CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209112Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505 (b)(2)
Application Number(s)	209112
Priority or Standard	Standard
Submit Date(s)	September 2, 2016
Received Date(s)	September 2, 2016
PDUFA Goal Date	October 2, 2016 due to major amendment received June 12, 2017.
Division / Office	DMEP/ODEII
Reviewer Name(s)	William Lubas, M.D., Ph.D.
Review Completion Date	September 22, 2017
Established Name	Sodium ascorbate
(Proposed) Trade Name	Ascor injection, 500 mg/mL
Therapeutic Class	Vitamin C
Applicant	McGuff Pharmaceuticals
Formulation(s)	Injection
Proposed Dosing Regimen	• (b) (4) • (b) (4)

- [redacted]
- [redacted]
- Dose Adults and Children age 11 years old or older- 200 mg [redacted]

Indication(s)	Treatment of scurvy
Intended Population(s)	Children > [redacted] months of age and adults with scurvy

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval in adults and pediatric patients 5 months of age and older for the treatment of the signs and symptoms of scurvy

1.2 Risk Benefit Assessment

The published literature including the pivotal efficacy trials of Krebs 1953 and Hodges et al. 1969 & 1971 showed that oral doses as low as 6.5 to 10mg/day of ascorbic acid were adequate to treat scurvy. However, higher doses of ascorbic acid such 66.5mg/day to 128mg/day, resulted in more rapid resolution of symptoms. While it is possible that even higher doses above 128mg/day may further improve the rate of recovery, it is likely that there is a limit to the benefit expected from higher doses so that at some point further dose increases would be expected to have minimal effect as the body pool becomes sufficiently saturated. It must also be considered that while repletion of body stores may be more rapid with higher doses, there is a limit as to the resolution of clinical symptoms as they require resynthesis of normally hydroxylated collagen and replacement of the abnormal collagen in damaged tissues, which may take weeks to months for complete recovery depending on the organ involved (e.g. skin, hair, gums or bone). The question therefore arises as to what is the appropriate dose of Ascor for the treatment of scurvy in different study populations, taking into account rapid repletion of body pools, without prescribing excessive doses which will eventually only end up being renally excreted. In this regards pharmacokinetic work by Levine et al. 1996 & 2001 helps provide justification for dose selection.

Levine et al. 1996 & 2001, showed that at oral doses up to 200mg/day there is maximal bioavailability, so that up to 100% of the ascorbic acid ingested is absorbed, but bioavailability decreases with higher oral doses, down to 33% for a single dose of 1250mg. With repeat daily dosing serum ascorbic acid levels reach steady state plateaus in the range of 75 to 85μM in both men and women at doses of 200mg/day and above[1]. As steady state levels plateau off at doses above 200mg/day there is limited benefit in efficacy with higher oral doses, (i.e. there is only a small 10% or so further increase in serum steady state ascorbic acid levels with higher oral doses even up to 2500mg/day). Given that most of the case reports of treatment of adult scurvy occurred with oral dosing and used doses between 250 and 2000mg/day the steady state serum levels in these cases were probably in the same range as would be expected with intravenous administration of 200mg/day of ascorbic acid. Therefore, the

1 See data from Levine et al. 1996 and 1971 presented in this review in Figure 1

intravenous dose of 200mg/day can be expected to be as effective as most treatments reported in the literature and is the adult treatment dose recommended for the treatment of scurvy by this medical reviewer. Considering that scurvy represents a case of severe vitamin C deficiency it seems appropriate that the treatment dose should be greater than the currently recommended maintenance dose and 200mg/day represents roughly double the Recommended Daily Associate (RDA) for adults which range from 75 to 125mg/day. While higher doses might be justified under certain conditions, for example a known rapid metabolizer, there is likely limited benefit in the vast majority of cases, and even though the risk for adverse reactions is still very small at higher doses such as 1000mg/day to 2000mg/day there is no clear advantage from such doses to justify any additional safety risk.

While children with scurvy have been safely treated with oral ascorbic acid doses of 100 to 1000mg/day, there is no similar pharmacokinetic data in children to help support dosing. Guidelines from the Harriet Lane Handbook (2012 edition) for pediatric dosing recommend 100 to 300mg/day either orally, intramuscularly, subcutaneously or intravascularly, without citing a primary source for these recommended doses. In general the RDA or Adequate Intake (AI) doses of ascorbic acid in children for daily maintenance are about half the adult maintenance dose. Assuming this relative two-fold difference in maintenance dosing between children and adults can be used to adequately control for the different dosing needs in children due to differences in body weight, metabolism, excretion, etc., then children who receive adequate maintenance levels of ascorbic acid with half the adult daily maintenance dose should also be effectively treated for scurvy at half the proposed adult dose of 200mg/day or 100mg/day. Therefore, this medical reviewer is recommending a dose of 100mg/day for pediatric patients age 5 months to 14 years. For older adolescent children 14 to 18yrs who require a higher maintenance dose of 75mg/day it is probably reasonable to recommend the adult dose of 200mg/day which is closer to double their daily maintenance dose.

With respect to safety, oral doses up to1000mg/day of ascorbic acid, which are more than adequate to replenish the body stores needed to prevent scurvy in one day (i.e. 300mg), have been shown to be safely given to children and adults with scurvy. In fact the tolerable upper intake level (UL) for ascorbic acid of 2000mg/day in adults and 440-1800mg/day in children is based primarily on the concern over gastrointestinal disturbance due to osmotic diarrhea, and even higher doses of ascorbic acid which would not produce the same gastrointestinal effects can be given safely intravenously. As such, intravenous doses up to 187,000mg/day have been given for off-label uses with the primary safety concerns being:

- an increase in urinary excretion of oxalic acid, a vitamin C metabolite, at doses above 1500mg/kg/day, equivalent to 105,000mg/day for a 70kg adult, which increases the risk for calcium oxalate kidney stones/oxalate nephropathy[2] and
- hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency[3] due to lower amounts of reduced glutathione in G6PD deficient red blood cells making them more susceptible to oxidative stress with ascorbic acid infusions above 25,000mg[4].

Such high intravenous doses while relatively safe for most individuals are not necessary for the proposed indication as demonstrated by the effectiveness of the very low doses used in the pivotal studies described above and by multiple case reports of effective oral treatment of scurvy with doses of 250 to 2000mg/day in adults and 100 to 1000mg/day in children. In general, oral therapy has been the treatment of choice in the literature, because of its ease of administration and demonstrated effectiveness, but there are also confirmed case reports of effective treatment of scurvy with intravenous doses of 200 to 1000mg/day in cases where that was considered necessary. Therefore, there is more than adequate safety data to support the recommended intravenous treatment doses of 200mg/day in adults and pediatric patients 14 years of age and older and 100mg/day in children 5 months to 14 years of age.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2 Phase I clinical trial of i.v. **ascorbic acid** in advanced malignancy. **Hoffer** LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L, Miller WH Jr. Ann Oncol. **2008** Nov;19(11):1969-74.
3 Acute **haemolysis** induced by high dose **ascorbic acid** in **glucose-6-phosphate** dehydrogenase deficiency. Rees DC, Kelsey H, Richards JD. BMJ. 1993 Mar 27;306(6881):

4 https://en.wikipedia.org/wiki/Glucose-6-phosphate_dehydrogenase_deficiency

2.1 Product Information

Ascorbic acid is an essential coenzyme for collagen formation, tissue repair and synthesis of lipids and proteins. Deficiency in vitamin C (ascorbic acid) results in the clinical syndrome of scurvy. Most otherwise healthy individuals have enough body stores to last about 2-4 months before symptoms of scurvy appear after starting a restricted diet deficient in ascorbic acid. In the United States, vitamin C deficiency is seen primarily in the poor, the elderly, tobacco smokers, alcoholics, and in individuals consuming unusually restrictive diets (e.g. rice, oils, bread and water).

Early symptoms include generalized fatigue, muscle and joint pain and weakness. These are followed by the classic skin, hair and gum findings which include: hyperkeratosis, perifollicular hemorrhage, ecchymosis, coiled body hairs and bleeding edematous gums. As the disease progresses there is poor wound healing and subjects can develop edema, fever, seizures, bone lesions and sudden death.

2.2 Currently Available Treatments for Proposed Indications

Treatment options include vitamin C containing supplements which are widely available over the counter. These include oral formulations as well as marketed but unapproved IV formulations (e.g. Mylan). Prescription based products include multivitamin formulations used to prevent vitamin deficiencies in subjects on chronic total parenteral nutrition (TPN) (e.g. INFUVITE ADULT, INFUVITE PEDIATRIC, M.V.I. ADULT and M.V.I. PEDIATRIC). Foods rich in vitamin C including most fruits and green leafy vegetables could also adequately contribute to providing a diet sufficient in vitamin C to treat or prevent the onset of scurvy.

2.3 Availability of Proposed Active Ingredient in the United States

See section 2.2.

2.4 Important Safety Issues With Consideration to Related Drugs

According to the Food and Nutrition Board, Institute of Medicine, National Academies report (IOM 2000) the recommended tolerable upper intake levels ULs for ascorbic oral dosing is 2000 mg/day for adults and 400-1800 mg/day for children, primarily based on osmotic diarrhea and gastrointestinal disturbances noted with higher oral doses and so is not relevant to the current IV formulation. A UL specific for intravenous dosing has not been defined but high daily doses > 500mg/day above can result in increased oxalic acid production and acidification of the urine both of which can promote kidney stone formation. Patients with glucose-6-phosphate dehydrogenase deficiency (G-6-PD) can develop a hemolytic anemia in response to IV ascorbic acid. According to the applicant ascorbic acid containing IV products are approved in other countries for use in children at doses from 35 to 500 mg/day and in adults at doses from 100 to 2000 mg/day.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In a Written Response issued Sept. 22, 2011 to the applicant's meeting request, the Division informed the applicant that the (b) (4) was not an appropriate reference drug product for a 505(b)(2) submission for their proposed drug product (b) (4) (b) (4)

A telecommunication was performed with the applicant on Oct. 16, 2014. During the meeting the Division informed the applicant that the Agency sees treatment of scurvy as a separate indication (b) (4). Treatment of scurvy results in clearly observable clinical benefit, while (b) (4) . The Agency was open to accepting an application for the treatment of scurvy but any application (b) (4) McGuff Pharmaceuticals responded that they understood the Agency's position and would only seek an indication for the treatment of scurvy in their NDA.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall submission quality is adequate.

3.2 Compliance with Good Clinical Practices

The pivotal studies were performed in accordance with clinical practice at the time they were designed.

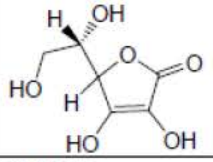
3.3 Financial Disclosures

Not applicable to this application, as the sponsor had no role in the design or execution of the pivotal studies from the published literature (i.e. Krebs 1953, and Hodges et al. 1969 and 1971).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Ascorbic Acid Chemical Structure

	Chemical Name: (2R)-2-[(1S)-1,2-Dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one
Structure	
Molecular Formula	$C_8H_8O_6$
Molecular Weight	176.1

The drug product is Ascorbic Acid Injection, a sterile, preservative-free solution to be diluted with 5% dextrose or Sterile Water for Injection (b) (4) for intravenous injection. Each 1 mL provides 562.5 mg sodium ascorbate, equivalent to 500 mg ascorbic acid. Excipients (per mL): 0.25 mg edetate disodium, sodium bicarbonate (b) (4)), water for injection ((b) (4)), and sodium hydroxide for pH adjustment to pH 5.6-6.6.The product is packaged in a 50 mL vial (containing 25 g ascorbic acid). The product is stable for 12 months at 5 °C. It is temperature-sensitive so it should not be stored at room temperature. (b) (4) .

The final OPQ recommendation is for Approval, including the overall manufacturing inspection recommendation.

> Medical officer's comment-
> Given that the dose (b) (4) proposed for this product is (b) (4) which can be given with (b) (4) there was concern that the large 50mL bottles might lead to dosing errors, or encourage misusing of the drug, with multiple entry into a container which contains no preservative, because of the large residual left over after removing a single dose. However, as the product will be labeled with Pharmacy Bulk Package (PBP) language and must be diluted prior to use, the specific procedures a pharmacist uses in dispensing PBP drug products should ensure that only a single appropriate aliquot is taken from the bottle when an appropriate diluent is admixed during the preparation of the to-be-administered intravenous infusion solution.

4.2 Clinical Microbiology

The product lacks an antimicrobial preservative; therefore, the in-use period of the to-be-administered diluted product is limited to four (4) hours. Given that it is to be marketed for single use administration antimicrobial effectiveness testing was not required. The endotoxins dose at the proposed endotoxins specification and (b) (4) dose as calculated by the microbiology reviewer is within the USP <85> recommendation of (b) (4) EU/kg/hr for intravenous administration.

The submission is recommended for approval on the basis of sterility assurance.

4.3 Preclinical Pharmacology/Toxicology

No nonclinical studies were conducted to support this 505(b)(2) marketing application for Ascorbic Acid Injection. Findings from nonclinical studies in the public literature support treatment with adequate safety margins at the proposed doses. The Pharmacology/Toxicology review by Dr. Espandiari recommends approval of Ascorbic Acid Injection for the treatment of scurvy.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ascorbic acid plays an essential role in the hydroxylation of collagen which is necessary for stabilizing the collagen triple helix. Tissues such as skin, gums, mucus membranes and bones contain a greater concentration of collagen and as such are more susceptible to deficiencies. Treatment of patients with scurvy restores the vitamin C pool which contributes to the repair of these damaged tissues.

Subjects at risk of scurvy are those with an inadequate intake (e.g. malnourished individuals, individuals eating highly restricted fad diets, alcoholics, anorexics, etc.), increased requirement (e.g. following recent surgery, serious infection, burn or trauma, smokers and dialysis patients, etc.) or decreased absorption (gastrointestinal malabsorption, short gut syndrome, etc.).

4.4.2 Pharmacodynamics

The pivotal efficacy trials of Krebs 1953 and Hodges et al. 1969 & 1971 showed that oral doses as low as 6.5 to 10mg/day of ascorbic acid were adequate to treat scurvy. Resolution of skin and hair symptoms begins with treatment within 1 to 2 weeks and is typically complete by 7 to 9 weeks in patients treated with 10mg/day of vitamin C. Gum swelling/lesions take longer to improve and may not normalize until 10 to 14 weeks after

the initiation of treatment with 10mg/day of vitamin C. However, higher doses of ascorbic acid such 66.5mg/day to 128mg/day, resulted in more rapid resolution of symptoms. While it is possible that even higher doses above 128mg/day may further improve the rate of recovery, it is likely that there is a limit to the benefit expected from higher doses so that at some point further increase would have minimal effect as the body pool becomes sufficiently saturated. It must also be considered that while repletion of body stores may be more rapid with higher doses, there is a limit as to the resolution of clinical symptoms as they require resynthesis of normally hydroxylated collagen and replacement of the abnormal collagen in damaged tissues, which may take weeks to months for complete recovery depending on the organ involved (e.g. skin, hair, gums or bone).

4.4.3 Pharmacokinetics

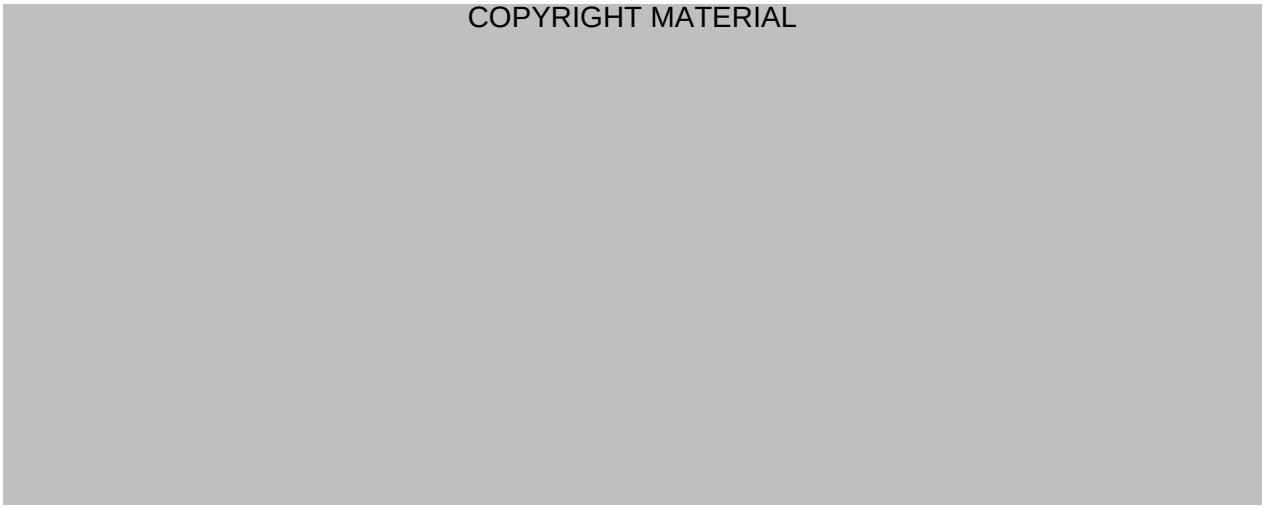
Levine et al. 1996 (in men)[5] and Levine et al. 2001 (in women)[6]
Vitamin C pharmacokinetics was studied in seven men age 20 to 26 years Levine et al. 1996 and in fifteen women ages 19 to 27 years Levine et al. 2001. Subjects were hospitalized for 4 to 6months on a diet low in ascorbic acid (< 5mg/day) in order to reduce vitamin C concentrations to 5 to 10μM (0.08-0.15mg/dL) without inducing scurvy. Subjects noted mild fatigue and irritability at the nadir of depletion which disappeared several days after the start of 30 or 60mg daily dosing. No other classic symptoms of scurvy were reported. After reaching an ascorbic acid nadir subjects were started on sequential repletion protocols with 15, 30, 50,100, 200, 500 and 1250mg of ascorbic acid dosed twice daily in the fasting state. Doses were maintained at each level until serum levels of ascorbic acid had reached steady-state plateaus. Steady state levels at each dose are shown in the following figure, with data from men in the left panel and data from women in the right panel. No adverse events were reported following IV doses up to 2500mg/day. While there was a trend for an increase in excretion of oxalate at higher doses which could potentially increase the risk for renal calculi, the increase at 1000mg/day was not statistically significantly higher than seen at 400mg/day and was still within the reported normal range. Data was not available for the 2500mg/day dose.

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

6 A new recommended dietary allowance of **vitamin C** for healthy young women. **Levine** M, Wang Y, Padayatty SJ, Morrow J. Proc Natl Acad Sci U S A. 2001 Aug 14;98(17):9842-6.

Figure 1 Steady-State Ascorbic Acid Serum Levels Based on Daily Dose

Left Panel Levine et al. 1996 in Men /Right Panel Levine et al. 2001 in Women



Bioavailability, comparing serum levels following oral and intravenous dosing, was measured at each steady-state dose level. Serum levels plateaued at each oral dose level at around 25 to 40 days. Serum levels reached a final maximal plateau in both men and women at around 75 to 85μM with doses of 200 to 500mg/day. Bioavailability was up to 100% for a single oral dose of 200mg but only 33% for a single oral dose of 1250mg due to increased renal excretion at the higher doses. Note the serum level at the current RDA is around 25μM (0.38mg/dL) or about 1/3 the maximum level that can be achieved with oral dosing.

Study MGP-101

The applicant submitted a Phase 1, single-dose PK study in 8 healthy volunteers (4 male and 4 female) ages 29 to 44 years. All subjects received a single dose of 1000 mg of ascorbic acid intravenously administered as a 20 mg/ml ascorbic acid solution (1000 mg in 50 mL dextrose 5% in water) infused over 30 minutes.

Ascorbic Acid deficient meals/snacks were available during the following study intervals:

(1) -120 minutes pre-dose to be consumed at least 30 minutes pre-dose,
(2) after the post-infusion +2 hour sample was taken and to be consumed before +3 hour sampling,
(3) after the post-infusion +6 hour sample was taken and to be consumed before +7 hour sampling and,
(4) after the +8 hour sample was taken and to be consumed before the +10 hour sampling.

Mean peak exposure to ascorbic acid was 436.173 μM and occurred as expected at the end of the infusion. Mean total exposure to ascorbic acid was 1340 μM*hr. Mean peak exposure to baseline-subtracted ascorbic acid was 395.287 μM and mean total

exposure to baseline-subtracted ascorbic acid was 912 µM*hr. The mean Cmax (baseline-subtracted) in women, 517.7 µM, was higher than that observed in men, 269.9 µM, which may be related to the smaller size of the women, lower weight (mean 141 vs. 182lbs) and lower BMI (22.2 vs. 26.2). Terminal elimination rate constants could not be reliably estimated in all patients in order to calculate AUC_{inf}, $T_{1/2}$, and CL. The terminal half-life ($T_{1/2}$) and clearance level (CL) estimated in 4 out of 8 subjects were 14.25 hr and 2.39 (L/hr), or in 3 out of 8 baseline-subtracted ascorbic acid subjects were 7.45 hr and 5.34 (L/hr), respectively. The only adverse reaction was a mild headache reported in one subject.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study No	Study Title
MGP-101	A Phase 1, Single-Dose Study to Evaluate the Pharmacokinetics of Intravenous Ascorbic Acid in Healthy Male and Female Volunteers

5.2 Review Strategy

This is a 505 (b) (2) application relying on data derived from the published literature for efficacy and safety. The pivotal studies include one article (Krebs 1953) in healthy pacifists volunteers who were relieved of their required military service obligations in WWII by volunteering for the study in which they developed scurvy by eating a diet deficient in vitamin C and two published studies (Hodges et al. 1969 and 1971) evaluating the use of vitamin C in prisoners who were also given diets low in vitamin C in order to induce scurvy and then had their recovery monitored as they were started on low doses of vitamin C to reverse the symptoms. Because of the ethical concerns about using these studies for an NDA approval an ethics consult was obtained during the review of this application. In his ethics review Kevin Prohaska at the Agency determined that these studies were designed and conducted in a manner consistent with the ethical standards for human subject protections that existed at the time the trials were conducted. Participation was voluntary, informed consent was obtained, subjects were informed of the risks, were permitted to withdraw, and were closely followed to assure safety until all symptoms of scurvy resolved. Therefore it was determined that it would be ethically acceptable to use the data from these trials in the evaluation of a new drug application.

Supportive studies that were reviewed included the PK studies of Levine et al. 1996 and 2001 which provide information on dosing requirements to provide sufficient saturation of ascorbic acid plasma and body pools, the study of Ratanachu-Ek et al. 2003

describing pediatric patients treated for scurvy in Thailand, and the reports from Grewar 1965 which dealt with case reports of infantile scurvy in Canada.

5.3 Discussion of Individual Studies/Clinical Trials

The sponsor performed one phase 1, single dose, PK study in healthy volunteers, MGP-101 in support of this application. This was not a bioequivalence study as the current formulation is for IV administration and there is no approved IV ascorbic acid product for comparison. There were no sponsor-conducted studies to support the safety and efficacy of ascorbic acid in the treatment of scurvy, instead all data to support this indication is derived from published literature. The pivotal trials supporting safety and efficacy consist of the depletion/repletion studies published by Krebs 1953[7] and Hodges et al. 1969[8] and 1971[9]. In addition the case reports in the published articles of Ratanachu-Ek et al. 2003 and Grewar 1965 are used to support efficacy in the treatment of pediatric patients. Additional studies using much high intravenous doses for other unapproved indications are also used to support the safety of the proposed doses: Fowler 2014[10], Hoffer 2008[11], Padayatty 2010[12], Stephenson 2013[13], Nielsen 2015[14], and Ludvigsson 1977[15].

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

8 Hodges, R. E., Baker, E. M., Hood, J., Sauberlich, H. E., March, S. C. (1969). Experimental scurvy in man. The American journal of clinical nutrition, 22(5), 535-548.

9 Hodges, R. E., Hood, J., Canham, J. E., Sauberlich, H. E., & Baker, E. M. (1971). Clinical manifestations of ascorbic acid deficiency in man. The American journal of clinical nutrition, 24(4), 432-443.

10 **Fowler** AA 3rd, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S; Phase I safety trial of intravenous **ascorbic acid** in patients with severe sepsis. Medical Respiratory Intensive Care Unit Nursing, Fisher BJ, Natarajan R. J Transl Med. 2014 Jan 31;12:32.

11 **Hoffer** LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L, Miller Phase I clinical trial of i.v. **ascorbic acid** in advanced malignancy. WH Jr. Ann Oncol. 2008 Nov;19 (11):1969-74.

12 **Padayatty** SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. **Vitamin C**: intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One. 2010 Jul 7;5(7):

13 **Stephenson** CM, Levin RD, Spector T, Lis CG. Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous **ascorbic acid** in patients with advanced cancer. Cancer Chemother Pharmacol. 2013 Jul;72(1):139-46.

14 **Nielsen** TK, Højgaard M, Andersen JT, Poulsen HE, Lykkesfeldt J, Mikines KJ. Elimination of **ascorbic acid** after high-dose infusion in prostate cancer patients: a pharmacokinetic evaluation. Basic Clin Pharmacol Toxicol. 2015 Apr;116(4):343-8

6 Review of Efficacy

Efficacy Summary

Scurvy had long been known as a problem for sailors during extensive sea voyages until the work of James Lind in the 18th century demonstrated that citrus fruits could be used to treat and prevent the illness. But it was not until the 20th century that vitamin C was identified as the likely component in citrus fruits that was responsible for curing the disease and it wasn't until the work of Krebs 1953 and Hodges et al. 1969 & 1971 that it was demonstrated that dietary deficiency of ascorbic acid alone resulted in all of the symptoms of scurvy and that repletion of vitamin C stores rapidly reversed the course of the potentially fatal disorder. While ascorbic acid plays an essential role in several enzyme reactions, its role in the hydroxylation of collagen at proline and lysine residues is primarily responsible for the symptoms that develop. Hydroxylation is necessary for the stabilization of the collagen triple helix structure and as such it is in tissues which contain greater concentrations of collagen such as skin, gums, hair, mucus membranes and bones in which symptoms of connective tissue weakness and capillary fragility typically develop in scurvy.

There is currently no single laboratory test that can be used to make the diagnosis of scurvy. Serum ascorbic acid levels < 0.3mg/dL were commonly associated with scurvy symptoms during the depletion phase in the pivotal studies. However, levels in the 0.05 to 0.3mg/dL range were still evident in recovering patients treated with low doses of 6.5mg/day, so serum ascorbic acid levels alone cannot be used to confirm a scurvy diagnosis. Diagnosis therefore depends on clinical symptoms characteristic of the disease as it typically presents in adults or children and a dietary history consistent with inadequate vitamin C intake or gastrointestinal malabsorption. Resolution of symptoms which typically occurs in days to weeks with adequate vitamin C exposure can be used to confirm the diagnosis.

The sponsor has developed an injectable vitamin C formulation which was previously available as a marketed unapproved drug for intravenous administration for the indication of the treatment of scurvy. This is a 505(b)(2) application referring to the work of Krebs and Hodges as the pivotal clinical studies to support the efficacy of ascorbic acid in the treatment of scurvy. While the work of Krebs was performed in healthy pacifist volunteers, who participated in the study in order to relieve them of their military service requirements, and the work of Hodges was performed in prisoner volunteers, a review of these studies by Kevin Prohaska at the Agency determined that they were designed and conducted in a manner consistent with the ethical standards for human subject protections that existed at the time the trials were conducted. Therefore, it is the

15 **Ludvigsson** J, Hansson LO, Tibbling G. **Vitamin C** as a preventive medicine against common colds in children.Scand J Infect Dis. 1977;9(2):91-8.

Agency's conclusion that it is ethically acceptable to use the data from these trials in the evaluation of a new drug application.

The studies of Krebs and Hodges were, in general, similar in design. Healthy individuals with adequate vitamin C stores were started on diets deficient only in vitamin C, but containing all other essential nutrients, for varying durations of time until they developed clear symptoms of scurvy. They were then replenished with various amounts of vitamin C per day to follow disease resolution. Onset of symptoms in the Krebs study took longer 17 to 20 weeks compared to the Hodges studies in which symptoms occurred within 4 to 7 weeks, likely because the diet used in the Krebs study still had small amounts of vitamin C that delayed complete depletion of body pools of ascorbic acid. The Krebs study demonstrated that doses as low as 10mg/day appear to be adequate to prevent the onset of scurvy and can treat scurvy that is already present, while Hodges et al. 1971 suggests that doses as low as 6.5mg/day are also adequate to treat scurvy in some patients. However, Hodges et al. 1971 shows that symptoms can resolve more rapidly with higher ascorbic acid doses of ascorbic acid such as 66.5 and 128mg/day. While it is possible that even higher doses above 128mg/day may further improve the rate of recovery, it is likely that there is a limit to the benefit expected from higher doses so that at some point further increase in dose would be expected to have minimal effect as the body pool becomes sufficiently saturated. The question therefore arises as to what is the appropriate dose of Ascor for the treatment of scurvy in different study populations, taking into account rapid repletion of body pools, without prescribing excessive doses which will eventually only end up being renally excreted. In this regards pharmacokinetic work by Levine et al. 1996 & 2001 helps provide justification for dose selection.

Levine et al. 1996 & 2001, showed that at oral doses up to 200mg/day there is maximal bioavailability, so that up to 100% of the ascorbic acid ingested is absorbed, but bioavailability decreases with higher doses, down to 33% for a single oral dose of 1250mg. With repeat daily dosing serum levels reach steady state plateaus in the range of 75 to 85μM in both men and women at doses of 200mg/day and above[16]. As serum ascorbic acid steady state levels plateau off at doses above 200mg/day there is limited benefit in efficacy with higher oral doses (i.e. there is only a small, 10% or so, further increase in serum steady state ascorbic acid levels with higher oral doses even up to 2500mg/day). Given that most of the published case reports of treatment of adult scurvy occurred with oral dosing and used doses between 250 and 2000mg/day, the steady state serum levels in these cases were probably in the same range as would have been expected with intravenous administration of 200mg/day of ascorbic acid. Therefore the intravenous dose of 200mg/day can be expected to be as efficacious as the treatment regimens reported in the literature and there is (b) (4) recommended by the sponsor. Considering that scurvy represents a case of severe vitamin C deficiency it seems appropriate that the treatment dose should be

16 See data from Levine et al. 1996 and 1971 presented in this review in Figure 1

greater than the currently recommended maintenance dose and 200mg/day represents roughly double the Recommended Daily Associate (RDA) for adults which range from 75 to 125mg/day. While higher doses might be justified under certain conditions, for example a known rapid metabolizer, there is likely limited benefit in the vast majority of cases, and even though the risk of adverse reactions is still very small at higher doses such as 1000mg/day to 2000mg/day there is no clear advantage from such doses to justify any additional safety risk.

While depletion, repletion studies are not available in pediatric patients, case reports of the onset of scurvy symptoms in children with diets low in ascorbic acid and the prompt resolution of these symptoms with the supplementation of the diet with ascorbic acid are clearly consistent with efficacy in the pediatric population. A retrospective chart review of 28 pediatric patients, 10 months to 9 ½ years of age, diagnosed with scurvy between 1995 and 2002 from Queen Sirikit National Institute of Child Health in Bangkok, Thailand[17] showed that all had clinical improvement within the first week after vitamin C supplementation with 150 to 300mg/day. In general, similar results were seen with infantile scurvy from 66 infants, mostly 5 to 12 months of age admitted to Children's Hospital, in Winnipeg Canada[18] between 1953 and 1965 after vitamin C supplementation with 100 to 1000mg/day. However there were three cases of sudden unexpected death, one which clearly occurred outside the hospital prior to the diagnosis and start of appropriate therapy, while information about the other two cases is not provided. Although higher doses of ascorbic acid, 100 to 1000mg/day, were used to treat scurvy in these two case report studies, Grewar et al. states that doses up to 7.5mg/kg/day are adequate for tissue saturation in infants and children, and typically 2 to 4 ounces of fresh orange juice which supplies 30 to 60mg of ascorbic acid is equally effective in providing for the resolution of symptoms in most cases. Unfortunately, there is no PK data in children to help in determining an optimum dose, which would lead to rapid resolution of symptoms without resulting in excessive unnecessary dosing. Guidelines for pediatric dosing from the Harriet Lane Handbook (2012 edition) for example recommend 100 to 300mg/day either orally, intramuscularly, subcutaneously or intravascularly, without citing a primary source for these recommended doses. This medical reviewer has chosen to recommend a dose of 100mg/day in pediatric patients 5 months up to 14 years of age and 200mg/day in children greater than 14 years of age similar to the adult dose recommendation, assuming that double the RDA/AI maintenance dose would be adequate replacement for this vitamin deficiency, similar to how optimum dosing was determined in adults using adult PK data (see 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations).

17 J Med Assoc Thai. 2003 Aug;86 Suppl 3:S734-40. Scurvy in pediatric patients: a review of 28 cases. Ratanachu-Ek S[1], Sukswai P, Jeerathanyasakun Y, Wongtapradit L.

18 INFANTILE **SCURVY**. **GREWAR** D. Clin Pediatr (Phila). 1965 Feb;4:82-9.

While the studies of Krebs and Hodges were performed with oral supplementation of vitamin C or dietary changes containing adequate vitamin C, there is no reason to suspect that intravenous vitamin C, the subject of this NDA, would not be at least as efficacious. Individual case reports in the literature confirm adequate treatment and resolution of symptoms in patients treated with commercially available unapproved intravenous ascorbic acid formulations at doses ranging from 200mg to 1000mg/day (see Table 15, pg49, sponsor's Summary of Clinical Safety). Given the current product has 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 too would be effective in the treatment of scurvy even though it has not been tested in patients with active scurvy. Intravenous administration could be beneficial in subjects unable to take oral supplements or with a history of gastrointestinal malabsorption, but there is no evidence to suggest that it would be more effective than oral administration in patients with normal gastrointestinal absorption. While much higher serum levels of ascorbic acid can be obtained with intravenous administration due to the decreased bioavailability of higher oral doses (e.g. bioavailability was up to 100% for a single oral dose of 200mg but only 33% for a single oral dose of 1250mg.) and so could potentially replenish body pools more rapidly, it is not known whether that would lead to a clinically beneficial difference in the resolution of symptoms which could still be delayed by the time required for resynthesis of normally hydroxylated collagen and replacement of the abnormal collagen in damaged tissues.

6.1 Indication

Treatment of scurvy.

The pivotal trials include a published article by Krebs 1953[19] and two published studies by Hodges et al. 1969[20] and 1971[21].

Krebs 1953
The Krebs 1953 article described a 16-month, double-blind, placebo-controlled trial in which subjects underwent vitamin C depletion until they developed symptoms of scurvy followed by vitamin C repletion under controlled conditions until all symptoms had

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

20 Hodges, R. E., Baker, E. M., Hood, J., Sauberlich, H. E., March, S. C. (1969). Experimental scurvy in man. The American journal of clinical nutrition, 22(5), 535-548.

21 Hodges, R. E., Hood, J., Canham, J. E., Sauberlich, H. E., & Baker, E. M. (1971). Clinical manifestations of ascorbic acid deficiency in man. The American journal of clinical nutrition, 24(4), 432-443.

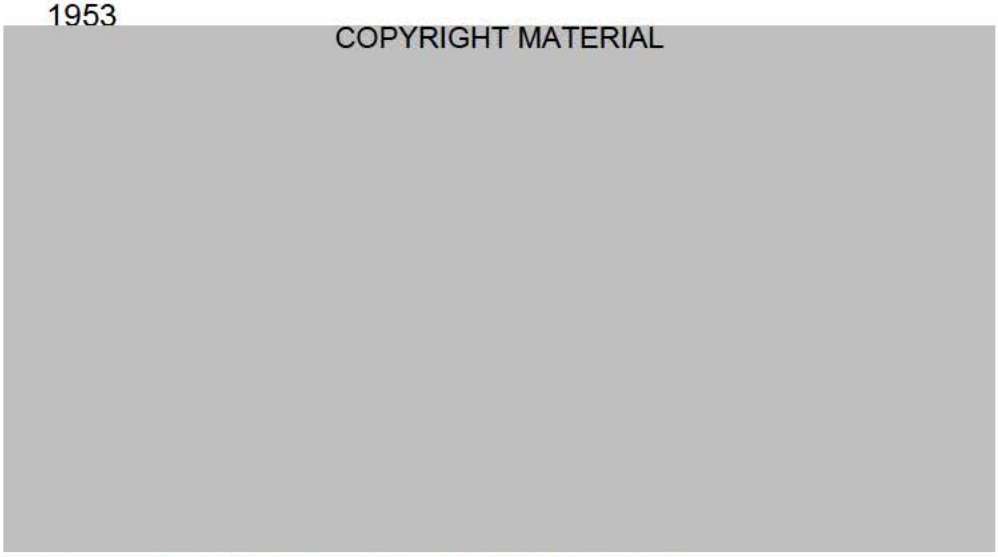
resolved. The study involved 20 subjects (19 men and 1 woman), 21 to 34 years of age, most of whom were conscientious objectors and were relieved of their required military service obligations in WWII by volunteering for this study. All subjects initially received a diet containing approximately 70 mg of ascorbic acid for 6 weeks to get baseline data. Subjects were then randomized into one of 3 treatment groups:

1. 10 subjects received no vitamin C supplementation (the deprived group)
2. 7 subjects received a supplement of 10 mg of vitamin C (the prophylactic group), and
3. 3 subjects received a supplement of 70 mg of vitamin C (the control group).

All subjects received the same diet that was designed to yield < 1 mg of vitamin C per day. The duration of this depletion phase varied depending on when patients developed symptoms and on the severity of the symptoms.

In the deprived treatment group no clinical signs were seen in the first 17 weeks. Between weeks 17 and 20 hyperkeratosis of the hair follicles was seen. Between weeks 26 and 34 perifollicular hemorrhages were seen. Between weeks 30 to 38 swelling and hemorrhages of the gums was seen. All seven deprived volunteers had clear symptoms of scurvy including multiple skin hemorrhages and gum lesions prior to the initiation of replacement therapy. A replacement dose of 10mg was chosen for most subjects with the intention of giving the smallest dose likely to produce a cure in a reasonable time. One subject received a dose of 20mg because the volunteer was not available for a long period of time. All subjects showed a similar response to treatment with an end to new perifollicular hemorrhages within a week and a loss of the dark purple color of older hemorrhages within 1 to 2 weeks. Within a month most of the hair follicles had normalized. Within in 7 to 9 weeks the skin appeared normal except for slight brown pigmentation at the site of the former hemorrhages. The gum swelling/lesions took longer to improve and did not normalize until 10 to 14 weeks later. Therefore the 10mg dose was sufficient to treat scurvy in all of these patients.

Table 1 Development and Treatment of Scurvy in the Deprived Treatment Arm-Krebs 1953



Source Table 4 Summary of Clinical Efficacy

The seven subjects on the 10mg prophylactic dose did not show any symptoms of scurvy for the first 23 weeks (160 days) of treatment. Therefore it was decided to deprive three of these volunteers and to continue four of them on the 10mg prophylactic dose. The volunteers continually on the 10mg dose never developed symptoms of scurvy even after treatment for up to a total of 60 wks (424 days). The volunteers deprived of all ascorbic acid for an additional 10 wks (71 days), the duration of the study, also did not develop symptoms in that period of time. Therefore treatment with 10mg of ascorbic acid was enough to prevent the development of scurvy and when given at baseline for several months was sufficient to prevent the new onset of scurvy for at least 10wks weeks after the dosing with ascorbic acid was stopped, but it is not known if the prevention of scurvy would have lasted for the full 17 to 20wks, which was the time at which scurvy symptoms appeared in subjects on a baseline dose of 70mg. Therefore it is not possible to tell if the lower dose of 10mg was as effective at preventing the onset of symptoms as the higher dose of 70mg. The higher dose is closer to the currently recommended US RDA doses of 90mg in males and 75mg in females.

The three volunteers continually on the 70mg dose acting as positive controls never developed any symptoms of scurvy during the entire length of the study. Therefore treatment with daily doses of 70mg of ascorbic acid appears enough to indefinitely prevent the development of scurvy in otherwise healthy subjects.

Average serum vitamin C concentrations ranged between 0.5 and 0.7mg/dL in subjects maintained on the standard 70mg dose of vitamin C throughout the study. Serum vitamin C levels dropped to below 0.1mg/dL by 3 to 4 weeks in both subjects receiving 10mg of supplementation who never developed scurvy and in those receiving no

vitamin C supplementation that later developed symptoms of scurvy starting at week 17. So serum vitamin C concentration appeared to be more useful in excluding a diagnosis of scurvy, if it was >0.5mg/dL, rather than confirming it if it was < 0.1mg/dL. The authors noted that vitamin C concentrations dropped more slowly in white cells reaching a nadir at weeks 12 to 14 and there appeared to be clear differences in white cell vitamin C concentrations in volunteers supplemented with 5, 10 and 20mg of vitamin C (e.g. 2.0, 2.7 and 3.6mg/100g, respectively) while all of these subjects had serum vitamin C levels < 0.1mg/dL below the lower level of detection of the assay suggesting that vitamin C levels in white cells might be of somewhat more diagnostic value. However the nadir in white cell vitamin C concentrations in volunteers, which occurred at 12 to 14 weeks, still occurred several weeks prior to the onset of symptoms, 17 to 20 weeks, so white cell vitamin C concentrations still could not be used to make a diagnosis of scurvy.

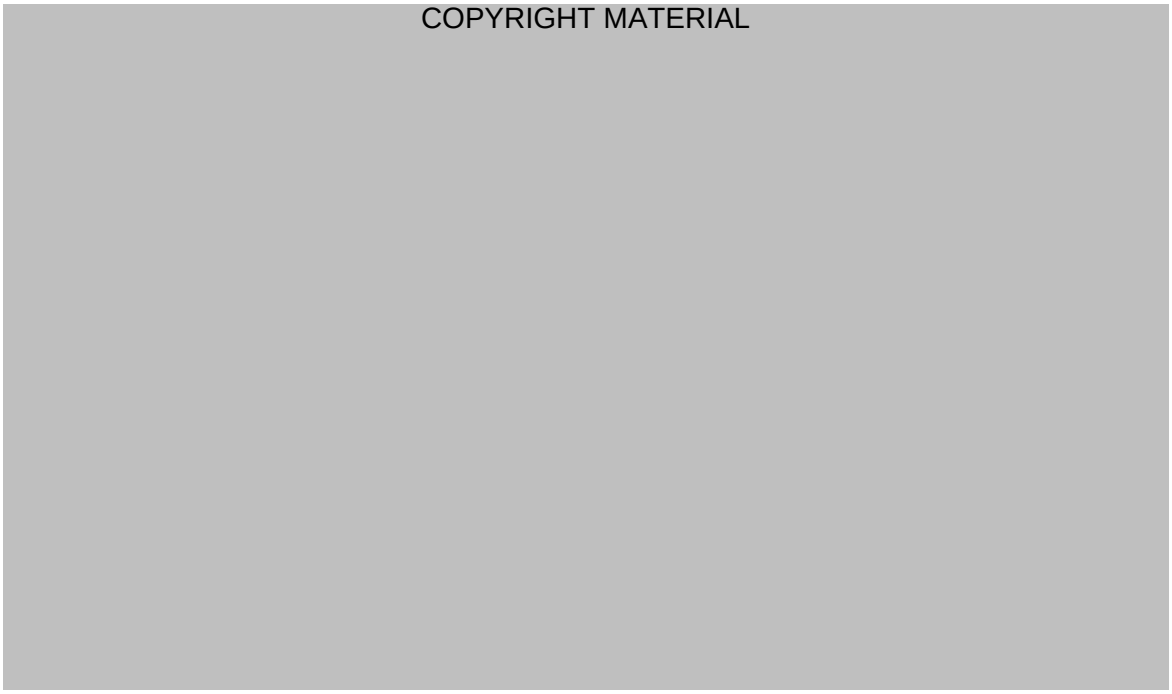
Medical officer's comments-

This study demonstrated that diets containing < 1mg of vitamin C can lead to the development of symptoms of scurvy within about 17 weeks without supplementation. Initial symptoms include hyperkeratosis of the hair follicles followed by perifollicular hemorrhages and finally swelling and hemorrhages of the gums. Daily intake of at least 10mg is sufficient to prevent the development of scurvy and will result in the gradual resolution of symptoms in subjects with scurvy. Resolution of skin and hair symptoms begins with treatment within 1 to 2 weeks and is typically complete by 7 to 9 weeks in patients treated with 10mg/day of vitamin C. Gum swelling/lesions take longer to improve and may not normalize until 10 to 14 weeks after the initiation of treatment with 10mg/day of vitamin C. The applicant argues that resolution of symptoms could have been faster had the subjects been treated with a higher dose than 10mg, but this cannot be concluded from the data in this current study.

Serum vitamin C levels are a poor measure of the bodies total pool of vitamin C and as such the risk for developing scurvy. Levels below 0.1mg/dL were consistent with the risk of developing scurvy but could also be observed in subjects taking low levels of supplementation (e.g. 10 to 20mg/day) that were unlikely to result in disease progression. Higher levels above 0.5mg/dL, however, were unlikely to be associated with scurvy. White cell vitamin C levels appear to correlate better with total body pools of vitamin C but they too are insensitive with respect to predicting the risk for the development of the symptoms of scurvy. Therefore a diagnosis of scurvy requires both a dietary history consistent with the risk of developing a deficiency and the development of classical symptoms associated with this condition. Serum or white cell vitamin C levels can help confirm a diagnosis, but are not diagnostic in and of themselves.

Hodges et al. 1969
The first of the two studies conducted by Hodges involved six male prisoner volunteers, 33 to 44 years of age, from the Iowa State Penitentiary. All subjects were housed in the metabolic ward of the University Hospitals in Iowa City and closely monitored for the duration of the study. There were three phases to the trial, a deprivation phase (Days 1 through 99) a repletion phase (Days 100 through 200) and a saturation phase (Days 200 to the end of the study). The men were taught to swallow a gastric tube through which they later administered three times a day a liquid diet totally deficient in ascorbic acid but adequate in all other nutrients. The repletion phase involved active administration of radiolabeled 14C ascorbic acid at various doses (4 to 32mg) until all evidence of scurvy resolved. In addition subjects were started on a modified solid diet containing 2.5mg of ascorbic acid from Day 114 to Day 200. During the saturation phase, starting with Study Day 200, all subjects were started on an ad lib diet containing 500mg of ascorbic acid until the end of the study. Two of the six subjects escaped from the hospital on Study Day 54, so study results are reported for only the four remaining subjects.

Figure 2 Study Design for Hodges et al. 1969



Subjects were required to walk 10 miles daily to help manifest the vitamin deficiency. Increased fatigue especially of the lower limbs and mild general malaise were observed about the time of development of objective signs of scurvy. The first petechial hemorrhages were seen in three subjects starting with Days 26 to 32 (4 wks). The first truly perifollicular hemorrhages were seen starting with Days 45 to 52 (6 wks). Bulbar conjunctival hemorrhages were noted in three of the four men between Days 84 and 91 (12 wks). Oral lesions including sublingual hemorrhages were seen starting with Days

36, 90 and 189 in three patients with swollen gums seen starting with Days 38, 42 and 105 (5-14wks). Hyperkeratosis was seen starting with Days 60, 77, 84 and 88 (8-12wks). Most findings were rated as either 1 or 2 on a four point scale with a few noted exceptions. The following adverse events were rated as 4 by one patient each: hyperkeratosis (Days 90-110), swollen gums (Days 70-110), follicular congestion (Days 150-160), and papillary swelling (Days 90-100).

Medical officer's comments-
Onset of symptoms was sooner in this study 4 to 5 wks (26 to 38 Days) than seen in subjects studied by Krebs in which symptoms didn't develop for 17 wks (119 Days). The authors speculate that this was because the later study included a diet with "not more than one mg" of vitamin C while the diet in the current study contained no vitamin C, so low levels of vitamin C in the < 1mg/day range may still have been partially protective in the Krebs study. Consistent with this, references sited in the Hodges et al. 1969 paper describe the onset of symptoms ranging from 60 to 225 days depending on the dietary conditions used to induce scurvy.

Clinical symptoms typically began to appear when the total body pools decreased to approximately 300mg and the rate of catabolism of vitamin C fell to < 2.5mg/day which would normally correlate to a total serum ascorbic acid level of < 0.2mg/dL. However, no lab measurements, including urinary excretion of vitamin C or total serum vitamin C, were useful in predicting the onset of symptoms.

The four remaining subjects in the study were treated with different amounts of ascorbic acid during the repletion phase: 4, 8, 16 and 32 mg. Most related symptoms had disappeared by the end of the repletion phase Day 210 except for the subject treated with the lowest dose, 4mg, who still had 1+ "hyperkeratosis" and 1+ "conjunctival lesions" noted at that time. However, uncertain assessments (±) were also reported at Day 210 for "hyperkeratosis" in the subject treated with the highest dose 32mg and for "gum swelling/congestion" in subjects treated with 4, 8 and 16mg of ascorbic acid (see Table III in the original reference). Looking at the symptoms scales reported for the subjects during the repletion phase it is this medical reviewer's impression that in general skin symptoms (e.g. "hyperkeratosis", "follicular congestion", "petechiae") and "conjunctival lesions" took longer to heal in the subject treated with 4mg compared to the subjects treated with 8mg, 16 and 32mg.

A wound healing assessment test was done early in the repletion phase that involved making a 5 cm surgical wound in the left thigh which was closed with suture and subsequently biopsied using a punch biopsy to assess for histological changes. Wounds healed equally in all four men despite being treated with

different doses ranging from 4 to 32mg of ascorbic acid so no convincing histological differences in healing rates were seen with this test.

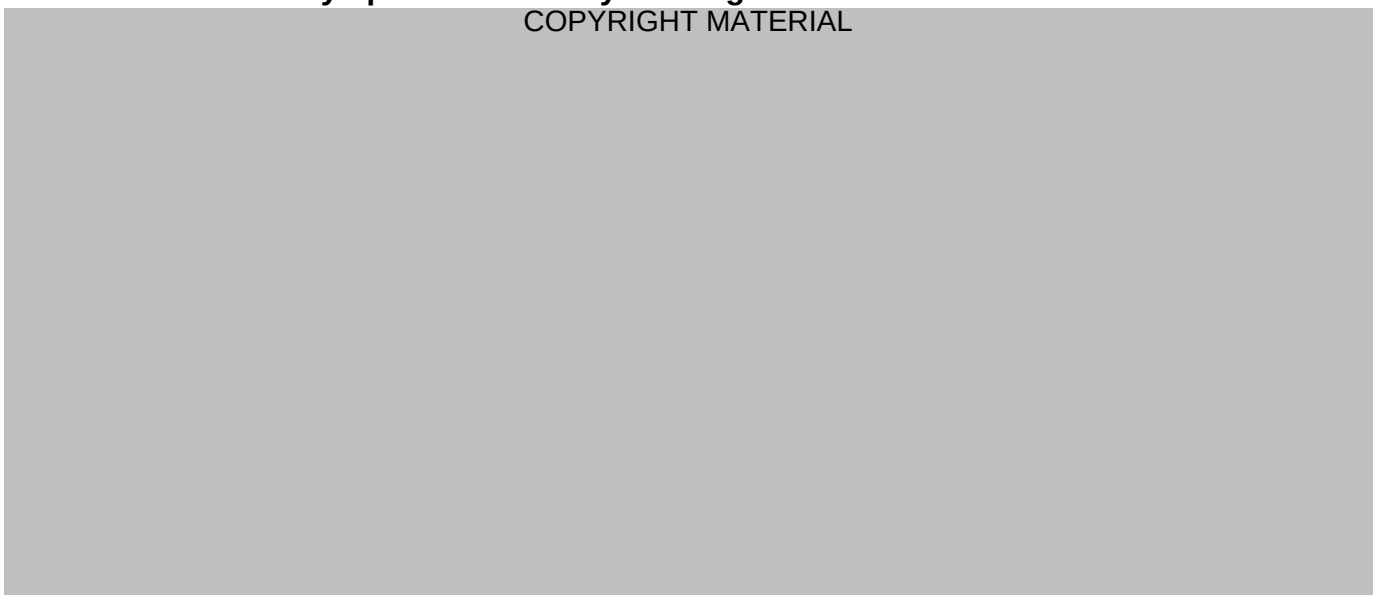
Hodges et al. 1971
This second study conducted by Hodges was designed similarly to the previous study Hodges et al. 1969 but more clearly attempted to assess the rate of repletion of the body pool of ascorbic acid and the rate of clinical recovery using a larger range of daily doses. Six male prisoners, 26 to 52 years of age, from the Iowa State Penitentiary were taught to swallow a gastric tube through which they could administer a liquid diet totally deficient in ascorbic acid but adequate in all other nutrients. Informed consent was obtained in all subjects and there is evidence that subjects were permitted to withdraw as one subject withdrew consent during the depletion phase prior to the development of clinical scurvy. All subjects were housed in the metabolic ward of the University Hospitals in Iowa City and closely monitored for the duration of the study.

Table 2 Dietary Intake of Ascorbic Acid in Hodges et al. 1971

There were four major phases to the trial. A control phase (Days 1 to 13), a deprivation phase (Days 14 to 97, 104 or 110), a repletion phase (Days 98, 105 or 111 to 227) and a saturation phase (Days 228 to 258). During the initial control period subjects were fed 77.5mg of ascorbic acid (2.5mg from a solid soy based diet and 75mg from supplements) for about two weeks. On Day 14 they were switched to the liquid diet containing no ascorbic acid until Days 97, 104 or 110, so the total duration time for the deprivation phase ranged from 84 to 97 days. During the beginning of the repletion phase some subjects were given low dose ascorbic acid 2.5mg for 12 days or 4mg for 5 days prior to receiving higher doses of 6.5, 66.5 or 128mg for the rest of the period. During the saturation phase subjects receives a regular solid diet containing 100mg of ascorbic acid ad lib plus supplements of 250 or 500mg daily of ascorbic acid.

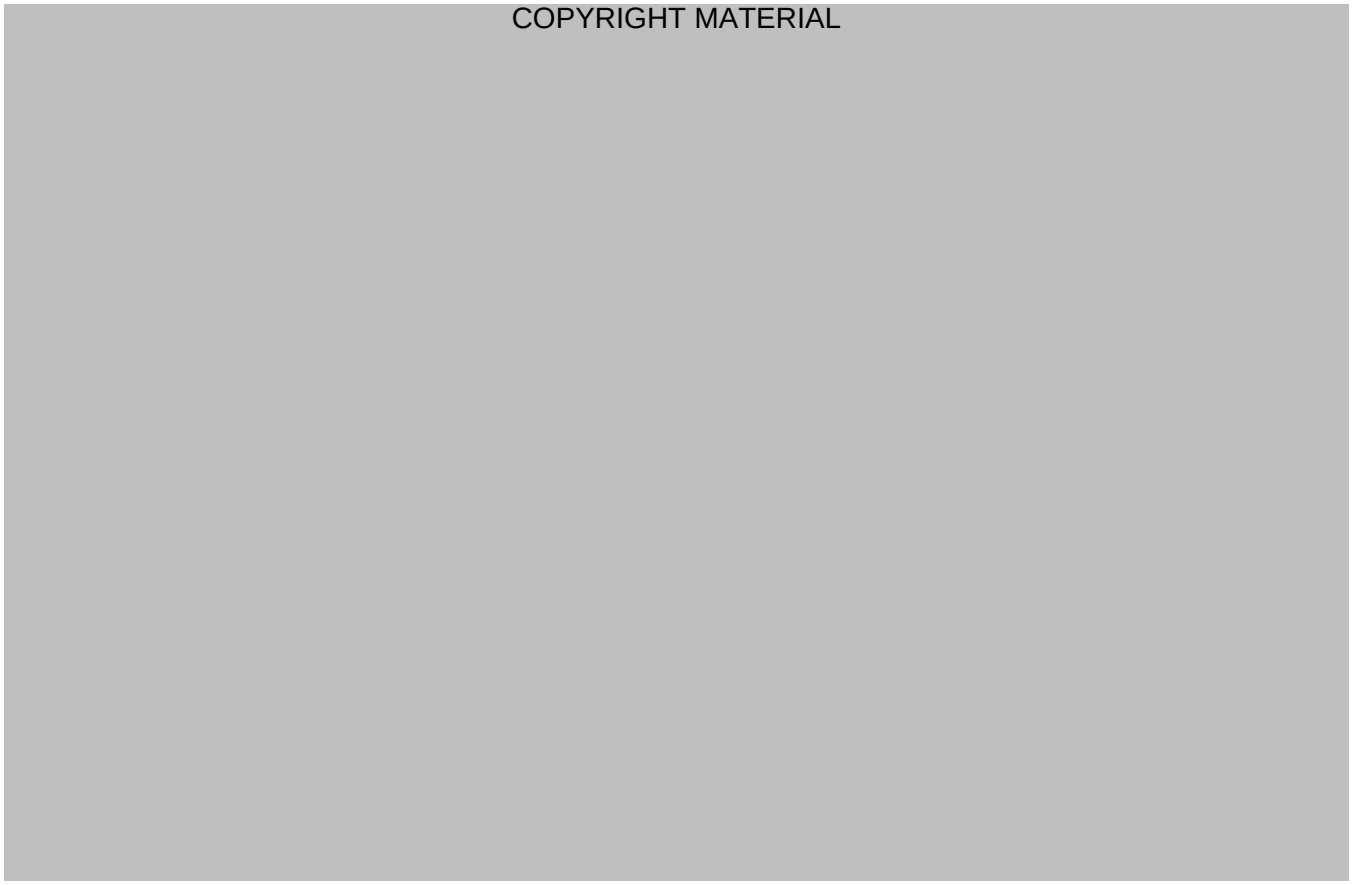
Clinical data is only reported for the 5 subjects who completed the study. The first signs of scurvy were “petechiae” which were seen as early as the 29th day of depletion (Day 42) in 4 of the 5 men (4/5) and appeared with plasma ascorbic acid levels of 0.13 to 0.24mg/dL. Additional clinical signs of scurvy seen in order of appearance were: “small spontaneous ecchymoses” seen in four of the five men (4/5) on legs only (Days 49-116), “coiled hairs” (2/5) seen between Day 55 and 87, “gum changes” (4/5) seen between Days 56 and 97, “hyperkeratosis” (5/5) seen between Days 58 and 113, and “congested follicles” (5/5) seen between Days 62 and 103. Other symptoms seen in this study likely due to scurvy but occurring less frequently included “sicca syndrome” (xerostomia, keratoconjunctivitis sicca, submandibular/parotid gland enlargement), “dyspnea”, “arthralgia”, “joint effusions”, “neuropathy” and “marked edema”. All these symptoms were reversed following treatment with ascorbic acid. Plasma ascorbic acid levels ranged from 0.0 to 0.30 mg/dL in patients with symptoms as shown in Table 3.

Table 3 Onset of Symptoms of Scurvy in Hodges et al. 1971



Recovery was seen with daily doses of 6.5, 66.5 or 128mg in patients during the repletion phase, therefore “the minimal amount of ascorbic acid needed to treat scurvy appears to be slightly less than 10mg daily.” However the rate of recovery was seemingly “proportional to the repletion dose” as patients with the higher doses recovered sooner. In the two patients treated with the low dose of 6.5mg/day of ascorbic acid serum levels of ascorbic acid continued to range between 0.05 and 0.3mg/dL during recovery in the repletion phase similar to what had been observed in the depletion phase. While the authors found poor correlation with plasma ascorbate levels and estimates of body pool size, they generally observed scurvy to appear when pool sized dropped below 300mg similar to what had been seen in their earlier study. The authors concluded that since rapid disappearance of symptoms was seen with the administration of modest doses of 66.5mg/day and since vitamin C is rapidly absorbed in the gastrointestinal tract “there seems little reason to treat scurvy with parenteral ascorbic acid or with massive doses.”

Figure 3 Serum Ascorbate Levels in Subjects Repleted with 6.5mg/day of Ascorbic Acid in Hodges et al. 1971



Medical officer's comments-
There is currently no single laboratory test that can be used to make the diagnosis of scurvy. Serum ascorbic acid levels < 0.3mg/dL were commonly associated with scurvy symptoms during the depletion phase. However, levels in the 0.05 to 0.3mg/dL range were still evident in recovering patients treated with low doses of 6.5mg/day, so these levels alone cannot be used to confirm a scurvy diagnosis. In addition, from the current data while there is evidence that higher oral doses up to 128mg/day may result in more rapid recovery of symptoms, it is not necessarily known if there would be significantly more rapid recovery at higher doses above 128mg/day as the recovery rate is likely to be maximal as some dose level.

While data from both Hodges references support the fact that most patients with scurvy can be adequately treated with moderate oral doses of vitamin C, it is true that in patients unable to take oral medications a parenteral formulation would be useful.

Other References Supporting Efficacy in Pediatric Patients-

Ratanachu-Ek et al. 2003
This is a retrospective case report study of 28 pediatric patients diagnosed with scurvy in Thailand between 1995 and 2002. Subjects were mostly male 61%, with an average age of 31.9 months (about 2.5 yrs) with a range of 10 months to 9.5years. Only 43% were considered underweight, while 36% were normal and 21% were overweight. Dietary histories included well-cooked foods (vitamin C is heat sensitive), small amounts or no vegetables and fruits, and supplementation with ultra heat temperature (UHT) milk.

Clinical manifestations included limp or inability to walk 96%, tenderness of lower limbs 86%, swollen knee or ankle joints 46%, bleeding gums/hypertrophy 36%, fever 18%, and petechial hemorrhage 4%. Other symptoms seen in individual patients included right sided heart failure due to pulmonary hypertension, systemic hypertension and pericardial effusion. All cases had abnormal findings on X-ray consistent with scurvy and low serum ascorbic acid levels < 0.31mg/dL. Iron deficiency anemia was seen in 95% of subjects.

Treatments included oral vitamin C at doses of 150 to 300mg/day. In 23 cases where follow-up was available, pain and tenderness in the lower limbs improved in 1 to 4 wks (mean 2.2wks), swelling and bleeding of gums improved in 1 to 3 wks (mean 1.5wks) and all cases of fever became afebrile within one week. Iron deficiency anemia in scurvy is multi-factorial due to blood loss, other vitamin deficiencies (e.g. folate) and decreased iron absorption in the absence of vitamin C.

Medical officer's comments-
Pediatric patients are more likely to present with difficulty walking, iron deficiency anemia and fever in contrast to skin and hair changes which are much more common presenting symptoms in adults. Ascorbic acid levels when measured were low < 0.31mg/dL but were not necessary for diagnosis which depended on a good dietary history and observation of the resolution of symptoms once supplementation with ascorbic acid was initiated.

Grewar 1965
66 cases of infantile scurvy were seen in infants admitted to Children's Hospital in Winnipeg, Canada from 1953 through 1965. Children were primarily between 5 to 12 months, with most 8 to 9 months of age. After 12 months of age the occurrence was rare except for children with feeding difficulties. Children were primarily bottle fed pasteurized/evaporated or boiled cow's milk. Cow's milk is an inadequate source of vitamin C as it contains only 1.5 to 2mg/dL of ascorbic acid compared to human milk which contains 4 to 8mg/dL. Cow's milk is nutritionally adequate for calves as they can synthesize their own vitamin C and are not dependent on maternal milk as a source.

Clinical manifestations include irritability especially more pronounced when the infants were handled or in anticipation of being handled. Pain, tenderness, weakness and disuse of lower limbs are attributed to subperiosteal hemorrhage. This was severe enough to lead to regression in interest in sitting, standing or walking in some cases. Fever was present in over half of the infants and is believed to be directly due to scurvy and not due to an infection as it was independent of treatment with antibiotics. Edematous gums could be seen as well as hemorrhage at sites of teeth eruptions. A hypochromic and microcytic anemia most commonly due to iron deficiency anemia was typical, as cow's milk can cause blood loss from the GI tract and oral ascorbic acid normally assists in iron absorption. In some cases the anemia could be complicated by a folic acid deficiency, due to poor dietary intake with unsupplemented cow's milk, which might present as a normocytic or more megaloblastic anemia. Sudden death while rare has been seen in both adults and children with scurvy.

Treatment in this article recommended dosages from 100 to 1000mg/day with either oral or intravenous administration. There was no advantage to treatment with larger doses due to renal excretion, although the authors point to a theoretical advantage of giving small amounts frequently in order to avoid exceeding the renal threshold. In the author's experience, treatment with 2 to 4 ounces of fresh orange juice daily (31 – 62mg/day) results in equally prompt resolution of symptoms.

Medical officer's comments-
Infantile scurvy occurs most frequently in primarily bottle fed children between 5 months and 12 months of age because most newborn infants have adequate fetal stores and breast feeding typically provides an adequate source of vitamin C. Infantile scurvy can theoretically occur in children less the 6 months of age if

mothers were already severely vitamin C deficient during the pregnancy although that has not been reported in the literature. There have been two case reports of "conditional scurvy" in infants born to mothers who took high doses of vitamin C estimated at 400mg/day during their pregnancies, but more recent findings have not substantiated these reports (see 7.6.2 Human Reproduction and Pregnancy Data). In conclusion, there was no mention of concern about toxicity when treating infantile scurvy with doses up to 1000mg/day in this study population.

6.1.1 Methods

The Krebs 1953 study was a double-blind, placebo-controlled study in healthy volunteers started on a diet deficient in vitamin C and randomized to one of three vitamin C supplementation groups:

- no vitamin C supplementation-the deprived group
- supplementation with 10mg of vitamin C-the prophylactic group and
- supplementation with 70mg of vitamin C-the control group.

Once clear symptoms of scurvy had been identified subjects were started on 10 or 20mg of ascorbic acid to follow resolution of symptoms.

Hodges 1969 and 1971 were open label studies in healthy volunteers consisting of three phases:

- A depletion phase- where subjects received a diet deficient in vitamin C
- A repletion phase- in which subjects received various low levels of supplementation with 6.5 to128mg of vitamin C until all symptoms resolved
- A saturation phase-in which subjects received 500mg/day of vitamin C and an ad lib diet to replenish body stores.

The exact details of these studies are described individually in greater detail in section 6.1 above.

6.1.2 Demographics

Of the 33 subjects in the three pivotal trials 32 were men between the ages of 21 and 54 years and one was a woman between the ages of 21 and 34 years. All subjects "were in good health as judged by medical history and physical exam".

6.1.3 Subject Disposition

Of the 33 subjects 4 withdrew from study prior to developing symptoms of scurvy during the depletion phase of the individual studies. Complete study data is available only on 29 subjects.

6.1.4 Analysis of Primary Endpoint(s)

The pivotal studies were not powered for a specific primary endpoint. Instead, onset and severity of clinical symptoms were recorded during the depletion phase as was the time to resolution of these symptoms following treatment with varying amounts of ascorbic acid during the repletion phase.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

All but one of the study subjects was male. The studies were too small to do subgroup analyses.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The pivotal efficacy trials of Krebs 1953 and Hodges et al. 1969 & 1971 showed that oral doses as low as 6.5 to 10mg/day of ascorbic acid were adequate to treat scurvy. However, higher doses of ascorbic acid such 66.5mg/day to 128mg/day, resulted in more rapid resolution of symptoms. While it is possible that even higher doses above 128mg/day may further improve the rate of recovery, it is likely that there is a limit to the benefit expected from higher doses so that at some point further increase would have minimal effect as the body pool becomes sufficiently saturated. It must also be considered that while repletion of body stores may be more rapid with higher doses, there is a limit as to the resolution of clinical symptoms as they require resynthesis of normally hydroxylated collagen and replacement of the abnormal collagen in damaged tissues, which may take weeks to months for complete recovery depending on the organ involved (e.g. skin, hair, gums or bone).

The studies of Levine go on to characterize the size of the body pools in men (Levine et al. 1996) and women (Levin et al. 2001) and estimate that symptoms occur when body pools drop below 300mg. Given the proposed adult [redacted] (b) (4), body pools could theoretically be restored [redacted] (b) (4) depending on how quickly the available ascorbic acid is utilized, metabolized and excreted. In adults the ascorbic acid RDA is 90 mg for males, and 75 mg for nonpregnant and nonlactating females, 85 mg in pregnant females and 120 mg in lactating females.

Table 4 Recommended Dietary Allowances (RDA) or Adequate Intakes* (AI)

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Source Dietary Reference Intakes for Vitamin C (2000) www.nap.edu Food & Nutrition Board, Institute of Medicine, National Academies

So the applicants proposed (b) (4) are roughly (b) (4) times the estimated RDAs. With oral doses up to 200mg/day there is maximal bioavailability, so that up to 100% of the ascorbic acid ingested is absorbed, but bioavailability decreases with higher doses, down to 33% for a single oral dose of 1250mg. With repeat daily dosing serum levels reach steady state plateaus in the range of 75 to 85μM in both men and women at doses of 200mg/day and above (well above the normal range 23- 50μM, see Figure 1). Given that the steady state levels plateau off at oral doses of 200mg/day and above there is limited benefit in efficacy with higher doses, (i.e. there is only a small, 10% or so, further increase in steady state serum ascorbic acid levels with higher oral doses even up to 2500mg/day). Given that most of the case reports of treatment of adult scurvy occurred with oral dosing and used doses between 250 and 2000mg/day, the steady state serum levels in these cases were probably in the same range as would have been expected with intravenous dosing of 200mg/day of ascorbic acid. Therefore, the intravenous dose of 200mg/day can be expected to give similar results to most cases of effective treatment reported in the literature. While higher doses might be justified under certain conditions, for example a known rapid metabolizer, there is likely limited benefit in the vast majority of cases. So even though the risk is still very small at higher doses such as 1000mg/day to 2000mg/day, there is no clear advantage from doses (b) (4).

While children with scurvy have been safely treated with oral ascorbic acid doses of 100 to 1000mg/day, there is no similar pharmacokinetic data in children to help support dosing. Guidelines from the Harriet Lane Handbook (2012 edition) for pediatric dosing recommend 100 to 300mg/day either orally, intramuscularly, subcutaneously or intravascularly, without citing a primary source for these recommended doses. In general the RDA or Adequate Intake (AI) doses of ascorbic acid in children for daily maintenance are about half the adult maintenance dose. Assuming this relative two-fold difference in maintenance dosing between children and adults can be used to adequately control for the different dosing needs in children due to differences in body weight, metabolism, excretion, etc., then children who receive adequate maintenance levels of ascorbic acid with half the adult daily maintenance dose should also be effectively treated for scurvy at half the 200mg/day proposed adult dose for the treatment of scurvy or 100mg/day. For older adolescent children 14 to 18yrs who require a higher maintenance dose of 75mg/day it is probably reasonable to recommend the adult dose of 200mg/day which is closer to double their maintenance daily dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no evidence of tolerance effects or lack of efficacy over time to the treatment of scurvy with ascorbic acid. That said the half-life reported here in Study MGP-1 in healthy adults treated with a single dose of 1000mg was 7 to 14 hours which is much longer than seen with off-label uses with much higher doses such as 51,000mg to 187,000mg where it ranged from 1.7 to 2.5 hours likely due to the induction of increased metabolism (Stephenson et al. 2013).

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The pivotal efficacy trials of Krebs 1953 and Hodges et al. 1969 & 1971 did not identify any drug-related safety concerns at the low oral doses of 6.5 to 128mg/day of ascorbic acid. Similarly, case reports from the literature have shown that higher oral doses of 250 to 2000mg/day in adults and 100 to 1000mg/day in children have also been used safely for the treatment of scurvy. In fact the tolerable upper intake level (UL) for ascorbic acid of 2000mg/day in adults and 440-1800mg/day in children is based primarily on the concern over gastrointestinal disturbance due to osmotic diarrhea, and even higher doses of ascorbic acid which would not produce the same gastrointestinal effects can

be given safely intravenously. Intravenous doses up to 187,000mg/day have been given for off-label uses with the primary safety concerns being:

- an increase in urinary excretion of oxalic acid, a vitamin C metabolite, at doses above 1500mg/kg/day, equivalent to 105,000mg/day for a 70kg adult, which increases the risk for calcium oxalate kidney stones[22] and
- hemolysis with infusions above 25,000mg[23] in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to lower amounts of reduced glutathione in G6PD deficient red blood cells making them more susceptible to oxidative stress[24].

However, while such high intravenous doses are still relatively safe for most individuals, they are not necessary for the proposed indication as demonstrated by the effectiveness of the much lower doses used in the pivotal studies described above and in multiple case reports of individuals treated for scurvy. In general, no unusual biochemical or hematologic abnormalities have been reported with intravenous administration of ascorbic acid. The primary adverse events which have been reported are few and mainly related to nonspecific symptoms such as vein irritation, transient hypertension, headache, nausea, and vomiting believed to be due to the rapid infusion of high-osmolarity solutions. In conclusion, there is adequate safety information from the published literature to support the safe use of the proposed intravenous doses of 200mg/day in adults and pediatric patients (b) (4) years of age and older and 100mg/day (b) (4) .

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The pivotal efficacy trials of Krebs 1953 and Hodges 1969 & 1971 did not identify any drug-related safety concerns at the low oral doses of 6.5 to 128mg/day of ascorbic acid. Additional studies using much high intravenous doses for other unapproved indications were reviewed below to support the safety of the proposed doses for the treatment of scurvy: Fowler 2014, Hoffer 2008, Padayatty 2010, Stephenson 2013, Nielsen 2015, and Ludvigsson1977.

22 **Hoffer** LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L, Miller WH Jr. Phase I clinical trial of i.v. **ascorbic acid** in advanced malignancy. Ann Oncol. **2008** Nov;19(11):1969-74.

23 https://en.wikipedia.org/wiki/Glucose-6-phosphate_dehydrogenase_deficiency

24 Rees DC, Kelsey H, Richards JD. Acute **haemolysis** induced by high dose **ascorbic acid** in **glucose-6-phosphate** dehydrogenase deficiency. BMJ. 1993 Mar 27;306(6881):

Fowler et al. 2014[25] was a Phase 1, randomized, double-blind, placebo controlled safety trial of intravenous ascorbic acid in the treatment of patient with sepsis. A total of 24 patients with severe sepsis admitted to the Medical Respiratory ICU at VCU Medical Center in Richmond Virginia were randomized to one of three different treatment arms:

- Low dose-50mg/kg/24hours (equivalent to 3,500mg/day in 70kg adult, n=8)
- High dose-200mg/kg/24 hours (equivalent to 14,000mg/day in 70kg adult, n=8) and
- Placebo (n=8)

to receive intravenous infusions of ascorbic acid or placebo every 6 hours for 4 days in additional to their regular care. The primary end points were ascorbic acid safety and tolerability, assessed as treatment-related adverse-event frequency and severity. On study Day 4, mean ascorbic acid levels were 15.6μM in the placebo group (0.26mg/dL), compared to 331μM (5.5mg/dL) in the low dose group and 3,082μM (51.4mg/dL) in the high dose group.

No adverse safety events were observed in ascorbic acid-infused patients.

Hoffer et al. 2008[26] was a Phase 1, open-label, safety trial of intravenous ascorbic acid in the treatment of patients with advanced malignancy. A total of 24 cancer patients were assigned to sequential cohorts receiving 400mg/kg, 600mg/kg, 900mg/kg and 1,500mg/kg of ascorbic acid intravenously three times weekly (based on a 70kg adult that would correspond to 28,000mg, 42,000mg, 63,000mg and 105,000mg of ascorbic acid). In addition, on non-infusion days subjects received 500mg BID to try to avoid ascorbic acid fluctuations. The average length of treatment was10 weeks, with a maximum length of treatment of 30 weeks (92 treatments). No unusual biochemical or hematologic abnormalities were reported. Adverse events included nonspecific symptoms which were believed to be typical for “the rapid infusion of any high-osmolarity solution.” In addition, patients in the highest dose cohort of 1,500mg/kg excreted 81.3 ± 18.8 mg of oxalic acid during and over the 6 hours following the infusion, which is above the normal range i.e. 10 to 60 mg/day. So in this very high dose cohort subjects could be at increased risk of renal calculi and obstructive nephropathy, but no information is reported on urine oxalic acid excretion at the lower doses.

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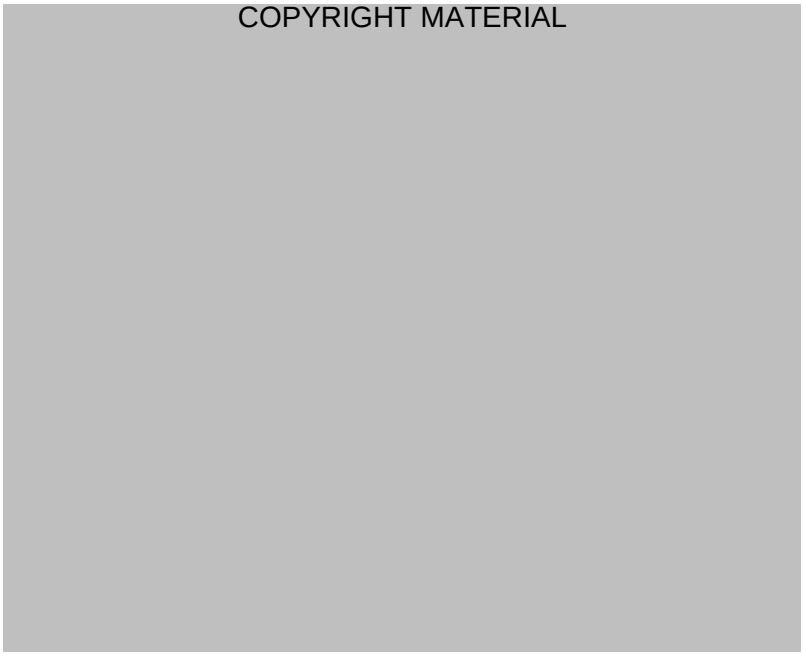
25 **Fowler** AA 3rd, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S; Phase I safety trial of intravenous **ascorbic acid** in patients with severe sepsis.Medical Respiratory Intensive Care Unit Nursing, Fisher BJ, Natarajan R. J Transl Med. 2014 Jan 31;12:32.

26 Phase I clinical trial of i.v. **ascorbic acid** in advanced malignancy. **Hoffer** LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L, Miller WH Jr. Ann Oncol. 2008 Nov;19 (11):1969-74.

Padayatty 2010[27] surveyed Alternative Medicine Practitioners attending a conference on Complementary and Alternative Medicine in 2006 and 2008 to detail their use of high dose intravenous vitamin C during the preceding months. A total of 172 practitioners responded that they had administered high dose vitamin C in the past year, with most of the patients treated by 48 physicians who had more than 100 patients per year and 5 physicians with more than 1000 patients per year. The average patient received 22 treatments with 28,000 mg of ascorbic acid every 4 days. While such survey information is anecdotal and of limited utility it is interesting that given such high treatment doses the main adverse events reported were nonspecific symptoms of lethargy and fatigue, vein irritation, mental status changes, nausea and vomiting. Of note there was a report of two patients with unspecified kidney stones, one patient each with oxalate and urate kidney stones and two cases of unspecified hemolysis. No adverse events were described as serious but practitioners may have been reluctant to describe events as serious despite the anonymity of the survey.

Table 5 Adverse Events in Padayatty et al. 2010



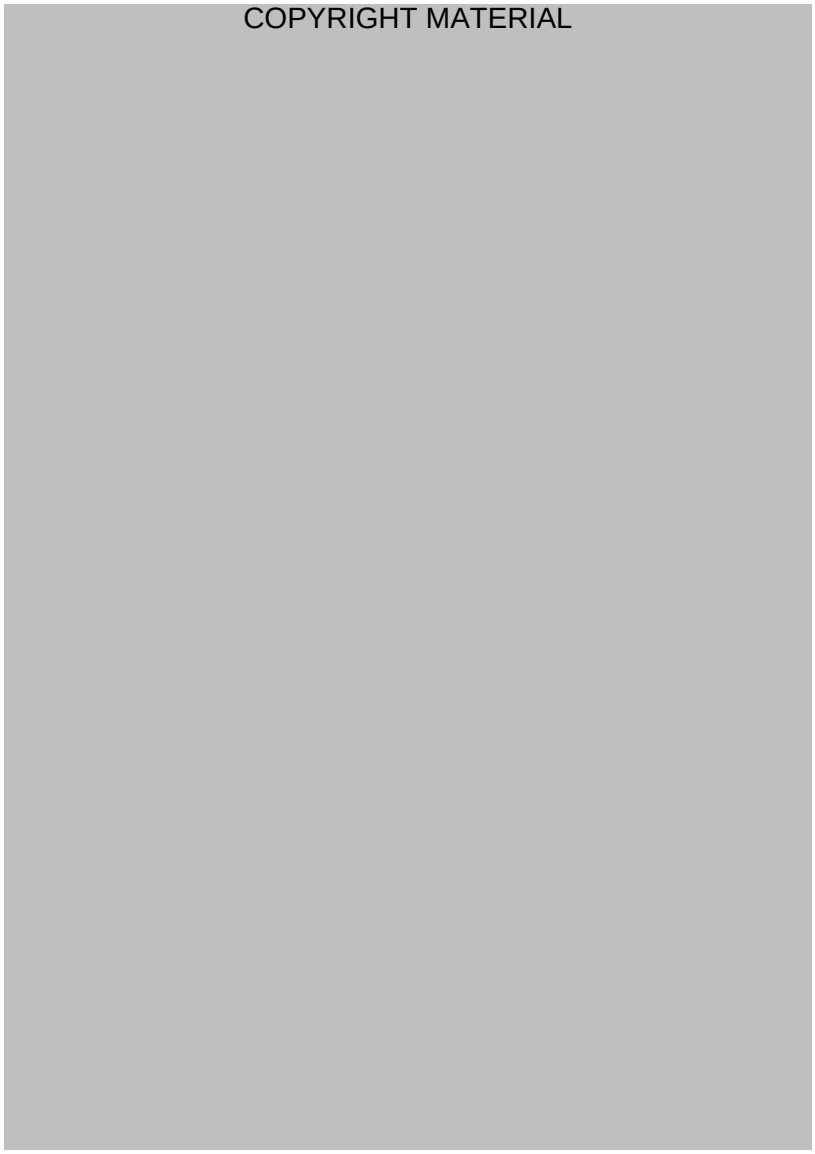
In addition, as part of a literature review of 187 papers published prior to 2010, on the use of high dose intravenous vitamin C, in the same publication, the authors were able to identify three cases of renal failure all in patients with pre-existing renal impairment and two patients with G6PD-deficiency who developed hemolysis.

27 **Vitamin C**: intravenous use by complementary and alternative medicine practitioners and adverse effects. **Padayatty** SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. PLoS One. 2010 Jul 7;5(7):

Stephenson 2013[28] was a Phase 1, safety, and tolerability, PK study in 17 cancer pts treated with high dose IV ascorbic acid for 4 consecutive days per week for 4 weeks. Doses of 30g/m^2, 50g/m^2, 70g/m^2, 90g/m^2 and 110g/m^2 (based on a 1.7m^2 adult that would correspond to doses of 51,000mg, 85,000mg, 119,000mg, 153,000mg and 187,000mg) were administered in 5 ascending dose cohorts of 3 patients each until a maximum tolerated dose was identified. In general, high-dose IV ascorbic acid was well tolerated, and most adverse events were mild and only possibly or probably related to the treatment. Treatment related nausea and headache were fairly common in all cohorts. Some patients had moderate to severe, hypercalcemia, hypernatremia and hypokalemia probably related to electrolytes concentrations in the infusion solution. Other reported adverse events seen in at least two subjects were transient hypertension and anemia. Cmax (49mM) and AUC (219h mM) appeared to peak at doses of 70g/m^2,so higher doses were not recommended for future studies even though there was no evidence of greater toxicity at the higher doses.

28 Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous **ascorbic acid** in patients with advanced cancer. **Stephenson** CM, Levin RD, Spector T, Lis CG. Cancer Chemother Pharmacol. 2013 Jul;72(1):139-46.

Table 6 Adverse Events Observed in Stephenson et al. 2013



Nielsen 2015[29] was an open-label, Phase 2, dose escalation study in 10 cancer pts with weekly single-dose intravenous infusions: Week 1-5,000mg, Week 2-30,000mg, Weeks 3 and 4-60,000mg. There were no serious adverse events. There was one case of transient arterial hypertension immediately after the infusion and two CTCAE Grade 1 "unrelated AEs" that were not further defined. The Cmax ranged from 1.5 to 37.8mM for

29 Elimination of **ascorbic acid** after high-dose infusion in prostate cancer patients: a pharmacokinetic evaluation. **Nielsen** TK, Højgaard M, Andersen JT, Poulsen HE, Lykkesfeldt J, Mikines KJ. Basic Clin Pharmacol Toxicol. 2015 Apr;116(4):343-8

doses up to 60,000mg. The elimination half-life was about 2 hours so it was not possible to maintain high ascorbic acid levels for long after the infusion was stopped.

Ludvigsson 1977[30] was a randomized (1:1), double-blind, placebo-controlled study comparing 10 or 30mg/day of oral ascorbic acid (placebo group) to 1000mg/day of ascorbic acid on the incidence and duration of the common cold symptoms in children age 9 to10yrs in Linkoping, Sweden. A 7-week pilot study enrolled 158 children from March to April 1973 and the 3-month main study enrolled 615 children from September to December 1973. Three subjects withdrew from the pilot study two due to stomach pains in the placebo group on 30mg of ascorbic acid and one due to headaches in the 1000mg group. Two subjects withdrew from the main study one due to a skin rash in the placebo group on 30mg of ascorbic acid and one due to nausea in the 1000mg group. A comparison of AEs by treatment group in the two studies shows a low percent of suspected adverse events <3% with slightly more headaches (1.3% vs. 0%) and nausea (1.9% vs. 0%) in the 1000mg ascorbic acid group compared to placebo.

Table 7 Adverse Events in Ludvigsson et al. 1977

There was no difference in any measured laboratory values [hemoglobin, hematocrit, red cell count, MCV, MCH, MCHC, serum iron, transferrin, cholesterol, triglycerides, blood sugar, serum ascorbic acid, prealbumin, albumin, alpha1antichymotrypsin, orosomucoid, alpha1antitrypsin, haptoglobin, alpha2macroglobulin, C3 (beta1e), fibrinogen, IgG, lgA, lgM, lgE and haemopexin] between treatment groups.

30 **Vitamin C** as a preventive medicine against common colds in children. **Ludvigsson** J, Hansson LO, Tibbling G. Scand J Infect Dis. 1977;9(2):91-8.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Bioavailability, comparing serum levels following oral and intravenous dosing, was measured at each steady-state dose level. Serum levels plateaued at each oral dose level at around 25 to 40 days. Serum levels reached a final maximal plateau in both men and women at around 75 to 85μM with doses of 200 to 500mg/day. Bioavailability was up to 100% for a single oral dose of 200mg but only 33% for a single oral dose of 1250mg due to increased renal excretion at the higher doses. Note the serum level at the current RDA is around 25μM (0.38mg/dL) or about 1/3 the maximum level that can be achieved with oral dosing. See Section 4.4.3 Pharmacokinetics Figure 1.

7.2.2 Explorations for Dose Response

Hodges et al. 1971 suggests that doses as low as 6.5mg/day can be adequate to treat scurvy in some patients. However, Hodges et al. 1971 shows that symptoms can resolve more rapidly with higher ascorbic acid doses of ascorbic acid such as 66.5 and 128mg/day. While it is possible that even higher doses above 128mg/day may further improve the rate of recovery, it is likely that at some point there would be a limit to the further benefit expected from higher doses as the body pool becomes sufficiently saturated.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

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. For example, ascorbic acid may lead to inaccurate results obtained for checking blood or urinary glucose levels if tested during or within 24 hours after infusion

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the pivotal efficacy trials of Krebs 1953 and Hodges et al. 1969 & 1971 at the low oral ascorbic acid doses of 6.5 to 128mg/day nor in the case reports from the literature included in this submission where adult subjects with suspected scurvy were treated with higher oral doses of 250 to 2000mg/day and children were treated with oral doses of 100 to 1000mg/day. There was one death out of 5 case reports of IV ascorbic acid in the treatment of severe suspected scurvy at doses of 200 to 1500mg in a 38 year old malnourished, anorexic, alcoholic with cirrhosis, anemia (Hct=20%) ascites and pedal edema[31]. He responded to IV ascorbic acid 1500mg/day with an increase in serum ascorbic acid from < 0.2mg/dL on admission to 1.3mg/dL on hospital day 4, but succumbed to septic shock from spontaneous bacterial peritonitis on hospital day 10 despite treatment with IV antibiotics and diuretics. This death was unlikely to be due to the treatment with intravenous ascorbic acid and was likely due to his concurrent illness. Padayatty et al. 2010, as part of their literature review of 187 papers published prior to 2010 noted two deaths in patients known to be at risk for high dose IV administration of ascorbic acid (one due to renal failure in a patient with nephrotic syndrome and one due to hemolysis in a patient with G6PD deficiency).

7.3.2 Nonfatal Serious Adverse Events

Intravenous doses up to 187,000mg/day have been given for off-label uses with the primary safety concerns being an increase in urinary excretion of oxalic acid, a vitamin C metabolite, at doses above 1500mg/kg/day, equivalent to 105,000mg/day for a 70kg adult, which increases the risk for calcium oxalate kidney stones[32] and hemolysis with infusions above 25,000mg[33] in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to lower amounts of reduced glutathione in G6PD deficient red blood cells making them more susceptible to oxidative stress[34].

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31 Scurvy in an **alcoholic** malnourished cirrhotic man with spontaneous bacterial peritonitis. **Maltos** AL, **Portari** GV, Saldanha JC, Bernardes Júnior AG, Pardi GR, da Cunha DF. Clinics (Sao Paulo). 2012;67(4):405-7.

32 Phase I clinical trial of i.v. **ascorbic acid** in advanced malignancy. **Hoffer** LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L, Miller WH Jr. Ann Oncol. **2008** Nov;19(11):1969-74.

33 https://en.wikipedia.org/wiki/Glucose-6-phosphate_dehydrogenase_deficiency

34 Acute **haemolysis** induced by high dose **ascorbic acid** in **glucose-6-phosphate** dehydrogenase deficiency. Rees DC, Kelsey H, Richards JD. BMJ. 1993 Mar 27;306(6881):

7.3.3 Dropouts and/or Discontinuations

Krebs 1953- One subject in the 10mg prophylactic group abandoned the study early at about 250 days without every developing any symptoms of scurvy. There were no other reports of early dropouts or discontinuations due to treatment with ascorbic acid.

Hodges 1969- Two of the six subjects escaped from the hospital on Study Day 54 before developing any symptoms of scurvy, so study results are reported for only the four remaining subjects.

Hodges 1971-One subject withdrew consent during the depletion phase of the study before developing any symptoms of scurvy, so study results are reported for only the five remaining subjects.

> Medical officer's comments-
> There is no evidence in these pivotal trials of the need to discontinue or limit dosing with ascorbic acid in patients with scurvy due to drug-related adverse events.

7.3.4 Significant Adverse Events

There were no serious adverse events in study MGP-101, nor reported as a result of treatment with ascorbic acid in the pivotal trials or safety trials reviewed in this submission. There were two subjects with chest pain and possible cardiac events during the depletion phase in Krebs 1953 who required emergency care but responded immediately to ascorbic acid replacement and recovered.

There are however individual case reports in the published literature of at least 3 cases of renal failure in patients with pre-existing renal impairment, after receiving high intravenous doses of 2,500 to 60,000mg. One of these subjects died after receiving a dose of 45,000mg. There are also individual case reports of at least 2 patients with GP6D deficiency who developed hemolysis after receiving 80,000mg intravenously, one of whom died as a result of the event.

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

All available results from the submitted literature are reviewed above. This section, therefore, will not include other specific findings such as laboratory results and ECGs.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no evidence of a dose response with respect to adverse reactions over the proposed (b) (4) in the pivotal or published safety trials which were reviewed in this application. There was evidence of increased oxalate excretion at very high intravenous doses i.e. 1500mg/kg (Hoffer 2008).

7.5.2 Time Dependency for Adverse Events

There was no evidence of drug-related adverse reactions in published studies using ascorbic acid to treat symptoms of scurvy at doses up to 1000mg/day. When used at high intravenous doses nonspecific symptoms including nausea, vomiting, headache, facial flushing, perspiration, dizziness, fatigue and weakness associated with the rapid infusions have been reported around the time of the infusion. These symptoms are usually self-limiting once the infusion is discontinued. With chronic dosing at very high doses subjects may be at increased risk of oxalate nephropathy. Monitoring is recommended in such cases.

7.5.3 Drug-Demographic Interactions

Due to the risk of oxalate nephropathy at very high intravenous doses, subjects with decreased renal function may be at greater risk of renal toxicity.

7.5.4 Drug-Disease Interactions

Hemolysis has been reported with administration of high doses of ascorbic acid in patients with glucose-6-phosphate dehydrogenase deficiency. Monitoring is recommended in such cases.

7.5.5 Drug-Drug Interactions

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

Ascorbic acid may decrease activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated in vitro by ascorbic acid.

Ascorbic acid may acidify the urine increasing renal excretion and lowering serum concentrations of certain medications (amphetamine, fluphenazine, mexiletine).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies have not been performed with ascorbic acid.

7.6.2 Human Reproduction and Pregnancy Data

There are no available data on use of this product in pregnant women to inform a drug-associated risk of adverse developmental outcomes. The published literature describes that pregnant women taking oral ascorbic acid for supplementation and through diet at doses ranging from 500 to 1000 mg/day did not experience adverse developmental outcomes. A published meta–analysis of randomized studies evaluating a large number of pregnant women who took oral ascorbic acid through diet and supplementation at doses ranging from 500 to1000 mg/day between the 9th and 16th weeks of pregnancy showed no increased risk of adverse pregnancy outcomes like miscarriage, preterm premature rupture of membranes, preterm delivery or pregnancy induced hypertension when compared to placebo.

Conditional scurvy occurring in newborn infants due to withdrawal from high intake of ascorbic acid during pregnancy had been reported in early literature in two cases but has not been substantiated with more recent findings and is no longer considered credible[35].

7.6.3 Pediatrics and Assessment of Effects on Growth

Infantile scurvy occurs most frequently in primarily bottle fed children between 5 months and 12 months of age because most newborn infants have adequate fetal stores and breast feeding typically provides an adequate source of vitamin C. Grewar 1965 describes 66 cases of infantile scurvy in children primarily between 5 and 12 months of age who were adequately treated with oral or intravenous vitamin C at doses of 100 to 1000mg/day. Older malnourished children or those on restricted diets can also develop scurvy if their diet is deficient in vitamin C. Ratanachu-Ek et al. 2003 describes 28 pediatric patients age 10 months to 9.5 years (mean age 2.5 yrs) with scurvy who were adequately treated with oral vitamin C doses of 150 to 300mg/day.

McGuff Pharmaceuticals has received orphan designation for the proposed indication "treatment of scurvy," so no waiver from pediatric assessment under PREA is required. However, the applicant has included recommended dosing for children > (b) (4) months based on age groups (b) (4).

(b) (4)

35 Vitamin and Mineral Safety 3rd Edition (2013) Council for Responsible Nutrition (CRN) https://www.crnusa.org

The applicant does not present a clear explanation for how the (b) (4) doses in children were determined by age group but describes that they are within the range of current recommendations of the Mayo Clinic[36], Pascorbin[37] (an ascorbic acid containing product marketed in Germany) and what had been reported in the literature (Ratanachu-Ek 2003).

The DPMH consult, after reviewing the relevant literature and the current submission, is recommending labeling for children 5 months of age and older but is proposing lower doses closer to those currently approved in multivitamin infusion products (i.e. 80mg/day for infants and children up to 11 years of age):

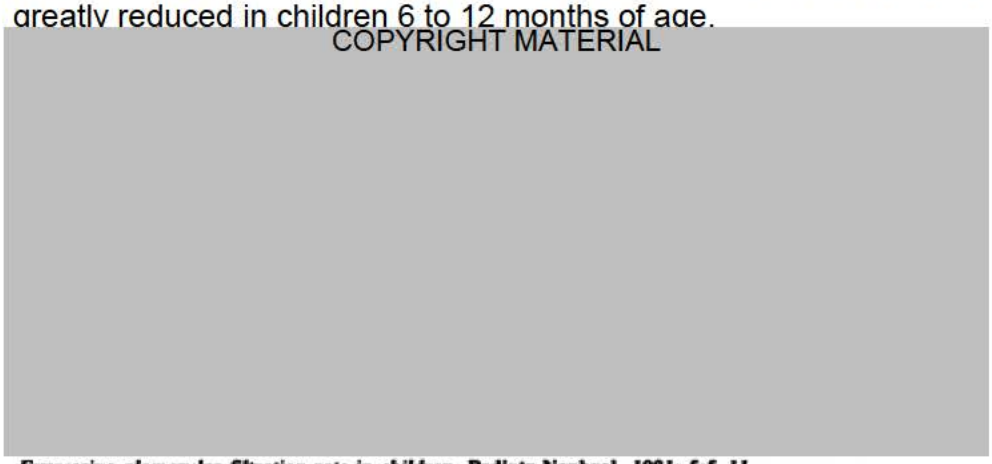
- 5 to 12months of age → 50mg/day
- 1 to 3 years of age → 100mg/day
- 4 to 10 years of age → 100mg/day
- 11 years and above → 200mg/day

with repeat dosing only recommended only for children 11 years and above.

Medical officer's comments-
The DPMH recommendations are similar but not exactly the same as proposed by this medical reviewer. Given that scurvy is a deficiency state it makes sense to this reviewer to treat with doses above the maintenance RDA levels in order to more rapidly treat the clinical symptoms of scurvy. This medical reviewer has concluded given the PK data for ascorbic acid in adults that 200mg/day is an appropriate adult dose (see Efficacy Summary). This dose is double the average adult maintenance dose and as such should replenish body pools of ascorbic acid more rapidly. In an analogous fashion double the pediatric maintenance dose seems an appropriate choice for the treatment of pediatric scurvy. Therefore this medical reviewer recommends doses of 100mg/day for children 5 months of age up to 14 years of age. At age 14 years the RDA goes from 45 to 75mg/day so 200mg/day seems to be a more appropriate dose for children 14 years and older and adults. The DPMH review recommends a lower dose of 50mg/day for children 5 to 12 months, primarily because of the concern over renal immaturity and the potential for inducing oxalate nephropathy in the younger children. It is this reviewer's assessment that such a concern is primarily theoretical as treatment is likely to be short term < one week and oxalate nephropathy has not been reported in children in the literature at these proposed low doses. In fact, Grewar 1965 demonstrates that doses of 100 too

36 http://www.mayoclinic.org/drugs-supplements/vitamin-c/dosing/HRB-20060322.
37 http://www.ndrugs.com/?s=pascorbin&t=dosage

1000mg/day were given safely to children 5 to 12 months of age. While it is true that renal function does not fully reach adult levels in all pediatric patients until 2 years of age, GFR nearly doubles in the first 6 months of life so that the risk is greatly reduced in children 6 to 12 months of age.



Expressing glomerular filtration rate in children, **Pediatr Nephrol.** *1991; 5:5–11.*

The DPMH consult recommends adult dosing of 200mg/day at age 11 years while this reviewer is recommending such dosing at age 14 years, given that the RDA is still 45mg in younger children 9 to 13 years of age (see Table 4). That said, either 11 or 14 years are probably reasonable ages to start the adult dosing given the adequate safety profile of ascorbic acid.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Drug abuse, withdrawal and rebound are unlikely with ascorbic acid. There is a potential for off-label use by health care professionals in Complementary and Alternative medicine (Padayatty et al. 2010) as well as for unproven indications such as wound healing, cancer chemotherapy, treatment of burns or sepsis.

Rapid infusion can result in nonspecific symptoms such as nausea, vomiting, facial flushing, headache, fatigue etc. which are typically self-limiting. Chronic use of high doses can result in oxalate nephropathy which should be treated by discontinuing therapy and giving supportive care.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Ascorbic Acid Injection, USP 500 mg/mL (Ascor L 500®) manufactured by McGuff Pharmaceuticals has been granted marketing authorization in Canada (approved 2010),

New Zealand (approved 2010), and Peru (approved 2015). The approved product labeling for Ascor L 500® in Canada includes the following dosing information.

> The average protective dose of ascorbic acid for adults is 70 to 150 mg daily. In the presence of scurvy, doses of 300 mg to 1 gram daily are recommended. However, as much as 6 grams have been administered parenterally to normal adults without evidence of toxicity.
>
> To enhance wound healing, doses of 300 to 500 mg daily for a week to ten days, both preoperatively and postoperatively, are generally considered adequate, although considerably larger amounts have been recommended. In the treatment of burns, doses are governed by the extent of tissue injury. For severe burns, daily doses of 1 to 2 grams are recommended. In other conditions in which the need for ascorbic acid is increased, three to five times the daily optimum allowances appear to be adequate.

MPI has received no reports of Adverse Events from New Zealand, Canada or Peru since commercial distribution commenced in those countries.

9 Appendices

9.1 Literature Review/References

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Ratanachu-Ek S1, Sukswai P, Jeerathanyasakun Y, Wongtapradit L. Scurvy in pediatric patients: a review of 28 cases. J Med Assoc Thai. 2003 Aug;86 Suppl 3:S734-40.

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9.2 Labeling Recommendations

Dose and Administration-
Recommend doses for the treatment of symptoms of scurvy:

- 100mg/day for children age 5 months to 14 years.
- 200mg/day for children > 14 years and adults.

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

Medical officer's comments-
Use of intravenous ascorbic acid at much higher doses has been studied in the published literature for the treatment of burns, wound healing, cancer

chemotherapy, etc. There is currently inadequate clinical evidence to support the efficacy and safety of these off-label uses.

Warning and Precautions-

- Oxalate nephropathy: 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.
- Hemolysis: Patients with glucose-6-phosphate dehydrogenase deficiency are at risk of severe hemolysis; a reduced dose is recommended.
- Laboratory Test Interference: Ascorbic acid may interfere with laboratory tests based on oxidation-reduction reactions, including blood and urine glucose testing.

Medical officer's comments-
Isolated cases of oxalate nephropathy and hemolysis have been reported in the literature but at much higher doses than those proposed for the treatment of scurvy (see 7.3.2 Nonfatal Serious Adverse Events).

Adverse Reactions-
Most common adverse reactions are pain and swelling at the site of infusion.

Medical officer's comments-
There was no evidence of drug-related adverse reactions in published studies using ascorbic acid to treat symptoms of scurvy at doses up to 1000mg/day. When used at high intravenous doses nonspecific symptoms including nausea, vomiting, headache, facial flushing, perspiration, dizziness, fatigue and weakness associated with the rapid infusions have been reported around the time of the infusion. These symptoms are usually self-limiting once the infusion is discontinued.

9.3 Advisory Committee Meeting

None

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

/s/

WILLIAM A LUBAS
09/27/2017

MARINA ZEMSKOVA
09/28/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 209112 Seq0000 **Applicant: McGuff Pharmaceuticals, Inc.** **Stamp Date: September 2, 2016**

Drug Name: Ascor (ascorbic acid) NDA/BLA Type: 505 (b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	No ISS is necessary as there is only one clinical PK study in this submission
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	No ISE is necessary as there is only one clinical PK study in this submission
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)(2)			The Applicant currently markets the Ascor L 500 as an unapproved drug. The submission relies on literature to support efficacy and safety.
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?			X	Dosage and schedule recommendations are based on literature.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and			X	No clinical efficacy

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Indication: Treatment of Scurvy				studies were performed by the Applicant. Clinical efficacy is based on the literature.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	See comment under item #14.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Clinical safety is based on the literature.
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	Clinical safety is based on the literature.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The Applicant has received orphan designation so no waiver for pediatric assessment is needed. The Applicant did submit dosing recommendations for children > (b) months of age.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Data was submitted for the one clinical PK study in this submission
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	See comment under item #14.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	See comment under item #14.
34.	Are all datasets to support the critical safety analyses available and complete?			X	See comment under item #14.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	See comment under item #14.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			No deaths or serious adverse events or adverse dropouts were observed in the single PK study.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	See comment under item #36.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	See comment under item #14.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	See comment under item #14. The best studies to support efficacy from the literature include

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					two studies performed in prisoner volunteers and one study performed in conscientious objectors who were able to avoid deployment during WWII by enrolling in the study. An ethics consult was obtained to evaluate whether appropriate informed consent was available to permit use of these data in the efficacy determination and it was determined that it was ethically acceptable to use data from these studies to support this indication.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

William Lubas MD, PhD	October 27, 2016
Reviewing Medical Officer	Date
Marina Zemskova MD	October 27, 2016
Clinical Team Leader	Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

WILLIAM A LUBAS
10/27/2016

MARINA ZEMSKOVA
10/27/2016