CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Distikstofoxide medicinaal AIR PRODUCTS, 100% v/v, medicinal gas, liquefied
Air Products Nederland B.V., the Netherlands

nitrous oxide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0862/001/MR
Registration number in the Netherlands: RVG 32959

Date of first publication: 22 July 2009
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Pharmacotherapeutic group:	Other general anesthetics
ATC code:	N01AX13
Route of administration:	inhalation
Therapeutic indication:	painful interventions of short duration
Prescription status:	prescription only
Date of first authorisation in NL:	28 March 2007
Concerned Member States:	Mutual recognition procedure with CZ, PT
Application type/legal basis:	Directive 2001/83/EC, 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Distikstofoxide medicinaal AIR PRODUCTS, 100% v/v medicinal gas, liquefied from Air Products Nederland B.V., the Netherlands. The date of authorisation was on 28 March 2007 in the Netherlands.

The product is indicated:

- for administration in equimolar concentration with oxygen (50% v/v nitrous oxide and 50% v/v oxygen) as an analgesic with weakly anaesthetic properties for painful interventions of short duration, as part of acute medical assistance in traumatology and burns, dental interventions, childbirth and Ear, Nose and Throat surgery.
- as a basic anaesthetic in combination with inhalation anaesthetics, intravenous anaesthetics (thiopental, propofol), opiates, and/or muscle relaxants. Medicinal oxygen is mixed-in in a minimum of 21% v/v.

A comprehensive description of the indications and posology is given in the SPC.

Nitrous Oxide Medicinal Air Products, containing nitrous oxide, is a relatively weak anaesthetic with good analgesic properties. The analgesic activity of nitrous oxide is based on an effect on opiate receptors; the anaesthetic action of nitrous oxide is brought about by interaction with GABA and glutamate receptors. Nitrous oxide has no muscle relaxant effect. In a concentration of 50% the effect of nitrous oxide is analgetic; an anesthetic effect occurs in a concentration of 105% (MAC). Anaesthesia can only be induced if nitrous oxide is combined with another anaesthetic administered intravenously or by inhalation.
In combinations with other inhalation anaesthetics, a concentration of 50-70% nitrous oxide will decrease the average minimal alveolar concentration (MAC) necessary for anaesthesia by about fifty percent.
Nitrous oxide has no direct effect on the lung function and gaseous exchange. However, nitrous oxide does have an indirect effect on gaseous exchange, as nitrous oxide dissolves better in the blood than nitrogen. Nitrous oxide is therefore taken up more rapidly in the lungs than nitrogen, as a result of which the concentrations (partial pressures) of other gasses, oxygen and potentially other anaesthetics inhaled at the same time increase.

Since the “Note for Guidance on medicinal gases: Pharmaceutical documentation” (CPMP/QWP/1719/00) was adopted in 2002, it is mandatory in the European Union to register medicinal gases as medicine replacing the status of medical device. Hence, a number of medicinal gases have now received a marketing authorisation.

The marketing authorisation is granted based on article 10a (well-established medicinal use) of Directive 2001/83/EC.

This application concerns a bibliographical application based on well-established medicinal use of nitrous oxide. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ‘’Medicinal use’’ does not exclusively mean ‘’use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

General
The active substance is nitrous oxide, an established active substance, described in the European Pharmacopoeia (Ph.Eur.*). Nitrous oxide is a colourless gas with a faintly sweet odour. It is heavier than air and non-flammable in air. Full documentation on the active substance has been included in the dossier.

Manufacturing process
The manufacturing process is sufficiently described for each production site. It consists of a thermal decomposition reaction: the main reaction is $NH_4NO_3 \rightarrow N_2O + 2\ H_2O$. This reaction is followed by purification steps. It has been demonstrated that the manufacturing process is sufficiently under control.

Impurities
The impurities routinely searched for at those described in the Ph.Eur. monograph: CO and CO_2; $NO+NO_2$ and H_2O. As the monograph is indeed intended for nitrous oxide formed by thermal decomposition; therefore no additional impurities are to be expected. The test methods are according to the Ph.Eur. monograph. The provided information is thus considered sufficient.

Specification of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for production scaled batches of each manufacturing site.

Stability of drug substance
Bibliographic evidence of stability is included, in which the behaviour of the molecule under normal and worst case scenario transport and storage conditions is discussed. No retest period is claimed. This is acceptable, since every batch will be tested for conformance to the Ph.Eur. monograph for nitrous oxygen prior to use (i.e. the filling of the cylinders).

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Distikstofoxide medicinaal AIR PRODUCTS consists of ≥ 98% nitrous oxide in the form of a liquefied gas. It is a colourless gas with a faintly sweet odour and without taste.

No excipients are present.

Pharmaceutical development
Nitrous oxide has been used as a medicinal gas for more than 50 years. The development of the product has been described. Several relevant physico-chemical properties are discussed and compatibility of the gas with the applied containers is also sufficiently guaranteed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of filling pure active substance N_2O from its storage tank into cylinders/packs, without any change of state. All operations are carried out in a closed circuit by means of a network of pipes with valves that are gas-specific and reserved solely for the nitrous oxide filling. The process has sufficiently been described. The fill weight is a critical parameter that should be validated if not tested on every unit. However, each cylinder is individually weighed and the requirements for fill weight of each cylinder size are stated. The process is therefore considered to be sufficiently under control.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form.
The drug substance specification is in line with the Ph.Eur., with additional requirements in line with the Note for Guidance on Medicinal Gases. Compliance with the release requirements is sufficiently demonstrated.
For the analytical methods reference is made to the Ph.Eur. Validation results are therefore not required.
Batch analytical data from the three proposed production sites have been provided on 3 full scaled batches, demonstrating compliance with the release specification.

Package
Distikstofoxide medicinaal AIR PRODUCTS is packed under its own vapour pressure in chromium molybdenum steel cylinders (Cr/Mb) and in aluminium cylinders (with or without outer hoopwrapped layer) of various capacities ranging from 0.5 to 50 litres. The cylinders are painted in line with EN 1089-3: blue shoulder. For NL (NF EN 1089-3) and CZ the body is white, for PT the body is black.
An overview is provided of the different cylinders and packs: water volume (l) and fill weight (kg) at 15 °C are stated. The valves are made of brass, steel or aluminium. All valves were brought into accordance with Directive 1999/36/EC. They have a Π-mark when complying. Compatibility of cylinder and valve materials is standardized in EN ISO 11114-:1997 for metallic materials and in EN-ISO 11114-2:2000 for non-metallic materials. The packaging is usual for this type of product.

Stability tests on the finished product
Nitrous oxide is a stable gas which has been used for a long time packaged in containers for which a long time of experience is available. Bibliographic data were therefore acceptable to support the claimed shelf-life. The MAH refers to the Stability and Compatibility in accordance with Framework Directive on Transport of Dangerous Goods by Road and to the NfG on Medicinal Gases. Compatibility of the gas with the containers is assured by compliance with this regulation. Common knowledge of the properties of nitrous oxide guarantees stability of the product at common storage temperatures. No additional impurities are to be expected to arise as a result of the filling process or storage. Small leakages may occur, but these would always be towards the atmosphere. The quality of the container and the closure valve is guaranteed by regular retests.
A shelf-life of three years was granted, under the conditions as described in section 6.4 of the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

Nitrous oxide has been available on the European market for several decades. Preclinical data have been superseded by clinical experience, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
No environmental risk assessment has been performed, which is acceptable for this application.

II.3 Clinical aspects

To support this application, the MAH submitted an expert report with a review of the literature. No new clinical studies were performed for this application. This is acceptable, since the current application concerns a product that is essentially similar to those already on the market in the Netherlands.

Pharmacokinetics
Nitrous oxide is administered by inhalation. Its absorption depends on the pressure gradient between inhaled gas and the blood passing through ventilated alveolar sections. Absorption is rapid, and nitrous oxide is readily distributed to well perfused organs such as the brain. It is not metabolised, but it is washed out by exhalation.

Pharmacodynamics
Nitrous oxide has both direct and indirect effects on the transmission of a number of neurotransmitters both in the brain and the spinal cord. An accepted concept for its mode of action is the direct interaction of nitrous oxide with membrane proteins, in particular ion channels and receptors involved in brain functions. Evidence is also provided that nitrous oxide may interact with the endogenous opioid system by the release of endogenous opioids and/or by direct action at the mu, delta, sigma and kappa receptors. Its effect on the endorphin system throughout the CNS is presumably one of the more central mechanisms underlying the analgesic effects. It has been postulated that the anxiolytic effect of nitrous oxide, may be mediated by selected subunits of the GABA-A receptor (Emmanouil & Quock, 2007).

Clinical efficacy
There is sufficient evidence from published randomised studies that the application of nitrous oxide in painful procedures where rapid analgesia and mild sedation is needed, such as in dental procedures and during labour, is useful and safe. Several studies show that nitrous oxide can be safely used in children.

Some indications that are discussed in the expert report are however not generally acknowledged, such as the use of nitrous oxide in the treatment of migraine, alcohol withdrawal symptoms, dyspnoea and pneumo-peritoneum. These indications are therefore not included in the SPC.

Though the application of nitrous oxide as analgesic drug is generally accepted, the usefulness of adding nitrous oxide to general anesthesia is currently under debate, especially as the incidence of post-operative nausea and vomiting is reported to be higher after general anesthesia where nitrous oxide had been used (Enlund, 2003). However, the prophylactic use of anti-emetics may negate this factor (Apfel, 2002). The most important reason for the continued use of nitrous oxide is that it has been reported to reduce the incidence of intra-operative awareness because it has a superior amnesic effect compared with other volatile anaesthetics (Tramèr *et al.*, 1996). In several studies it was confirmed that nitrous oxide has a propofol-sparing effect, which is also beneficial. By enabling reduced doses of more potent anaesthetics, nitrous oxide limits cardio-respiratory side effects of these other anaesthetic drugs. Nitrous oxide is therefore still an option in general anaesthesia (Hopkins, 2005).

Clinical safety
Side effects of nitrous oxide are generally minor and reversible. The main complications following the use of nitrous oxide are those due to varying degrees of hypoxia. As nitrous oxide is rapidly washed out of the body after discontinuation of administration, patients in general recover rapidly. Nitrous oxide does not significantly impair higher cognitive tasks (Beckman, 2006) and is well tolerated in elderly (Leung, 2006). Euphoria is commonly reported, and nitrous oxide dependence may occur for those who have access.

The safety concerns and precautions to be taken to prevent adverse events and to protect the staff to chronic exposure are adequately described in the SPC. In general, nitrous oxide can be safely used in painful procedures in elderly, children and cardiovascular patients.

In general anaesthesia, nausea may be more common when nitrous oxide is applied in combination with other anaesthetics. Nitrous oxide may expand air-filled caveties and should therefore not be used in pneumothorax, bullous emphysema, et cetera.

As nitrous oxide interferes with folate and vitamine B12 metabolism, long term exposure should be avoided, as well for patients as for staff. Especially pregnant staff members should avoid exposure to nitrous oxide, as it may cause birth defects. This is adequately reflected in the SPC.

Limited data on short-term use of nitrous oxide in pregnancy in humans do not reveal an increased risk of congenital abnormalities. A study from Lewinska et al. (2005) suggests that inhalation exposure to anesthetics, with nitrous oxide as a predominant chemical, may induce genotoxic effects in peripheral blood lymphocytes of exposed operating-room nurses. Possible reproductive and teratogenic effects of anesthetics, particularly to nitrous oxide, in animal studies have been reported (Yagiela 1991). However, retrospective reviews and individual case reports have not shown nitrous oxide anesthesia to be foeto-toxic or teratogenic in humans (Aldridge et al. 1986, Park et al. 1986). It is however recommended that pregnant staff members should confine from working with nitrous oxide, and that frequent and prolonged use of nitrous oxide should be avoided, especially in early pregnancy.

Whether nitrous oxide can be safely used in anaesthesia in cardiovascular patients is a matter of debate. Folate and vitamine B12 deficiency may lead to elevated homocysteine (Hcy) levels, which are considered a risk factor for cerebro- and cardiovascular disease. It has been postulated that nitrous oxide, as it interferes with folate metabolism, may be a significant risk factor for cardiac complications. However, this was not confirmed in the ENIGMA I trial. In this blinded randomized trial in 2050 patients undergoing general anaesthesia for more than 2 hours with nitrous oxide or oxygen (with or without nitrogen), there was a non-significant reduction of myocard infarcts in the nitrous oxide study arm (Myles, 2007). As relatively few patients with pre-existent cardiovascular diseases or risks were included in the ENIGMA trial, a new trial (ENIGMA II, N = 7000) has recently started in Australia and New Zealand including these patients at risk. Of note, in the ENIGMA I study, a significantly increased risk of postoperative wound infection, severe vomiting, pneumothorax or atelectasis, and pneumonia was observed (all $P<0.05$). Median duration of hospital stay did not differ substantially between groups (7 days).

Pharmacovigilance plan

The Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Minimisation Plan

Concerning the need for a risk minimisation plan the MAH declares no such plan is deemed necessary. The application concerns a product for which no safety concerns requiring additional risk minimisation activities have been identified. This is considered acceptable.

Product information

Readability test

The MAH has not performed a readability test on its package leaflet based on the following justifications:

- reference is made to the readability test performed on the Dutch package leaflet for Noxap (nitric oxide in nitrogen).
- the same lay-out and design is applied as in the Dutch package leaflet for Noxap;
- the route of administration is the same as for Noxap;
- Nitrous Oxide Medicinal is not used directly by the patient but by a healthcare professional.

Based on the 'Guidance for the Pharmaceutical Industry on the use of Bridging Studies to demonstrate compliance with article 59(3) of Council Directive 2001/83/EC (Consultation with Target Patient Groups), it can be concluded that the same key messages for safe use are applied within the range of medicinal gases as a group of medicines. Therefore, no readability test was deemed necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nitrous oxide has been used since the 19th century for analgesia during painful procedures and anaesthesia in combination with other anaesthetics. There is sufficient evidence from randomised studies that the application of nitrous oxide in painful procedures where rapid analgesia and mild anaesthesia is needed, such as in dental procedures and during labour, is useful and safe. Several studies show that nitrous oxide can be safely used in children and elderly, provided that the safety measures and contraindications, as stated in the SPC, are taken into account.

The use of nitrous oxide in anaesthesia is under debate, as it may cause nausea and it might enhance the risk on post-operative cardiovascular events. However, it has not been confirmed in a large clinical trial that nitrous oxide indeed induces cardiovascular adverse events. A benefit of nitrous oxide may be the reduction of intra-operative awareness, and the dose sparing effect of more potent anaesthetics with a less favourable safety profile, such as propofol and halogenated gas. Nitrous oxide is therefore still an option in general anaesthesia.

The MEB, on the basis of the data submitted, considered that Distikstofoxide medicinaal AIR PRODUCTS, 100% v/v, medicinal gas, liquefied demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Distikstofoxide medicinaal AIR PRODUCTS, 100% v/v was authorised in the Netherlands on 28 March 2007.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, have granted a marketing authorisation. The mutual recognition procedure was finished on 9 April 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from March 2007 to March 2010.

The date for the first renewal will be: 28 March 2012.

There were no post-approval commitments made during the procedure.

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List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Repeat use procedure with DE and SK.	NL/H/0862/ 001/E/001	Repeat Use	23-3-2010	21-6-2010	Approval	Y, Annex I

ANNEX I – Repeat use procedure (NL/H/0862/001/E/001)

The Repeat use procedure started on 23 March 2010. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states (DE and SK), on the basis of the data submitted, considered that well-established use has been demonstrated for Distikstofoxide medicinaal AIR PRODUCTS, 100% v/v, and have therefore granted a marketing authorisation. The repeat use procedure was finished on 21 June 2010.

The date for the first renewal will be: 28 March 2012.

The PSUR submission cycle will follow a harmonised birthdate of 26 March 2010, with a 3 year PSUR cycle.

The following post-approval commitment has been made during the procedure:

- The MAH committed to submit a type II variation in order to bring the SPC more in line with the SPC of Livopan, SE/H/0831/01/MR.