IPAR

UPDATED FINAL RENEWAL ASSESSMENT REPORT

on

Beclazone 50 micrograms CFC-Free Inhaler
Beclazone 100 micrograms CFC-Free Inhaler
Beclazone 250 micrograms CFC-Free Inhaler
(Beclometasone Dipropionate)

MR No. IE/H/0118/001-003

ADMINISTRATIVE INFORMATION

Name of the medicinal product in the European Union:	**Beclazone 50, 100 & 250 micrograms CFC-Free Inhaler**
Name(s) of the active substance(s)	**Beclometasone Dipropionate Anhydrous Ph. Eur.**
Pharmacotherapeutic classification (Group + ATC code)	**Anti-asthmatics, Inhalants Glucocorticoids R03B A01**
Pharmaceutical form and strength	**Pressurised inhalation, solution, 50,100 & 250 mcg**
Reference No. for the Mutual Recognition Procedure	**IE/H/0118/001-003/R/002**
Reference Member State	**IE**
Concerned Member States:	**BE, LU, PT,**
Name, telephone and fax number of the contact point in the Reference Member State	**Aisling O'Brien** **Post Licensing Unit** **Irish Medicines Board** **Kevin O'Malley House** **Earlsfort Centre** **Earlsfort Terrace** **Dublin 2** **Tel: 01 634 3387** **Fax: 01 676 2517** **E-mail: aisling.obrien@imb.ie**
Names of the assessors	**David Lyons (Clinical)** **Laurence O'Dwyer (Quality)**
Day 40, PRAR circulated	**30th July 2007**
Day 55, Comments Due from CMSs	**14th August 2007**
Day 59, FRAR circulated	**3rd April 2008**
Day 85, Comments Due from CMSs	**29th April 2008**

Assessors: Module 3 Mr. L O'Dwyer; Module 4 & 5 Dr. D Lyons
Marketing Authorisation Holder: Norton Waterford

I INTRODUCTION

1. Introduction and Background

Norton Waterford (now Ivax Pharmaceuticals) made a national application in Ireland in November 1996, for a product authorisation for a range of beclometasone dipropionate (BDP) containing products using the non-CFC propellant HFA 134a.

The company then used the Mutual Recognition Procedure (MRP) to gain approval for the MDI in Belgium, Finland, Italy, and Portugal, with a subsequent 'second wave' MRP in Spain and with Germany.

Beclazone is presented as a conventional 'press and breathe' metered dose inhaler (MDI) delivering 50 µg, 100 µg, 250 µg beclometasone diproprionate per actuation.

2. Documents Submitted

The marketing authorisation holder (MAH) submits EU renewal application forms with copies of the currently approved SPC, PIL, labelling, manufacturing license, GMP Certificate. A quality expert statement is provided.

3. Post Approval Commitments

None.

4. Regulatory action during period of review

A list of variation applications that have been submitted since the original grant of the marketing authorisation has been provided. All variations have now been approved apart from Type II variations to harmonise the leaflet and labelling throughout the concerned member states which are in progress.

5. Patient Exposure

Beclazone is marketed in thirty-seven countries worldwide. In the period November 2001 to October 2006 approximately 2×10^9 defined daily doses were sold. Due to the major variability in duration of treatment the MAH cannot translate this into a population treatment estimate.

The renewal documentation does not distinguish between the sales due to the Easi-Breathe and non-Easi-Breathe delivery devices. From a clinical safety and efficacy point of view this is not an important omission as both delivery systems should have clinically indistinguishable clinical effects.

6. Manufacturing Licences

The MAH submitted the current manufacturing licence for:

Norton Waterford, T/A IVAX Pharmaceuticals Ireland, IDA Industrial Park, Cork Road, Waterford, Ireland.

A declaration of GMP compliance for active substance manufactured at Sicor S.r.L Tanuta D Alessandro, I-13048 Santhia, Vercelli, Italy and Sicor S.p.A. Via Senato 19, 20120 Milan, Italy has been provided signed by the Qualified Person at the currently approved Norton Waterford manufacturing and batch release site.

7. New Clinical Data

No new clinical data are provided.

8. Summary of Product Characteristics (SPC)

The MAH has proposed changes to sections 1 and 2 of the SPC in line with current guidelines. The RMS considers these changes to be acceptable. The following additional changes should be made to the proposed SPC:

Pharmaceutical form (3)
A visual description of the product should be included in this section. The MAH is requested to propose the text to be included.

Special Precautions for Storage (6.4)
In line with the current '*Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalation Products'* (CPMP/QWP/2845/00) the following additional statements should be included in this section:

'The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.'

Section 6.6

The heading of this section should be updated in line with the current SPC guideline.

MAH Response dated 10/03/08:
The MAH agrees with all of the additional changes proposed by the RMS. The MAH proposes to submit a variation to update the SPC as requested.

Assessor Comment in original FRAR:
The response provided by the MAH is acceptable. However the above changes are relatively minor and in line with current guidelines – therefore it is felt that these changes can be made as part of the renewal. Issue resolved.

MAH Response to FRAR:
The MAH notes that the additional changes to the SPC will be made as part of the renewal.

Assessor Comment:
Issue resolved.

9. Labels & Package Leaflet

The MAH has submitted Type II Variations to harmonise the labels and leaflet (IE/H/0118/001-003/II/023). These variations will be processed separately. Therefore the RMS proposes that comments on the labels and package leaflet should be made as part of the variation applications rather than the renewals.

Assessor comment: The type II variation referred to above has now been approved and the label and leaflet text has been harmonised.

II QUALITY ASPECTS

MODULE 3 – QUALITY/PHARMACEUTICAL ASSESSMENT

Active Substance Specifications

The MAH is requested to submit a complete list of the active substance specifications as the currently approved specifications include additional tests to those listed in the Ph. Eur. monograph e.g., residual solvents, particle size.

MAH Response dated 10/03/08:

A complete list of the active substance specifications has been submitted.

Additional queries to MAH arising from response dated 10/03/08 (included in original FRAR):

1. The limits for a number of tests listed in the submitted active substance specifications (e.g. specific optical rotation, related substances) are not in line with the limits listed for the corresponding tests in the current Ph. Eur. monograph for beclometasone dipropionate, anhydrous. A type IA No. 25 notification was approved on 27/03/07 to update the active substance specifications in line with Ph. Eur. requirements (IE/H/118/001-003/IA/019). Therefore it is assumed that the active substance specifications submitted by the MAH in their response document dated 10/03/08 were submitted in error.

   The MAH is requested to submit the currently approved active substance specifications for this product and confirm that the active substance is fully tested in line with the requirements of the current Ph. Eur. monograph for beclometasone dipropionate, anhydrous.
2. The MAH has indicated that a variation to amend the active substance specifications in line with the Ph. Eur. monograph is currently under preparation. Any such variation will be independently assessed but the RMS would like to make it clear at this time that it is not requesting the deletion of any tests that are not listed in the Ph. Eur. monograph from the active substance specifications. If the deletion of any such tests is proposed by the MAH, this would have to be fully justified in the variation application and it would have to be demonstrated that the remaining tests are sufficient to ensure the quality of the active substance.

MAH Response to FRAR dated 16/04/08:

1. A copy of the currently approved active substance specifications is submitted in appendix 1 of the MAH's response document. The active substance is fully tested in line with the Ph. Eur. monograph with some additional tests.
2. The MAH submitted a variation to update the API specification on 2nd April 2008. At the recommendation of the pharmaceutical assessor the MAH will resubmit the variation to address the issues that arose during the assessment. The revised variation is currently being prepared and will be submitted as part of the renewal conditions.

Assessor Comment:

The MAH's responses to both points are acceptable and these issues are now considered to be resolved. The variation referred to in the MAH's response was a Type IA No. 25b) notification (IE/H/0118/001-003/IA/027). The variation was deemed unacceptable due to the failure to meet the conditions for that category and a number of issues with the submitted documentation. The MAH has committed to submit a new variation application to address the issues raised and the assessment of the active substance specifications will be performed as part of that variation. The variation should be submitted within 1 month of the completion of this renewal application.

Finished Product Specifications

The MAH is requested to resubmit the relevant page of the quality expert statement in order to confirm both the release and shelf-life specifications.

MAH Response dated 10/03/08:

A complete list of the currently approved release and shelf-life finished product specifications has been submitted.

Assessor comment:

The MAH's response is acceptable. Issue resolved.

From a review of the shelf-life finished product specifications on the RMS' files it appears that the limits for related substances in the finished product specifications are wider than those listed in the BP monograph for Beclometasone Pressurised Inhalation. The MAH is requested to comment on this and if necessary provide a commitment that a variation will be submitted to tighten the limits for related substances in the specifications.
MAH Response dated 10/03/08:
The MAH has committed to submitting a variation to tighten the limits for related substances in the finished product specifications in line with BP requirements.
Assessor comment:
The MAH's commitment is noted. The relevant variation should be submitted immediately following the completion of this renewal application. Issue resolved.

The finished product specifications indicate that the colourimetric identification test is a Ph. Eur. method. While it is acknowledged that this test was listed as an identification test in previous versions of the Ph. Eur. monograph for the active substance, it is no longer listed in the current Ph. Eur. monograph. Therefore the MAH is requested to provide a commitment that the finished product specifications will be updated by variation to clarify this point.
MAH Response dated 10/03/08:
The MAH has committed to addressing this issue as part of the variation to tighten the limits for related substances in the finished product specifications in line with BP requirements.
Assessor comment:
The MAH's commitment is noted. The relevant variation should be submitted immediately following the completion of this renewal application. Issue resolved.

Quality Expert Statement
The MAH is requested to resubmit the declaration by the quality expert as the declaration should state that the products comply with all relevant CHMP Quality guidelines and not just the two guidelines referred to in the current statement.
MAH Response dated 10/03/08:
A revised quality expert statement has been submitted.
Assessor Comment:
The revised quality expert statement is acceptable. Issue resolved.

III NON-CLINICAL ASPECTS

No pre-clinical data are presented.

IV CLINICAL ASPECTS

No new clinical data are presented.

PERIODIC SAFETY UPDATE REPORT

The bridging PSUR contains reports of 132 serious adverse events (AE) and 55 non-serious AEs arising in 90 patients, which are presented as line listings. The MAH also presents an analysis of selected cases chosen on the basis that they were fatal or reporting serious unexpected findings. Unfortunately, but not unusually, the cases are unassessable for a causal relationship to beclametasone due to lack of clinical detail, confounding by co-medication or co-morbidity or a combination of all three.

V OVERALL CONCLUSIONS

The outstanding issues raised in the original FRAR have been satisfactorily addressed by the MAH and the marketing authorisations may be renewed.

VI REVISION DATE

July 2008