

# **Public Assessment Report**

## **Scientific discussion**

**Actynox, 50%/50% v/v,  
medicinal gas, compressed  
(oxygen/nitrous oxide)**

**NL/H/3036/001/DC**

**Date: 7 January 2015**

This module reflects the scientific discussion for the approval of Actynox, 50%/50% v/v, medicinal gas, compressed. The procedure was finalised on 31 July 2014. For information on changes after this date please refer to the module 'Update'.

A list of literature references is given on page 9.

## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Actynox, 50%/50% v/v, medicinal gas, compressed from Air Products Nederland B.V.

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. Actynox is indicated in adults and children older than 1 month.

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

This decentralised procedure concerns an application for nitrous oxide/oxide 50/50, a well known analgesic gas, based on well-established use. The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

The concerned member states (CMS) involved in this procedure were Belgium, Spain and Portugal.

The equimolar mixture of N<sub>2</sub>O and O<sub>2</sub> has been on the market in the European Community for more than 10 years, which is a criterion for a well-established use application.

## II. QUALITY ASPECTS

### II.1 Introduction

Actynox, 50%/50% is a colourless, odourless gas, supplied in cylinders containing nitrous oxide (N<sub>2</sub>O) 50% v/v and oxygen (O<sub>2</sub>) 50 % v/v at a pressure of 185 bar (15°C)

The steel or aluminium 2, 5, 15 or 50 Litre gas cylinders with a filling pressure 185 bar have a shut-off valve with or without integrated pressure regulator. The shoulder of the gas cylinder is marked in white and blue (oxygen/nitrous oxide). The body of the gas cylinder is white (medicinal gas).

No excipients are present in the medicinal product.

### II.2 Drug Substances

The active substances nitrous oxide and oxygen are both described in the European Pharmacopoeia (Ph.Eur.). Both are colourless gasses.

#### **Nitrous oxide**

##### Manufacturing process

The nitrous oxide (N<sub>2</sub>O) is obtained by continuous thermal decomposition of the ammonium nitrate (NH<sub>4</sub>NO<sub>3</sub>). 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 confirms 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 is stored under liquid form, balanced with its own gaseous phase at -18°C. Storage pressure of nitrous oxide depends on the liquid temperature.

Stability studies support a re-test period of three years in a gas cylinder at 45 bar pressure (pressure calculated with reference to a temperature of 15°C) when stored between 0°C and 50°C.

## **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.

## **II.3 Medicinal Product**

### 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 pharmaceuticals have been adequately described. The MAH addressed the issues of pressure increase, liquefying of the N<sub>2</sub>O (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.

### 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, NO<sub>x</sub> 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, 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. Moreover, nine months stability data obtained at room temperature are available in which no significant changes or trends have been observed. 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.

The MAH additionally showed that the drug product should be stored in horizontal position at a temperature above +10°C for at least 48 hours before use if the drug product has accidentally been stored at too low temperatures. The mixture is homogeneous again after 48 hours at temperatures above +10°C. A corresponding statement has been included in the SmPC.

#### **II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Actynox, 50%/50% v/v has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

### **III. NON-CLINICAL ASPECTS**

#### **III.1 Ecotoxicity/environmental risk assessment (ERA)**

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

#### **III.2 Discussion on the non-clinical aspects**

Pharmacodynamic, pharmacokinetic and toxicological properties of nitrous oxide and oxygen, 50%/50% are well known. 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 for this bibliographical application.

### **IV. CLINICAL ASPECTS**

#### **IV.1 Introduction**

N<sub>2</sub>O has been used for well over 150 years in clinical settings as an anaesthetic gas. N<sub>2</sub>O is now primarily used as an analgesic and sedative in dental or clinical setting in Europe, as a pre-mixed gas mixture with O<sub>2</sub>.

A 50% N<sub>2</sub>O/O<sub>2</sub> 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.

#### **IV.2 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 physiochemical properties explain the rapid onset of analgesia and the fact that the effects of N<sub>2</sub>O rapidly subside following discontinuation of administration. The gas is eliminated exclusively by respiration. N<sub>2</sub>O is not metabolised in the human body.

#### **IV.3 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.

#### IV.4 Clinical efficacy

The MAH 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 MAH, 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<sub>2</sub>O 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<sub>2</sub>O 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 SmPC 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 flatus gas in laparoscopy and as combustion gas in cryosurgery. These indications are not included in the SmPC.

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.

#### IV.5 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 anaesthetics, 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 analgesics (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 SmPC.

**IV.6 Risk Management Plan**

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Actynox 50%/50% v/v.

- Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
<b>Important Identified Risks</b>		
Inactivation of vitamin B12, Anaemia megaloblastic and leukopenia	SmPC sections 4.5 and 4.8	N/A
Polyneuropathy	SmPC sections 4.5 and 4.8	N/A
Myelopathy	SmPC sections 4.5 and 4.8	N/A

Paraparesis	SmPC sections 4.5 and 4.8	N/A
Decreased efficacy in children under 3 years	SmPC section 4.2	N/A
Respiratory depression in neonates (when the product is used during labour)	SmPC section 4.4	N/A
Pressure in middle ear and other air-filled cavities	SmPC section 4.4	N/A
Interaction with centrally acting medicinal products	SmPC section 4.5	N/A
<b>Important potential risks</b>		
Reduced fertility in medical and paramedical personnel	SmPC section 4.4	Training to medical and paramedical personnel
Reproductive and developmental toxicity	SmPC section 4.4	Training to medical and paramedical personnel
Misuse	Routine Pharmacovigilance	N/A
<b>Missing information</b>		
None	N/A	N/A

The member states agreed that the defined pharmacovigilance activities and risk minimisation measures are sufficient to control the risks and areas of missing information.

#### **IV.7 Discussion on the clinical aspects**

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 clinical 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 are taken into account. The SmPC adequately reflects its intended use, safety measures to be taken and characteristics.

#### **V. USER CONSULTATION**

The package leaflet has been evaluated via a user consultation study. A bridging report has been submitted, referring to a similar product, Donopa 50%/50% v/v (NL/H/2233/001/DC). The bridging report submitted by the applicant has been found acceptable. The member states agree that separate user testing is not required.

#### **VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Actynox, 50%/50% v/v, medicinal gas, compressed 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.

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 Actynox 50%/50% v/v, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 31 July 2014.

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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