RECLASSIFICATION SUBMISSION

BECONASE HAYFEVER™

(Beclomethasone dipropionate aqueous nasal spray 50 μg/metered dose)

From Restricted Medicine

To Pharmacy Medicine

APRIL 1999 MEETING

PART A

1. International non-proprietary name (INN) and British approved name (BAN) of the medicine.

Beclomethasone dipropionate BP

2. Trade name.

BECONASE Hayfever™

3. Company requesting reclassification.

GlaxoWellcome (NZ) Ltd
Eighth Floor, Quay Tower
cnr Customs & Albert Streets
Pte Bag 106600
Downtown, Auckland
NEW ZEALAND

4. Dose form and strength.

Aqueous nasal spray, 200 doses
50 μg/metered dose.

5. Pack size and other qualifications.

BECONASE Hayfever™ is an aqueous suspension delivered by a metering, atomising pump containing beclomethasone 50 μg/actuation. The product is supplied in amber glass bottles, each containing 22g of suspension or 200 doses. BECONASE Hayfever™ is packaged into a carton with an accompanying consumer information leaflet.

6. Indication for which change sought.

Prevention and treatment of seasonal allergic rhinitis, including hayfever.

7. Present classification of medicine.

Restricted Medicine

8. Classification sought.

Pharmacy Medicine

9. Classification in other countries where marketed.

Beclomethasone dipropionate aqueous nasal spray 50μg is marketed on prescription in approximately 70 countries and has been licensed for non-prescription use in Germany, New Zealand, South Africa, Finland, Switzerland and the United Kingdom.

10. Extent and duration of usage.

Intranasal beclomethasone dipropionate 50μg was first marketed as an aerosol formulation available on prescription in New Zealand under the tradename BECONASE Nasal Spray™ in December 1974. Later an aqueous formulation of the same dose strength called BECONASE Aqueous Nasal Spray™ was also launched on prescription in August 1983. The aerosol formulation was discontinued in this country in November 1995. In September 1997, the 50μg dose strength of BECONASE Aqueous Nasal Spray™ was reclassified from a Prescription Medicine to a Restricted Medicine with a change in tradename to BECONASE Hayfever™.

Between August 1983 and October 1998, 1,505,500 units of 200 dose pack of BECONASE Aqueous Nasal Spray™ 50μg were sold in New Zealand on a Prescription Medicine basis. An additional 100,800 units of 200 dose pack of BECONASE Hayfever™ were sold on a Restricted Medicine basis between September 1997 and October 1998.

In the UK 3,495,284 units of 100 dose pack and 848,555 units of 180 dose pack of BECONASE™ OTC were sold between launch in March 1994 and October 1998.

11. Proposed labelling.

Draft primary and secondary container labelling for the reclassified presentation of BECONASE Hayfever™ is contained in Appendix 1.

12. Proposed 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*."

The above two statements are included in the Dosage and Administration section of the currently approved Data Sheet for this product (see Appendix 2).

13. Other products containing the same active ingredient which may be affected by the proposed classification change.

Other intranasal corticosteroid sprays containing beclomethasone dipropionate 50 μg/metered dose which are presently marketed in this country are:

ALANASE Aqueous™ (Pacific)
ALDECIN Aqueous Nasal Spray™ (Schering Plough)
ATOMASE Aero™ (Douglas)
ATOMASE Aqueous™ (Douglas)
ATOMIDE JUNIOR™ Aerosol (Douglas)

Like BECONASE Hayfever™, all of the above products are presently available on a Prescription Medicine and Restricted Medicine basis for use in adults and children. These products would not be affected by reclassification of BECONASE Hayfever™ to Pharmacy Medicine in view of the increased age limit of 18 years and older proposed for this product (see Entry 12 of this section).

PART B

1. Expected benefits to the consumer and/or public from the proposed change in classification.

Seasonal allergic rhinitis, or hayfever, is an inflammatory disorder of the nasal mucosa which occurs in susceptible individuals in response to inhalation of airborne allergens, particularly pollen grains from weeds, grasses, flowers and trees during spring and early summer. Hayfever is the most common allergic disease encountered in the community, affecting an estimated 10% to 15% of the general population [Appendix 3]. Associated signs and symptoms of hayfever include nasal congestion, rhinorrhoea, sneezing, nasal itching and watery eyes. These symptoms can be very troublesome and may result in sleep loss and inability to concentrate.

Allergen avoidance is clearly the best strategy for prevention of seasonal allergic rhinitis, but is rarely practical. Several therapies are used for the prevention and/or treatment of seasonal allergic rhinitis, including antihistamines, oral and intranasal decongestants, anticholinergic sprays, intranasal corticosteroids, immunotherapy and sodium cromoglycate. Of these therapies, oral antihistamines, intranasal decongestants, sodium cromoglycate and intranasal corticosteroids are presently available to consumers in New Zealand on a non-prescription basis.

Oral antihistamine preparations have been the mainstay of prevention and treatment of allergic rhinitis for many years. A number of these products are freely available in New Zealand as Pharmacy Medicines, including AVIL™ (pheniramine, HMR), CLARATYNE™ (loratadine, Schering-Plough), PHENERGAN™ (promethazine, RPR), POLARAMINE™ (dextrochlorpheniramine, Schering-Plough) and TELFAST™ (fexofenadine, HMR). Although these products are particularly effective in the suppression of sneezing they are less effective for rhinorrhoea and have little influence on nasal blockage. Moreover, most antihistamines produce a degree of dose-related sedation, although the newer agents claim to be non-sedating at therapeutic doses. Some of the newer antihistamines have been associated with cardiac toxicity when taken in higher doses or concomitantly with medicines metabolised via the cytochrome p_{450} system. Some antihistamines also have well-documented interactions with other commonly used medicines. In particular, they potentiate the effects of alcohol.

Several intranasal decongestants are marketed in New Zealand as Pharmacy Medicines for the short term treatment of nasal blockage associated with allergic rhinitis, including AVIL™ Nasal Spray (pheniramine + phenylephrine, HMR), DRIXINE™ Drops and Spray

(oxymetazoline, Novartis), OTRIVINE™ (xylometazoline, Novartis) and VICKS SINEX™ Spray (oxymetazoline, Procter & Gamble). These agents have a rapid onset of action, providing initially effective symptomatic relief. However, the disadvantages of these products for consumers are that rebound hyperaemia may occur some hours after dosing, and continued use may cause rhinitis medicamentosa.

An intranasal formulation of sodium cromoglycate (RYNACROM™, RPR) is presently marketed as a Restricted Medicine in this country. Unfortunately, use of this agent tends to be limited by the short duration of action of sodium cromoglycate necessitating dosing 4 to 6 times daily which is impractical for most hayfever sufferers.

Intranasal corticosteroid preparations such as BECONASE Hayfever™ have a potent anti-inflammatory effect on the nasal mucosa and have been used worldwide, including in New Zealand, for over 25 years for the prevention and treatment of seasonal allergic rhinitis. Topically administered corticosteroids have been shown to provide effective relief for nasal congestion, sneezing, rhinorrhoea and nasal itching. These agents also have low oral bioavailability, so the swallowed portion of an intranasal dose does not produce detectable systemic levels or the unwanted effects and/or drug interactions of the oral antihistamines and intranasal decongestants.

The role of intranasal corticosteroids has evolved over time from second-line to first-line treatment of seasonal allergic rhinitis and prevention of symptom recurrence. The results of a recently published meta-analysis of 16 randomised controlled trials involving 2267 subjects indicate that intranasal corticosteroids are more effective than oral antihistamines for alleviating most nasal symptoms of allergic rhinitis, and suggest no difference between these treatment modalities for relief of associated eye symptoms [Appendix 4, Weiner et al; 1998]. The authors recommend intranasal corticosteroids for cost-effective first-line treatment of allergic rhinitis, and suggest a role for oral antihistamines as ancillary treatment, especially for eye symptoms or nasal itch if inadequately controlled by intranasal corticosteroids.

BECONASE Hayfever™ has been available in the United Kingdom for five years as a non- prescription product and in this country as a Restricted Medicine for over 12 months without untoward events. Reclassification of BECONASE Hayfever™ to Pharmacy Medicine status would allow adult hayfever sufferers easier access to a more effective and safer product for prevention and treatment of their seasonal allergic rhinitis than many of the alternative products presently marketed as Pharmacy Medicines.

2. Ease of self-diagnosis for seasonal allergic rhinitis.

Hayfever is a common allergic disease, affecting an estimated 10% to 15% of the population (see Appendix 3). The condition is easily self-diagnosed by the characteristic symptoms of rhinorrhoea, sneezing and nasal stuffiness, as well as possible itching of the eyes, nose, ears and/or palate. Seasonal allergic rhinitis is easy to distinguish from other forms of rhinitis because it tends to occur only in spring or summer with the release of pollens from flowers, weeds, grasses and trees. Hayfever is also a self-limiting disorder which requires no special investigations, and is unlikely to mask a more serious underlying disease.

Indeed, hayfever has long been recognised as being appropriate for self-diagnosis, as reflected by the extensive range of oral antihistamine and intranasal decongestant products which have been marketed for many years worldwide on an OTC basis. The symptoms of seasonal allergic rhinitis are also well documented in the consumer information leaflet accompanying BECONASE Hayfever™ (see Appendix 5).

3. Relevant data for like compounds.

As discussed in Entry 1 of this section, the superiority of intranasal corticosteroids compared with oral antihistamines for first-line treatment of allergic rhinitis has been documented in the meta-analysis included as Appendix 4.

The findings of a range of published studies which have compared the efficacy and safety of beclomethasone dipropionate with that of alternative treatments for seasonal allergic rhinitis are also reviewed in Appendix 3. This review concludes that " ... with demonstrated clinical advantages in efficacy, safety in long term use, and good patient acceptance with either the nasal spray or aerosol forms of administration, beclomethasone dipropionate has been shown to provide unsurpassed efficacy in controlling the persistent and troubling symptoms of allergic rhinitis".

4. Local data or special considerations relating to New Zealand.

GlaxoWellcome (NZ) Ltd has identified no local data or special considerations with regard to BECONASE Hayfever™ which could be regarded as being specific to New Zealand.

5. Interactions with other medicines.

Consistent with the statement in the British National Formulary that drug interactions " ... do not generally apply to corticosteroids with potent topical action such as beclomethasone", there have been no documented interactions between BECONASE Aqueous Nasal Spray™ 50µg or BECONASE Hayfever™ and other medicines. This is in contrast with a number of the oral antihistamines presently classified as Pharmacy Medicines which are known to interact with a wide range of commonly used medicines, including alcohol. Furthermore, there is no evidence of any particular adverse event profile in association with concomitant use of alternative anti-hayfever preparations, for example antihistamines and decongestants.

6. Contraindications.

BECONASE Hayfever™ is contraindicated in patients with a history of hypersensitivity to any of its components. Review of the GlaxoWellcome worldwide spontaneous safety database for skin, respiratory and ENT systems indicates a possibility for rare local hypersensitivity reactions, including rash/urticaria, facial/lip swelling, pruritus and local irritation, all of which resolve upon treatment withdrawal. There is no clear evidence of anaphylactic problems of major clinical significance.

Infections of the nasal passages and paranasal sinuses should be appropriately treated but do not constitute a specific contraindication to treatment with intranasal beclomethasone dipropionate (see Appendix 6).

7. Potential for development of drug resistance.

Nil.

8. Safety profile of BECONASE Hayfever™

Extremely rare cases of nasal septal perforation have been reported following the use of intranasal corticosteroids. As with other nasal sprays, dryness and irritation of the nose and throat, unpleasant taste and smell and epistaxis have been occasionally reported. There have been rare reports of headache. Rare cases of raised intraocular pressure or glaucoma in association with intranasal formulations of beclomethasone dipropionate have been reported. Hypersensitivity reactions including rashes, urticaria, pruritus, erythema and oedema of the eyes, face, lips and throat have also been reported (see Data Sheet, Appendix 2).

In the past 14 years, 15 adverse events have been reported to GlaxoWellcome (NZ) Ltd in association with the BECONASE™ aerosol or aqueous formulation in New Zealand, of which only two were classified as serious. One report of nasal ulceration had a probable causal relationship. The other report concerned an eleven-year-old child who experienced generalised shaking, loss of balance, rapid breathing, increased heart rate, visual disturbance, hallucination, sweating and incoherent speech, in whom the relationship with BECONASE Aqueous Nasal Spray™ was considered to be almost causal. Non-serious events included three reports each of headache and epistaxis, and one each of headache and lack of efficacy, violent sneezing, wheeziness and tight chest, vomiting, hirsutism in a child, hyperactivity in a child, burning nasal passages and burning in the mouth and throat.

A recent search by the Centre for Adverse Reactions Monitoring in Dunedin has identified two further adverse events in association with BECONASE Aqueous Nasal Spray™ both of which were reported as not serious. One report of skin atrophy and purpura in an elderly man was considered probably related to intranasal and/or inhaled beclomethasone. Another report of transient visual disturbance was considered to have a possible causal relationship.

An international beclomethasone dipropionate safety update for the period 01 February 1995 to 31 January 1998 is enclosed as Appendix 7.

9. Potential for abuse or misuse.

Review of the GlaxoWellcome worldwide safety database has shown that abuse or misuse of BECONASE Hayfever™ does not pose particular problems. The most likely harmful effect that would be expected to follow inhalation of large amounts of beclomethasone dipropionate over a short time period is suppression of hypothalamic-pituitary-adrenal (HPA) function. No special emergency action need to taken. Treatment with BECONASE Hayfever™ should be continued at the recommended dose so that full therapeutic benefit can be maintained. HPA function recovers in one to two days. If treatment is discontinued there may be a delay before relief of symptoms is obtained after recommencing treatment.

A volunteer study showed a reduction in plasma cortisol levels at a BECONASE Hayfever™ dose of 8mg (20 times the recommended daily dose) which occurred in some but not all subjects, and levels returned to normal within 48 hours of treatment cessation (see Appendix 8). The consumer information leaflet contains the statement "*Do not use more than 8 sprays in a day*" (see Appendix 5).

There have been very rare reports of misuse of intranasal beclomethasone dipropionate. One patient suffered scarring of the conjunctiva after spraying it into the eye and another developed a perforated ear drum after using the spray to relieve impacted earwax; both events occurred with the pressurised aerosol. The consumer information leaflet contains the statement "*Only use Beconase Hayfever in the nose*" (see Appendix 5).

10. Summary

Intranasal beclomethasone diproprionate 50μg has been marketed worldwide since 1974 and is currently available on a prescription or OTC basis in at least 70 countries.

Assuming a daily dose of 400μg, it can be estimated from worldwide volume sales that there have been at least 13 million patient years of exposure to intranasal beclomethasone dipropionate aqueous nasal spray since launch in 1983 until January 1998 (Appendix 7). Spontaneous reporting during this time indicates an adverse event rate of 1.2 per 10,000 patient years of treatment, suggesting an extremely favourable safety profile for BECONASE Hayfever™. Moreover, intranasal beclomethasone dipropionate lacks the important adverse effects and/or drug interactions commonly found with the oral antihistamines and intranasal decongestants which are freely marketed in this and many other countries for prevention and treatment of seasonal allergic rhinitis.

Like other intranasal corticosteroids, the role of intranasal beclomethasone dipropionate has evolved over time from second-line to first-line therapy for seasonal allergic rhinitis, and the superiority of intranasal corticosteroids compared with oral antihistamines for cost-effective first-line treatment of hayfever is now well documented (Appendix 4).

Hayfever is easily self-diagnosed by its characteristic nasal symptoms and its seasonal nature. Furthermore, it is a self-limiting disorder which does not require special investigation and is unlikely to mask a more sinister underlying disease. Indeed, hayfever has long been recognised as being appropriate for self-diagnosis, as reflected in the extensive range of antihistamines and decongestants which have been freely marketed direct to consumers for many years worldwide.

BECONASE Hayfever™ has been available in the United Kingdom for five years as a non prescription product and in New Zealand as a Restricted Medicine for over 12 months without untoward events. With appropriate labelling amendments, reclassification of BECONASE Hayfever™ to Pharmacy Medicine status will allow adult hayfever sufferers easier access to a safer and more effective product for

prevention and treatment of their symptoms than many of the alternative products presently marketed as Pharmacy Medicines for treatment of seasonal allergic rhinitis.

APPENDICES

1. Proposed primary and secondary container labelling for BECONASE Hayfever ™ as a Pharmacy Medicine.

2. Proposed Data Sheet for BECONASE Hayfever™ as a Pharmacy Medicine.

3. Fireman, P**.** "A Comparison of Intranasal Beclomethasone Dipropionate with Other Agents in the Treatment of Rhinitis – A Review of the Published Clinical Experience".*Today's Therapeutic Trends* 1991; 9(1): 21-34

4. Weiner JM, et al; "Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials". *BMJ* 1998; 317: 1624-9

5. Proposed consumer information leaflet for BECONASE Hayfever™ as a Pharmacy Medicine.

6. Published articles in support of claim that infections of the nasal passages and paranasal sinuses do not constitute a specific contraindication to treatment with intranasal beclomethasone.

7. Safety Update

8. Harris DM, et al; "The effect of intranasal beclomethasone dipropionate on adrenal function". *Clinical Allergy* 1974; 4: 291-4