LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Medicinsk Lustgas Air Liquide 100%, medicinal gas, liquefied
(nitrous oxide)

SE/H/1071/01/MR

This module reflects the scientific discussion for the approval of Medicinsk Lustgas Air Liquide 100%, medicinal gas, liquefied. The procedure was finalised at 2011-05-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Air Liquide Santé International has applied for a marketing authorisation for Medicinsk Lustgas Air Liquide 100%, medicinal gas, liquefied . The active substance is nitrous oxide. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Medicinsk Lustgas Air Liquide is presented in form of **medicinal gas, liquefied** containing 100% of Nitrous oxide substance. There is no other excipient. The drug product is nitrous oxide medicinal filled in gas cylinders as a liquefied gas. The only component used in the manufacturing process is medicinal nitrous oxide.

II.2 Drug Substance

Nitrous oxide has a monograph in the Ph Eur. Nitrous oxide is an odourless and colourless gas and has Boiling point of -88.5 °C at 1 bar (760 mmHg). Vapour pressure at 20 °C is 50 bars. The physico-chemical properties of Nitrous oxide are sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, and reagents.

The active substance specification includes relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated.

II.3 Medicinal Product

Medicinsk Lustgas Air Liquide 100%, medicinal gas, liquefied contains nitrous oxide as active substance. There is no other ingredient in the drug product.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions other than those applying to gas containers and gas under pressure.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The active ingredient of Medicinsk Lustgas Air Liquide 100% is nitrous oxide (N_2O). Prolonged exposure to high concentrations of nitrous oxide has been shown to be associated with neurotoxicity, adverse effects on the hemopoietic system and teratogenicity in animals. The mechanism responsible for its toxicity presumably involves the inhibition of methionine synthetase which results in reductions in S-adenosylmethionine and tetrahydrofolate levels. However, the wide human clinical experience with Medicinal nitrous oxide should form the basis for the safety assessment.

IV. CLINICAL ASPECTS

IV.1 Discussion on the clinical aspects

Efficacy:

The indications for Medicinsk Lustgas AL are:

- For use in anaesthesia, in combination with other inhalation anaesthetics or intravenous anaesthetics.
- For the treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted.

The use of nitrous oxide for general anaesthesia has a long history. It is used primarily as an adjunct to other inhalational or intravenous anaesthetics. Nitrous oxide substantially reduces the requirement for inhalational anaesthetics and consequently, reduces the overall cost of anaesthesia.

Due to several factors among them occupational hazards, its adverse profile and environmental impact, the use of nitrous oxide has been questioned during the last decades. However, by many anaesthesiologists it is still considered highly valuable and is widely used.

The analgesic/sedative effects of nitrous oxide have long been used during labour, in pre-hospital settings, in dental practice and during endoscopic procedures. End-tidal concentrations from 15 - 45% have shown quantifiable and subjectively meaningful increases in the thresholds for both sensation and pain although in labour pain, the individual response is variable and the peak pain relieving effect may be reached when the contraction is over.

No differences concerning efficacy between the sexes have been found.

The potency of nitrous oxide increases in the elderly. When nitrous oxide is combined with a second inhaled anaesthetic, the effects of nitrous oxide are more pronounced in the elderly.

In infants and children, it has been demonstrated that the predicted MAC for nitrous oxide is almost identical to the MAC in adults.

Safety:

Nitrous oxide increases the ICP and can cause cerebral damage in susceptible patients. Nitrous oxide should be carefully used in neuroanaesthesia.

Nitrous oxide causes alterations in myocardial performance that affect both systolic and diastolic function which for risk patients can cause regional ischemia. The use of nitrous oxide cannot be recommended in patients with significant cardiovascular risk factors who are undergoing either cardiac and/or non-cardiac procedures.

The concentration at which nitrous oxide in oxygen can elicit clinically relevant respiratory depression and loss of protective laryngeal reflexes for different groups of patients is not clear.

When nitrous oxide is used in dentistry concentrations up to 70% have been described. At such concentrations loss of consciousness usually occurs.

The use of nitrous oxide is contraindicated when there is a suspicion of intestinal obstruction. Nitrous oxide has an expanding effect in gas filled spaces. Examples are microbubbles in the blood, pneumothorax, injected gas in the eye bulb and gastrointestinal gas.
Nitrous oxide interacts with cobalamine. Patients with established or relative B_{12} due to any reasons are especially at risk. In otherwise healthy patients the maximum exposure time recommendations varies between 6 and 12 hours.
Even if modern scavenging systems can greatly reduced the anaesthesia personnel exposure to nitrous oxide the risks for reduced fertility, spontaneous abortion and malformations cannot be ignored.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The efficacy of nitrous oxide is well known after its use for more than a century. It has its own analgetic and sedative effects and can act as part of the carrier gas for more potent inhalation anaesthetics. As the art of anaesthesia is evolving as new drugs are developed the place for nitrous oxide has slowly changed. Today there are some anaesthesiologists who recommend that nitrous oxide should be abandoned in routine anaesthesia while other considers the gas a natural part in an anaesthetic drug mix.
If nitrous oxide is used according to the recommendations in the SPC the benefit/risk for the patient must be judged as positive.

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has not been performed. The applicant has committed to submit the results of a user test in a variation within three months after finalisation of the procedure.

The risk/benefit ratio is considered positive and Medicinsk Lustgas Air Liquide 100%, medicinal gas, liquefied is recommended for approval.

VI. APPROVAL

The Mutual recognition/Decentralised procedure for Medicinsk Lustgas Air Liquide 100%, medicinal gas, liquefied was successfully finalised on 2011-05-18.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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