L-ARGININE

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLA) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient. It is a referenced document to be used as a labelling standard.

Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion. The solidus (/) indicates that the terms are synonyms or that the statements are synonymous. Either term or statement may be selected by the applicant.

Background information:

- L-Arginine is a conditionally essential amino acid (IOM 2006).
- L-Arginine plays a role in the formation of important physiologic factors, including nitric oxide (NO, a vasodilator), urea (an excretory product), creatine (required for storage of high-energy phosphates), all proteins (as a part of the structures), and growth hormone release (Shao and Hathcock 2008).
- In healthy adults with adequate protein intakes, L-Arginine is synthesized by the body in sufficient quantity to meet physiologic needs. It is only under specific diseased states such as congenital defects or catabolic states that supplementation is essential (Shils et al. 2006; IOM 2005).
- The claim "May help support a modest improvement in exercise capacity in individuals with stable cardiovascular diseases" is based on evidence from clinical trials showing that L-Arginine supplementation, in patients with cardiovascular diseases (CVD), may enhance their endurance exercise tolerance or exercise capacity, an important measuring factor of daily-life activity (Doutreleau et al. 2010; Doutreleau et al. 2006; Nagaya et al. 2001; Bednarz et al. 2000; Ceremużyński et al. 1997; Rector et al. 1996). The claim is also based on its mechanism of action, where clinical trials showed that L-Arginine supplementation enhances endothelium-dependant vasodilation by increasing nitric oxide (NO) production in these patients, who have lower levels of NO (Lim et al. 2004; Palloshi et al. 2004; Bode- Böger et al. 2003; Lekakis et al. 2002; Sydow et al. 2002; Nagaya et al. 2001; Hambrecht et al. 2000; Lerman et al. 1998; Adams et al. 1997; Clarkson et al. 1996). Increasing NO production through L-Arginine supplementation might therefore be beneficial by restoring vasodilatation and improving muscular metabolism in patients with cardiovascular compromised systems.
- The minimum dose for the claim "L-Arginine is a non-essential amino acid that is involved in protein synthesis" is based on 5% of the daily average intake, i.e. 4.2 g per day (IOM 2005).
- The maximum dose where no duration of use is required is based on 10% of the daily average intake.

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Proper name(s):

- (*S*)-2-Amino-5-[(aminoiminomethyl)amino]pentanoic acid (O'Neil et al. 2009)
- L-Arginine (NIH 2009; O'Neil et al. 2009)

Common name(s): L-Arginine (NIH 2009; O'Neil et al. 2009)

Source material(s):

- L-Arginine monohydrochloride / L-Arginine hydrochloride (USP 32; Ph. Eur. 2007)
- Synthetic (BP 2009; USP 32; Ph. Eur. 2007)

Route(s) of administration: Oral

Dosage form(s): The acceptable pharmaceutical dosage forms include, but are not limited to, chewables (e.g. gummies, tablets), caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons.
This monograph is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Use(s) or Purpose(s): Statement(s) to the effect of:

- May help support a modest improvement in exercise capacity in individuals with stable cardiovascular diseases (CVD) (Doutreleau et al. 2010; Doutreleau et al. 2006; Lim et al. 2004; Palloshi et al. 2004; Bode- Böger et al. 2003; Lekakis et al. 2002; Sydow et al. 2002; Nagaya et al. 2001; Bednarz et al. 2000; Hambrecht et al. 2000; Lerman et al. 1998; Adams et al. 1997; Ceremużyński et al. 1997; Clarkson et al. 1996; Rector et al. 1996).
- L-Arginine is a non-essential amino acid that is involved in protein synthesis (Shils et al. 2006; IOM 2005; Groff and Gropper 2000).

Dose(s):

Improvement in exercise capacity in individuals with stable CVD:
Preparations equivalent to 6-21 g per day; not to exceed 8 g per dose (Doutreleau et al. 2010; Shao and Hathcock 2008; Doutreleau et al. 2006; Evans et al. 2004: Lim et al. 2004; Palloshi et al. 2004; Bode-Bogër et al. 2003; Bednarz et al. 2000; Hambrecht et al. 2000; Lerman et al. 1998; Adams et al. 1997; Ceremużyński et al. 1997; Clarkson et al. 1996; Rector et al. 1996)

Protein synthesis: Preparations equivalent to 0.21-21 g, per day; doses > 8 g per day must be in divided doses and must not exceed 8 g per dose (Shao and Hathcock 2008; IOM 2005; Evans et al. 2004; Bode-Bogër et al. 2003; Sydow et al. 2002)

See Appendix 1 for examples of dosages and frequencies of use, according to cited references. The purpose of Appendix 1 is to provide guidance to industry.

Duration(s) of use:

For products containing 0.21-0.42 g:
No statement required.

For products containing > 0.42 g:
If you suffer from a cardiovascular disease, consult your health care practitioner for use beyond 6 weeks (Shao and Hathcock 2008; Sydow et al. 2002; Hambrecht et al. 2000; Clarkson et al. 1996; Rector et al. 1996).

For products containing > 9-14 g:

- If you suffer from a cardiovascular disease, consult your health care practitioner for use beyond 6 weeks (Shao and Hathcock 2008; Sydow et al. 2002; Hambrecht et al. 2000; Clarkson et al. 1996; Rector et al. 1996).
- Consult a health care practitioner for use beyond 6 months (Alexander et al. 2005; De Nicola et al. 1999).

For products containing > 14 g:

- If you suffer from a cardiovascular disease, consult your health care practitioner for use beyond 6 weeks (Shao and Hathcock 2008; Sydow et al. 2002; Hambrecht et al. 2000; Clarkson et al. 1996; Rector et al. 1996).
- Consult a health care practitioner for use beyond 12 weeks (Tangphao et al. 1999).

Risk information: Statement(s) to the effect of:

Caution(s) and warning(s):

All products: Consult a health care practitioner prior to use if you are pregnant or breastfeeding.

For products containing 0.42-21 g:

- Consult your health care practitioner prior to use if you are taking medication for cardiovascular diseases, erectile dysfunction, and/or blood thinners (Huynh et al. 2002; Parker et al. 2002; Siani et al. 2000; Adams et al. 1995).
- Consult a health care practitioner prior to use if you suffer from a cardiovascular disease and are attempting an increase in physical activity (Doutreleau et al. 2010; Doutreleau et al. 2006; Schulman et al. 2006; Nagaya et al. 2001; Bednarz et al. 2000; Ceremużyński et al. 1997; Rector et al. 1996).
- Consult a health care practitioner if your cardiovascular condition worsens.
- Consult a health care practitioner prior to use if you have a renal/kidney disease or if you are following a low protein diet (Goldman and Ausiello 2004).

Contraindication(s):

For products containing 0.42-21 g:

Do not use if you have had a heart attack/myocardial infarction (Schulman et al. 2006).

Known adverse reaction(s):

For products containing 0.42-21 g:

Some people may experience gastrointestinal discomfort (such as diarrhea) (Grimble 2007; Evans et al. 2004; IOM 2005; Clarkson et al. 1996).

Non-medicinal ingredients: Must be chosen from the current NHPD *Natural Health Products Ingredients Database* and must meet the limitations outlined in the database.

Specifications:

- The finished product must comply with the minimum specifications outlined in the current NHPD *Compendium of Monographs*.

- The medicinal ingredient may comply with the specifications outlined in the pharmacopoeial monographs listed in Table 1 below.

Table 1: Monographs published in the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) and the U.S. Pharmacopeia (USP)

Pharmacopoeia	Monograph
BP	Arginine
Ph. Eur.	Arginine Arginine Hydrochloride
USP	Arginine Arginine Hydrochloride

References cited:

Adams MR, McCredie R, Jessup W, Robinson J, Sullivan D, Celermajer DS. 1997. Oral L-arginine improves endothelium-dependent dilatation and reduces monocyte adhesion to the endothelial cells in young men with coronary artery disease. Atherosclerosis 129(2):261-269.

Adams MR, Forsyth CJ, Jessup W, Robinson J, Celermajer DS. 1995. Oral L-arginine inhibits platelet aggregation but does not enhance endothelium-dependent dilation in healthy young men. Journal of the American College of Cardiology 26(4):1054-1061

Alexander JW, Metze TJ, McIntosh MJ, Goodman HR, First MR, Munda R, Cardi MA, Austin JN, Goel S, Safdar S, Greenberg N, Chen X, Woodle ES. 2005. The influence of immunomodulatory diets on transplant success and complications. Transplantation 79:460-465.

Bednarz B, Wolk R, Chamiec T, Herbaczyńska-Cedro K, Winek D, Ceremużyński L. 2000. Effects of oral L-arginine supplementation on exercise-induced QT dispersion and exercise tolerance in stable angina pectoris. International Journal of Cardiology 75(2-3):205-210.

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Ceremużyński L, Chamiec T, Herbaczyńska-Cedro K. 1997. Effect of supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. The American Journal of Cardiology 80(3):331-333.

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Goldman L, Ausiello D, editors. 2004. Cecil Textbook of Medicine, Volume 1, 22nd edition. Philadelphia (PA): Saunders.

Grimble GK. 2007. Adverse gastrointestinal effects of arginine and related amino acids. The Journal of Nutrition 137(6 Suppl 2):1693S-1701S.

Groff J, Gropper S. 2000. Advanced Nutrition and Human Metabolism, 3rd edition. Belmont (CA): Wadsworth/Thomson Learning.

Hambrecht R, Hilbrich L, Erbs S, Gielen S, Fiehn E, Schoene N, Schuler. 2000. Correction of endothelial dysfunction in chronic heart failure: additional effects of exercise training and oral L-arginine supplementation. Journal of the American College of Cardiology 35(3):706-713.

Huynh NT, Tayek JA. 2002. Oral arginine reduces systemic blood pressure in type 2 diabetes: Its potential role in nitric oxide generation. American College of Nutrition 21(5):422-427.

IOM 2006: Otten JJ, Pitzi Hellwig J, Meyers LD, editors. 2006. Institute of Medicine Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington (DC): National Academies Press.

IOM 2005: Institute of Medicine. Panel on Dietary Reference Intakes for Electrolytes and Water, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. 2005. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. Washington (DC): National Academies Press.

Lekakis JP, Papathanassiou S, Papaioannou TG, Papamichael CM, Zakopoulos N, Kotsis V, Dagre AG, Stamatelopoulos K, Protogerou A, Stamatelopoulos SF. 2002. Oral L-arginine improves endothelial dysfunction in patients with essential hypertension. International Journal of Cardiology 86(2-3):317-323.

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Appendix 1: Examples of dosage and frequencies of use

- 6 g, 2 times per day (Doutreleau et al. 2010)
- 6 g, 2 times per day (Doutreleau et al. 2006)
- 1 g, 3 times per day (Evans et al. 2004)
- 3 g, 3 times per day (Evans et al. 2004)
- 7 g, 3 times per day (Evans et al. 2004)
- 3 g, 2 times per day (Lim et al. 2004)
- 2 g, 3 times per day (Palloshi et al. 2004)
- 8 g, 2 times per day (Bode-Bogër et al. 2003)
- 2 g, 3 times per day (Bednarz et al. 2000)
- 3 g + 2 g + 3 g, per day (Hambrecht et al. 2000)
- 3 g, 3 times per day (Lerman et al. 1998)
- 7g, 3 times per day (Adams et al. 1997)
- 2 g, 3 times per day (Ceremużyński et al. 1997)
- 7 g, 3 times per day (Clarkson et al. 1996)
- 2.8 g, 2 times per day (Rector et al. 1996)
- 4.2 g, 3 times per day (Rector et al. 1996)