LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Medicinsk lustgas Yara Industrial, 100% medicinal gas, liquefied
Nitrous oxide

SE/H/659/01/DC

This module reflects the scientific discussion for the approval of Medicinsk lustgas Yara Industrial. The procedure was finalised at 2007-10-16 (day 210). For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Yara Industrial AS has applied for a marketing authorisation for Medicinsk lustgas Yara Industrial, medicinal gas, liquefied. The active substance is nitrous oxide, with analgetic and sedative effects and in use for over one century. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Medicinal nitrous oxide is presented in the form of medicinal gas, liquefied containing 100% nitrous oxide. The product is filled in gas cylinders.

II.2 Drug Substance

The drug substance, nitrous oxide, is produced by thermal decomposition of ammonium nitrate, an old and well-known method, which is described in the literature.

$$NH_4NO_3 \rightarrow N_2O + 2\ H_2O$$

Nitrous oxide is an odourless and colourless gas and has Boiling point at 1 bar (760 mmHg). -88.5 °C. Vapour pressure at 20 °C is 50 bars.
The route of synthesis is sufficiently described, and the critical parameters in the synthesis of Nitrous oxide are controlled during the reaction. Acceptable specifications on starting materials, solvent and reagents have been presented.

The tests and limit specifications for Nitrous oxide are appropriate to control the quality of Nitrous oxide and the specifications comply with Ph. Eur. requirements. The proposed limits are achievable by the manufacturing process and are supported by batch analysis data.

The bulk nitrous oxide (API) is stored in insulated steel tanks with double walls for later use in filling of final products.

II.3 Medicinal Product

The drug product is medicinal nitrous oxide filled in gas cylinders as a liquefied gas.
The only component used in the manufacturing process is medicinal nitrous oxide.
The manufacturing process is very simple as filling of Medicinal nitrous oxide into cylinders is the only process to be performed.
A batch of nitrous oxide in cylinders is defined as the number of cylinders filled from the same tank of liquid nitrous oxide in one day. The cylinders are filled from the storage tank of liquid nitrous oxide.

The tests and limit specifications for the drug product (Nitrous oxide) are appropriate to control the quality of Nitrous oxide and the specifications comply with Ph. Eur. requirements. The proposed limits are achievable by the manufacturing process and are supported by batch analysis data.

The gas cylinders are made from steel and conform with EU Council Directive 84/525/EEC relating to seamless, steel gas cylinders. The steel cylinders are seamless, manufactured from rolled metal. Each cylinder can be traced by an engraved code made by the manufacturer. The colour of the gas cylinders follows European standard: NS-EN 1089-3. The cylinder body is painted white while the shoulder is painted blue for nitrous oxide. The standard valve is made of brass, an alloy of copper and zinc.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The active ingredient of Medicinsk Lustgas Yara Industrial 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. The RMS will not circulate a non-clinical assessment report.

IV. CLINICAL ASPECTS

IV.1 Clinical efficacy

The applied indications ***as an anaesthetic agent*** and ***as an analgesic/sedative agent*** are those traditionally associated with nitrous oxide ("well established use"). The scientific basis for the effectiveness, including its limitations, of nitrous oxide is firm. Although safety aspects and the use of alternative gaseous anaesthetics have question the place of nitrous oxide, no new data has been published in recent years to challenge the **efficacy** profile of this substance.

IV.2 Clinical safety

Nitrous oxide has been used for over one century and still new aspects on the safety of its use are published.
However, for patients not burden by any of the risk factors described above the use of nitrous oxide in anaesthesia and for short term analgesia/sedation according to recommendations must be considered as safe. It also contributes to a decreased risk of awareness.
The SmPC covers the situations and conditions where nitrous oxide should not be used or carefully used.

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 consider the gas a natural part in an anaesthetic drug mix.
If nitrous oxide is used according to the recommendations in the proposed SmPC the benefit/risk for the patient must be judged as positive.

User testing of the package leaflet has been performed and is acceptable.

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

VI. APPROVAL

The Decentralised procedure for Medicinsk Lustgas Yara Industrial, 100% medicinal gas, liquefied, was successfully finalised on 2007-10-16.

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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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