LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Kalinox
(nitrous oxide, oxygen)

SE/H/1168/01/MR

This module reflects the scientific discussion for the approval of Kalinox. The procedure was finalised at 2011-09-12. 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 Kalinox inhalation gas containing nitrous oxide 50% and oxygen 50% (mol/mol). The active substances are nitrous oxide and oxygen and there is extensive clinical experience with the use of this nitrous oxide/oxygen combination. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Kalinox is presented in the form of Medicinal gas, compressed containing 50% of nitrous oxide and 50% of oxygen. Kalinox 50%+50% are filled in the cylinders.

II.2 Drug Substance

Nitrous oxide and oxygen has a monograph in the Ph Eur., respectively.

Nitrous oxide

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.

Oxygen

Oxygen is obtained from liquid air by fractionated distillation at low temperature.
Principle of the manufacture of oxygen:
Liquefaction of air requires that it is cooled to a temperature much lower than the critical temperature of its constituents (- 122 °C for argon, - 147 °C for nitrogen and -119 °C for oxygen) so that a very low temperature cold source is required.
The specification for the drug substance complies with Ph. Eur. requirements.

II.3 Medicinal Product

Kalinox 50%+50% Medicinal gas, compressed contain only 50% of nitrous oxide and 50% of oxygen.

The product development has taken into consideration the physico-chemical characteristics of the active substances.
Nitrous oxide can be readily liquefied. It has long been known that N_2O/O_2 mixtures are not physically stable at low temperatures. The critical separation temperature for an equimolar mixture of N_2O/O_2 — when bottled at 125 bar — is around -5°C.
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 “Do not store below -5°C”.

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 and well known, no further studies are deemed necessary.
The nonclinical overview on the nonclinical pharmacology, pharmacokinetics and toxicology is adequate and is considered sufficient to support the application.

III.1 Ecotoxicity/environmental risk assessment

No ERA is required for this product.

III.2 Discussion on the non-clinical aspects

There are no objections of Kalinox from a nonclinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Both uptake and elimination of nitrous oxide occur exclusively via the lungs. Due to the low solubility of nitrous oxide in blood and other tissues, saturation of blood and central nervous system is achieved rapidly. These properties explain the rapid onset of analgesia and that the effects of nitrous oxide quickly subside following discontinuation of administration. Nitrous oxide is eliminated by respiration.

IV.2 Pharmacodynamics

Nitrous oxide, like gaseous anaesthetics with low solubility in oil, is a weak anaesthetic. A mix of 50%/50% N_2O/O_2 does not induce general anaesthesia. In contrast, analgesic capability is already marked. The 50% oxygen content in the mixture ensures that the patient remains well oxygenated.
The time to action onset of nitrous oxide is fast, as is its elimination, due to its low solubility in the blood. Thus, the effect is induced in 3 to 10 minutes, depending on the study, and appears to have resolved 10 to 20 minutes after discontinuation of short-term inhalation.

The exact mechanism through which nitrous oxide produces its effects is not fully known. It is thought that N_2O induces opioid peptide release in the periaqueductal grey area of the midbrain, leading to inhibition of GABA-ergic neurons that are tonically inhibiting the descending inhibitory pathways, which results in activation of the descending noradrenergic inhibitory neurons. Activation of these inhibitory neurons results in modulation of pain processing. The anxiolytic effect may be mediated through interaction with GABA type A (GABA-A) receptors.

IV.3 Clinical efficacy

The applicant has submitted five clinical studies. However, the clinical part of the application is mainly based on bibliographic data.

Nitrous oxide has sedative and limited analgetic effects. Its major advantage is a fast onset of effect and, importantly, a fast offset when administration ceases. These properties make the fixed combination of 50% nitrous oxide combined with 50% oxygen (Kalinox) suitable to ease the discomfort in various moderately painful and anxiety-provoking investigations, procedures, and treatments of relatively short duration. As the safety of the mixture is high, it can be used as a rescue analgesic, even if poor, until more advanced analgesia can be provided (eg, epidural analgesia during labour). However, the place for Kalinox in labour pain seems limited; it has a long history of use in this setting, but placebo-controlled studies have shown no better effect than compressed air. The timing of administration in relation to contractions could be of influence.

Some of the studies indicated a lower degree of efficacy in younger children (<8 years) compared with older children. It is not clear whether this could be due to a less effective use of the mask by younger children. The sole use of Kalinox in more painful conditions (for example, fracture reduction) cannot be recommended.

IV.4 Clinical safety

Reported common adverse events included nausea, vomiting, dizziness, light-headedness, and drowsiness, and excitement. Reported frequencies of adverse events varied widely between various published articles, which can only be partly explained by differences in the N_2O concentration used in the gas mixture (ranging from 10% to 80%). In a study of self-administered N_2O/O_2 50%/50% in 1243 patients in a prehospital emergency setting, approximately 21% of the patients reported side effects such as: nausea or vomiting (5.7%), dizziness or light-headedness (10.3%), drowsiness (7.6%), and excitement (3.7%). Oversedation has been reported in few patients. However, the effects of inhaled N_2O/O_2 could be potentiated by combinations with other sedative drugs, which increase the risk of respiratory adverse events.

Self-controlled intermittent administration of nitrous oxide/oxygen 50/50% has not demonstrated any significant respiratory depressive effects or loss of laryngeal reflexes. However, continuous administration of the gas mixture (ie, not controlled by the patient) could lead to impairment of the laryngeal reflexes and patients need to be appropriately monitored.

Nitrous oxide oxidizes the cobalt in vitamin B_{12}, converting it from the active, reduced form cob(I)alamine to the inactive form cob(II)alamine. Cobalt is an indispensable cofactor in methionine synthetase activity. Irreversible oxidation by nitrous oxide thus induces inhibition of this enzyme. Methionine synthetase with vitamin B_{12} as cofactor enables the transmethylation reaction starting from homocysteine and 5-methyltetrahydrofolate, which produces methionine and tetrahydrofolate. Depletion of tetrahydrofolate creates a risk for megaloblastic anemia. Methionine is a precursor of S-adenosyl-methionine, a methyl group donor that plays a role in a large number of methylation reactions such as the conversion of norepinephrine to epinephrine, the synthesis of arachidonic acid, and myelinisation. Since methionine synthetase inhibition occurs fast and recovery is slow, the cumulative effect of repeated, short-term exposure or continuous exposure to inhaled N_2O/O_2 may increase the risk for toxicity. The chronic use (or abuse) of N_2O/O_2 has been associated with the development of myeloneuropathy and/or toxic bone marrow effects such as megaloblastic anemia.

Nitrous oxide increases the intracranial pressure (ICP) due to an increase in cerebral blood flow both in normal individuals and in patients with intracranial pathology.

During myocardial infarction, 50%/50% N_2O/O_2 has been used to alleviate pain. However, N_2O has a slight myocardial depressive effect and could cause regional ischemia in at-risk patients.

Due to the low solubility of nitrous oxide in plasma compared with other gases, nitrous oxygen will diffuse from plasma into gas containing cavities faster than the original gas will diffuse into the blood. Examples are microbubbles in the blood, pneumothorax, injected gas in the eye bulb and gastrointestinal gas. These gas cavities will expand during nitrous oxide administration.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nitrous oxide has sedative and limited analgetic effects. Its major advantage is a fast onset of effect and, importantly, a fast offset when administration ceases. These properties make the fixed combination of 50% nitrous oxide combined with 50% oxygen (Kalinox) suitable to ease the discomfort in various moderately painful and anxiety-provoking investigations, procedures, and treatments of relatively short duration.
The potential risks for Kalinox are almost entirely related to its 50% nitrous component. The fixed concentration and self administration by the patient will substantially reduce the risk profile.
The situations where Kalinox will be used are typically 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 Kalinox for both patients and health personnel must be considered as very low. However, continuous administration of Kalinox (ie, not controlled by the patient) could lead to impairment of the laryngeal reflexes. If used according to the recommendations as outlined in the SPC, the benefit/risk assessment for Kalinox is favourable.
The clinical risk/benefit ratio is considered positive and Kalinox inhalation gas containing nitrous oxide 50% and oxygen 50% is recommended for approval from a clinical view.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Kalinox inhalation gas containing nitrous oxide 50% and oxygen 50% is recommended for approval.

User consultation
The Applicant has committed to perform a user test of the patient information leaflet after the conclusion of the MRP.

VII. APPROVAL

Kalinox inhalation gas containing nitrous oxide 50% and oxygen 50% was approved in the national procedure in Sweden on 2009-10-16. The Mutual recognition procedure was successfully finalised on 2011-09-12.

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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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