LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Livopan
(nitrous oxide and oxygen)

SE/H/831/01/MR

This module reflects the scientific discussion for the approval of Livopan. The procedure was finalised at 2008-04-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

AGA AB has applied for a marketing authorisation for Livopan, 50%/50% medicinal gas, compressed. The active substance is nitrous oxide and oxygen. Nitrous oxide has been used as an anaesthetic and analgesic therapeutic agent since the mid 19th century. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Livopan is presented in the form of *medicinal gas compressed* containing *50% nitrous oxide and 50% oxygen* . The finished product is filled in gas cylinders of type aluminium or steel.

II.2 Drug Substance

Both nitrous oxide and oxygen have a monograph in the Ph Eur.

Oxygen is manufactured by distillation of liquefied air in a distillation column, a physical separation process. The products are separated according to their boiling points. The main products are nitrogen (78%) and oxygen (21%). Oxygen is colourless, odourless, and tasteless and has a Boiling point: -182.95 °C (101.325 kPa).

The specification for the oxygen complies with Ph. Eur. requirements. The analytical methods used are those specified in the European Pharmacopoeia. As the methods are according to Ph. Eur. no validation has been performed.

The liquid oxygen bulk product is stored and transported in insulated containers. The containers are gas industry standard for storage and transport of cryogenic gases. The parts of the container in contact with the product, that is the inner vessel and the product piping, are made of aluminium or stainless steel. These materials are inert to liquid oxygen.
Valves are made from stainless steel and/or bronze and are specially designed for low temperatures. The vessels are closed to the atmosphere. The pressure in the storage and transport vessels is always above atmospheric pressure. The storage tanks at the filling stations are used for medicinal oxygen only.

Drug substance (Nitrous oxide)
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 manufacturing process is sufficiently described, and the major phases in the process of nitrous oxide are controlled during the reaction and purification. Acceptable specifications on starting materials, solvent and reagents have been presented. The manufacturing process is considered to be acceptable.
The specification for the drug substance complies with Ph. Eur. requirements and the batch analysis data presented confirms the capability of the manufacturing process to produce

Nitrous oxide of consistent quality, complying with the designed specification (Ph. Eur. requirements).
The transport tanked used for shipping nitrous oxide raw material is a vacuum insulated tank intended for transport of liquefied gases such as at low temperature. The tank used for shipment of nitrous oxide medicinal is dedicated to nitrous oxide medicinal service.
No separate stability studies have been performed on the drug substance.

II.3 Medicinal Product

The drug product Livopan consists of 50% nitrous oxide and 50% oxygen. The finished product is filled in gas cylinders dedicated to the product. The gas cylinders are made of aluminium or steel.
The gas cylinders are equipped with valves which is equipped with separate ports for filling and withdrawal of gas.
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, (do not store below -5 ºC).

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of nitrous oxide and oxygen are well known. As nitrous oxide and oxygen are widely used, well-known active substances, no further studies are required. Overview based on literature review is, thus, appropriate.
The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and is considered sufficient to support the application. The proposed SPC describes the pharmaco/toxicological properties of oxygen and appropriate warning and contraindication statements are made.
There are no objections for approval of Livopan from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

LIVOPAN (nitrous oxide 50% + oxygen 50%) gas is intended for self-administration in situations when a fast onset and offset of analgesia and sedation is wanted. Its analgetic potency is moderate and for more severe painful conditions, is insufficient. However, in many painful or unpleasant conditions, investigations or treatments it can act as an analgetic support. The fast recovery is commonly an advantage. The risks for the patients if the recommendations in the SPC are followed are low. If properly used, including adequate scavenging equipment, the occupation exposure should also be considered fully acceptable.

IV.2 Pharmacokinetics

The pharmacokinetic profiles of oxygen and nitrous oxide are well established.
"Nitrous oxide in concentration of 50% is associated to analgesia and sedation but without major impact on protective reflexes. Nitrous oxide uptake and distribution is fast, it is solely eliminated by exhalation, there is no metabolism of nitrous oxide within the human body. There is an approximately 2.5 times higher oxygen content in the [LIVOPAN] gas mixture compared to ordinary ambient air, this will improve safety and ensure that the patient is well oxygenated. The gas not taken up by the patients will be diluted into the ambient air." (cited from the Expert report)

IV.3 Pharmacodynamics

Nitrous oxide, N2O
Recent studies demonstrating region-dependent effects of nitrous oxide on dopamine and/or norepinephrine concentrations or turnover in the brain have provided direct evidence for the involvement of these substances in transducing some of nitrous oxide's effects in the central nervous system.
The anaesthetic mechanism of nitrous oxide (as for ketamine) has been linked to depression of the glutaminergic synaptic transmission. Recent investigations have led to the hypothesis that the analgesic effects of nitrous oxide are induced by a opioid peptide release in the peri-aqueductal grey area of the midbrain which leads to inhibition of GABAergic neurons *via* opioid receptors by multiple mechanisms that work together. The descending noradrenergic inhibitory neurons, which are tonically inhibited by gamma-aminobutyric acid neurons, are activated and modulate the pain processing in the spinal cord and stimulate descending noradrenergic neuronal pathways, which modulate nociceptive processing.

Oxygen, O2
Carbohydrates, proteins and fat are fed into the tricarboxylic acid cycle, producing reducing equivalents that are fed into the electron transport chain in the mitochondria, which produces potential energy in the form of adenosine triphosphate (ATP). Oxygen is the terminal electron acceptor, with water and ATP being produced. Continued production of ATP is required for long-term cell survival. Mitochondrial oxygen utilisation accounts for about 90% of total cellular oxygen consumption, with much of the remainder used in reactions with mixed-function oxidases, dioxygenases, the cytochrome P-450 system and NADPH oxidase.
The critical level of oxygen required for oxidative phosphorylation to proceed normally *in vivo* is unknown, but it appears that the intramitochondrial oxygen partial pressure (PO_2) needed is only about 0.13 kPa. However, the neurons will no longer function when the PO_2 at their surface is reduced below about 2.7 kPa.
Oxygen is very difficult to store in a biological system. There is no satisfactory method of physical storage in the human body. Haemoglobin is the most efficient chemical carrier, but more than 0.5 kg is required to carry 1 g of oxygen. The quantity of oxygen in the blood when breathing room air is barely sufficient for 3 minutes metabolism in the resting state. Breathing supplemental oxygen can cause a substantial increase in total oxygen stores.

The biological effects of oxygen are well understood. Despite intensive research, the exact molecular mechanisms behind the analgesic and anaesthetic effects of nitrous oxide (as well as for other anaesthetic agents) are still unknown.

IV.4 Clinical efficacy

Introduction
The idea behind Livopan is to administer nitrous oxide in an effective but also safe combination together with oxygen, the latter to ensure sufficient oxygenation.

Overall conclusions on clinical efficacy
The efficacy data for N2O/O2 50/50% is generally of low scientific quality. However, the combination of data from such studies and the description of its behaviour from numerous publications make it possible to draw some efficacy conclusions.
Clinical investigations with variable concentrations of nitrous oxide have demonstrated that with up to approximately 50% of this gas mostly leave the vital respiratory reflexes intact. If this concentration is then combined with self administration the safety will significantly increase.
Nitrous oxide has a sedative and a limited analgetic effect. Its major advantage is its fast onset and more important a fast offset when administration ceases. It is also possible to hasten the elimination by forced external ventilation. These properties makes the fixed combination of 50% nitrous oxide combined with 50% oxygen (Livopan) suitable to ease the discomfort in moderate painful and anxiety evoking investigations, procedures and treatments of relatively short duration. As the safety (see below) is high it can also be used as a rescue analgesic, even if poor, until further more advanced analgesia can be delivered, e.g. epidural analgesia in labour. For short pain treatment in children when an i.v. line is not possible or desirable the mixture can have a place.
The sole use of Livopan in more painful conditions, e.g. fracture reduction, cannot be recommended, at least not in children. The place for Livopan in labour pain is controversial. It has a long record in this setting, but the only placebo-controlled study showed no better analgesia than air. The administration technique (foremost the temporal aspect) could have influenced these results.

IV.5 Clinical safety

Introduction
The oxygen component in Livopan should be of no safety concern.
Adverse events connected to nitrous oxide, both related to exposed patients and to health care staff, have been frequently reported. Environmental effects and abuse of nitrous oxide have also been described.

Overall conclusion on clinical safety
The potential risks for Livopan are almost entirely related to its 50% nitrous component. The fixed concentration and the self administration will substantially reduce the risk profile. The situations where Livopan will be used are of relatively short duration. If relevant contraindications are observed and the gas mix is only administrated as recommended (including scavenging systems) the risks with the use of Livopan for both patients and health personnel must be considered as very low. However, it should be noted that it is technically possible to administer Livopan continuously and in these cases the risks increase considerably as impairment of laryngeal reflexes has been described when N2O/O2 50/50% was administered continuously for 30 minutes.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Livopan, 50%/50% medicinal gas, compressed is recommended for approval.

User testing of the package leaflet has not been performed. The justification for absence of user testing is acceptable since the applicant has referred to the reports on user tests of the package leaflets of similar products (one product containing nitrous oxide and another product containing oxygen).

VI. APPROVAL

Livopan, 50%/50% medicinal gas, compressed was approved in the national procedure on 2007-12-07. The mutual recognition procedure, with Sweden as RMS, was successfully finalised on 2008-04-16.

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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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