PASCOE NATURMEDIZIN

PASCORBIN®

1. NAME OF THE MEDICINAL PRODUCT

PASCORBIN®
Active substance: ascorbic acid 150 mg per ml of solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 150 mg ascorbic acid.

Each 5-ml ampoule contains:
Pharmacologically active ingredient: ascorbic acid 750 mg.

Each injection vial of 50 ml of solution for injection contains:
Pharmacologically active ingredient: ascorbic acid 7.5 g.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of clinical vitamin C deficiency states that cannot be corrected by dietary intervention or substituted orally.

Methaemoglobinaemia in childhood.

4.2 Posology and method of administration

PASCORBIN® is provided for peripheral-intravenous injection.
Unless otherwise prescribed, administer 5 ml daily by slow intravenous injection, up to 50 ml solution for injection when added to an infusion.

Vitamin C replacement therapy during parenteral nutrition:
For prophylaxis of vitamin C deficiency during prolonged parenteral nutrition:

- adults should be given 100 to 500 mg ascorbic acid per day (equivalent to 0.7 ml to 3.3 ml PASCORBIN®) by the intravenous route .
- children should be given 5 to 7 mg ascorbic acid/kg of body weight per day by the intravenous route.

Methaemoglobinaemia in childhood:
A single dose of 500 to 1000 mg ascorbic acid (equivalent to 3.3 ml to 6.6 ml PASCORBIN®) should be administered by intravenous injection.
If necessary, the same dose can be repeated.
A dose of 100 mg/kg of body weight per day should not be exceeded.

Method of administration and duration of treatment
The product should be given by slow intravenous administration.
The duration of treatment depends on the clinical picture and the results of laboratory testing.

4.3 Contraindications

PASCORBIN® should not be used in patients with oxalate urolithiasis or iron storage disorders (thalassaemia, haemochromatosis, sideroblastic anaemia).

Use in children under 12 years of age:

- In children under 12 years of age receiving parenteral nutrition, an IV dose of 5-7 mg ascorbic acid/kg of body weight per day should not be exceeded.
- In the treatment of childhood methaemoglobinaemia, a dose of 100 mg ascorbic acid/kg of body weight per day should not be exceeded.

4.4 Special warnings and precautions for use

Intravenous injection of high doses of PASCORBIN® may lead to acute renal failure due to renal calculi from precipitation of calcium oxalate crystals in the kidneys. This has been observed at doses as low as 1.5-2.5 g. Patients with pre-existing renal insufficiency are at particular risk of this event. Adequate fluid intake (approximately 1½ to 2 l per day) should be ensured. Therefore, the daily vitamin C dose should not exceed 100 to 200 mg in patients with renal calculi.
Patients with advanced or end-stage renal disease (dialysis patients) should not receive more than 50 to 100 mg daily.
Each ampoule of 5 ml solution for injection contains 4.2 mmol (97.2 mg) sodium, and each injection vial of 50 ml solution for injection contains 42.3 mmol (972 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.
In patients with erythrocyte glucose-6-phosphate dehydrogenase deficiency given high doses of vitamin C (4 g daily), there have been isolated reports of haemolysis, in some cases severe. Therefore, it should be avoided to exceed a dose of 100-500 mg ascorbic acid per day.
Patients with known respiratory problems (such as obstructive or restrictive bronchial and pulmonary diseases) may, in isolated instances, experience acute dyspnoea when treated with high doses of PASCORBIN® (7.5 g and higher). Therefore, it is recommended to start these patients on lower doses.

4.5 Interaction with other medicinal products and other forms of interaction

PASCORBIN® may (because of its high redox potential) chemically alter other drugs; compatibility with other drugs must therefore be verified on a case-by-case basis when co-administration is considered.

Ascorbic acid has the potential to interfere with the effects of anticoagulants.

Co-administration of ascorbic acid and fluphenazine results in reduced fluphenazine plasma concentrations, and co-administration of ascorbic acid and acetylsalicylic acid results in reduced acetylsalicylic acid excretion and increased ascorbic acid excretion in the urine. Salicylates inhibit ascorbic acid uptake by leukocytes and platelets.

The use of higher doses of vitamin C during chemotherapy should be separated from chemotherapy administration by appropriate intervals (1-3 days depending on the half-life of the chemotherapeutic agent) because no clinical data on potential interactions are available.

Special information for diabetics:
Parenteral administration of ascorbic acid interferes with blood glucose tests.

4.6 Pregnancy and lactation

During pregnancy and lactation, a dose of 100 to 500 mg ascorbic acid daily should not be exceeded. Ascorbic acid is excreted in breast milk and crosses the placental barrier.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following frequency categories are used for reporting undesirable effects:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Respiratory and cutaneous hypersensitivity reactions have been observed very rarely.
In isolated cases, patients may briefly experience circulatory problems (e.g. dizziness, nausea, visual disturbances).
Patients with acute infections have very rarely experienced reactions such as chills and elevated temperature.

4.9 Overdose

For risk of haemolysis and renal calculi see ”Special warnings and precautions for use” section.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
ascorbic acid (vitamin C)

ATC code: A11GA01

Ascorbic acid is essential to human health. Ascorbic acid and dehydro-ascorbic acid, formed in the body from ascorbic acid,

constitute a redox system of great physiological importance.

Its redox potential makes vitamin C a co-factor of numerous enzyme systems (collagen formation, catecholamine synthesis, hydroxylation of steroids, tyrosine and xenobiotics, biosynthesis of carnitine, regeneration of tetrahydrofolic acid and alpha-amidation of peptides, e.g. ACTH and gastrin).

In addition, vitamin C deficiency impairs immune defence reactions, especially chemotaxis, complement activation and interferon production. The functions of vitamin C at the molecular level have not yet been completely elucidated.

Ascorbic acid reduces ferri ions and forms iron chelates, thus improving the absorption of iron salts. It blocks oxygen free radical-induced chain reactions in aqueous body compartments. Its antioxidative functions involve intimate biochemical interactions with those of vitamin E, vitamin A and carotinoids. Reduction of potential carcinogens in the gastrointestinal tract by ascorbic acid has not yet been adequately established.

5.2 Pharmacokinetic properties

Ascorbic acid is subject to concentration-dependent absorption from the proximal small intestine. With increasing single doses, bioavailability decreases to 60-75% after dosing with 1 g, to approximately 40% after 3 g and to as little as approximately 16% after 12 g. Unabsorbed ascorbic acid is broken down by the colonic flora mainly to CO_2 and organic acids.
In healthy adults, maximum metabolic turnover of 40 to 50 mg/day is reached at plasma concentrations of 0.8 to 1.0 mg/dl. Total daily turnover is approximately 1 mg/kg of body weight. At extremely high oral doses, plasma concentrations of up to 4.2 mg/dl are briefly attained after approximately 3 hours.
Under these conditions, more than 80% of ascorbic acid is excreted unchanged in the urine. Mean half-life is 2.9 hours. Renal excretion is by glomerular filtration followed by re-absorption in the proximal tubule. Upper limit concentrations in healthy adults are 1.34 +/- 0.21 mg ascorbic acid/dl plasma in men and 1.46 +/- 0.22 mg ascorbic acid/dl plasma in women.
Total body ascorbic acid is at least 1.5 g following administration of high doses of approximately 180 mg daily. Ascorbic acid accumulates in the pituitary, adrenals, lenses of the eyes, and white blood cells.

5.3 Preclinical safety data

a) Acute toxicity
See section 4.9 "Emergency management".

b) Subchronic and chronic toxicity
Subchronic and chronic studies in rats produced no evidence of substance-related effects.

c) Mutagenic and tumourigenic potentials
Long-term studies in mice produced no evidence of a tumourigenic potential.
Cell culture and/or animal studies produced no evidence of a mutagenic effect in the therapeutic dose range.

d) Reproductive toxicity
Studies in two animal species using daily doses of up to 1000 mg/kg of body weight demonstrated no foetotoxic effects.

Ascorbic acid is excreted in breast milk and crosses the placental barrier by simple diffusion.

5.4 Further information

Following the administration of gramme doses, urinary ascorbic acid concentrations may increase to the point of interfering with the measurement of various clinical chemistries (glucose, uric acid, creatinine, inorganic phosphate). In addition, the administration of gramme doses may give a false-negative result in a test attempting to detect occult blood in stool.
In general, there may be interference with chemical detection methods based on colour reactions.
Dietary sources and meeting requirements
Fruits and vegetables are the only dietary sources that supply vitamin C in a density that readily meets requirements. As vitamin C is easily oxidisable and soluble, cooking results in substantial loss (green leafy vegetables up to 60%, potatoes up to 25%). Ascorbic acid is quite stable in fruits because of the acidic pH range. In leafy vegetables, enzymatic breakdown by peroxidases starts immediately after harvesting (over 50% loss within 48 hours at room temperature) which can be prevented by blanching, e.g. for preservation. The vitamin C content of cow's milk does not protect infants from vitamin C deficiency disease.

Deficiency symptoms
Clinically manifest vitamin C deficiency disease (scurvy or Moeller-Barlow disease) develops insidiously over several months from a state of latent vitamin C deficiency. Systemic diseases such as measles, epidemic hepatitis, major trauma, malabsorption syndromes or the prolonged use of various drugs (including salicylates and tetracyclines) may substantially accelerate this.
Non-specific early symptoms include reduced physical performance and psychometrically objectifiable dysfunctions such as increased exhaustability or irritability. Later on, patients develop

increased capillary fragility with petechiae, microhaematuria, reduced resistance to infection (mainly as a result of decreased phagocytosis), accompanied by gingivitis (following tooth eruption), and eventually skin and mucosal haemorrhages over larger areas (ecchymoses and bruises), first evident on the sublingual mucosa and the marginal border of the gums. A frequent concomitant syndrome is hypochromic, microcytic, frequently iron-refractory anaemia.
Wound healing is delayed and connective tissue scarring impaired at the same time. Infants additionally develop subperiostal haematomas and bleeding into the growth zones of the long tubular bones, which may be extremely painful (Moeller-Barlow disease). Vitamin C deficiency disease may be fatal in both adults and infants. Appropriate treatment with ascorbic acid is likely to achieve full recovery with no late complications even in severe cases.

The aetiology of the alterations should be objectified by measuring a greatly reduced ascorbic acid concentration in the blood plasma (less than 0.1 mg/dl or 6 µmol/l) and in the white blood cells (less than 5 mg/dl or 280 µmol/l).
Measurements of the vitamin C concentration in the blood plasma can be used to document that requirements are met. Concentrations below the threshold levels indicating that requirements are still met (0.5 mg/dl in men, 0.55 mg/dl in women) are rarely observed in healthy individuals in Germany. This also applies to pregnant women and nursing mothers. However, women who have been breastfeeding for several months often show a fall in plasma and milk ascorbic acid concentrations. The same applies to preserved human milk. The increased vitamin C requirements of heavy smokers are usually met in younger and middle-aged adults.
Groups at risk include elderly people over 65 years of age (men more often than women), individuals who regularly consume large amounts of alcohol, smokers, pregnant women and nursing mothers and people eating an unbalanced diet. Long-term use of drugs (especially salicylates, tetracyclines and corticosteroids) may reduce vitamin C reserves.
Substantial decreases in the vitamin C concentration in the blood plasma and leukocytes are seen in acute infectious diseases, severe diseases of the hepatic parenchyma, major trauma and in haemodialysis patients. Low vitamin C concentrations in plasma and leukocytes are also observed in chronic infectious diseases, severe malabsorption syndromes and terminal cancer.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: sodium bicarbonate, water for injections.

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6.2 Incompatibilities
Ascorbic acid has a strong redox potential. Chemical compatibility with other drugs must therefore be verified on a case-by-case basis when co-administration is considered.

6.3 Shelf life
2 years.
This medicinal product should not be used after the expiry date.

6.4 Special precautions for storage
Ampoules: Do not store above 20°C.
Injection vials: Do not store above 25°C.
Protect from light.
The solution for injection is free from preservatives and intended for single dispensing only. The product must be used immediately after opening the ampoule or injection vial. Any solution remaining after use must be discarded.
The mixture of PASCORBIN® and normal saline solution for brief peripheral intravenous infusion must be used without delay. Any solution remaining after use must be discarded.

6.5 Nature and contents of container
Original packs of
5 ampoules 5 ml
10 ampoules 5 ml
50 ml injection vial
Hospital packs of
100 ampoules of 5 ml
1000 ampoules of 5 ml
Original packs of
1 injection vial 50 ml
Bundle packs of
20 injection vials 50 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER
German MA No.: 6727989.00.00

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION
14.12.2005

10. DATE OF REVISION OF THE TEXT
07 / 2012

11. LEGAL STATUS
Pharmacy only (P).