Public Assessment Report

Scientific discussion

Ipramol Steri-Neb 0.5 mg / 2.5 mg per dose Nebuliser Solution

(ipratropium bromide and salbutamol sulphate)

PA 282/79/1
IE/H/163/001/E01

This module reflects the scientific discussion for the approval of <Ipramol>.

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Ipramol Steri-Neb 0.5 mg/2.5 mg Nebuliser Solution was authorised for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium bromide and salbutamol.

II. QUALITY ASPECTS

II.1 Introduction

This application is for Ipramol Steri-Neb 0.5 mg / 2.5 mg per dose nebuliser solution. Each single-use ampoule contains 0.5 mg ipratropium bromide (as monohydrate) and 2.5 mg salbutamol (as sulphate) in 2.5 ml of a sterile nebuliser solution. The ampoules are composed of low-density polyethylene and are supplied as strips of five ampoules. Each strip is individually sealed in a foil overwrap pouch and these are packed into cardboard cartons containing 20 or 60 ampoules.

II.2 2.2 Drug Substances

The drug substances are ipratropium bromide and salbutamol sulphate, both of which are established active substances described in the European Pharmacopoeia. They are manufactured in accordance with the principles of Good Manufacturing Practice (GMP). An EDQM certificate of suitability has been issued for the source of ipratropium bromide and a European drug master file was submitted by the manufacturer of the salbutamol sulphate.

The specifications for both active substances meet current pharmacopoeial requirements and batch analytical data demonstrating compliance with this specification have been provided.

II.3 Medicinal Product

Composition

The nebuliser solution contains 0.5 mg ipratropium bromide (as monohydrate) and 2.5 mg salbutamol (as sulphate) in 2.5 ml of solution. The excipient are sodium chloride (to adjust tonicity), dilute hydrochloric acid (to adjust pH), and water for injections.

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at a suitably qualified manufacturing site. The manufacturing process has been validated according to relevant European guidelines.

Control of excipients

All ingredients comply with the requirements of the European Pharmacopoeia.

Control of finished product

The finished product specification meets the requirements of the European Pharmacopoeia for preparations for inhalation. It includes controls on appearance and colour of the solution, particulate matter, weight per ampoule, pH, assays of both drug substances, related substances, and sterility.

The analytical methods used are described in sufficient detail and are supported by appropriate validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

Packaging material

The product is supplied in low-density polyethylene ampoules.

Evidence has been provided that the grades of polyethylene used in the ampoules complies with the requirements of the European Pharmacopoeia for polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations.

Stability of the finished product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years without the need to specify a maximum storage temperature . The product should not be frozen as this might rupture the ampoules and compromise sterility. The European Pharmacopoeia monograph for salbutamol sulphate directs that it should be stored protected from light and it is therefore recommended that the ampoules should be stored in their outer carton to protect from light.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product is sterile. It contains no novel excipients or excipients that are of animal or human origin.

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

The application is a generic one, abridged under Article 10.1(a) iii of Directive 2001/83/EEC claiming essential similarity with Combivent UDV®. Therefore, in order to avoid repetitious and unnecessary animal testing there are no self-generated data. The existing pre-clinical pharmacology and toxicology of salbutamol and ipratropium are reviewed by the company.

IV. CLINICAL ASPECTS

The application is generic claiming essential similarity with Combivent UDV®. Due to the difficulty measuring plasma concentrations of ipratropium and its lack of an easily measurable and repeatable pharmacodynamic effect the demonstration of equivalence is based on the nebulised plume geometry. Variation in the particle distribution size is equivalent within and between the test and reference products giving reassurance that their clinical performance will be equivalent.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The innovator product Combivent UDV has been in clinical use for the treatment of COPD for many years and has proven to be a safe and effective treatment. The generic product has demonstrated, in as far as possible given the pharmaceutical form, that it is similar to the innovator product and thus the risk benefit profile will be similar.