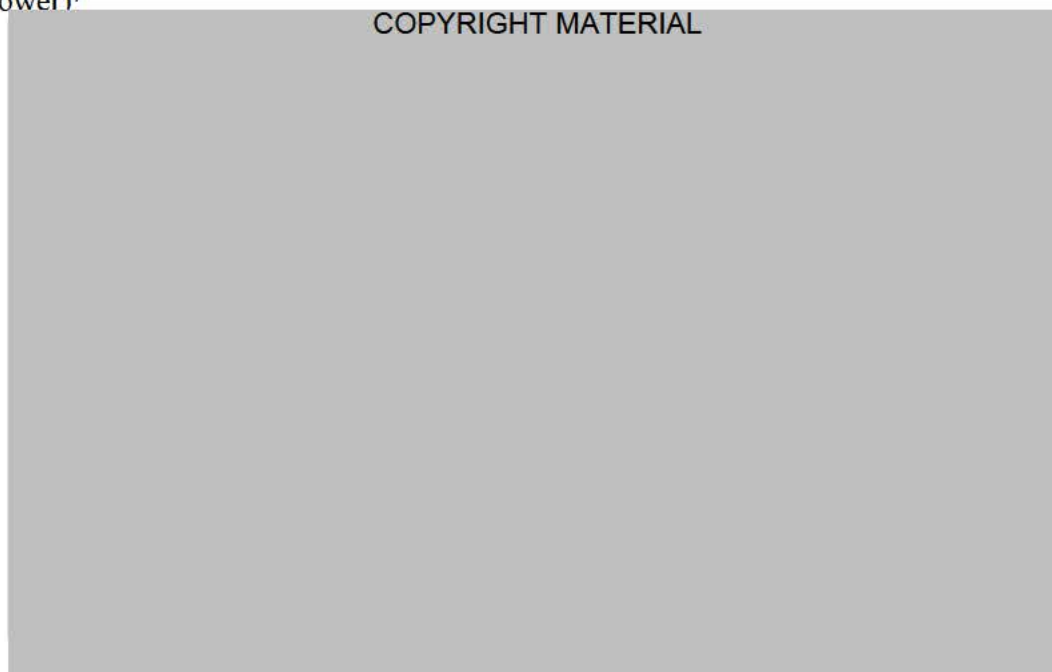
Figure 1. Plasma ascorbic acid concentrations (μM) in volunteers as a function of daily dose.



Source: Clin.Pharm review, page 11

The study also demonstrated comparable kinetics of ascorbic acid doses following oral and i.v. administration at steady state dose levels (Figure 2).

Figure 2. Ascorbic acid bioavailability in plasma for 200 mg dose (*Upper*) and 1250 mg (*Lower*)⁷



⁷ Levine M, Conry-Cantilena C, Wang Y, Welch RW, Washko PW, Dhariwal KR, Park JB, Lazarev A, Graumlich JF, King J, Cantilena LR. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci U S A. 1996 Apr 16;93(8):3704-9.

○- oral doses; ●-i.v. doses; baseline is indicated by dashed lines.

- The PK parameters obtained from studies investigating the use of multiple high i.v. doses of ascorbic acid (5- 187 g)^{8 910} in cancer patients demonstrated t_{1/2} of 1.8-2.5 hours and CL rate ranging from 6.02 L/hr to 2.3 L/hr/m².

- The PK parameters obtained from the Sponsor's PK study using a single i.v. dose of 1000 mg in healthy volunteers are as follows: the mean peak exposure to ascorbic acid is 436.2 μM and occurred at the end of the 30 min infusion, the mean t_{1/2} is 7.4 (±1.4) hr.

- Distribution and elimination:

There is a renal threshold for ascorbic acid; 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. When body tissues are not saturated and plasma concentration is low, administration of ascorbic acid results in little or no renal excretion.

- Metabolism:

Ascorbic acid converts to urinary oxalate- through intermediate formation of its oxidized product, dehydroascorbic acid.

- Drug-drug interactions (DDI)

Drug-drug interactions were not studied in the Ascorbic Acid Injection development program; all information regarding DDI is obtained from the literature. The Sponsor proposed to include information regarding Ascorbic Acid Injection interactions with fluphenazine, amphetamines, and antibiotics in the label. The reviewers recommended that (b) (4) should be deleted; all other information regarding DDI was found to be acceptable.

- Clinical Pharmacology reviewers reviewed the proposed doses of Ascorbic Acid Injection and found these doses to be acceptable for all age groups; the proposed doses are supported by sufficient evidence from published literature.

Based on the results of published studies using ascorbic acid (clinical studies in healthy volunteers and patients with vitamin C deficiency, scurvy, cancers, etc.), PK data from the MGP10 study, and current IOM recommendations regarding tolerable upper intake level, the reviewers concluded that the proposed i.v. daily doses of Ascorbic Acid Injection are associated with an increase in ascorbic acid plasma levels that are expected to normalize the depleted body stores, that “do not exceed the recommended upper intake levels [2000 mg/day],

⁸ Nielsen, T. K., Højgaard, M., Andersen, J. T., Poulsen, H. E., Lykkesfeldt, J. and Mikines, K. J. Elimination of Ascorbic Acid After High-Dose Infusion in Prostate Cancer Patients: A Pharmacokinetic Evaluation. *Basic Clin Pharmacol Toxicol*, 2015, 116: 343–348.

⁹ Padayatty, S. J., Sun, H., Wang, Y., Riordan, et al.. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Annals of internal medicine*, 2004, 140(7), 533-537

¹⁰ Stephenson, C. M., Levin, R. D., Spector, T., & Lis, C. G. Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced cancer. *Cancer chemotherapy and pharmacology*, 2013, 72(1), 139-146.

and that are within the safety margins noted in those treated for scurvy and for the massive IV doses utilized in cancer patients [up to 187 g/day]”.

No PK data are available for the pediatric population. However, Dr. Pisal concluded that the pediatric doses can be extrapolated from adult doses “with downward dose adjustment for weight”, since “the PK and safety of ascorbic acid have been well characterized with oral and IV dosing in adults”. Dr. Pisal indicated that the proposed pediatric doses (b) (4)

Lastly, multiple pediatric studies using ascorbic acid in doses of up to 1000 mg/day reported improvement in scurvy symptoms in 24-hours-5 days (refer to the Clinical Pharmacology review for a detailed discussion on the results of these studies).

- Intrinsic factors that could potentially influence exposure and activity

Age and Hepatic Impairment: The clinical pharmacology reviewers indicated that, based on the information from published literature, no dose adjustment is required for the geriatric population or patients with hepatic impairment.

Renal Impairment: The reviewers also did not recommend dose adjustment in patients with renal impairment, since the proposed doses and duration of treatment are below threshold where hyperoxaluria and renal calculi formation are expected. However, they recommend including a statement in the label that the drug should be used with caution in patients with renal abnormalities and that renal function and oxalate levels should be monitored during treatment in patients at high risk for this complication. In addition, Division of Pediatric and Maternal Health (DPMH) recommended also including in the label the risk of oxalate toxicity in infants due to the renal immaturity.

- Use in Special Populations

Although ascorbic acid may increase absorption of iron when administered orally and thus contribute to iron overload in patients with iron overload disorders (hemochromatosis, thalassemia, major sideroblastic anemia, etc.), the reviewers indicated that this risk is not relevant to the i.v. formulation and recommended no dose adjustment in these patient populations. However, they recommend monitoring iron/ferritin levels (as per standard of care) in patients with these disorders during treatment of scurvy. I disagree with the reviewers’ recommendations and recommend not including monitoring that is not directly relevant to the i.v. formulation in the label.

The reviewers recommend using lower doses of ascorbic acid in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the known risk of hemolytic anemia.

6. Clinical Microbiology

The microbiology review was completed as part of the product quality review. Quality microbiology data was reviewed by Drs. Maria I. Cruz-Fisher and Jesse Wells on 8/02/2017. No concerns were identified by the reviewers.

7. Clinical/Statistical- Efficacy

The data to support the efficacy of Ascorbic Acid Injection for the treatment of scurvy is derived exclusively from published literature including three prospective controlled studies and multiple case reports using ascorbic acid for treatment of scurvy, and PK studies evaluating kinetics of ascorbic acid in healthy volunteers and asymptomatic patients with vitamin C deficiency.

Dr. Lubas reviewed all publications that the applicant submitted to support a determination of efficacy for Ascorbic Acid Injection in scurvy. Overall, the published literature provides the necessary evidence in all age groups to establish that intravenous ascorbic acid injection effectively improves symptoms of scurvy.

Below, I will briefly summarize the data that supports the establishment of efficacy of Ascorbic Acid Injection, at the proposed doses, for adults and children. Refer to Dr. Lubas's review for a detailed discussion of all publications submitted to support the efficacy of ascorbic acid.

Efficacy of Ascorbic Acid Injection in adults with scurvy

The data to support the efficacy of Ascorbic Acid Injection in adults is obtained from 3 controlled prospective (pivotal) studies^{11 12 13} evaluating use of ascorbic acid in prisoners and pacifists with diet-induced scurvy, but healthy otherwise, from studies of ascorbic acid in asymptomatic vitamin C deficient subjects¹⁴, and multiple case reports of ascorbic acid use in patients with scurvy (refer to Dr. Lubas's review for the detailed discussion of the studies). It should be noted that the Agency found the above pivotal studies to be ethically acceptable (refer to Regulatory section above).

Data in the prospective studies "consistently demonstrated that oral administration of ascorbic acid in doses 6.5-128 mg orally was associated with improvement in scurvy symptoms within 1 week of treatment initiation in patients with diet-induced scurvy. Although, these studies used oral formulations of ascorbic acid, Dr. Lubas noted "there is no reason to suspect that intravenous vitamin C...would not be at least as efficacious. Given the current product has

¹¹ Krebs, H. A. The Sheffield experiment on the vitamin C requirement of human adults. Proceedings of the Nutrition Society, 1953, 12(03), 237-246.

¹² Hodges RE, Baker EM, Hood J, Sauberlich HE, March SC. Experimental scurvy in man. Am J Clin Nutr. 1969 May;22(5):535-48

¹³ Hodges, RE., Hood, J., Canham, JE., Sauberlich, H E., Baker, EM. Clinical manifestations of ascorbic acid deficiency in man. Am J Clin Nutr. 1971, 24(4), 432-443

¹⁴ Levine M, Conry-Cantilena C, Wang Y, Welch RW, Washko PW, Dhariwal KR, Park JB, Lazarev A, Graumlich JF, King J, Cantilena LR. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci U S A. 1996 Apr 16;93(8):3704-9.

been chemically confirmed to contain vitamin C and to result in an increase in serum vitamin C levels in healthy volunteers, it is reasonable to assume that it would be effective in the treatment of scurvy even though it has not been tested in patients with active scurvy". Furthermore, Dr. Lubas' conclusion is supported by comparable PK kinetics of oral and i.v. doses as discussed above. The Sponsor's proposed (b) (4) dose (200 mg/day) is supported by data demonstrating that symptoms resolve more rapidly with higher ascorbic acid doses (66.5 and 128 mg/day Hodges et al, 1971); published data also demonstrated that higher doses (200-500 mg/day) may reach faster a maximum serum concentration plateau compared to high oral doses that have decreased bioavailability at doses > 200 mg/day (refer to Clin.Pharm review). Lastly, multiple case reports using i.v. ascorbic acid in doses up to 1500 mg/day for 1-2 weeks consistently demonstrated improvement/resolution of scurvy symptoms.

The Sponsor proposes (b) (4) However, as Clinical and Clin.Pharm reviewers noted, (b) (4)

In conclusion, the applicant's proposed i.v. dose of 200 mg/day appears to be sufficient to replenish the body pool and treat the symptoms of scurvy, and is within the range studied and consistent with doses recommended by medical textbooks¹⁵.

Lastly, intravenous formulations will be most advantageous in patients who are unable to take oral supplements or in patients with a history of gastrointestinal malabsorption. Patients who have an intact GI tract can be treated with oral ascorbic acid formulations and there is no evidence from the published literature to suggest that the i.v. formulation is more effective than oral administration. Thus, I recommend that Ascorbic Acid Injection should be indicated only for the population of patients with limited oral intake and/or impaired GI absorption.

I also agree with Dr. Lubas that diagnosis and monitoring of treatment should be based on signs and symptoms of scurvy rather than on ascorbic acid levels. As demonstrated in the published literature, patients with low ascorbic acid levels are not always symptomatic and low plasma ascorbic acid levels may persist in the recovery phase during treatment when the symptoms begin to improve and/or resolve.

Efficacy of Ascorbic Acid Injection in pediatric patients

The published data to support the efficacy of Ascorbic Acid Injection in children with scurvy was reviewed by Dr. Bill Lubas and by DPMH reviewers (Drs. Elizabeth Durmovicz and Mona Khurana, refer to DPMH review in DARRTS from 9/20/2017).

The reviewers agreed that the efficacy of ascorbic acid in children can be extrapolated from available adult data. Additional evidence of efficacy of ascorbic acid at the proposed doses for treatment of pediatric patients with scurvy is obtained from retrospective review of pediatric

¹⁵ Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015.

patients with scurvy (n=28 cases)¹⁶ and pediatric case reports (n=21). In these publications, children > 5 month old with scurvy were successfully treated with ascorbic acid in doses 100 - 1000 mg/daily (oral and injectable) for up to 3 months. All studies consistently reported resolution of symptoms associated with scurvy within 24-hours-5 days (refer to Dr. Lubas review and DPMH review for details).

The reviewers recommend [REDACTED] (b) (4)

The reviewers recommend approving the [REDACTED] (b) (4) of ascorbic acid for the treatment of scurvy, since data from published literature demonstrated improvement in scurvy symptoms with even [REDACTED] (b) (4) of ascorbic acid and there is insufficient safety data supporting the [REDACTED] (b) (4).

Based on the adult and pediatric data, pediatric data from published literature, recommended dietary allowance (RDA), and tolerable upper intake levels for ascorbic acid (IOM 2000)¹⁷, the recommended doses are as follows: 1 year-11 years - 100 mg/daily, and > 11 years 200 mg/daily. DPMH recommends a more conservative dosing approach for < 12 months age group, because of “the potential for increased ascorbic acid exposure [and toxicity] ...due to the renal immaturity” in this age group; thus, the recommended dose for children 5-12 months old is 50 mg daily. The proposed doses are also in line with doses recommended by textbooks for treatment of scurvy in pediatric patients^{18 19}.

I also agree with reviewers’ recommendation that treatment with Ascorbic Acid Injection should be restricted to patients > 5 months old. Scurvy has not been reported in patients < 5 months old and it is not expected to develop in the first 6 months of life given that children are usually born with sufficient ascorbic acid pools and, thus, are generally protected from scurvy through the first 6 months of life.

8. Safety

Ascorbic acid has a long history of use as a dietary supplement and in different clinical situations. Overall, use of ascorbic acid is associated with low toxicity even at high doses. Ascorbic acid is generally recognized as a safe (GRAS) substance and is included as an excipient in multiple FDA approved drug products, as a chemical preservative in foods, and alone or as a combination of marketed dietary supplement ingredients. A tolerable upper intake level of oral ascorbic acid of 2 g/day established by the Food and Nutrition Board of the National Academy of Sciences (2000) is based on reports of diarrhea and other gastrointestinal disturbances that are not relevant to i.v. administration.

¹⁶ Ratanachu-Ek S, Sukswai P, Jeerathanyasakun Y, Wongtapradit, L. Scurvy in pediatric patients: a review of 28 cases. *Journal of the Medical Association of Thailand*. 2003;86.:S734

¹⁷ Institute of Medicine-Food and Nutritional Board. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids*. Washington, DC: National Academy Press, 2000

RDA (Upper Tolerable Intake Level): 6-12 months- 50 mg/day (not established), 1- 8 years 15-25 mg/day (400-650 mg/day), 9-18 years -45-65 mg/day (1200-1800 mg/day).

¹⁸ Custer JW, Rau RE. eds. *The Harriet Lane Handbook*. 18th ed. Philadelphia, PA: Elsevier Mosby; 2009. 738. *Scurvy: (oral, i.m, i.v, s.c.): child-100-300 mg/daily for at least 2 weeks*

¹⁹ Micromedix Solutions 2.0. <http://www.micromedixsolutions.com>

The Sponsor included data from published literature using oral and i.v. formulations of ascorbic acid in adults and children with vitamin C deficiency, with scurvy, and with other conditions (e.g. cancer, critically ill patients) to support the safety of the proposed doses of Ascorbic Acid Injection in patients with scurvy. These publications were reviewed by Dr. Lubas and discussed in detail in his clinical review (refer to his review for details). Dr. Lubas concluded that no new or unexpected safety signals for ascorbic acid were identified in the literature, although the estimation of the frequency of AEs is complicated due to the limitations of published data (e.g. publications present limited information on safety or on how safety was evaluated during the study).

The Sponsor also included an analysis of adverse events associated with ascorbic acid products approved for use in scurvy and other conditions in Canada, New Zealand and Peru. Dr. Lubas reviewed this data and did not reveal any significant safety concerns with i.v. dosing of ascorbic acid.

Briefly, as per Dr. Lubas, **no** drug-related safety concerns were reported in the studies using ascorbic acid in doses up to 2000 mg/day in adults and in doses up to 1000 mg/day in children > 5 months old with scurvy. Ascorbic acid formulations were safely administered in doses up to 187,000 mg/day administered i.v. to patients with cancer and other serious conditions for up to 3 months.

One of the potential risks associated with administration of ascorbic acid in high doses is an increase in oxalate and uric acid excretion that may precipitate oxalate nephropathy. This complication is related to duration of treatment (> 1 week), doses (> 1000 mg/day) and preexisting medical conditions (e.g., renal impairment, history of kidney stones). In addition, DPMH reviewers stated that pediatric patients < 2 years old may be at increased risk for oxalate nephropathy due to the renal immaturity and recommend including the risk of oxalate toxicity in children with immature renal function in the label. Overall, oxalate-related complications are preventable by administration of the lowest effective dose over a short period of time, monitoring of kidney function in patients at risk, and proper discontinuation of the drug if needed.

There are rare reports of hemolytic anemia during i.v. administration of very high doses of ascorbic acid^{20 21} in patients with glucose-6-phosphate dehydrogenase deficiency (G-6-PD). This adverse reaction is not expected with the Sponsor's proposed (b) (4) doses (50 mg-200 mg) for the treatment of scurvy. DPMH reviewers also confirmed that hemolysis is not expected in healthy infants even at high doses. However, I agree with the recommendation to use (b) (4) doses in the population at risk for development of hemolytic anemia (refer to Clinical Pharmacology review).

The other more common and less severe complications associated with use of ascorbic acid are injection site reactions, headache, fatigue, nausea, vomiting, and transient hypertension that is most frequently caused by rapid administration of high-osmolality solutions. All adverse

²⁰ Campbell Jr, G. D., Steinberg, M. H., Bower, J. D. Letter: Ascorbic acid-induced hemolysis in G-6-PD deficiency. 1975, *Annals of internal medicine*, 82(6), 810.

²¹ Rees, D. C., Kelsey, H., Richards, J. D. Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. *BMJ: British Medical Journal*, 1993, 306(6881), 841.

reactions typically resolve with supportive care. These complications are preventable by administration of a diluted ascorbic acid solution at a slow rate and by appropriate monitoring during ascorbic acid administration.

The Sponsor proposed

(b) (4)

The Sponsor proposed container of Ascorbic Acid Injection is filled with a volume (50 ml) that greatly exceeds the recommended daily doses (0.1-0.4 ml). It is unlikely that ~200 patients in a single hospital would ever need ascorbic acid at once. The risks associated with use of large volumes single use drug product like Ascorbic Acid Injection (overdose, microbial contamination, medication errors, off-label use) were discussed in details in the CMC, clinical, DPMH and DMEPA reviews (refer to corresponding reviews in DARRTS). All reviewers agreed that these risks are mitigated through the proper labeling of the product and through clear dosage and administration instructions. The reviewers also searched the FAERS database and did not identify any medication error cases attributable to the packaging. I agree that the risk of overdose is low considering wide safety margins of vitamin C and that **no** drug-related safety concerns were reported in the studies using ascorbic acid in doses up to 2000 mg/day in adults and in doses up to 1000 mg/day in children > 5 months old with scurvy and in doses up to 187,000 mg/day in patients with cancer or in post-marketing reports. I therefore do not believe that re-packaging is absolutely required for approval. Further, it is unlikely that the applicant would repackage this drug and FDA may lose its opportunity to bring this marketed unapproved drug into compliance. While the packaging is not optimal, I believe it is in FDA's and the public's best interest to bring this drug into regulatory compliance. I recommend that the Sponsor consider nevertheless repackaging the product in smaller volume vials in the future so that the vial size more closely approximate the recommended use. We will monitor post-marketing reports for medication errors related to vial size through our ongoing routine pharmacovigilance efforts and revisit this issue if the need arises.

Drs. Lubas, Durmowicz and Khurana concluded that the application provided sufficient data on the safety profile of the drug at the proposed dose in all age groups to be included in the label. Overall, the safety profile of ascorbic acid at the proposed doses is well understood and there is extensive clinical experience with the use of oral and injectable ascorbic acid for the treatment of scurvy. More importantly, the risks associated with the use of ascorbic acid can be adequately mitigated through product labeling, appropriate population and dose selection.

Finally, I am in agreement with Dr. Lubas that the benefits for the dosing regimen proposed outweigh the risks.

²² Institute of Medicine-Food and Nutritional Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids. Washington, DC: National Academy Press, 2000

9. Advisory Committee Meeting

The AC meeting was not need to seek input from the Advisory Committee for any issues in this application and a meeting was not held.

10. Pediatrics

Ascorbic Acid Injection has received orphan-drug designation on July 22, 2016 for “treatment of scurvy”. Therefore, the requirements of the Pediatric Research Equity Act do not apply to this application. However, the Sponsor proposes to include information regarding pediatric doses in patients (b) (4) months old with scurvy in the label (refer to the discussion above).

11. Other Relevant Regulatory Issues

None

12. Labeling

Proprietary name

The proposed proprietary name, Ascor, was found to be acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on November, 18, 2016.

Labeling

The label was reviewed by the Division of Pediatric and Maternal Health (refer to reviews in DARRTS from 9/20/2017 and 9/19/2017) and by the Division of Medication Error Prevention and Analysis (DMEPA) (refer to review in DARRTS from 3/15/2017).

The following major recommended changes to the label were made:

- The indication should be restricted to adult and pediatric patients with scurvy who cannot take oral formulations of ascorbic acid or have impaired GI absorption. Patients with intact GI tract can be successfully treated with oral formulations.
- Limitation of use should be included in the label stating that the drug should not be used for treatment of vitamin C deficiency without symptoms and signs of scurvy. Vitamin C insufficiency is not a well-defined entity and there isn't sufficient evidence that restoration of vitamin C levels in asymptomatic patients is associated with clinical benefit.
- (b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval as benefits of use outweigh the risks

I recommend that the proposed indication for Ascorbic Acid Injection be modified as follows (pending the agreement on the final labeling language):

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.

Distinguishing between patients with impaired oral intake and GI absorption from patients with intact GI tract is critical for determining the appropriate form of therapy. In patients who are unable to take ascorbic acid orally, the administration of ascorbic acid by i.v. infusion is the only way to replete body stores and treat symptoms. In contrast, oral treatment in patients with an intact GI tract is more appropriate because incurring the risks associated with infusion is not justified.

I recommend that Ascorbic Acid Injection be indicated for short term treatment only, to avoid potential safety issues associated with longer use (e.g. oxalate stones). Published data demonstrated that 1 week treatment with ascorbic acid is sufficient to improve scurvy symptoms, although the complete resolution of symptoms may take longer it isn't clear that additional ascorbic acid is required. Thus, patients should be monitored until the resolution of symptoms and should be retreated with ascorbic acid (oral or i.v.) as needed.

Indication should be restricted to adults and pediatric patients > 5 months old, since scurvy is not expected to develop in the first few months of life for the reasons described above in this memorandum and there are no published reports of scurvy in children < 5 months.

- Risk Benefit Assessment

Benefits:

As indicated in the body of this memorandum, scurvy may be associated with life-threatening medical complications if left untreated. The natural history of scurvy is predictable and the depleted vitamin C body pool and associated symptoms of scurvy cannot be corrected spontaneously without timely exogenous ascorbic acid administration. In the setting of tissue depletion of vitamin C, exogenous ascorbic acid repletes body stores and improves signs and symptoms of scurvy. It is thus self-evident that this drug's benefit lies in its ability to prevent the serious life-threatening medical complications caused by depletion of tissues of ascorbic acid.

The data from the submitted published literature demonstrated that ascorbic acid at (b) (4) proposed in the label effectively treat symptoms of scurvy by repletion of the body ascorbic acid pool in all age groups. These data provide sufficient information to conclude that the benefits of Ascorbic Acid Injection in patients with scurvy outweigh the risks associated with the drug. The effect of ascorbic acid on symptoms and signs of scurvy is consistent across all studies. The recommended doses are also in line with doses recommended by medical textbooks and used in practice for the treatment of scurvy.

Risks:

Ascorbic acid is associated with low toxicity at the proposed doses. The potential risks associated with oral and injectable ascorbic acid formulations are well recognized. The most common adverse reactions associated with ascorbic acid infusion include injection site reactions, fatigue, nausea, and headache. Dilution of the drug product, rotation of intravenous sites and timely discontinuation of the infusion when appropriate mitigates these risks.

The most serious risks associated with parenteral ascorbic acid infusion at high doses are oxalate nephropathy and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. The overall risk of these AEs is low in patients with scurvy when the drug is used at doses 50 mg-200 mg for < 1 week. More importantly, these risks can be mitigated by using the lowest dose for the shortest period of time, appropriate monitoring of populations at risk, and by communicating these risks through labeling.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

The Sponsor should consider repackaging Ascorbic Acid Injection to ensure the size of the packaging is consistent with how this drug will most likely be used in the care setting (i.e., dispensing a single dose to a few patients at once).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARINA ZEMSKOVA

09/30/2017

JEAN-MARC P GUETTIER

10/02/2017

Dr. Zemskova's review serves as the Summary Basis for approval. The product was a "marketed unapproved drug" and the applicant was encouraged by FDA to obtain the required evidence necessary support use of the drug for the intended indication and to submit an application. The application brings this drug into compliance as the applicant has provided the evidence necessary to establish the efficacy and safety of ASCOR (ascorbic acid injection), for intravenous use, when used as recommended in the product labeling, 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.