CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Distikstofoxide medicinaal SOL, medicinal gas, liquefied 100% v/v SOL SpA, Italy

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/2783/001/MR
Registration number in the Netherlands: RVG 32961

Date of first publication: 8 May 2013
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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:	31 July 2009
Concerned Member States:	Mutual recognition procedure with BE, BG, LU, SI, UK
Application type/legal basis:	Directive 2001/83/EC, Article 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 SOL, medicinal gas, liquefied 100% v/v from SOL SpA. The date of authorisation was on 31 July 2009 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 weak anaesthetic properties for painful interventions of short duration, as part of acute medical treatment in the field of traumatology and for burns, dental surgery, childbirth and ear, nose and throat surgery in adults and children from the age of 1 month.
- as a basic anaesthetic in combination with inhalation anaesthetics, intravenous anaesthetics (thiopental, propofol), opiates, and/or muscle relaxants in adults and children from the age of 1 month. Medicinal oxygen is added at a concentration of at least 21% v/v.

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

Nitrous oxide is a relatively weak anaesthetic with good analgesic properties. The analgesic action of nitrous oxide is based on an effect on opiate receptors and its anaesthetic action on an effect on GABA- and glutamate receptors. Nitrous oxide has no muscle-relaxing effect. At a concentration of 50%, nitrous oxide has an analgesic action; an anaesthetic effect is only obtained at a concentration of 105% (MAC). Anaesthetic action is only achieved with the simultaneous administration of intravenous anaesthetics or other inhalation anaesthetics. A concentration of 50% - 70% nitrous oxide in such a combination with other inhalation anaesthetics reduces the mean minimal alveolar concentration (MAC) required for anaesthesia by about half.

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
The active substance is nitrous oxide, an established active substance, described in the European Pharmacopoeia (Ph.Eur.*). It is a colourless and odourless gas, with a faintly sweet odour. It is heavier than air and non-flammable in air.

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.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. The requirements are acceptable. Compliance has been demonstrated by inclusion of batch analysis results from each manufacturing site.

Stability of drug substance
The substance is tested for compliance with the Ph.Eur. requirements prior to filling the cylinders. Therefore a retest period is not applicable.

** 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 SOL is a colourless and odourless gas.

The product consists of 100% nitrous oxide v/v in the form of a liquefied gas under its own vapour pressure (45 bar at 15°C) in seamless steel or aluminium cylinders of various capacities and in cylinder bundles.

No excipients are present.

Pharmaceutical development
The development of the product is satisfactorily performed and explained. Nitrous oxide has been used as a medicinal gas for more than 50 years. The packaging material is deemed suitable for the product at issue. Background information on cylinders, valves and bursting discs was provided. For compatibility issues reference is made to the Framework Directive on transport of Dangerous Goods by Road (ADR). Additionally 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. This is acceptable.

Manufacturing process
The manufacturing process consists of transfilling pure active substance N2O 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 and is under control.

After finalisation of the MRP, an additional manufacturer was approved through variation procedure NL/H/2783/IB/001/G.

Quality control of drug product
The drug substance specification is in line with the Ph.Eur., with additional requirements in line with the NfG on Medicinal Gases. The requirements are acceptable. Compliance with the release requirements is sufficiently demonstrated. In the dossier analysis results of several batches including different cylinder volumes per batch have been presented. The weight has been laid down for each individual batch, the % N2O is measured for one cylinder and the content of H2O is mentioned. The results indicate that the cylinders can be filled in compliance with the proposed specification.

Stability of drug 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 may therefore be used to support the claimed shelf-life. Compatibility of the gas with the containers is assured by compliance with the first 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. The claimed shelf-life of three years is deemed acceptable, 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. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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 literature review. 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 transported in blood as free gas; it does not bind to hemoglobin. As hypoxia may occur due to dilution effect in the alveoli, N2O is always mixed with oxygen at clinical use (50-70% N2O/O2).

Nitrous oxide is not metabolized by enzymes, but it is washed-out by exhalation. No PK interactions at enzyme level are expected, as nitrous oxide is not metabolized by enzymes. No accumulation is expected in renal or hepatic patients, or children.

Pharmacodynamics
N2O is a weak anaesthetic (minimum alveolar concentration - MAC around 105%) and analgesic, that may need combination with other substances, in particular for general anaesthesia. The equivalent analgesic effect of N2O in an adult patient has been estimated to require around 10-15 mg of morphine.

The underlying mechanisms of N2O-induced analgesic effects have been partly elucidated. It has been

suggested in the literature that endogenous opioid peptide release, and inhibition of GABA-ergic and glutamate-mediated excitatory neurotransmission, may play a role.

Clinical efficacy

The use of nitrous oxide at induction and maintenance of anaesthesia, in a 70%/30% N2O/O2 mixture, is well-established. N2O cannot provide sufficient level of anaesthesia on its own, but is combined with more potent other anaesthetics (e.g. inhalation anaesthetics, propofol, opioids). N2O is mainly used in anaesthesia for its analgesic properties. It reduces the need of other anaesthetics significantly, contributing to better tolerability of anaesthesia, as inhalational anaesthetic agents may be cardiotoxic, hepatotoxic, or increase cerebral flow and intra-cranial pressure. The benefits are that the use of N2O shortens induction of anaesthesia, and reduces the needs op opioids and other anesthetics at induction and maintenance. It also appears to reduce retrograde amnesia.

However, N2O causes Post-Operative Nausea and Vomiting. According to the ENIGMA trial, N2O as adjuvant in maintenance of general anesthesia may even be associated with enhanced perioperative cardiovascular (CV) risks and wound infection, although confounding was not excluded, as there were differences in depth of anesthesia and O2 use between N2O arm and control. Recently, a prospective trial in 1773 patients undergoing carotid surgery did not confirm an enhanced CV risk. (GALA trial, Sanders et., 2012)[1].

The safety and efficacy of this commonly used inhalant anesthetic is under discussion among anesthesiologists. There is no general European guideline available on the use of N2O in general anesthesia. However, there is still a place for N2O in European practice, as a part of as analgesic component in 'balanced anaesthesia' add-on to other anaesthetic drugs, and because of its well-established safety record, or low costs. There are advantages of the use of nitrous oxide in renal or hepatic compromised patients, as there is no accumulation in these special patients.

Nitrous oxide, as 50/50 N2O/O2 mixture is a strong analgesic drug, which is well established and can be safely used in labor and a broad range of painful procedures. It has a rapid onset and off-set of effect. It is also anxiolytic. It is as effective as other drugs commonly used in painful procedures (midazolam, propofol), but with lower sedation rate.

Clinical safety

The safety profile of nitrous oxide depends on the clinical context where it is used, and dose and duration of exposure.

At short-term use in procedural pain and labor, at a 50%/50% N2O/O2 mixture, nitrous oxide is in general well tolerated. Nausea and neuropsychiatric events are commonly reported, but severe cases are rare. N2O at short term use in labor in low doses (50%) is not harmful for the fetus and neonate.

Nitrous oxide, as used in general anaesthesia at higher doses (70%/30% N2O/O2), is associated with a higher risk of Post-Operative Nausea/Vomiting (PONV) compared to placebo. Recently, N2O at maintenance of anaesthesia is discussed, as it may be associated with wound infections and cardiovascular risk, as reported in the ENIGMA trial, a RCT in about 2000 subjects. Especially patients with enhanced homocysteine plasma levels, as a signal of vitamin B12 depletion, may be at risk. However, any cardiovascular risk of N2O is not confirmed by another recent study in 1773 carotid surgery patients (GALA trial).

Long-term exposure to nitrous oxide is associated with vitamin B12 depletion, and consecutively megaloblastic anemia and spinal cord damage, or, in pregnant women, neural tube closure disorders. Probably as it has opioid effects, nitrous oxide has an abuse/addition potential. Health care professionals and patients need to be protected against long term exposure. Adequate warnings and measures are proposed in the SPC.

[1] Sanders RD, Graham C, Lewis SC, Bodenham A, Gough MJ, Warlow C; GALA Trial Investigators. Br J Anaesth. 2012 Sep;109(3):361-7. Epub 2012 Jun 17.

Nitrous oxide can be safely used in special populations like children, renal and hepatic patients. As there is a lack of clinical data of the use of N2O in neonates, and this age group may be more vulnerable to vitamin B12 depletion and neurotoxicity, the use in this age group is not recommended.

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

On the basis of the safety specification and considering the extensive clinical experience, the applicant does not regard it necessary to establish specific risk minimisation activities. Routine risk minimisation activities, such as warnings included in the product information and a careful labelling and packaging should be adequate for avoiding the risks that may be associated with this product. No additional risk minimisation activities (such as educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes) will be required.

Product information

SPC

The content of the SPC approved during the mutual recognition procedure is adequate. Health care professionals and patients need to be protected against long term exposure. Adequate warnings and measures are included in the SPC.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Both rounds of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The use of nitrous oxide at lower doses as analgesic and anxiolytic drug is well established, and has a good safety record. Also the use as an analgesic component in general anaesthesia is well established; Although there are some concerns about higher risk of post-operative nausea/vomiting and potential risk of CV events, the latter is not confirmed in some studies. Other analgesics used in general anaesthesia, like opioids, may cause nausea as well, or have longer carry-over effect post-operative.

Nitrous oxide has the advantage that it can be used in renal and hepatic patients, without dose adjustments. The use in children is well-established, except in neonates, where data are sparse. Therefore, neonates are excluded from the indication.

The MEB, on the basis of the data submitted, considered that Distikstofoxide medicinaal SOL, medicinal gas, liquefied 100% v/v demonstrated adequate evidence of efficacy for the approved indications 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 contain adequate information and warnings, and are in the agreed templates.

The Board followed the advice of the assessors. Distikstofoxide medicinaal SOL, medicinal gas, liquefied 100% v/v was authorised in the Netherlands on 31 July 2009.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The concerned member states, on the basis of the data submitted, have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 2 December 2012.

The date for the first renewal will be: 2 December 2017.

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

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	Cardiovascular
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
MAC	Minimum Alveolar Concentration
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
Addition of SOL S.p.A., Cremona as a manufacturing site for the finished product, primary and secondary packaging site, batch release and batch control/testing site.	NL/H/2783/ IB/001/G	IB/G	18-7-2013	13-9-2013	Approval	N