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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Donopa 50%/50% v/v medicinal gas, compressed SOL SpA, Italy

oxygen/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/2233/001/DC
Registration number in the Netherlands: RVG 109415

22 August 2012

Pharmacotherapeutic group:	other general anesthetics
ATC code:	N01AX63
Route of administration:	inhalation
Therapeutic indication:	treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted in adults and children older than 1 month
Prescription status:	prescription only
Date of authorisation in NL:	6 June 2012
Concerned Member States:	Decentralised procedure with BE, DE, IT, LU, 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 Donopa 50%/50% v/v medicinal gas, compressed from SOL SpA. The date of authorisation was on 6 June 2012 in the Netherlands.

The product is indicated for the treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted. Donopa is indicated in adults and children older than 1 month.

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

Nitrous oxide in concentrations of 50% has analgesic effects, raises the pain threshold for various painful stimuli. The intensity of the analgesic effect depends mainly on the psychological state of the patient. At this concentration (50%), nitrous oxide has limited anaesthetic effects. At these concentrations nitrous oxide provides a sedative and calming effect but the patient remains conscious, easily arousable but with a certain detachment from his/her surroundings.
The 50% concentration of oxygen (more than twice the concentration in ambient air) guarantees good oxygenation and optimally oxygen saturation of the haemoglobin.

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.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of oxygen/nitrous oxide 50%/50% v/v, medicinal gas, compressed. This type of application does not require submission of the results of preclinical 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.

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

No scientific advice has been given to the MAH with respect to these products.

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 substances
The active substances, nitrous oxide and oxygen, are both described in the European Pharmacopoeia (Ph.Eur.*).

Nitrous oxide
Manufacturing process
The nitrous oxide (N_2O) is obtained by continuous thermal decomposition of the ammonium nitrate (NH_4NO_3). The produced gas is thus purified, pressurised, dried and liquefied. Nitrous oxide is an odourless and colourless gas and has a boiling point at 1 bar (760 mmHg) -88.46 °C.
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 have been presented. The manufacturing process is considered to be acceptable.

Quality control of drug substance
The specification for the drug substance complies with Ph. Eur. requirements and the batch analysis data presented confirm the capability of the manufacturing process to produce nitrous oxide of consistent quality, complying with the designed specification (Ph. Eur. requirements).

Stability of drug substance
The nitrous oxide, used for many years, does not show any known instability. Despite its high chemical reactivity, nitrous oxide is stable within normal temperature and pressure conditions and in the absence of reactive substances. No separate stability studies have been performed on the drug substance; literature reference data on the stability have been included.

** 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.*

Oxygen
Manufacturing process
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 and oxygen. The starting material is ambient atmospheric air. There are no specifications on the purity of the air and no controls are performed. The oxygen production process is a continuous distillation process. There are no intermediates during the production process.

Quality control of drug substance
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.

Stability of drug substance
Oxygen, used since numerous years, does not present known instabilities. It can therefore be considered that oxygen, despite its enormous chemical reactivity, is a stable gas in normal conditions of temperature and pressure and in the absence of reactive substances. No separate stability test has been performed on the drug substance as such. A shelf-life of one year was assigned.

Medicinal Product

Composition
Donopa 50%/50% v/v medicinal gas, compressed consists of 50% nitrous oxide and 50% oxygen at 135 or 185 bar. It is a colourless, odourless gas.

No excipients are used.

The medicinal gas is packed in steel or aluminium gas cylinders.

Pharmaceutical development
The analgesic properties of the medicinal nitrous oxide are known from the description by Sir Humphrey Davy of an infected tooth pain relief obtained after treatment by nitrous oxide. The mixture medicinal nitrous oxide – medicinal oxygen (50/50 molar) presented in cylinders was developed by BOC in 1961.
No overages are used in the product. The development pharmaceutics haven been adequately described. The MAH addressed the issues of pressure increase, liquefying of the N_2O (temperature), stability after storage at low temperature and the cylinder suitability. Homogeneity of the mixture was studied.

Manufacturing process
The manufacturing consists of introducing the two gases into the cylinder. This introduction can be done by two different ways; by gravimetric method with introduction of the 2 gases successively or introduction of the mixture under well defined temperature and pressure conditions. Details of both methods have been provided. The process has been validated for 7 batches at both 135 bar and 185 bar.

Container closure system
The finished product is filled in gas cylinders dedicated to the product. The cylinders are either made of steel, aluminium or hoop wrapped aluminium. They are used with standard valve or with integrated pressure regulator, with or without flow-meter. Compliance with European Directives and (N)EN and/or ISO standards was shown. The quality of the container closure system is therefore considered sufficiently guaranteed.

Quality control of drug product
The specification for the finished product includes tests for assay of oxygen and nitrous oxide and pressure. The impurities in medicinal gases like carbon monoxide, carbon dioxide, NOx and water are analysed in the drug substances. The tests and limit specifications for the oxygen and nitrous oxide and pressure are considered to be acceptable. Batch analyses results were provided for three batches at 135 bar and three batches at 185 bar, demonstrating compliance with the specification.

Stability of drug product
Stability tests at -5°C and 50°C on product filled to 135 bar and 180 bar were provided. Results from 24 months of storage show no significant change in concentration in any of the measured parameters. The proposed shelf life for the drug product of 24 months and the proposed storage conditions of “Store between 0°C and 50°C. Do not freeze” are therefore 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

Pharmacodynamic, pharmacokinetic and toxicological properties of nitrous oxide and oxygen, 50%/50% are well known. As nitrous oxide and oxygen, 50%/50% are widely used, well-known active substances, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is thus appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. There are no objections to approval of Donopa 50%/50% from a non-clinical point of view.

Environmental risk assessment
No environmental risk assessment has been performed, as Donopa is not expected to pose a risk to the environment.

II.3 Clinical aspects

N_2O has been used for well over 150 years in clinical settings as an anaesthetic gas. N_2O is now primarily used as an analgesic and sedative in dental or clinical setting in Europe, as a pre-mixed gas mixture with O2.

A 50% N_2O/O_2 ratio is considered optimal for the sought indication, i.e. treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted.
These short-term procedures involve procedural pain like e.g. wound and burn dressing, wound debridement, suturing, treatment of fractures, and dental procedures such as tooth extraction. The gas is also used for labour pain.

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 both blood and the target organ (CNS) is achieved rapidly. These physio-chemical properties explain the rapid onset of analgesia and the fact that the effects of N_2O rapidly subside following discontinuation of administration. The gas is eliminated exclusively by respiration. N_2O is not metabolised in the human body.

Pharmacodynamics
At the 50% concentration, it causes analgesia without deeper anaesthesia. For induction of general anaesthesia, higher nitrous oxide concentrations should be used (e.g.70%). Oxygen 50% (more than twice the concentration in ambient air) provides normal oxygen saturation of the haemoglobin.

Clinical efficacy
The applicant discussed several studies that support the sought indication of acute pain during medical and dental procedures, and labour.

Besides the studies that were discussed by the applicant, the following publications are considered relevant; In several randomized studies, nitrous oxide was superior to placebo in painful procedures like e.g. implantation of venous access ports in cancer patients (Douard, 2006) and bronchoscopy in pediatric patients (Fauroux, 2004). N_2O was superior to combinations with other anaesthetics like ketamine + midazolam/propofol in several painful procedures in children (e.g. acute fracture reduction (Luhman, 2006), voiding cysto-urethrography (Keidan, 2005), and continuous sciatic block for lower limb surgery (Vas, 2005)). Especially the recovery time and nausea was less after application of N_2O compared to the ketamine combinations.

In dental practice, the use of nitrous oxide reduced significantly the fear and avoidance for following dental procedures in extreme frightened patients (Collado, 2006), compared to local anaesthetic measures.

Rosen (2002) conducted a systematic review to determine the efficacy and safety of nitrous oxide for labour analgesia. Eleven randomized controlled trials, with adequate control groups and outcome assessment by parturients during or shortly after the intervention, were used to determine efficacy. Although nitrous oxide is not a potent analgesic, studies suggest a beneficial effect for many parturient women. It is easy to administer and, despite some early reports of unconsciousness, particularly with 75% nitrous oxide, 50% nitrous oxide appears to have been safely used by very large numbers of women over many years.
In the SPC a warning is included that nitrous oxide should not be combined with opioids during the partus, as it may enhance the sedative effects of opioids. Of note, in a small-scaled double-blind cross-over study by Volmanen in 2005, 15 parturients received remifentanil i.v. and nitrous oxide in random order, with

wash-out period of 20 minutes in between. Remifentanil was superior over nitrous oxide in pain relief, but sedation scores were higher compared to nitrous oxide.

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 and as a flateous gas in laparoscopy and as combustion gas in cryosurgery. These indications are not included in the SPC.

In conclusion, 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.

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.

Interaction with folate and vitamin B12

Prolonged administration may be associated with megaloblastic anemia and peripheral neuropathy, due to interaction of nitrous oxide with folate or vitamin B12. Depression of white cell formation might also occur. The period of treatment should therefore not exceed 24 hours. In order to prevent long-term exposure to the personnel, specific precautions should be made that the atmosphere in the treatment rooms remain below specific toxicity levels.

Pregnancy

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). Limited data on short-term use of nitrous oxide in pregnancy in humans do not reveal an increased risk of congenital abnormalities. To be on the safe side, it is 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.

Nausea

In analgesic procedures the incidence of nausea is reported to be low and less than other analgetics (Kanagasundaram, 2001 /Petersen-Felix, 1998/ Hovorka, 1989), but in general anaesthesia the use of nitrous oxide has been reported as a significant risk factor (Nader , 2004/ Tramer, 2004/ Divatia, 1996). Nader observed barometric changes in the middle ear in patients undergoing general anaesthesia for arthroscopic knee surgery, and postulated that this may contribute to postoperative emesis.

Increased volume of air-filled cavities

There is a risk of increased pressure and volume from the diffusion of nitrous oxide into air-containing cavities. Nitrous oxide exchanges with nitrogen, the latter having a blood gas solubility which is 34 times lower compared to nitrous oxide. More nitrous oxide will be delivered to the body than nitrogen removed. This will result in increased volume and pressure of air trapped in pockets such as in intestines, pneumothorax, middle ear and the eye, in case a volatile or gaseous drug is injected (Dale and Brown, 1987). The use of nitrous oxide is therefore contraindicated for these conditions.

Cardiovascular

Hohner et al. (1994) concluded that nitrous oxide, known to have both sympathomimetic and cardiodepressive actions, produced a decrease in myocardial contractility during sympathetic stimulation. As nitrous oxide exerts a sympathomimetic action, Yoo et al (2003) investigated whether it modifies the cardiovascular responses to tracheal intubation during general anesthesia. They observed an attenuation

of the pressor response and an augmentation of the norepinephrine response to laryngoscopy and endotracheal intubation, caused by nitrous oxide. The clinical relevance of these findings remains unclear. Both Hohner (1994) and Mitchel et al. (1989) concluded, that nitrous oxide did not induce clinically detectable myocardial ischemia in patients who had coronary artery disease before the operation despite changes were observed regarding cardiac function.

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

Risk management plan

The safety profile of medicinal gaseous nitrous oxide/oxygen can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The SPC adequately reflects the intended use of the product, safety measures to be taken and characteristics.

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, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question met the criterion of 81% correct answers. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Donopa 50%/50% v/v is essentially similar to other medicinal nitrous oxide/oxygen products considering the same pharmaceutical form, the same route of administration, the consistent manufacturing as required according to the European Pharmacopoeia and the similar impurity profile.

The MAH presented an adequate overview of the available clinical and non-clinical data on the medicinal use of the product, supporting the well-established medicinal use of the product. The benefit/risk ratio is favourable for the proposed indications if nitrous oxide/oxygen is used correctly and under well-controlled circumstances.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other medicinal gaseous oxygen/nitrous oxide containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Donopa 50%/50% v/v, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 April 2012. Donopa 50%/50% v/v medicinal gas, compressed is authorised in the Netherlands on 6 June 2012.

The date for the first renewal will be: 6 June 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	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
N_2O	Nitrous oxide
O_2	Oxygen
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

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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