CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Niontix, medicinal gas, liquefied 100% v/v
Linde Gas Therapeutics Benelux 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/2163/001/MR
Registration number in the Netherlands: RVG 33168

18 January 2012

Pharmacotherapeutic group:	Other general anesthetics
ATC code:	N01AX13
Route of administration:	inhalation
Therapeutic indication:	painful interventions of short duration; as basic anaesthetic in combination with inhalation or intravenous anaesthetics (thiopental, propofol), opiates and/or muscle relaxants
Prescription status:	prescription only
Date of first authorisation in NL:	29 July 2009
Concerned Member States:	Mutual recognition procedure with BE and LU
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 Niontix, medicinal gas, liquefied 100% v/v, from Linde Gas Therapeutics Benelux B.V. The date of authorisation was on 29 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 weakly anaesthetic properties for painful interventions of short duration, as part of acute medical treatment in the field of traumatology and for 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 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.
Nitrous oxide has no direct effect on lung function and gas exchange. Nitrous oxide does have an indirect effect on gas exchange because nitrous oxide dissolves better in blood than nitrogen. This means that nitrous oxide is taken up into the lungs more quickly than nitrogen so that the concentrations (partial pressures) of other gases, oxygen and any other anaesthetics inhaled simultaneously, are increased.

According to the “Note for Guidance on medicinal gases: Pharmaceutical documentation” (CPMP/QWP/1719/00), adopted in 2002, it is mandatory in the European Union to register medicinal gases as medicine, replacing the status of medical device as was the case before 2002.

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.*). Nitrous oxide is a colourless and odourless gas. It is heavier than air and non-flammable in air. The boiling point at 1 bar is -88.5ºC. The vapour pressure at 20ºC is 50 bar. Full documentation on the active substance has been included in the dossier.

Manufacture
Nitrous oxide is produced by thermal decomposition of starting material ammonium nitrate: $NH_4NO_3 \rightarrow N_2O + 2\ H_2O$. The purified nitrous oxide is then compressed, dried and liquefied. The liquefied gas is transferred to a refrigerated storage tank. This is the general process to manufacture nitrous oxide which is also the basis of the Ph.Eur. monograph. Sufficient information has been provided on the production process for each production site. Full documentation on the active substance has been included in the dossier.

Impurities
The impurities routinely searched for are those described in the Ph.Eur. monograph: nitrogen/oxygen, ammonia/nitric acid, nitric oxide/nitrogen dioxide, chlorine/hydrogen chloride, carbon dioxide/carbon monoxide and water. The monograph is 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 drug substance specification is in line with the Ph.Eur.; this specification is acceptable. The process at all production sites is deemed sufficiently under control. Batch analytical data demonstrating compliance with this specification have been provided for production scaled batches of each manufacturing site.

Stability
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
The product consists of 100% nitrous oxide v/v (EP) in the form of a liquefied gas in steel cylinders of various capacities and in cylinder bundles.

No excipients are present.

Pharmaceutical development
Nitrous oxide is used for more than 50 years. The development of the product has been described. No overages are used, and the properties of the gas have been discussed in the substance section. 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. The available process description is deemed sufficient. The in-process controls are indicated in the flow chart. 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.
Tabulated batch analysis results for 12 cylinders have been enclosed, demonstrating compliance with the release specification.

Package

Niontix, medicinal gas, liquefied 100% v/v is packed under its own vapour pressure in chromium molybdenum steel cylinders (Cr/Mb) with cylinder size (water capacity) of 2, 10, 40, 50, or 12 x 50 litres, with respectively a nominal content of 1.5, 7.5, 30, 37.5 and 450 Kg nitrous oxide.
The cylinders are painted in line with EN 1089-3.
On/off valves are used. To seal and lubricate the threads between the cylinder and the valve PTFE (polytetrafluorethene) tape or, for cylindrical threads, an O-ring is used. A unique connection is used. The valve outlet is a Pin Index Safety System (PISS).
The cylinders and valves comply with Directive 1999/36/EC; this is also called the TPED or pi-mark directive. 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. Nitrous oxide is stable according to literature at ambient temperature, even at high pressures. A discussion is enclosed on the decomposition reaction and the concluded stability. Reference is made to literature references. The literature confirms that degradation of nitrous oxide does not take place at temperatures up to 420°C. At room temperature no degradation occurs at pressures up to 600 atm. The product is therefore considered as stable. This is confirmed by the additionally included stability data.
Cylinders (several sizes) from 3 different batches were tested at several temperatures, to show that the nitrous oxide in the cylinders is stable during the shelf life. The data available demonstrate compliance with the specifications.
The proposed shelf-life of 5 years is granted. The storage conditions mentioned in the SPC (-20°C to +65°C) are acceptable.

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.
The MAH provided a non-clinical literature overview, including information on primary pharmacodynamics, drug interactions and single dose toxicity. Information regarding neurotoxic effects of nitrous oxide was included in the SPC (section 5.3).

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 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.

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 (Tramer *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
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 Clinical Overview and 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 cavities and should therefore not be used in pneumothorax, bullous emphysema, et cetera.

As nitrous oxide interferes with folate and vitamin 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.

Whether nitrous oxide can be safely used in anaesthesia in cardiovascular patients is a matter of debate. Folate and vitamin 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 were included in the ENIGMA trial with pre-existent cardiovascular diseases or risks, 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 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 pilot test with 5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

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 Niontix, medicinal gas, liquefied 100% v/v 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. Niontix, medicinal gas, liquefied 100% v/v was authorised in the Netherlands on 29 July 2009.

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 4 October 2011.

The date for the first renewal will be: 29 July 2014.

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

References

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Emmanouil D.E., Quock R.M. Advances in Understanding the Actions of Nitrous Oxide. Anesth Prog 54:9–18 2007

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Hopkins PM. Nitrous oxide: a unique drug of continuing importance for anaesthesia.Best Pract Res Clin Anaesthesiol. 2005 Sep;19(3):381-9.

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Tramèr M, Moore A, McQuay H. Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. Br J Anaesth. 1996 Feb;76(2):186-93.

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