

Shortage Prevention Plan

Nitric Oxide / Nitric Oxide Mixtures up to 1000ppm in Nitrogen

Introduction:

This document covers the medicinal product Nitric Oxide (NO), with concentrations up to 1000ppm, in Nitrogen (N₂). The active substance in these mixtures is Nitric Oxide.

Nitric oxide can be produced from either the reaction of sulfuric acid (diluted 55%) with liquid sodium nitrite, with the resulting gas being counter-current injected in a washing cycle containing sodium hydroxide and then fed into a condenser/decanter, or from the large-scale production as a by-product in the Ostwald process from the synthesis of nitric acid from ammonia.

After both processes the nitric oxide gas is then filled at a defined pressure into aluminum cylinders. Later the nitric oxide active substance is mixed with nitrogen to create a so called intermix of about 1-5% (V/V) Nitric Oxide in Nitrogen. The last step of the manufacturing process is the actual production of the final mixture, where the intermix is further diluted with nitrogen.

This product has had a Ph.Eur. monograph, 1550, for many years and is a commonly used medicinal product worldwide.

Usually, Nitric oxide/Nitrogen mixtures are supplied to healthcare facilities as licensed medicinal products in defined packages of a compressed gaseous mixture in aluminum cylinders.

EIGA emphasizes that in Europe, and as confirmed with the European Medicines Agency (EMA), although there was a significant increase in the use/consumption of nitric oxide/nitrogen medicinal gas products during the COVID-19 pandemic, our member companies confirmed that at no time was there a shortage of these mixtures to patients in healthcare facilities.

EIGA has used Technical Report No. 68, "Risk-Based Approach for Prevention and Management of Drug Shortages", as prepared by the Parenteral Drug Association (PDA) in 2014 as part of the inter-association collaborative contribution to the EMA (European Medicines Agency) Initiative on medicinal product shortages caused by manufacturing and GMP compliance issues. The document can be freely downloaded from the PDA website.

The risk triage method is a simple four-step process that uses a preliminary hazards analysis approach to evaluate the risk of a drug shortage by considering the therapeutic use of a product, availability of alternatives, and likelihood of occurrence. The process assigns a risk priority level based on a combination of the potential impact to the patient and likelihood of a drug shortage, and then recommends risk controls for the assessed product. The

© EIGA grants permission to reproduce this publication provided the Association is acknowledged as the source

EUROPEAN INDUSTRIAL GASES ASSOCIATION AISBL
AVENUE DE L'ASTRONOMIE 30 • B-1210 BRUSSELS
PHONE +32 2 217 70 98 • E-mail : info@eiga.eu www.eiga.eu

The AVA logo features the letters "AVA" in a stylized, bold, yellow font. To its right, the word "Documents" is written in a blue, sans-serif font, and below it, "Document Sharing Hub" is written in a smaller, blue, sans-serif font.
Document Sharing Hub

method uses discrete information and key words to assign a priority level for each element, making the assessment focus on product information and avoiding discussions on general subjective terms.

The steps in the triage process are as follows:

1. Identify risk level (impact to patient) based on therapeutic use and availability of alternatives.
2. Determine the likelihood of a drug shortage for the product.
3. Determine the risk priority level based on a combination of impact to patient and likelihood of a drug shortage for the product.
4. Plan and implement the suggested risk controls for the assessed product based on the risk priority level.

Step 1:

			Availability of Alternatives		
			No Alternatives Available	Alternative Products Available: Similar Therapy	Exact Product Available but in Other Presentations
Therapeutic Use & Consequences if Product is not Available	Medically necessary product, life supporting or life sustaining	Fatal or severe irreversible harm if the patient is not treated with the product	Risk Level A	Risk Level A	Risk Level B
	Acute short term or chronic long term	Severe harm but reversible if patient is not treated with the product	Risk Level A	Risk Level B	Risk Level C
	Other indications	inconvenience if patient is not treated with the product	Risk Level B	Risk Level C	Risk Level C

Typical Indications of Nitric Oxide/Nitrogen mixtures are:

They are used in conjunction with ventilatory support and other appropriate active substances, as indicated:

- for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.
- as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

Therefore, the assessment is that Nitric Oxide/Nitrogen mixtures are for acute short term or chronic long term uses. Furthermore, it should be noted that for inhaled nitric oxide there are other alternatives, such as inhaled prostacyclin and alternative prostaglandin preparations such as inhaled iloprost, treprostinol and beraprost (Lowson SM. Alternatives to nitric oxide. Br Med Bull. 2004 Nov 5; 70:119-31).

In the assessment of alternatives, the outcome is that there are many "Exact products available" as there are many Marketing Authorisation Holders (MAHs) within each EU member state having authorisations for Nitric Oxide/Nitrogen mixtures. It should also be noted that these products are present in the exact same presentation, therefore lowering the risk even further.

With the assessment of "Therapeutic Use & Consequences if Product is not Available" as "Acute short term or

© EIGA grants permission to reproduce this publication provided the Association is acknowledged as the source

EUROPEAN INDUSTRIAL GASES ASSOCIATION AISBL
AVENUE DE L'ASTRONOMIE 30 • B-1210 BRUSSELS
PHONE +32 2 217 70 98 • E-mail : info@eiga.eu www.eiga.eu

AVA Documents
Document Sharing Hub

chronic long term uses” and “Availability of Alternatives” as “Exact Product Available” – it is classed as **RISK LEVEL C**.

© EIGA grants permission to reproduce this publication provided the Association is acknowledged as the source