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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

IPRAXA Steri-Neb 250 micrograms/1 ml, nebuliser solution
IPRAXA Steri-Neb 500 micrograms/2 ml, nebuliser solution
IVAX Farma B.V., the Netherlands

ipratropium bromide (as monohydrate)

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/1138/001-002/MR
Registration number in the Netherlands: RVG 27815, 27816

18 May 2010

Pharmacotherapeutic group:	other drugs for obstructive airway diseases, inhalants: anticholinergics
ATC code:	R03BB01
Route of administration:	inhalation
Therapeutic indication:	reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD); reversible airway obstruction in asthma in combination with inhaled beta$_2$-agonists.
Prescription status:	prescription only
Date of first authorisation in NL:	17 December 2003
Concerned Member States:	Mutual recognition procedure with AT, BE, DE, DK, FI, FR, HU, IT, LU, NO, PT, RO, SE, SI
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 IPRAXA Steri-Neb 250 micrograms/1 ml and IPRAXA Steri-Neb 500 micrograms/2 ml, nebuliser solution, from IVAX Farma B.V. The date of authorisation was on 17 December 2003 in the Netherlands.

The product is indicated for:

- treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD).
- treatment of reversible airway obstruction in asthma, when used concomitantly with inhaled beta$_2$-agonists.

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

Anticholinergics prevent an increase in the intracellular concentration of cyclical guanosine monophosphate (cyclical GNP), which is caused by the interaction of acetylcholine and the muscarinic receptors on the bronchial smooth muscle.
The dilation of the bronchi which occurs after the inhalation of ipratropium bromide, is mainly a place-specific, local effect and is not a systemic effect.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Atrovent Unit dose 250 µg/1 ml and Atrovent Unit Dose 500 µg/2 ml which have been registered in the United Kingdom by Boehringer Ingelheim Limited since 1986. In the Netherlands, Atrovent Unit dose 250 µg/1 ml and Atrovent Unit Dose 500 µg/2 ml have been registered since 1999 and 1988, respectively (NL License RVG 23418 and 12869). In addition, reference is made to Atrovent Unit Dose authorisations in the individual member states (reference product). For RO and SI, reference is made to the innovator products authorised in the UK (European reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As IPRAXA Steri-Neb 250 micrograms/1 ml and IPRAXA Steri-Neb 500 micrograms/2 ml, nebuliser solution are products for inhalation use, these are exempted for biostudy. Essential similarity is demonstrated by comparative *in vitro* data only. This is acceptable and in line with the NfG CPMP/EWP/4151/00.The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

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 these product types 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 ipatropium bromide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white to almost white, crystalline powder. It is present in the monohydrate form.

The CEP procedure is used for both active substance suppliers. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Specification
The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents and microbiological quality. One overall specification for both suppliers has been laid down. The active substance specification is considered adequate to control the quality. One typical Certificate of Analysis for drug substance generated by the finished product manufacturer has been provided for each manufacturer. This is deemed sufficient since further batch analysis results have been assessed by the EDQM during the CEP procedure.

Stability
The stability of the substance is covered by the CEP. The re-test period applied is 2 years and the storage conditions are *'No special storage conditions. Store in the original packaging in order to protect from light'*.

* 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
IPRAXA Steri-Neb 250 micrograms/1 ml contains as active substance 261 micrograms of ipratropium bromide monohydrate equivalent to 250 micrograms of anhydrous ipratropium bromide.

IPRAXA Steri-Neb 500 micrograms/2 ml contains as active substance 522 micrograms of ipratropium bromide monohydrate equivalent to 500 micrograms of anhydrous ipratropium bromide.

The drug product is an isotonic sterile solution containing no preservatives. Both products are clear, colourless solutions with a pH of 3.0–4.0 and an osmolarity of 257-284 mOsm/kg.

The nebuliser solution is packed in transparent LDPE ampoules with a twist-off top.

The excipients are: sodium chloride, hydrochloric acid (1M) (for pH adjustment), water for injections.

The primary container is a 3 ml LDPE ampoule (called Steri-Neb). It is hermetically sealed and has a twist-off top.

Pharmaceutical development
The development of the product is satisfactorily performed and explained. The excipients used are common in the manufacture of comparable formulations and are also present in the innovator product. The packaging material is deemed suitable for the product at issue. The product is a simple, aqueous solution. Its composition is derived from the composition of the innovator product. Therefore, no formal formulation studies were performed. Comparative analysis results of test products and innovator products have been provided. The product is designed for single use and as such does not contain anti-microbial preservatives.

No clinical trials have been performed since ipratropium nebuliser solution is a well established product. Considering the simplicity of the solution, only characterised by the active substance content, sodium chloride content, pH and absence of microorganisms, the solution of the originator and the proposed solutions are almost identical. No overages are applied. No reconstitution diluents are required. The product is administered using a nebuliser. The SPC additionally mentions that the product should not be mixed with other nebulisation solutions. This is deemed sufficient.

The LDPE packaging material is demonstrated to be of acceptable quality. Stability studies confirm that the product does not deteriorate in this packaging material. It was committed to perform a leachable study to assess the potential levels of leachables, arising from migration of components of ink, adhesives or the label used for labelling the immediate packaging, into the drug product. See also post-approval commitment on page 7 of this report.

Manufacturing process
The manufacturing process is relatively simple. It consists of dissolution of the ingredients and sterilisation by filtration. The process has sufficiently been validated. The solution is filled out into the vials by a Blow-Fill-Seal procedure. A justification for not applying a terminal sterilisation method on the finished product is not provided, however, it is known that polyethylene polymers are sensitive to gamma-irradiation, and also heat treatments are not feasible, therefore sterile filtration is acceptable. Validation results have been provided for a total of three batches of which two were filled out in 1 ml ampoules and one in 2 ml ampoules. These results show that the process is sufficiently under control.

Product specification
The product specification for the powder includes tests for description, identity, assay, degradation, sterility, fill weight, pH and osmolality. The specification has been adequately justified. Batch analysis data have been provided on five batches of each strength. Compliance with the release requirements is sufficiently demonstrated.

Stability tests on the finished product
Stability data of two pilot batches and one full-scale batch per product strength were submitted. The powder and solvent have been stored at 25°C/40% RH (24 months) and 40°C/NMT 25% RH (6 months). The results show that a significant water loss occurs. Due to this water loss, the content of the active substance and sodium chloride increases. The water loss is deemed acceptable as all the parameters remain within the specification. A shelf-life of 2 years, when stored below 25°C, could be granted. Photostability studies showed degradation of the active substance when exposed to light. Therefore, an additional storage requirement '*Store the ampoules in the original outer carton for protection against light*' is applicable.

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

These products is generic formulations of Atrovent Unit dose 250 µg/1 ml and Atrovent Unit Dose 500 µg/2 ml, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ipratropium bromide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ipratropium bromide is a well-known active substance with established efficacy and tolerability.

No specific clinical studies have been performed, as it concerns a generic application.
Therapeutical equivalence if demonstrated by comparative *in vitro* data only. This is acceptable and in line with the NfG CPMP/EWP/4151/00, since:

- The product contains the same active substance.
- The physical state of the active substance is the same (dissolved).
- The delivered dose is the same
- The inhalation device is identical in all parts which influence performance: any of the available nebulisers currently available on the market can be used.
- Test and reference solutions have an nearly identical composition.

The SPC of the originator does not describe the type of nebuliser. Considering the simplicity of the solution, only characterised by the active substance content, sodium chloride content, pH and absence of microorganisms, the solution of the originator and the proposed solutions are almost identical. For this reason, and taking into account that solutions are usually further diluted and nebulising apparatus is not defined in the SPC of the innovator, the absence of bioequivalence data is justified.

Risk management plan
Ipratropium bromide was first approved in 1975, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ipratropium bromide 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. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. 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 has been harmonised with the product information of the reference product Atrovent (Netherlands and UK) and other generics registered by European procedures, and with current state of the art, SPC guideline and QRD templates.

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 two rounds with 10 participants

each. All selected volunteers were users of anticholinergic bronchodilators, selected from the patient files of a local pharmacy to reflect gender, age, and social class characteristics of the pharmacy files.
Diagnostic testing was performed. The questionnaire consisted of 15 questions, presenting a good mix of findability, understandability and applicability questions and covering all significant safety issues for safe and correct use of the product.
After the first round, no amendments were made. After two rounds, however, 2 questions did not meet the criterion of 80% correct answers, since the information could not be found adequately. This led to a revision of the PL in order to improve the findability of this information. Weaknesses in findability/ applicability of some information were identified and led to modifications on the PL with respect to lay-out and wording.
The report is of sufficient quality and the results show that the readability of the PL is sufficient, however could be improved by modifications which have been implemented in a revised PL. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

IPRAXA Steri-Neb 250 micrograms/1 ml and IPRAXA Steri-Neb 500 micrograms/2 ml, nebuliser solution have a proven chemical-pharmaceutical quality and are generic forms of Atrovent Unit dose 250 µg/1 ml and Atrovent Unit Dose 500 µg/2 ml. Atrovent Unit Dose is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for inhalation use, no bioequivalence study is deemed necessary. As with the innovator product any of the available nebulisers currently available on the market can be used.

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 and are in agreement with other ipratropium bromide containing products.

The Board followed the advice of the assessors. IPRAXA Steri-Neb 250 micrograms/1 ml and IPRAXA Steri-Neb 500 micrograms/2 ml, nebuliser solution were authorised in the Netherlands on 17 December 2003.

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, considered that essential similarity has been demonstrated for IPRAXA Steri-Neb 250 micrograms/1 ml and IPRAXA Steri-Neb 500 micrograms/2 ml with the reference products, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 21 January 2008.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from January 2008 to January 2011.

The date for the first renewal will be: 21 January 2013.

The following post-approval commitment has been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to supply the authorities with a full report of the extractables and leachables study of the label. The product will not be marketed France, Germany and Italy before assessment of this report by the authorities. This commitment has been fulfilled.

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
Submission of an updated CEP for an active substance manufacturer currently approved.	NL/H/1138/ 001-002/ IA/001	IA	14-7-2008	28-7-2008	Approval	N
Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change outside the range of the currently approved pack sizes.	NL/H/1138/ 001-002/ IB/002	IB	15-7-2008	14-8-2008	Approval	N
Change in the address of the MAH in IT only.	NL/H/1138/ 001-002/ IA/003	IA	17-7-2008	31-7-2008	Approval	N
Change to batch release arrangements and quality control testing of the finished product; Replacement or addition of a manufacturer responsible for batch release; not including batch control/testing.	NL/H/1138/ 001-002/ IA/004	IA	18-11-2008	2-12-2008	Approval	N
Change in the specification of the finished product. Tightening of specification limits.	NL/H/1138/ 001-002/ IB/005	IB	10-3-2009	9-4-2009	Approval	N
Change in the name and/or address of the marketing authorisation holder in FR.	NL/H/1138/ 001-002/ IA/006	IA	14-4-2009	28-4-2009	Approval	N
Withdrawal of marketing authorisation in SI.	--	--	--	14-10-2009	Approval	N
Change in the name and/or address of the marketing authorisation holder in DE.	NL/H/1138/ 001-002/ IA/007	IA	26-10-2009	9-11-2009	Approval	N