LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Protoxan
(nitrous oxide and oxygen)

SE/H/1274/01/DC

This module reflects the scientific discussion for the approval of Protoxan. The procedure was finalised at 2013-02-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Praxair Euroholding S.L. has applied for a marketing authorisation for Protoxan medicinal gas, 50% + 50%. The active substance is nitrous oxide and oxygen. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Protoxan is presented in the form of a medicinal gas containing 50% of nitrous oxide and 50% of oxygen. There are no excipients in the medicinal product.

II.2 Drug Substance

Nitrous oxide and oxygen have both monographs in the Ph. Eur.

Nitrous oxide is a colourless gas. The identity of nitrous oxide has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have not been conducted as the drug substance manufacturer refers to bibliographic data. This has been accepted. The data provided are sufficient to confirm the retest period.

Oxygen is a colourless gas. The identity of oxygen has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have not been conducted as the drug substance manufacturer refers to bibliographic data. This has been accepted. The data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Protoxan, medicinal gas is free from excipients. All raw materials used in the product are of vegetable origin/has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substances.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions are going to be performed and data presented support the shelf life claimed in the SPC, when stored above -5 °C.

III. NON-CLINICAL ASPECTS

No new non-clinical studies were conducted to support the submission for PROTOXAN (nitrous oxygen 50% / oxygen 50%).
Pharmacodynamic, pharmacokinetic and toxicological properties of nitrous oxygen / oxygen are well-known. As nitrous oxygen / oxygen are widely used, well-known active substances, no further studies are required. An overview and summaries on pharmacology, pharmacokinetics and toxicology based on literature review are, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment

The product contains equal parts of oxygen and nitrous oxide. No ERA has been submitted and the applicant has presented a justification. It is accepted that the no ERA is required for this product.

III.2 Discussion on the non-clinical aspects

There are no objections to approval of PROTOXAN from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Nitrous oxide in a 50% / 50% mixture with oxygen is considered to be well established in clinical practice. No new clinical data was required for this application and clinical aspects have been assessed based on an overview of literature data.

IV.2 Pharmacokinetics

N/A

IV.3 Pharmacodynamics
The mechanism behind analgesic effects of nitrous oxide has to some extent been clarified in recent years while the precise mechanisms behind loss of consciousness are still elusive.

IV.4 Clinical efficacy
Nitrous oxide is considered well established in clinical practice. The clinical efficacy is considered well known and supportive literature data was adequately reviewed in the application. No new clinical studies were conducted to support the application for PROTOXAN (nitrous oxygen 50% / oxygen 50%).

IV.5 Clinical safety
No new safety studies were conducted to support the application for PROTOXAN (nitrous oxygen 50% / oxygen 50%). In view of the extensive use of nitrous oxide the safety profile is well known and benign. It was adequately reviewed in the application. If relevant contraindications are observed and the gas mix is only administrated as recommended (including scavenging systems) the risks with the use of Protoxan for both patients and health personnel must be considered as very low.

IV.6 Discussion on the clinical aspects
There are no objections to approval of PROTOXAN from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
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 language used for the purpose of user testing the PIL was Portuguese.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Protoxan medicinal gas, 50% + 50% is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Protoxan medicinal gas, 50% + 50% was successfully finalised on 2013-02-21.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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