Australian Product Information
Biological Therapies Sodium Ascorbate Solution
Injection for Intravenous Infusion 30 g in 100 mL, 15 g in 50 mL, 15 g in 100 mL, 45 g in 500 mL

AUST R 47757, 47750, 22283, 22254, 22282, 22284, 22286

1. Name of the Medicine

Sodium ascorbate

2. Qualitative and Quantitative Composition

Each Biological Therapies Sodium Ascorbate Injection for Intravenous Infusion contains sodium ascorbate and water for injections.

All of the Sodium Ascorbate Solution Injections mentioned in this product information sheet are hypertonic and single use. The pack sizes for these products are as described below.

Ingredients per mL:

Product	Sodium Ascorbate	Water for Injections
30 g in 100 mL	300 mg/mL	qs.
15 g in 50 mL	300 mg/mL	qs.
15 g in 100 mL	150 mg/mL	qs.
45 g in 500 mL	90 mg/mL	qs.

Summary Information:

Sodium Ascorbate Solution 30 g in 100 mL (300 mg/mL)
AUST R 47757 (vial) & AUST R 47750 (bag)

Osmolality	Sodium/mL			Ascorbate/mL		
mOsm/kg	mg	mmol	mEq	mg	mmol	mEq
2366	34.8	1.50	1.50	265.2	1.50	1.50

Sodium Ascorbate Solution 15 g in 50 mL (300 mg/mL)
AUST R 22283 (vial) & AUST R 22254 (bag)

Osmolality	Sodium/mL			Ascorbate/mL		
mOsm/kg	mg	mmol	mEq	mg	mmol	mEq
2366	34.8	1.50	1.50	265.2	1.50	1.50

Sodium Ascorbate Solution 15 g in 100 mL (150 mg/mL)
AUST R 22282 (vial) & AUST R 22284 (bag)

Osmolality	Sodium/mL			Ascorbate/mL		
mOsm/kg	mg	mmol	mEq	mg	mmol	mEq
1268	17.4	0.75	0.75	132.6	0.75	0.75

Sodium Ascorbate Solution 45 g in 500 mL (90 mg/mL)
AUST R 22286 (bag)

Osmolality	Sodium/mL			Ascorbate/mL		
mOsm/kg	mg	mmol	mEq	mg	mmol	mEq
782	10.44	0.45	0.45	79.56	0.45	0.45

Sodium ascorbate is a white, or very slightly yellow crystalline powder which is odourless and has a slightly salty taste. It is freely soluble in water (1 g is soluble in 3 mL water) and dissolves to give a clear, colourless or slightly yellow solution.

3. Pharmaceutical Form

Biological Therapies Sodium Ascorbate Injection for Intravenous Infusion is a clear and colourless to straw coloured solution with a pH range of 6.0 to 8.0. Presentation is in plastic bags or glass vials.

Biological Therapies Sodium Ascorbate Solution Injection for Intravenous Infusion is a sterile, non pyrogenic concentrated solution in sterile Water for Injections.

4. Clinical Particulars

4.1 Therapeutic Indications

Biological Therapies Sodium Ascorbate Injections are indicated for the treatment of vitamin C deficiency when oral treatment is not feasible.

4.2 Dose and Method of Administration

Treatment of ascorbate deficiency is usually achieved with oral ascorbate. Biological Therapies Sodium Ascorbate Solution Injection for Intravenous Infusion may be used when oral treatment is not feasible. The recommended dose in adults is 100-500 mg daily, and in children, 100-300 mg daily. Treatment may continue for up to three weeks.

Single entry only should be made into the bag or vial and the appropriate dose removed under strict aseptic conditions. The dose may then be given as a straight push or added to an infusion bag of sterile Water for Injections, saline or dextrose.

If the solution is injected too concentrated and/or too quickly into a small vein, there may be substantial pain in the vein. It is recommended if possible, to only inject into a large vein - usually the cubital vein although the veins on the back of the hand have been used. Pain can be minimised by slowing the infusion rate, or by diluting the infusion, initially 50:50 with sterile Water for Injections. Further dilution and/or slowing of the infusion rate may be necessary for patients with fine veins or who are unable to tolerate the pain. Where veins are very fine or very damaged even diluting to isotonicity may be required. Isotonic strength is 30 grams sodium ascorbate in 1000 mL of sterile Water for Injections. Gently massaging the arm along the course of the vein can also help relieve pain. Pain may also be reduced by warming the IV solution to near body temperature.

Care should be exercised to avoid extravasation during the infusion. If this occurs with the hypertonic infusion it can cause quite severe pain. Under these circumstances the needle should be withdrawn and an ice pack (wrapped in cloth) applied to the injection site. Pressure over the site should be maintained for 5 to 10 minutes during which time the pain will usually subside. Provided the patient (and the doctor) are amenable, the other cubital vein may then be tried. Pain usually limits the amount infused/injected extravenously resulting in no long term after effects. However, if pain is blocked and extravasation occurs then significant sclerosing and/or ulceration could occur.

4.3 Contraindications

Biological Therapies Sodium Ascorbate Solution Injection for intravenous infusion is contraindicated in those persons who have shown hypersensitivity to any component of this preparation.

4.4 Special Warnings and Precautions for Use

Use with caution in the following circumstances:

1. Hyperoxaluria
People with hyperoxaluria or who are prone to kidney stones should exercise caution in consuming or being injected with large amounts of Vitamin C. Ascorbate may cause acidification of the urine, occasionally leading to precipitation of urate, cystine or oxalate stones or drugs in the urinary tract.

2. Iron overload and Iron absorption
Large doses of Vitamin C may be dangerous in patients with haemochromatosis, thalassaemia, polycythemia, leukaemia or sideroblastic anaemia due to enhanced absorption of dietary iron, although this enhancement occurs primarily with orally administered Vitamin C.

3. Hypernatraemia, congestive cardiac failure or severely impaired kidney function
Care should be exercised in administering intravenous sodium ascorbate to those patients who either have hypernatraemia, congestive cardiac failure or may be unable to handle the increased sodium load as a result of renal insufficiency.

4. Uricosuria
Vitamin C tends to increase the excretion of uric acid and to correspondingly lower serum uric acid. However, no effect of Vitamin C on uric acid excretion has also been reported.

5. Sickle Cell Crisis
Rarely, high doses of Vitamin C have been associated with sickle-cell crisis in patients with sickle-cell anaemia.

6. Glucose-6-phosphate dehydrogenase (G6PD) Deficiency
In this condition red cells become highly sensitive to many different drugs and conditions. There have also been a few reports in the literature of high dose Vitamin C inducing haemolysis in G6PD deficient patients.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

Ascorbic acid, as a strong reducing agent, interferes with laboratory tests involving oxidation and reduction reactions. Falsely elevated or false negative measurements may be obtained in plasma, faeces or urine depending on such factors as the concentration of ascorbate, pH and the specific method employed. Interference may be obtained with glucose measurement by glucose oxidase, or older methods employing reduction of copper, zinc or iron. Vitamin C also interferes with autoanalyser determinations of transaminases and lactic dehydrogenase. It can also affect some tests for occult blood and serum theophylline levels. Provided attention is paid to the test method and to avoiding supplements before such testing there should be no problems.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Aspirin: Increased urinary excretion of ascorbic acid and decreased excretion of aspirin occur when the drugs are administered concurrently. Aspirin has been found to reduce the absorption of ascorbic acid by about a third.

Dicoumarol: An isolated case where the prothrombin time is reduced following intake of ascorbic acid.

Warfarin: Several cases have been reported in which ascorbic acid appeared to reduce the effect of warfarin. These reports have not been confirmed in subsequent trials.

Ethinyloestradiol: Ascorbic acid in an oral dose of 1 g has been reported to increase the bioavailability of ethinyloestradiol in oral contraceptive preparations. This effect can be important if ascorbic acid supplementation is discontinued, as the drop in hormone absorption may lead to breakthrough bleeding or even contraceptive failure. However, there are no studies on this ethinyloestradiol effect when the Vitamin C has been administered as an intravenous or intramuscular injection.

Iron (Oral): Oral ascorbic acid can increase absorption of iron. However, feedback mechanisms usually control its excessive absorption.

Desferrioxamine: Ascorbic acid may increase the excretion of iron when given concomitantly with desferrioxamine. However, cases of cardiomyopathy and congestive heart failure have occurred in patients on concomitant treatment. It may be that ascorbic acid mobilises iron from spleen and other reticuloendothelial tissues resulting in increased iron deposition in visceral organs. In general it is recommended that the dose of ascorbic acid be administered an hour or two after the infusion of desferrioxamine has started.

Isoprenaline: The chronotropic effect of isoprenaline decreases when administered concurrently with ascorbic acid.

Alcohol: Alcohol reduces ascorbic acid levels.

Disulfiram: Chronic use or high doses of ascorbic acid may interfere with the disulfiram - alcohol interaction when used concurrently.

Mexiletine: High doses of ascorbic acid may accelerate renal excretion of mexiletine when the drugs are administered concurrently.

Barbiturates or primidone: The urinary excretion of ascorbic acid may increase when administered together with barbiturates or primidone.

Fluphenazine and other phenothiazines: Ascorbic acid has been reported to decrease the therapeutic effect of phenothiazines. The concentration of fluphenazine may also be reduced.

Amphetamine and tricyclic anti-depressants: Ascorbic acid decreases renal tubular reabsorption of amphetamines and tricyclic anti-depressants.

General: Because ascorbate is a urinary acidifier in large doses, the excretion of drugs that are weak acids may be decreased and the excretion of drugs that are weak bases may be increased.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available.

Use in pregnancy

Australian pregnancy classification:

Exempt from classification.

As there are no documented formal studies studying intravenous Vitamin C during pregnancy, caution should be exercised in treating pregnant women. Ingestion of large doses of ascorbate during pregnancy has resulted in scurvy in neonates.

Use in lactation

Vitamin C crosses the placenta and passes freely into human breast milk. However, as there are no documented formal

studies studying intravenous Vitamin C during lactation, caution should be exercised in treating breastfeeding women.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Reported adverse effects include:

Body as a whole: fever, fatigue, malaise, somnolence.

Gastrointestinal: nausea, vomiting, diarrhoea, abdominal pain, pancreatitis.

Haematological: haemolysis, sickle-cell crisis (refer to **Section 4.4 Special Warnings and Precautions for Use**).

Metabolic: gout.

Neurological: headache, dizziness, cerebrovascular disorder, encephalopathy, meningitis-like reaction.

Renal: renal impairment, renal pain, haematuria, hyperoxaluria, hyperuricosuria, renal calculi.

Skin: Rash, urticaria.

Too rapid intravenous administration of the solution may cause temporary faintness or dizziness. Such reactions are infrequent and if they do occur are usually mild and pass within 15 to 20 minutes. These symptoms may be related to the hypoglycaemic action of Vitamin C.

Being a potentially irritating solution to the vein, thrombophlebitis is a theoretical possibility and a potential side effect of short-term venous catheterisation. Therefore, the administering physician should be aware of its possibility and if it does occur, manage appropriately.

Some dehydration usually occurs, so adequate fluid replacement should be given. Water should be kept close by. It is not uncommon to drink several glasses of water during and after a sodium ascorbate infusion. Patients may also usually experience some diuresis following sodium ascorbate infusion.

There may be a transient increase in serum cholesterol in atherosclerotic patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

There have been a few reports of renal failure reportedly due to excessive oxalate formation following massive doses of intravenous Vitamin C. However, some doubt has recently been cast upon the laboratory methods for determination of oxalate. Vitamin C is inherently unstable in body fluids once these are removed from the body or post mortem without homeostatic control mechanisms, resulting in the in vitro formation of oxalate. Also, many of the earlier test methods for estimation of oxalate have subsequently been found to be over-estimated as a result of interference by Vitamin C. Nevertheless, because the increase in oxalate excretion is controversial, care should be exercised in those patients with renal impairment or who exhibit hyperoxaluria. It may be wise during prolonged sodium ascorbate infusion to monitor kidney function.

Within the many decades of clinical use of sodium ascorbate infusion, there have been no reported severe over-dosage effects, other than pain or a transient light headed feeling. This light-headedness may be related to the hypoglycaemic action of Vitamin C. This feeling usually passes after 15 to 20 minutes and is helped by eating fruit, having a meal or drinking some fruit juice.

Haemolytic anaemia has been reported in few cases of individuals with glucose-6-phosphate dehydrogenase deficiency.

Treatment of Overdosage:

In event of overdosage, symptomatic or supportive measures should be taken. Sodium ascorbate infusion should be discontinued.

Should an allergic reaction occur, 0.5 – 1 mL of Adrenaline Injection BP (Adrenaline 1 in 1,000) can be administered intramuscularly and repeated every 10 minutes until improvement occurs. Antihistamines and corticosteroids by slow intravenous injection are a useful adjunctive measure.

For information on the management of overdose please contact the Poisons Information Centre on 13 11 26 (Australia).

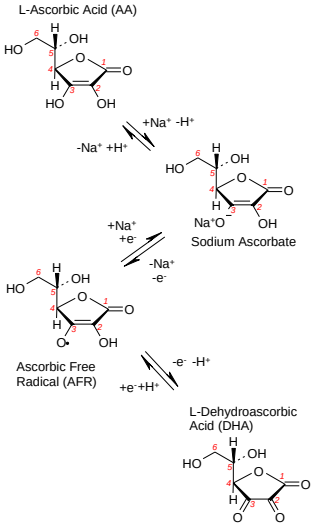
5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Vitamin C, a water-soluble vitamin, is essential for the synthesis of collagen and intracellular material. Vitamin C deficiency develops when dietary intake is inadequate. It is rare in adults, but may occur in infants, alcoholics or the elderly. Deficiency leads to the development of a well-defined syndrome known as scurvy. This is characterised by capillary fragility, bleeding (especially from small blood vessels and the gums), normocytic or macrocytic anaemia, cartilage and bone lesions and slow healing of wounds. Body stores of vitamin C in health are about 1.5 to 3 g. Symptoms of deficiency develop when body stores are less than 0.5 g.

Mechanism of action/effect:

Ascorbic Acid is reversibly oxidised to dehydroascorbic acid (DHA).

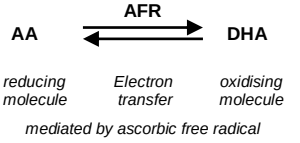


DHA may also exist in a hydrated form involving C_2 and C_3. The conversion between the ascorbate anion and DHA involves a transient, very short-lived ascorbic free radical (AFR). The formation of the ascorbic free radical has been implicated as an important energised molecule in several metabolic reactions. The oxygen atom attached to C_3 in the AFR has an unpaired electron which makes it very reactive.

The hydrogen atoms of the hydroxyl groups attached to C_2 and C_3 of the ascorbic acid molecule (AA) are quite labile because of the tendency of high density electrons in the $C_2 = C_3$ double bond to be displaced towards the oxygen of the carbonyl groups.

Ascorbic Acid (AA), ascorbic free radical (AFR) and dehydroascorbic acid (DHA) are known to participate in biochemical reactions. Ascorbic Acid (or ascorbate, such as sodium ascorbate) acts as a strong reducing agent, ascorbic free radical acts as both a reducing agent and as an oxidising agent as appropriate, and DHA as an oxidising agent.

In shorthand biochemical terminology, AA and DHA act as a redox couple.



DHA is inherently unstable and consequently does not normally accumulate in the body. Under optimal physiological conditions the body can convert DHA back to AA using reduced glutathione or other SH groups. If this reconversion does not occur, the excess DHA undergoes spontaneous hydrolytic ring rupture (delactonization) to form molecules such as 2,3 diketogulonic acid, L-xylose, L-lyxonic acid, L-threonic acid and ultimately oxalic acid.

At physiological pH, ascorbic acid exists as an anion (ascorbate) and is more water soluble (hydrophilic) whereas dehydroascorbic acid is hardly ionised and is more lipid soluble (lipophilic). This difference in solubility may help account for the successful transport of AA via vitamin C transporters into the intracellular and intramitochondrial environments. Small quantities of DHA in the cell membranes, or intraorganelle membranes encourage the transport of ascorbates. Alternatively, DHA may be reduced by glutathione or other SH groups to form ascorbic acid thereby releasing it into the cytosol. The formation of a redox pair between DHA in the cell or organelle membrane and AA is a mechanism for allowing the ordered transfer of electrons. Ascorbate transporters can become faulty leading to impaired vitamin C transport.

Clinical trials

No data available.

5.2 Pharmacokinetic Properties

Absorption:

The disposition of ascorbic acid was studied in seven healthy males aged 20 to 26 years. Doses of 15 mg to 1250 mg were administered twice daily in an oral solution at least 90 minutes before meals. Absorption of ascorbate was saturable, the plasma concentration reaching 80% saturation at a dose of 200 mg/day and 100% saturation at 1 g/day. Concentrations in neutrophils, monocytes and lymphocytes reached plateaux at a dose of 100 mg per day. Eighty percent of 100 mg/day dose was absorbed, but only 46% of a 1.25 g/day dose.

Distribution:

Ascorbate is widely distributed to body tissues.

Metabolism:

Ascorbate is metabolised to dehydroascorbic acid, ascorbate-2-sulphate, diketogulonic acid and oxalic acid, which are excreted by the kidneys.

Excretion:

Once the body stores are saturated, ascorbate is eliminated unchanged by the kidneys. In healthy volunteers, 50% of a 200 mg dose was excreted and almost the entire dose of doses above 500 mg. Therefore, doses above 500 mg/day had little impact on body stores. The plasma terminal elimination half-life is 3h. Oxalate and urate excretion were increased in healthy volunteers at doses of 1 g/day compared with lower doses.

5.3 Preclinical Safety Data

Genotoxicity

Studies demonstrating the mutagenic effect of Vitamin C have nearly all been *in vitro* usually in the presence of copper or chromium which may induce the ascorbyl free radical without any of its *in vivo* control mechanisms. Therefore the relevance of this data to clinical use in man is not known.

Presently there is no evidence that high intakes of Vitamin C will be mutagenic in man, and studies have concluded that 10 g/day will not be mutagenic or teratogenic in humans.

Carcinogenicity

No data available.

6. Pharmaceutical Particulars

6.1 List of Excipients

Water for injections.

6.2 Incompatibilities

Sodium ascorbate (as ascorbic acid injection) is reported to be incompatible with ferric salts, oxidising agents, and salts of heavy metals, particularly copper.

Injections of sodium ascorbate are reported to be incompatible with aminophylline, bleomycin sulfate, erythromycin lactobionate, nafcillin sodium, doxapram hydrochloride, cephazolin sodium, nitrofurantoin sodium, conjugated oestrogens, and sulphafurazole diethanolamine. Incompatibility, dependent on pH or concentration, has been reported with chloramphenicol sodium succinate, chlorothiazide sodium, hydrocortisone sodium succinate and penicillin G potassium.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Store at 2 °C to 8 °C (Refrigerate. Do not freeze). Biological Therapies Sodium Ascorbate Solution should not be used if there is visible turbidity or crystallisation. Normal colour is colourless to straw coloured. However, under extreme conditions or post expiry date the solution gradually darkens to very dark yellow and finally orange/brown. Excessive darkening is an indication of increased break down.

6.5 Nature and Contents of Container

Container type:

Vials: Clear glass vial with rubber stopper and aluminium seal with a tear-away centre.

Bags: Semi-opaque PVC bag with pigtail tubing in a clear plastic pouch.

Pack sizes:

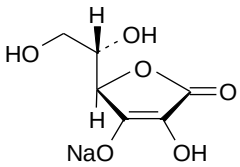
Vial products: 1 vial per carton.
Bag products: 1 bag per pouch.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical Properties

Chemical structure



$C_6H_7O_6Na$

Molecular weight = 198.11

CAS number

134-03-2

7. Medicine Schedule (Poisons Standard)

Not scheduled

8. Sponsor

Biological Therapies Sodium Ascorbate Solution Injections for Intravenous Infusion are manufactured in Australia by:

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Website: www.biologicaltherapies.com.au
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9. Date of First Approval

11 October 1999

10. Date of Revision

11 September 2018

Summary Table of Changes

Section Changed	Summary of New Information
8	Sponsor's fax number and website address added