PRODUCT MONOGRAPH

L-ARGININE HYDROCHLORIDE INJECTION

250 mg/mL

SANDOZ STANDARD

Sandoz Canada Inc.
145 Jules-Léger
Boucherville, Québec, Canada
J4B 7K8

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Control no.: 106555

L-Arginine Hydrochloride Injection
250 mg/mL

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ACTION AND CLINICAL PHARMACOLOGY

The precise mechanism by which arginine stimulates pancreatic release of insulin and glucagon has not yet been elucidated.

The elevation in serum levels of growth hormone and prolactin following IV administration of L-arginine hydrochloride is also not fully understood. As compared to patients with normal pituitary function, patients with impaired pituitary function have lower or no increases in plasma concentrations of growth hormone after arginine administration.

Arginine increases blood glucose concentration. This effect may be direct; the amount of glucose released from the liver is reported to be directly related to the quantity of amino acid infused. Glycogenolysis and gluconeogenesis may also be mediated by stimulation of glucagon release by arginine.

INDICATIONS AND CLINICAL USE

Growth hormone reserve test
L-Arginine Hydrochloride Injection given by intravenous injection is often used as a diagnostic agent of the pituitary function.

Acidification of urines
Rapid infusion of L-Arginine Hydrochloride Injection is among the safest means of rapid acidification of urines, particularly in cases of intoxications with basic drugs whose elimination is dependent on urinary pH.

Metabolic alkalosis
In cases of severe metabolic alkalosis when sodium administration should be restricted. Use of arginine for metabolic alkalosis should not preclude the use of IV sodium chloride and/or potassium chloride.

Hyperammonemia
In prophylaxis against hyperammonemia following parenteral administration of amino acid mixtures.

As a detoxifying agent in pathological conditions with hyperammonemia (hepatic coma, hepatic encephalopathy, liver failure).

CONTRAINDICATIONS

L-arginine hydrochloride should not be used in patients with allergic tendencies.

PRECAUTIONS

L-arginine hydrochloride should be administered with caution in patients with hyperchloremic acidosis or with renal failure.

Because arginine contains a high content of metabolizable nitrogen, the temporary effect of a high nitrogen load on the kidneys should be evaluated before giving the drug.

ADVERSE REACTIONS

Adverse reactions such as nausea, vomiting, numbness, headache and venous irritation are among the most frequently reported side effects following IV administration of amino acids, especially if administered too rapidly. Nevertheless, L-arginine hydrochloride is particularly well tolerated and the above-mentioned adverse effects are not too frequent.

Leakage of IV solutions of L-arginine hydrochloride into the surrounding tissue may cause necrosis and superficial phlebitis.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

DRUG INTERACTIONS

Estrogens and estrogen-progestin combination oral contraceptives may elevate growth hormone response, and reduce glucagon and insulin response to arginine. Reduction of arginine-induced growth hormone response by medroxyprogesterone acetate and of insulin response by norethindrone has also been reported.

Plasma insulin concentrations following arginine stimulation may be further elevated by thiazide diuretics, xylitol and aminophylline. The latter two drugs may also reduce glucagon response to arginine.

Long-term administration of sulfonylurea oral antidiabetic agents may suppress plasma glucagon response to arginine. In one study, phenytoin reduced the plasma insulin response to arginine when glucose intolerant patients were given a glucose load.

Severe, potentially fatal, hyperkalemia has occurred following L-arginine hydrochloride therapy for metabolic alkalosis in several patients with severe hepatic disease who had recently received spironolactone. Severe hyperkalemia, requiring treatment, developed within several hours after initiating arginine therapy; spironolactone had been discontinued two to three days prior to initiation of arginine. Death occurred in one patient subsequent to ventricular tachycardia and asystole despite attempts to decrease serum potassium concentrations and treat cardiac abnormalities. Severe hyperkalemia in these patients probably resulted from an arginine-induced extracellular shift of potassium from cells, impaired hepatic metabolism of arginine, and/or a spironolactone-induced decrease in renal excretion of the ion; spironolactone's effect on potassium persists for several days following discontinuance of the drug. Patients receiving a potassium-sparing diuretic are at increased risk of arginine-induced hyperkalemia and, therefore, combined use of the drugs should be avoided.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

L-Arginine Hydrochloride Injection should only be administered by IV infusion after dilution to 10% (100 mg/mL) with water or Dextrose 5 - 10%.

Growth hormone reserve test
This test should be done in the morning after the patient has been maintained in basal conditions (fast and bed rest) for 12 hours. Bed rest should be continued during the test. Blood samples for growth hormone assay and glycemia should be taken 30 minutes prior to, and immediately before beginning the arginine infusion, and at 30-minute intervals for 2.5 hours thereafter.

Adults: The L-Arginine Hydrochloride Injection dose is 30 g administered by IV infusion of a 10% aqueous solution at constant rate over 30 minutes.

Children: In children of less than 50 kg, the recommended dosage is 0.5 g/kg of body weight.

Acidification of urines
A dose of 20 to 40 g by rapid IV infusion with a 10% solution in water.

Metabolic alkalosis
42 g/L of L-Arginine Hydrochloride Injection in water for injection, by IV infusion, to provide 198 mEq H^+ (pH 5.6).

Hyperammonemia
A dose of 20 to 40 g by slow IV infusion (4 hours) with a 10% solution in Dextrose 5 or 10%.

PHARMACEUTICAL INFORMATION

Drug substance

Proper name:	L-arginine hydrochloride
Classification:	Amino Acid
Molecular Formula:	$C_6H_{14}N_4O_2$ •HCl
Molecular Weight:	210.66
Physicochemical properties:	L-arginine hydrochloride is a crystalline solid which melts with decomposition between 225 – 235°C. It is freely soluble in water and slightly soluble in warm ethanol. Its isoelectric point is 10.76 and its respective pKa's are: $pKa_1 = 2.18$, $pKa_2 = 9.09$ and $pKa_3 = 13.20$. L-Arginine Hydrochloride Injection 250 mg/mL is hypertonic, has a pH of 5.0 - 6.5. Aqueous solutions of L-arginine hydrochloride are isotonic at concentrations of 3 to 4%.

COMPOSITION, STORAGE AND STABILITY

Each mL of aqueous solution contains L-arginine hydrochloride 250 mg, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection.

Store between 15 and 30°. Discard unused portion.

PACKAGING

Unidose vials of 30 mL.

REFERENCES

1. Saap C, et al. Sodium chloride equivalent cryoscopic properties and hæmolytic effects of certain medicinals in aqueous solutions. III Supplemental Values. J Pharm Sciences, 1975; 64: 1884.

2. AMA Drug Evaluations, Third Edition, PSG Publishing Company, pp. 228-230.

3. Milne DM. Pharmacology of amino acids. Clinical Pharmacology and Therapeutics, 1968; 9: 484.

4. Gold EM. Hypothalamic-pituitary function tests current status. Post-Graduate Medicine, 1977; 62: 105-114.

5. Merimee TJ, et al. Effect of Arginine on serum levels of human growth-hormone. The Lancet, 1965; p. 668.

6. Pierron H. et al. Le test à l'arginine dans les retards staturaux hypophysaires et idiopathiques. Pédiatrie T XXVI, 1971; : 703-721.

7. Josefsberg Z, et al. Comparative HGH response to IV glucagon and IV arginine stimulation tests in children and adolescents. Europ J Pediat, 1976; 121/149/154.

8. Raiti S, et al. A comparison of the effects of insulin hypoglycemia and arginine infusion on release of H.G.H. The Lancet, 1967; ll83.

9. Floyd JC, et al. Stimulation of insulin secretion by amino acids. Journal of Clinical Investigation, l966; 45: 1487-1502.

10. Aronoff SL, et al. Arginine-stimulated hyperglycemia in diabetic Lima Indians. Diabetes, 1976; 25: 404.

11. Meschi F, et al. Glucagon response to arginine stimulation in obese and diabetic children. Diabetes, 1977; 26: 558-560.

12. Del Prete GF, et al. Insulin and glucagon response to glucose and arginine in two patients with "autoimmune" diabetes Mellitus. Horm Metab Res, 1976; 8: 149-150.

13. Marchina MM, Renzi G, Serofilli S. Medical treatment of hyperammonemia in the elderly. Controlled clinical study. Minerva Med, 1979; 70(11):811-818.

14. Tolentino P. Liver failure. Pædiatrician, 1978; 7(4-5):166-175.

15. Soeters PB, Weir G, Ebeid AM, et al. Insulin, glucagon, portal systemic shunting, and hepatic failure in the dog. J Surg Res, 1977; 23(3):183-188.

16. Fischer JE, Funovics JM, Aguirre A, et al. The role of plasma amino acids in hepatic encephalopathy. Surgery, 1975; 78(3):276-290.

17. Chang JJ, Scott CF, Colman RW. Role of arginine residues in the coagulant activity of high molecular weight kikinogen blood. 1986; 67(3):805-810.

18. Naidoo C, Jialal I, Joubert SM. Arginine-stimulated acute phase of insulin secretion in non-insulin-dependent diabetes in the young. Diabetes Res Clin Exp, 1986; 3(3):127-130.

19. Schrier RW. Role of arginine vasopressin in regulation of systemic arterial pressure. Annu Rev Med, 1986; 37:13-20.

20. Nussey SS, Ang VTY, Bevan DH, et al. Human platelet arginine vasopressin. Clin Endocrinol, 1986; 24(4):427-434.

21. Barbul A. Arginine: Biochemistry, physiology, and therapeutic implications. J Parent Enter Nutr, 1986; 10(2):227-238.

22. Brown MA, Gallery EDM. Sodium excretion in human pregnancy: a role for arginine vasopressin. Amer J Obstet Gynecol, 1986; 15(4):914-918.