Beconase Hayfever
(Beclomethasone dipropionate, 50μ per actuation)

Proposal
To reclassify Beconase Hayfever (beclomethasone 50μg/actuation) from Restricted Medicine to Pharmacy Medicine

Background to current classification position
Prescription medicine in NZ as an aerosol formulation in 1974. The aqueous formulation, called Beconase Aqueous Nasal Spray, became available in 1983. Aerosol formulation discontinued in 1995.
Reclassified to a Restricted Medicine in 1997, change in trade name to Beconase Hayfever.

Recommendation
Accept reclassification. Discuss merits of age restriction.

Investigation

1. **The proposed strength, quantity, dosage form, dose and route of administration of the medicine including indication**
   Beclomethasone dipropionate aqueous nasal spray 50μg/metered dose.
   Metering atomising pump, amber glass bottles containing 22g of suspension or 200 doses.
   Dose: 100μg each nostril twice daily, total daily administration should not normally exceed 400μg.

2. **Approved indication(s)**
   Current: prevention and treatment of seasonal allergic rhinitis, including hayfever. In adults and children over 12 years of age.
   Proposed: prevention and treatment of seasonal allergic rhinitis, including hayfever. In adults 18 years and over.
   [Note Beconase Aqueous Nasal Spray, prescription medicine, is also approved for perennial allergic rhinitis and vasomotor rhinitis. In adults and children over 6 years of age (the datasheet claims there is insufficient clinical data to recommend use in children under 6 years.)]

3. **How long has the particular product been marketed?**
   Prescription medicine in NZ as an aerosol formulation in 1974. The aqueous formulation, called Beconase Aqueous Nasal Spray, became available in 1983. Aerosol formulation discontinued in 1995.
   Reclassified to a Restricted Medicine in 1997, change in trade name to Beconase Hayfever, more restricted age range and indication.

4. **Overseas regulatory status**
   Beclomethasone dipropionate aqueous nasal spray 50μg is marketed on prescription in approximately 70 countries and has been licensed for non-prescription use in Germany, South Africa, Finland, Switzerland and the UK.

Australia: Schedule 3 (pharmacist only, i.e. restricted medicine also), as "beclomethasone in aqueous nasal sprays delivering 50μg or less per actuation when the maximum recommended daily dose is no greater than 400μg, for the treatment of seasonal and allergic rhinitis."

5. **Demonstrated efficacy (i.e. its ability to produce a wanted pharmacological effect at the proposed dosage)**
   The company has submitted two papers dealing with efficacy. The first compares intranasal beclomethasone dipropionate (BDP) with other agents in the treatment of rhinitis. BDP compares well with antihistamines and sodium cromoglycate, especially in clearing nasal symptoms. Some of the studies used doses higher than in this proposal.

   A second study compared various intranasal corticosteroids with oral antihistamines in a meta-analysis of 16 studies and 2267 subjects. Again the corticosteroids seemed to be particularly effective and superior to the antihistamines in reducing nasal symptoms, with no difference in efficacy for nasal discomfort and eye symptoms for intranasal corticosteroids or oral antihistamines.

   Intranasal corticosteroids have been shown to be effective in treating chronic sinusitis. In the acute situation it is recommended first to treat with antibiotics and decongestants.

6. **Is the product intended for treatment of a minor ailment or symptom readily identifiable by the user, which is capable of rapid spontaneous resolution and for which a medical consultation is not necessary?**
   Hayfever affects approximately 10-15% of the general population. The seasonal variety is easy to self-diagnose, coinciding with spring/summer and the release of pollens. Signs and symptoms are nasal congestion, rhinorrhoea, sneezing, nasal itching and watery eyes. It is self-limiting.

7. **Likelihood of mis-diagnosing, masking or compromising the appropriate medical management of a disease**
   Unlikely to mask or compromise appropriate medical management if restricted to short-term use.

8. **Requirement for professional advice from a medical practitioner, dentist or pharmacist**
   Only if prolonged course required or more severe symptoms such as bloody nasal discharge.

9. **Requirement for supervision of sale by a pharmacist**
   Nil.

10. **Proposed labelling and warning statements**
    It is proposed to amend the presently approved primary and secondary container labelling to include the statements:
    1. For use only by adults aged 18 years and older

2. Do not use continuously for more than three months without consulting your doctor.

11. **Hazard potential, including likelihood for any adverse effects**

The company has submitted a safety update from launch until January 1998. The company spontaneous reporting database has received approximately 2000 reports since 1983. Most are local (epistaxis, irritation, dryness, burning), hypersensitivity type (urticaria, skin rash, facial oedema) and disorders of taste and smell.

The main areas of concern with intranasal corticosteroids are:

- Growth suppression 4 cases have been reported to the company.
- Cushing's syndrome 13 cases. 3 involving children.
- Adrenal insufficiency/HPA suppression 17 cases. 3 involving children.
- Hyperglycaemia or loss of diabetes control or increased insulin requirements. Most cases were in known diabetics.
- Cataracts 9 cases. Most had been using the steroid for years. Average age was 55 years. Equal numbers male and female.
- Glaucoma 7 cases. 3 had pre-existing glaucoma. Average age 63 years.
- Raised intraocular pressure 18 cases, most asymptomatic and found on routine examination. Average age 45 years.
- Hypersensitivity Severe reactions rare.
- Necrosis of the femoral head 3 cases.
- Infections few isolated reports of severe chicken pox.

Most of these are covered in the datasheet.

Growth suppression remains a debated issue. Certainly it is agreed that oral steroids can affect growth and suppress the hypothalamic-pituitary-axis (HPA). It is suspected that inhaled and intranasal may do this also, although systemic levels are obviously lower and therefore the risk of suppression is likely to be lower.

In 1998 the FDA tightened its labelling on inhaled and intranasal corticosteroids to include mandatory statements regarding growth suppression in the precautions and paediatric sections on all these products. At that time there were 8 reports of growth suppression with intranasal steroid use and 12 reports with inhaled steroids. They assessed the international literature on the subject and found only a few good studies examining growth suppression (including the study in 12. below). Problems with studies included inaccurate height measurement, difficulties in adjusting for puberty, the possibility of later growth recovery after stopping steroids, and difficulties in developing a model to predict final adult height.

The FDA then concluded, "The finding of growth inhibition was robust". However, they could not predict the effects of intranasal or inhaled corticosteroids on final adult height, nor the impact of different products on growth. They recommended that growth needs to be monitored with

treatment adjusted if growth is suppressed. They commented that more studies are required. The FDA went on to say that they are not suggesting that inhaled/intranasal corticosteroids are unsafe in children and are not considering restricting use in children. However they wanted properly labelled medications to promote their safest use.

In summary, one must weigh up the risks and benefits. With regard to asthma treatment the benefits of steroids are perhaps better known and one would accept a slightly greater risk than with intranasal steroids. The New Zealand Medicines Adverse Reactions Committee (MARC) has also considered the issue. The MARC examined recent literature on growth suppression with inhaled and intranasal steroids and the FDA decision at their June 2000 meeting. They concluded that long term well-controlled studies are required to confirm whether there is growth suppression, and whether it has an impact on adult height. They will continue to monitor the literature.

Drug interactions There is no evidence of significant drug interactions with BDP.

Pregnancy There is inadequate evidence of safety of BDP in pregnancy; however, animal reproductive studies show foetal adverse events with high systemic exposure to steroids (these levels do not occur with intranasal preparations). The company advises that the patient should consult their doctor before use in pregnancy.

12. **Any relevant data on post-marketing experience**

Estimated exposure between 1983 (launch of aqueous formulation) and January 1998 is 13 million patient years. The company adverse event rate is 1.2/10000 patient years.

The submission includes a Periodic Safety Update Report (PSUR) for 1/2/95-31/1/98. In this it is mentioned that the statement under the Precautions section has been amended to include a reference to growth retardation:

> If recommended doses of intranasal BDP are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic therapies, systemic effects may occur, *including reduction in growth velocity.*
> (This is included in the proposed NZ datasheet.)

The reason for this change has been the results of a study in 1997 comparing Vacenase (also intranasal BDP but another manufacturer) and placebo and their effects on growth and hypothalamic-pituitary axis (HPA) function. The dose was 168μg twice daily for 12 months. A small but significant reduction in growth rate was seen in the steroid treated group (0.9cm), and no effect on the HPA. The study had several flaws including poor technique in height measurement, excessive dose, and baseline differences (correcting for these left a 0.68cm difference). However, this resulted in expanding the systemic warnings as above. The PSUR

explains, “since use of the non-prescription product does not involve management of the patient by a clinician, the use of Beconase OTC has been restricted to adults aged 18 years or over. In addition, non-supervised use has been restricted to a maximum period of three months.

A review of the General Practice Research Database (GPRD) in the UK on which 200000 people were prescribed intranasal BDP over 4 years, found that there was no evidence of growth retardation, although only 10% were scripts to children and under 1% were for chronic use. This database also reviewed safety in 70000 cases and found adverse effects were infrequent. And a retrospective cohort study did not find a higher incidence of cataract or glaucoma for intranasal steroid use. (The submission does mention a study, however, which has shown that inhaled high doses of steroids for over 3 months give a slightly higher (just statistically significant) incidence of cataracts and glaucoma.)

13. **Potential for inappropriate use of the medicine**
Low but the company has received a report of a person using the spray in the eye causing scarring conjunctivitis, and another report of its use to relieve impacted earwax resulting in a perforated eardrum.

14. **Potential for abuse of the medicine (e.g. non-therapeutic use of the medicine for self-gratification)**
The PSUR reports a case of a 10 year old boy being found with altered conscious level “inebriated” and headache after spray use.

15. **Current availability of other products with similar benefits**
Other OTC products used in treatment of hayfever are oral antihistamines, intranasal and oral decongestants, sodium cromoglycate and anticholinergic nasal sprays. All pharmacy only.
Other intranasal steroids are restricted medicines.

16. **Any public health advantage associated with the availability of these medicines**
Possibility of earlier treatment of symptoms and improved quality of life, if better accessibility. *However the lower classification may restrict access for those aged between 12 and 18 years.*

17. **Patient convenience including geographical factors**
No additional benefit as will still be sold in pharmacies.

18. **Pharmacokinetics**
Following intranasal administration an undefined amount of BDP is absorbed through the nasal mucosa, the remainder is swallowed. After a 200μg dose there was no measurable BDP in the plasma (limit is 100pg/ml). The majority of BDP undergoes first pass metabolism in the liver. Excretion is mainly in the faeces.

Conclusion

Safety and efficacy data support reclassification. There is insufficient evidence supplied to support a further age restriction to 18 years and over given that the product will still need to be purchased at a pharmacy and the labelling is clear that the spray is for short term seasonal use only. In addition, most of the studies monitored growth over the period of a year, and actual numbers of spontaneous reports of growth suppression are few.