Application to reschedule the entries for:

(1) FLIXONASE™ Aqueous Nasal Spray (fluticasone propionate)

(2) BECONASE™ Hayfever Aqueous Nasal Spray (beclomethasone dipropionate)

from Restricted Medicine to Pharmacy Medicine

GlaxoSmithKline
Consumer Healthcare
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30 July, 2003

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Sponsor’s Declaration

I certify that to the best of my knowledge, the information contained within the current application is true and correct.

John Tabar
Scientific Affairs Manager
GlaxoSmithKline Consumer Healthcare

Executive Summary

- This application seeks approval for the rescheduling of **fluticasone propionate (FLIXONASE™ Aqueous Nasal Spray; 50μg/metered dose) (FP)** and **beclomethasone dipropionate (BECONASE™ Hayfever Aqueous Nasal Spray; 50μg/metered dose) (BDP)** from **Restricted Medicine** to **Pharmacy Medicine** status for the prophylaxis and treatment of allergic rhinitis (AR) in adults and children aged 12 years and over. It is important to note that this application **does not** propose to extend the period of usage of these intranasal steroids beyond the currently approved maximum of 6 months.

- AR is a high prevalence disorder[1,2] that can seriously affect quality of life.[3] Around 1 in 3 Australians suffer from this condition at some stage in their lives; and the symptoms can have a debilitating impact on quality of life — they can affect mood, learning, work performance, sleep and account for 500,000 sick days per year in Australia. The public health benefit of reducing this burden is therefore substantial.

- AR has traditionally been described as seasonal or perennial. Importantly, the vast majority of patients with AR have perennial disease, but it may be so mild that the symptoms do not impact on daily activities.[4] During the pollen season these patients then experience an exacerbation of symptoms during which their disease becomes moderate to severe.

- In 2001 the World Health Organization, in conjunction with ARIA,* suggested some changes to the classification of AR. The aim of these changes was to reclassify the disease into categories similar to those for asthma. Consequently, **AR is now classified into two subcategories — intermittent and persistent — and the symptoms are graded based on severity.**[5] In light of this new medical approach to the classification of AR, this submission refers to AR rather than distinguishing between seasonal and perennial.

- Intranasal corticosteroids, such as FP and BDP, have been established as the first-line therapy of choice for people with AR for a number of years.[1] This first-

*ARIA = Allergic Rhinitis and its Impact on Asthma

line position is based on the efficacy and safety of these products. Intranasal corticosteroids have been demonstrated to provide superior, and more complete, symptom control than any other medication class in the control of AR.[1,2]

- At the February 2003 meeting of the National Drugs and Poisons Subcommittee (NDPSC), recommendations were made to reschedule BDP for the treatment of AR from Restricted Medicine to Pharmacy Medicine of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). At the subsequent NDPSC meeting in June 2003, the intranasal corticosteroids budesonide and mometasone were considered for similar rescheduling. FP nasal spray belongs to the same class of drugs, and has a comparable safety and efficacy profile to the other corticosteroids. This opinion is supported by the Australian Drug Evaluation Committee (ADEC), who during their consideration of FPANS (meeting dated 8–9 October 1999), agreed that 'fluticasone nasal spray was not different from the other intranasal steroids and possessed the same safety profile'.

- Whilst much of the literature pertaining to intranasal corticosteroids relates to this group of medicines as a class, this application seeks for a change in scheduling only with respect to two products — FP and BDP. Post-marketing surveillance confirms that neither of these two products poses any safety concerns different to those corticosteroids sold as Pharmacy Medicine products.

  – FP has been available as a non-prescription medicine in New Zealand for almost 4 years and in Australia for 1 year.
  – BDP has been available as a non-prescription medicine in New Zealand for 6 years and in Australia for 3 years.

- AR is a condition that does not require medical diagnosis and can be easily identified by the consumer. It requires no special investigations and is unlikely to mask a more serious underlying disease. Indeed, research conducted in 2000 has shown that 79% of hayfever sufferers know what causes their allergy and are able to identify the main symptoms of their disorder.[6] Whilst rescheduling of FP and BDP to Pharmacy Medicine status would remove the mandatory requirement for personal pharmacist intervention, a Pharmacy Medicine classification would still allow the products to be supplied under the supervision of the pharmacist with intervention and involvement by the pharmacist on an as-needed basis.

The criteria (in Australia and New Zealand one would assume) for classification of a medicine as a Pharmacy Medicine assert that the ailment or symptoms to be treated should:

- not require ongoing or close medical diagnosis or management.
- be easily recognised by the consumer.
- be amenable to short treatment, or
- be capable of being monitored and self managed by the consumer, with advice and counselling if necessary.

The recurrent nature of the symptoms of AR and the recognition by most sufferers of factors that trigger them facilitates self-diagnosis. The long-standing, widespread range of antihistamines, e.g., Claratyne™ (loratadine) and Zyrtec™ (cetirizine hydrochloride), and decongestants, which have been freely marketed direct to consumers for many years worldwide reflects the medical view that this condition is suitable for self-diagnosis and self-medication.

- Antihistamines, whilst a valuable treatment option for some AR sufferers, are not the first line choice of medication for AR. Despite this, they dominate the AR market. This market position is more likely to be attributable to their Pharmacy Medicine availability than to their efficacy.

  This is exemplified by recent research amongst Australian allergy sufferers, which has revealed that of those sufferers that treat their condition, only 1 in 4 say that their medication works every time.[7] Furthermore, the majority of sufferers (48%) self-select their medication in the pharmacy, yet 50% of the sufferers surveyed claimed to have never spoken to a pharmacist about which treatments are best for them. The availability of FP and BDP as Pharmacy Medicines within the pharmacy, and the associated medical education and marketing that would accompany this de-scheduling, would provide renewed impetus for customers to consider alternative options to antihistamine tablets. In doing so, it would provide opportunities for the consumer to ask questions of the pharmacist.

- Used correctly, intranasal corticosteroid sprays control symptoms more completely than do antihistamine tablets.[1,2] In view of the well-recognised systemic effects of corticosteroids, there has been considerable interest in the

potential for intranasal corticosteroids to produce systemic effects. However, the consensus from a large body of scientific evidence is that **the risk of systemic steroid-like effects with these products is small**,[2,8-11] although events may rarely occur in susceptible individuals with prolonged use.[5]

Negative perceptions regarding the use and safety of intranasal corticosteroids have meant that until recently consumers suffering from AR either had to make do with antihistamine tablets or visit their GP for a prescription. Given that intranasal corticosteroids are now acknowledged as first-line treatment for and prevention of AR, increased consumer access to BDP and FP would alleviate the public-health burden of this condition. Enabling both antihistamines and these well-established intranasal corticosteroids to share a side-by-side placement on the pharmacy shelf provides consumers with a wider choice of drug class with which to manage their condition.

Most importantly, such a position can be achieved without increasing the risk of harm. The long-established efficacy and safety of both BDP and FP for the symptomatic treatment of seasonal and perennial AR meet the criteria for a Pharmacy Medicine. Indeed, the excellent safety profile of these products has been established in short- and long-term clinical studies, and confirmed in post-marketing data gained from over a quarter of a century of use. Additionally, the risks of misuse with these products are minimal.

- The data comparing intranasal corticosteroids with non-sedating antihistamines are uniform in their demonstration that intranasal corticosteroids offer clinical superiority. **Moreover, since the cost per treatment day is less with intranasal corticosteroids, cost-effectiveness considerations favour these medications over antihistamines**.[12]

- Today's patients are becoming increasingly involved in their own healthcare management. The wider availability of medicines has facilitated this process. However, it is important that consumers understand fully the differences between medications such that they can make informed choices.

  Ensuring the correct and appropriate use of any medication is vital if the public health benefits of wider access are to outweigh the risks from adverse events and misuse. As has already been demonstrated, FP and BDP have excellent efficacy

and safety profiles. **The appropriate use of these products, as Pharmacy Medicines, will be further enhanced by the development of new, performance-based labelling.** (For examples of performance-based labelling for FP and BDP, please refer to Appendix 1.)

In summary

- Existing Pharmacy Medicines, such as antihistamine tablets, are indicated for the treatment of perennial and seasonal AR.
- Used correctly, intranasal corticosteroid sprays control symptoms more completely than do antihistamine tablets.[1,2]
- There is extensive experience of these medications in the treatment of AR and the data have demonstrated these drugs to be safe with minimal risk of systemic side effects.
- Intranasal corticosteroids are effective when used on an as-needed basis.[12]
- The appropriate use of these products, as Pharmacy Medicines, will be further enhanced by the development of new, performance-based labelling.
- Cost-effectiveness considerations favour these medications over antihistamines.[12]
- Beclomethasone dipropionate and fluticasone propionate aqueous nasal sprays satisfy all the MCC criteria for classification as Pharmacy Medicines.

Relevant considerations for fluticasone propionate and beclomethasone dipropionate

1. Performance-based labelling

As a manufacturer of a wide range of over-the-counter medicines, GlaxoSmithKline has taken expert design and comprehension advice to develop performance-based labels, enhancing the readability and assimilation of the information. As such new labels will ensure that a consumer wishing to self-select an over-the-counter product will be able to quickly ascertain:

a) if the product is right for their condition, and
b) if they can use the product.

Independent testing of this concept has revealed excellent results.

The concept of performance-based labelling would be applied to the new FPANS and BDPANS Pharmacy Medicine packaging, with consideration given to ensuring that the label clearly shows:

- Product name
- Active ingredient
- Conditions that the product is indicated for
- Symptoms of these conditions
- What causes/triggers these symptoms
- When the product should not be used
- That the product should not be used for more than 6 months without the advice of a doctor/pharmacist
- That if symptoms are not relieved within 7 days, a doctor/pharmacist should be consulted.

As can be seen from the proposed draft labels (Appendix 1) much of this information will be portrayed in both words and visual icons, further enhancing label comprehension.

2. Previous considerations and trans-Tasman harmonization

It is relevant to note that the Medicines Classification Committee first considered the reclassification of BDP in New Zealand (from Restricted Medicine to Pharmacy Medicine status) in November 2000 (Appendix 2). The committee raised three concerns to this reclassification:

- Long-term and even year-round use of the product
- Concomitant use of the product with other steroids
- The minimum age restriction of 18 years that had been proposed by the company.

Chronic use is not an issue in this case. The application is not seeking to change current restrictions regarding the use of the product (limited to 6 months) and will have additional on-pack information advising the user to seek medical advice if the symptoms are not resolved within 7 days.

International Safety Updates confirm the lack of adverse effects of long-term use of BDP nasal spray. (Please refer to Appendix 3 for International Safety Updates for BDP.) Clearly, the data suggest that long-term use of BDP does not have a detrimental effect. Furthermore, post-marketing experience in Australia and New Zealand has confirmed that intranasal FP does not pose any safety concerns different to those corticosteroids currently included as Pharmacy Medicine products in Australia.

The label will also contain a warning regarding concomitant use of the product with other steroids. Additionally, the currently approved age limit of 12 years is considered appropriate and justifiable on the basis of the available clinical data.

A post-marketing study was conducted to assess the usage of one intranasal corticosteroid (FP) in New Zealand 2 years after OTC launch. Specifically, the study was designed to identify whether consumers (n=100) were compliant in the areas of dosage, contraindications and usage with other medicines. The results showed:

- No evidence of underage use

- Around 30% of respondents were using the product more than once per day, but most had been advised to do so by a doctor
- Of 16 people who had been using the product for more than 6 months, 10 had been advised to do so by a healthcare professional
- Although there are no contraindications on the NZ pack regarding concomitant use with other medicines, only one person used it concomitantly on the advice of their GP
- Only one person increased the dosage without GP advice
- Of 30 people who co-used asthma steroids with FP, 66% were advised to do so by their healthcare professional.

3. Current pharmacotherapies for allergic rhinitis

In the management of AR, allergen avoidance is clearly the best strategy, but this is rarely practical. If avoidance fails then pharmacotherapy is the next step. It is now widely established that intranasal corticosteroids provide more complete symptom control than do any other class of medications.[1,2] Moreover, because intranasal corticosteroids have lower average wholesale prices than non-sedating antihistamines, they offer clinical superiority in conjunction with a lower cost per treatment day. [13]

Antihistamines

Oral antihistamines have been used for many years for the prevention and treatment of AR. A number of these are available as Pharmacy Medicines for short-term, 10-day treatment e.g., loratadine (Claratyne™) and cetirizine hydrochloride (Zyrtec™). They can be used to treat some of the histamine-mediated symptoms of rhinitis, such as nasal itching, sneezing and watery rhinorrhoea, by blockade of histamine H1-receptors.[3]

Even though H1 antihistamines are effective at reducing the neurally mediated symptoms of itch, sneeze, and rhinorrhoea they have little objective effect on nasal blockage.[3,14] The reason for this is that histamine is not the main cause of nasal obstruction following allergen challenge; here other mediators such as prostaglandins, leukotrienes and kinins play a significant role.[15,16] Newer antihistamine plus decongestant combinations such as Clarinase™ are reputed to relieve nasal congestion arising from the late-phase inflammatory response.

However, unlike intranasal corticosteroids, they do not treat the underlying inflammation that leads to nasal congestion.

Antihistamines vary widely in their onset of activity. Generally, the onset of the antihistaminic effect begins within one hour and is greatest 5–7 hours after oral administration of the compound.[17]

Symptoms of sedation, drowsiness, fatigue, performance impairment and somnolence are the most problematic adverse effects of the first-generation antihistamines. Second-generation antihistamines clearly cause less sedation and impairment than their predecessors, but none of them are entirely devoid of CNS activity. Indeed, all antihistamines possess the potential to cause a degree of somnolence as a function of the histaminergic mechanisms involved in the control of CNS arousal.[18,19]

Topical anti-histamines, such as levocabastine aqueous nasal spray (Livostin™ nasal spray and eye drops) and azelastine HCl (AZEP™ Hayfever relief) are also Pharmacy Medicines. Topical intranasal agents are reported as having a slightly more rapid onset of action than oral preparations and are quite effective in relieving pruritis, sneezing, and rhinorrhoea. However, like H1-receptor antagonists administered orally, they are not highly effective in relieving nasal blockage.[17]

Mast cell stabilisers

Mast cell stabilisers, such as sodium cromoglycate (Rynacrom™), reduce nasal itching, sneezing, hypersecretion and nasal blockage in AR. Mast cell stabilisers inhibit the release of histamine and other mediators of inflammation from sensitised mast cells. These medications prevent the early- and late-phase reactions of AR, but do not relieve pre-existing symptoms. As such, they are prophylactic agents and need to be started before the onset of symptoms for maximum effect. They reduce the symptoms of AR, but are clearly less effective than nasal corticosteroids.[3]

Sodium cromoglycate is effective immediately, but for effective use it must be used 4–6 times a day. This need for frequent dosing (which can lead to poor patient compliance) is its major disadvantage.[2]

Topical decongestants

Topical decongestants, such as ephedrine nasal drops, can provide symptomatic relief from nasal congestion associated with vasomotor rhinitis and the common cold. They contain sympathomimetic drugs, which exert their effect by vasoconstriction of the mucosal blood vessels, which in turn reduces oedema of the nasal mucosa. They are of limited value because they can give rise to rebound congestion (rhinitis medicamentosa) when their effects wear off. This is because secondary vasodilation causes a subsequent temporary increase in nasal congestion.[20]

The more potent sympathomimetic drugs oxymetazoline (Logicin™), phenylephrine and xylometazoline (Otrivin™) are more likely to cause a rebound effect. All of these agents can cause a hypertensive reaction if used during treatment with a monoamine oxidase inhibitor.

Intranasal corticosteroids

Topical corticosteroids are effective in reducing nasal blockage, itching, sneezing and rhinorrhoea in all forms of rhinitis. They have effects on cells and mediators involved in both early- and late-phase reactions (Table 1). They have proved to be more effective in symptomatic control of AR than sodium cromoglycate, antihistamines and decongestants.[3] When formulated as aqueous nasal sprays, they can have an immediate soothing effect[21,22] and are well tolerated, with a low incidence of side effects.[23] It may be three to four days before the maximum benefits of the anti-inflammatory effect of the corticosteroid are attained.

Beclomethasone dipropionate

BDP aqueous nasal spray 50μg has been marketed on prescription since 1974 in approximately 70 countries. It has been available without prescription in a number of countries including the UK, New Zealand, Australia, Finland, Ireland, Poland, Switzerland, Sweden and South Africa for up to 6 years.

For over 25 years, BDP in an aqueous nasal spray format has been widely utilized in over 30 countries with over 11 million patient years of exposure. During this time, BDP has been shown to be extremely safe for use in the treatment of seasonal and perennial AR. The most common adverse events have primarily been associated with minor irritation of the nasal mucous membranes, which is commonplace with the use of nasal sprays.

Fluticasone propionate

FPANS has been available as a Restricted Medicine in New Zealand for over 3 years (i.e., since June 2000).

The product was approved for registration in Australia on 13th January 2000, as a Schedule 4 product. It was rescheduled to Restricted Medicine status in November of 2000 and then launched as a non-prescription product in July 2002 (under the brand name Beconase Hayfever & Allergy 24 Hour™ aqueous nasal spray).

It is pertinent to note however that FP has been available in Australia as a metered dose inhaler (Flixotide™) since August 1994 and is currently marketed in three different inhaled dosage forms (Flixotide™ Accuhaler™, Inhaler and Nebules™) for the treatment of asthma and associated diseases. This prior local experience with other dosage forms of the active ingredient, coupled with the extensive safety data collated from exposure to intranasal FP world-wide (16.3 million patient years) provides sufficient product exposure to support rescheduling to Pharmacist Only status.

4. Positive public health implications

AR is much more than just having a blocked or runny nose. It is associated with impairments in how people function in their everyday lives and can create difficulties at work or school.[24] In Australia alone it is estimated that 500,000 sick days every year are attributed to the symptoms of this condition.[25] Effective management of AR can therefore have a significant effect on quality of life and work performance.[24]

Recent research conducted amongst Australian allergy sufferers has revealed that many are obtaining inadequate symptom relief with the current products that they self-select in the pharmacy. The consensus from this research is that consumers will put up with what they have access to and are reluctant to bother their GP or pharmacist for advice on a more suitable, or more effective, product.

This unfortunate situation is perpetuated by the products available to consumers. Currently a wide variety of medications for the symptomatic control of AR are available as Pharmacy Medicines. Whilst these medications do confer some benefits

to people with AR, they are not regarded as the first-choice treatment option. Intranasal corticosteroids, currently held as Restricted Medicines, are the first-choice treatment option because they provide superior symptom control as well as prophylactic benefits with no increase in risk from adverse events.

Descheduling FP and BDP to Pharmacy Medicines would provide an alternative treatment option to consumers. Moreover, patients would be able to find these products in the same place that they find their current products. Presented with a new treatment choice, consumers would have an increased chance of successfully controlling their symptoms and in doing so avoid the negative health consequences that result from inadequate symptom management.

Taking into consideration the safeguards of professional intervention through pharmacist counselling (with the option of referral to a physician if warranted), and adequate labelling (via packaging and Product Information Leaflets) to provide clear and simple instructions for the use of these products, it is difficult to argue that their rescheduling from Restricted Medicines to Pharmacy Medicines will pose any added risk to public health and safety to consumers. On the contrary, there are tremendous public health benefits in having safe, efficacious first-line agents available as Pharmacy Medicines. This will potentially reduce the number of physician visits and result in a subsequent reduction in medical costs for a condition that can be effectively managed by pharmacists and referred to physicians if necessary.

5. Ease of self-diagnosis

AR (seasonal and perennial) is a common condition, affecting an estimated 10% to 15% of the population. The condition is easily self-diagnosed by the characteristic symptoms of rhinorrhoea, sneezing and nasal stuffiness, as well as occasional itching of the eyes, nose, ears and/or palate. It is a recurring yet self-limiting disorder, which requires no special investigations, and is unlikely to mask a more serious underlying disease.

Indeed, AR has long been recognised as being appropriate for self-diagnosis, as reflected by the extensive range of oral antihistamine and intranasal decongestant products that have been marketed worldwide for many years on an OTC basis. The

symptoms of AR are well documented in the revised Product Information Leaflet accompanying FPANS and BDPANS.

PART A1: FPANS technical data and general information

1. Company requesting rescheduling

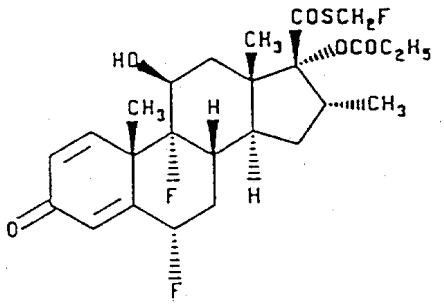
GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue
Ermington
NSW 2115

2. Company contact

Mr John Tabar
Scientific Affairs Manager
Ph: (02) 9684 0204
Fax: (02) 9684 6958
Email: john.n.tabar@gsk.com

3. Name of the drug

Proprietary name: Fluticasone propionate
Trade name: FLIXONASE™ Aqueous Nasal Spray
Structural formula:



Full chemical name: S-fluoromethyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1, 4-diene-17β-carbothioate.
CAS: 80474-14-2
Molecular formula: $C_{25}H_{31}F_3O_5S$

4. Dose form

Aqueous nasal spray

5. Pack size and strength

60 or 120 doses
50μg/metered dose

6. Proposed dosage

Two sprays into each nostril once a day, preferably in the morning. Dose may be increased to two sprays into each nostril twice daily if necessary. The maximum daily dose should not exceed four sprays into each nostril.

7. Packaging details

FPANS is an aqueous suspension delivered by a metering, atomising pump containing FP 50μg/actuation. The product is supplied in amber glass bottles, each containing 60 or 120 doses. The carton label for this product has been redesigned in accordance with the principles of performance-based labelling to enhance readability and assimilation of information. (Please refer to Appendix 1 for draft carton labelling.) Each FPANS bottle is packaged into a carton, together with an accompanying patient information leaflet. (Please refer to Appendix 5 for patient information leaflet.)

8. Indications

Current approved Restricted Medicine indication
"Prophylaxis and treatment of seasonal AR in adults and children aged 12 years and over."

Indication proposed for rescheduling to Pharmacy Medicine
"Prophylaxis and treatment of AR in adults and children aged 12 years and over."

9. Present classification of medicine

Restricted Medicine

10. Classification sought

Pharmacy Medicine

11. Classification in other countries where marketed

FP aqueous nasal spray 50μg is marketed on prescription in approximately 100 countries.

FP has been available for OTC use as a Restricted Medicine in New Zealand for 3 years (since June 2000) and in Australia for 1 year (since July 2002). An application has been submitted to the Australian NDPSC to consider the re-scheduling of FP to Pharmacy Medicine Status in the November 2003 meeting. It is worth noting that other intranasal corticosteroids have either been rescheduled to Pharmacy Medicine status (e.g., beclomethasone) or have applications pending for a similar switch in status (e.g., budesonide and mometasone, both heard at the June 2003 NDPSC).

12. Extent and duration of usage

Intranasal FP 50μg was first registered in the United Kingdom in March 1990, where it has been on the market since April 1991. FPANS was approved for registration in New Zealand on 7th November 1991

Up to 28 February 2003, there have been approximately 16.3 million patient years of exposure for intranasal formulations of FP.

13. Safety

The safety of FP is reviewed in Part B1.

14. Known side-effects

As with other nasal sprays, dryness and irritation of the nose and throat, unpleasant taste and smell, and epistaxis have been reported. Hypersensitivity reactions including skin rashes and oedema of the face or tongue have also been reported. There have also been rare reports of anaphylaxis/anaphylactic reactions and bronchospasm. (Please refer to the 'Adverse Reactions' section of the approved Product Information, Appendix 6.)

15. Abuse or habituation

Evidence of abuse or habituation with FP has not been reported.

16. Proposed warning statements

It is proposed that the PI document for Pharmacy Medicine FPANS will include the following warning statements:

- See your doctor if you are already taking another steroid product (e.g., tablets, asthma or nasal inhaler, eye/nose drops).
- See your doctor if you have infection in the nasal passages or sinuses.
- See your doctor if you have recently had an injury or surgery to your nose, or problems with ulceration in your nose.
- See your doctor if nasal symptoms are not relieved after 7 days of treatment.
- See your doctor if you develop:
  - fever, nasal or facial pain, or swelling
  - purulent or discoloured nasal discharge
  - bleeding from the nose
  - acute eye pain or visual disturbance.
- Do not use for more than 6 months except on medical advice.
- Once the full effect has been obtained, a lower maintenance dose should be used.
- Do not exceed the maximum stated dose.

17. Other products containing the same active ingredient that may be affected by the proposed scheduling change

None

PART A2: BDPANS Technical Data and General Information

1. Company requesting rescheduling

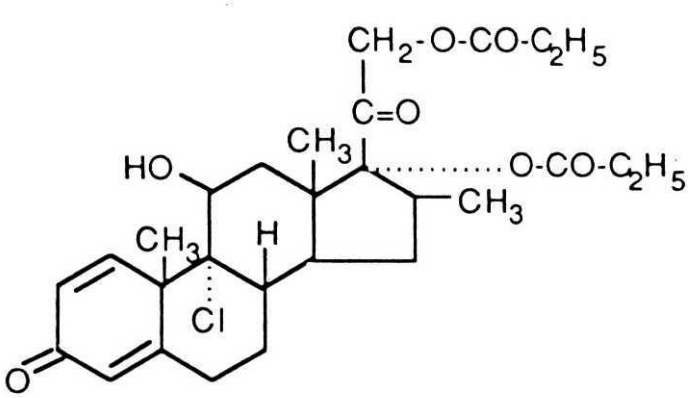
GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue
Ermington
NSW 2115

2. Company contact

Mr John Tabar
Scientific Affairs Manager
Ph: (02) 9684 0204
Fax: (02) 9684 6958
Email: john.n.tabar@gsk.com

3. Name of the drug

Proprietary name: Beclomethasone dipropionate
Current trade name: BECONASE Hayfever™
Proposed trade name: BECONASE Hayfever 12 Hour™
Structural formula:



Full chemical name: 9-chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-doine-17,21-dipropionate

CAS: 5534-09-8

Molecular formula: $C_{27}H_{23}ClO_7$

4. Dose form

Aqueous nasal spray.

5. Pack size and strength

200 doses

50 μg/metered dose

6. Proposed dosage

Two sprays into each nostril twice daily. The maximum daily dose should not exceed 4 sprays into each nostril (i.e., 400μg).

7. Packaging details

BDPANS is an aqueous suspension delivered by a metering, atomising pump containing BDP 50μg/actuation. The product is supplied in amber glass bottles, each containing 20g of suspension, equivalent to 200 doses. Each BDPANS nasal spray bottle is packaged into a carton with an accompanying patient information leaflet.

8. Indications

Current approved Restricted Medicine indication

"Short-term (3–6 months) treatment of seasonal AR in adults and children aged 12 years and over."

Indication proposed for rescheduling to Pharmacy Medicine

"Short-term (3–6 months) prophylaxis or treatment of AR in adults and children aged 12 years and over."

9. Current classification of medicine

Restricted Medicine

10. Classification sought

Pharmacy Medicine

11. Classification in other countries where marketed

BDP aqueous nasal spray 50μg has been marketed on prescription since 1974 in approximately 70 countries. It has been available without prescription in a number of countries including New Zealand, Finland, Ireland, Poland, Switzerland, Sweden and South Africa for many years (Table 1). In addition, it was recently de-scheduled to become a general sales medicine in the UK and a Pharmacy Medicine in Australia.

Table 1. Current scheduling status of BDP.

Country	**Product Name**	**Approval date**	**Legal status**
Australia	Beconase Aqueous Nasal Spray 50μg	16 Dec 99	Pharmacy Medicine (S2)
Azerbaijan	Beconase Aqueous Nasal Spray 50μg	4 Feb 00	OTC
Finland	Beconase Aqueous Nasal Spray 50μg	29 Dec 98	OTC
Germany	Beconase Aqueous Nasal Spray 50μg		OTC
Ireland	Beconase Aqueous Nasal Spray 50μg	17 Sep 99	OTC
Israel	Beconase Aqueous Nasal Spray 50μg	17 Sep 00	OTC
Jordan	Beconase Aqueous Nasal Spray 50μg	15 Jan 97	OTC

Kirghizia	Beconase Aqueous Nasal Spray 50μg	4 Mar 97	OTC
Lebanon	Beconase Aqueous Nasal Spray 50μg		OTC
Malaysia	Beconase Aqueous Nasal Spray 50μg	14 Dec 94	OTC
New Zealand	Beconase Aqueous Nasal Spray 50μg	1 Apr 97	OTC
South Africa	Beconase Aqueous Nasal Spray 50μg	2 Oct 95	OTC
Sweden	Beconase Aqueous Nasal Spray 50μg	1 Dec 99	OTC
Switzerland	Beconase Aqueous Nasal Spray 50μg	5 Nov 98	OTC
UAE	Beconase Aqueous Nasal Spray 50μg	1 Jun 90	OTC
UK	Beconase Aqueous Nasal Spray 50μg	2002	GSL
Ukraine	Beconase Aqueous Nasal Spray 50μg	26 Oct 95	OTC

12. Extent and duration of usage

For over 25 years, BDP in an aqueous nasal spray format has been widely utilized in over 30 countries with over 10 million patient years of exposure. During this time, BDP has been shown to be extremely safe for use in the treatment of seasonal AR. The most common adverse events have been primarily associated with minor irritation of the nasal mucous membranes, events that are commonplace and anticipated with the use of nasal sprays.

13. Safety

The safety of BDP is discussed in Part B2.

14. Known side-effects

A review of the GlaxoSmithKline worldwide safety database has shown that abuse or misuse of BECONASE Hayfever and Allergy 12 Hour™ does not pose particular problems. The most likely harmful effect that would be expected to follow inhalation of large amounts of BDP over a short time period is suppression of hypothalamic-pituitary-adrenal (HPA) function. No special emergency action needs to be taken. Treatment with BECONASE Hayfever and Allergy 12 Hour™ should be continued at the recommended dose so that full therapeutic benefit can be maintained. HPA function recovers in 1–2 days. If treatment is discontinued, there may be a delay before relief of symptoms is obtained after recommencing treatment.

A volunteer study showed that a reduction in plasma cortisol levels at a BECONASE Hayfever and Allergy 12 Hour™ dose of 8mg (20 times the recommended daily dose) occurred in some but not all subjects, and levels returned to normal within 48 hours of treatment cessation. The patient information leaflet contains the warning statement "Do not use more than 8 sprays in a day”.

There have been very rare reports of misuse of intranasal BDP. One patient suffered scarring of the conjunctiva after spraying it into the eye and another developed a perforated eardrum after using the spray to relieve impacted earwax; both events occurred with the pressurised aerosol. The current patient information leaflet contains the statement "Only use Beconase Hayfever in the nose”. The future patient information leaflet would contain the same instruction.

15. Abuse or habituation

Please refer to Part B2.

16. Proposed warning statements

It is proposed that the ‘Product Information Leaflet’ document for Pharmacy Medicine BECONASE Hayfever and Allergy 12 Hour™ will include the following warning statements:

- See your doctor if you are already taking another steroid product (e.g., tablets, asthma or nasal inhaler, or eye/nose drops).
- See your doctor if you have infection in the nasal passages or sinuses.
- See your doctor if you have recently had an injury or surgery to your nose, or problems with ulceration in your nose.
- See your doctor if nasal symptoms are not relieved after 7 days of treatment.
- See your doctor if you develop:
  - fever, nasal or facial pain or swelling
  - purulent or discoloured nasal discharge
  - bleeding from the nose
  - acute eye pain or visual disturbance.
- Do not use for more than 6 months except on medical advice.
- Once the full effect has been obtained, a lower maintenance dose should be used.
- Do not exceed the maximum stated dose.

17. Other intranasal corticosteroid sprays containing beclomethasone dipropionate that may be affected by the proposed scheduling change

ALDECIN™ Aqueous Nasal Spray (Schering Plough)

PART B1: FPANS – Reasons for requesting classification change

1. Product overview

Pharmacological properties

FP is a highly lipophilic corticosteroid molecule, which facilitates its uptake and retention in target tissues, and penetration through the cell membrane. It has increased intrinsic activity at the glucocorticoid receptor but a low dissociation rate. This results in an estimated half-life for the FP–receptor complex of 10 hours. The relative affinity for the glucocorticoid receptor is 3- and 1.5-fold higher than that of budesonide and the active metabolite of beclomethasone, respectively. As a result, FP exhibits high topical anti-inflammatory activity where it has been shown to be more potent than many other corticosteroids, including BDP, mometasone furoate, flunisolide, budesonide and triamcinolone acetonide.[26] Such activity, coupled with a high rate of conversion to a metabolite of negligible activity at the glucocorticoid receptor, low affinity for other steroid receptors [including the mineralocorticoid, oestrogen, androgen and progestogen receptors[14]] results in a high therapeutic index and potentially an improved safety profile.

In the early studies the quantitation of systemic exposure following FP aqueous nasal spray (FPANS) administration was not readily accomplished due to the very low plasma levels achieved via this dosing route. Initially, a radioimmunoassay was used for FP plasma measurements (lower limit of quantification [LLOQ] 0.05ng/mL). Later, a liquid chromatography mass spectrometry (LCMS) assay was developed with a LLOQ of 0.025 ng/mL. The data from these earlier studies with FPANS have been summarised: although the majority of subjects had undetectable plasma levels of FP, six separate studies concluded that at 10 times the clinical dose, absorption from the nasal mucosa was low (<2%) and insufficient to exert a measurable effect on the HPA axis (Richards DH, GW R&D UK). A more recent study using LCMS has confirmed that the absolute oral and nasal bioavailability of FPANS is negligible (<1%).[27]

Effects on pituitary–adrenal function

The use of systemic and inhaled corticosteroids can cause suppression of the HPA-axis, as their presence in the systemic circulation can mimic the effects of naturally occurring corticosteroids. However, systemic effects with the intranasal use of FP would appear unlikely, as the systemic bioavailability of this drug is very low (<1%). Large placebo-controlled studies that measured serum and urinary cortisol levels have shown that the intranasal use of FP does not suppress HPA function. Although urinary free cortisol is a test best used to detect oversecretion of cortisol, it is widely used and accepted as an indicator of adrenal function.[23] Significant changes in urinary free cortisol were not detected following FP intranasally at single doses of up to 2mg or at doses of 2mg or 4mg/day for up to 7 days.

These findings have been confirmed with the more recent studies. In study FLTB1016, no significant change in either 24-hour serum cortisol AUC (ratio FPANS:placebo 1.01; 90% CI: 0.90, 1.14) or 24-hour urinary cortisol excretion (ratio 0.78; 90% CI: 0.58, 1.04) was observed following FPANS 200μg/day for 4 days.

Pharmacokinetic–pharmacodynamic modelling of plasma cortisol and plasma FP data in healthy subjects further supports this conclusion. Using a wide range of inhaled, oral, and intravenous doses, a relationship has been established between the FP plasma concentration and effects on the HPA axis.[28] The FP plasma AUC24 required to cause 50% plasma cortisol AUC24 reduction was 3.2ng/mL/h with no significant changes in plasma cortisol observed below a FP AUC24 of approximately 1ng/mL/h.(Richards DH, GW R&D UK) In study FLTB1016, the highest observed FP AUC following FPANS 200μg/day was 0.016 ng/mL/h, this is approximately 60-fold below the threshold for detectable effects on cortisol levels. FPANS was also administered at 800μg TDS (12 times the daily clinical dose) in this study. Although this was associated with a small reduction in serum and urinary cortisol compared with placebo, this was not considered clinically significant. In study FNM10001, FPANS was again administered at 800μg TDS and no significant change in serum or urinary cortisol was observed compared with baseline.[29] Clinical data concur with these findings. No effect on HPA axis function was detected following 800μg/day of intranasal FP 400μg b.i.d. compared with placebo for four weeks. This conclusion was based on data from 6-hour cosyntropin infusion stimulation tests, performed at screening and at 4 weeks. In this study FP 800μg/day was not different from placebo,

whereas two groups of patients receiving oral prednisone (7.5 and 15mg/day) both showed evidence of HPA axis suppression.[30]

Pharmacokinetics

Absorption

Following intranasal dosing with FPANS it is estimated that the major portion of the dose is cleared by the nasal cilia and eventually swallowed. Since FPANS is an aqueous suspension and has poor aqueous solubility (0.14μg/mL), the contact time and surface area probably limit the opportunity for dissolution and direct absorption across the nasal mucosa.

Following intranasal dosing of FP 200μg/day, steady-state maximum plasma concentrations were not quantifiable in 9 of 12 subjects (<0.01ng/mL; study FLTB1016). The highest C_{max} observed was 0.017ng/mL. As the majority of the intranasal dose is swallowed and oral bioavailability of FP is <1% due to poor absorption and pre-systemic metabolism, the total systemic absorption arising from both nasal and oral absorption of the swallowed dose is negligible.

Low systemic absorption of FP for high intranasal doses has also been found. In study FLTB1016, the steady-state, geometric-mean FP C_{max} with FPANS 800μg TDS was 0.037ng/mL (range: 0.011–0.067ng/mL) compared with 10.53ng/mL (range: 4.03–38.7ng/mL) with FPANS 1mg intravenous, confirming the negligible nasal bioavailability. This was confirmed in study FNM10001[29] and study FLTB1009,[31] which found mean C_{max} values of 0.277ng/mL and 0.314ng/mL, respectively, with FPANS 800μg TDS.

There are no data to suggest that the presence of nasal inflammation increases the absorption of FP. Evidence with other intranasal corticosteroids supports this finding. In this case, solubility and not permeability most likely limit absorption. Therefore, even for a more soluble intranasal corticosteroid (e.g., triamcinolone acetonide), rhinitis has been shown not to influence nasal absorption.[32]

Distribution

At steady-state, FP has a large volume of distribution of approximately 318L. Plasma protein binding is also moderately high at 91%.

Metabolism

FP is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite by the cytochrome P450 enzyme CYP3A4. Swallowed FP is also subject to extensive first-pass metabolism. There is potential for increased systemic exposure to FP when co-administering potent CYP3A4 inhibitors such as ketoconazole and ritonavir.

Excretion

The elimination rate of intravenous administered FP is characterised by a high plasma clearance of 1.1L/min. Peak plasma concentrations are reduced by approximately 98% within 3–4 hours and only low plasma concentrations were seen at the 7.8-hour terminal half-life. [33] The renal clearance of FP is negligible (<0.2%) as is that of the carboxylic acid metabolite (<5%). The major route of elimination is the excretion of FP and its metabolites in bile.

The elimination rate of intravenously administered FP is linear over a 250–1000µg dose range. The difficulty in detecting systemic concentrations of FP following intranasal dosing has prevented formal proportionality studies being performed for this route of administration.

Clinical experience

Full data are available from over 4000 patients who have received FP in open and comparative studies for seasonal AR and perennial rhinitis in adults and children. All patients with rhinitis have inflammation of the nasal mucosa. Thus, all these studies used standard assessment criteria, with minor variations only.

Efficacy evaluations included symptom assessments recorded daily by patients and at clinic visits by the investigators. The four most reported symptoms were rhinorrhoea, sneezing, nasal blockage and nasal itching. Symptoms were scored either using a four-point scale (some studies used a three-point scale for eye symptoms) or a 100mm line visual analogue scale (VAS). Efficacy was analysed in the total population of all patients randomised to treatment (i.e., the intent-to-treat population). Safety assessments were based on recordings of adverse events, and routine laboratory data and vital signs. Plasma cortisol levels were measured in

studies of FPANS in perennial rhinitis in adults and both in seasonal and perennial rhinitis in children.

As of 31 December 2002, the most current Periodic Safety Update (PSUR) for intranasal FP estimates that there have been 16.3 million patient years of exposure worldwide. (Please refer to Appendix 7 for the PSUR.)

Adverse reactions in controlled clinical studies with FPANS have been primarily associated with irritation of the nasal mucous membranes, and are consistent with those expected from application of a topical medication to an already inflamed membrane. The adverse reactions reported by patients treated with FPANS were similar to those reported by patients receiving placebo.

Global analysis of efficacy

Over 2000 adults and 350 children have been treated with FPANS for the management of seasonal AR. The patients had a history of seasonal rhinitis symptoms, specified in most studies as at least two years' duration, and a positive skin prick test with the seasonal allergen. FPANS has also been used to treat over 1200 adults and 100 children with perennial rhinitis. Patients recruited in two of the perennial rhinitis studies were selected on the basis of having had symptoms for at least two years. In the other studies, selected patients had symptoms severe enough to warrant treatment and showed a positive skin prick test with at least one perennial allergen to which they had continuous exposure.

The dosage regimens given to adults ranged from 25μg twice daily for two weeks to 800μg twice daily for four weeks but the majority of adults received 200–400μg daily administered as 200μg once daily, 100μg twice daily or 200μg twice daily. Treatment cut-offs with these doses were at 1 month, 6 weeks, 3 months, 6 months and 12 months. Children received FPANS 100μg or 200μg once daily for 2, 4 or 12 weeks.

Results and dose justification

Conclusions based on data from dose-ranging studies indicated that, in general, symptomatic improvement would not be further increased by FP doses greater than 200μg twice daily.

A once-daily dosage of FPANS 200µg has been shown to be efficacious in treating adult patients with seasonal rhinitis, and it has been proposed that in the small numbers of patients whose symptoms are not fully controlled with this regimen, 200µg twice daily should be recommended. In the relief of adult perennial rhinitis, FPANS 200µg given as a single daily dose was as effective as 100µg twice daily. Furthermore, in the year-long study, FPANS 200µg twice daily was more efficacious than BDP aqueous nasal spray (BDPANS) 200µg twice daily. In the paediatric studies, FPANS 100µg once daily was as effective as 200µg once daily for treating seasonal AR as well as perennial rhinitis.

FPANS 200µg once daily was also more effective than sodium cromoglycate nasal spray used four times daily and compliance was better with the once-daily treatment regimen. No significant differences were seen between FPANS 200µg once daily and flunisolide at 100µg twice daily. A recently published study compared the efficacy and safety of FPANS 200µg once daily with triamcinolone acetonide aerosol spray 220µg once daily in 233 patients aged 12 to 70 years in the treatment of spring AR.[34] The rhinitis index score (sum of scores of symptoms on a scale from 0 to 3) was evaluated before morning drug administration every day for 21 days. The results demonstrated that triamcinolone acetonide aerosol and FPANS were equally effective and safe. In a comparison with antihistamines, FPANS was found more effective than either terfenadine 60mg twice daily or loratadine 10mg once daily in controlling symptoms of nasal blockage and rhinorrhoea. A randomised, double blind study compared the efficacy and safety of FPANS 200µg with cetirizine 10mg once daily for the treatment of seasonal AR in 237 patients aged 12 years and above over a 21-day treatment period. Improvement in total symptom score was significantly greater in the FPANS group than in the cetirizine group. Differences favouring FPANS were also observed both in the number of symptom-free days and in the percentage of days when patients did not require terfenadine as rescue therapy. Additionally, FPANS had comparable if not better tolerability compared with cetirizine. No differences in nasal symptoms were seen between patients treated with FPANS or astemizole 10mg once daily or budesonide aqueous nasal spray 200µg twice daily.

A 1-year placebo-controlled study investigated the influence of FPANS on Langerhans' cells, T-cells, mast cells, eosinophils and macrophages in the nasal

mucosa in 42 patients with perennial AR. Efficacy was evaluated by nasal symptom score. The results demonstrated that FPANS treatment results in a decrease in nasal inflammatory cells. Furthermore, the efficacy of FPANS improves after prolonged treatment.[34]

Clinical trials have shown an improvement in ocular symptoms with the use of FPANS compared with other corticosteroids and antihistamines and with placebo or baseline.[35-39] Meta-analyses conducted by independent groups have reported corticosteroids to have equal efficacy with regard to eye symptoms.[40,41] The precise mechanism for the efficacy of FPANS in relieving ocular symptoms remains unclear, but the effectiveness of FPANS in AR has been demonstrated as a result of its topical rather than its systemic activity.[42] Furthermore, the low bioavailability of FP (<1%) means that the therapeutic effect is unlikely to be due to systemic absorption of FP.

Comparisons with other intranasal corticosteroids

In large, double-blind, randomised studies the efficacy of FP 200μg/day in relieving nasal symptoms was found to be similar to that of intranasal beclomethasone 336–400μg/day. In addition, FP 200μg/day showed similar efficacy to flunisolide 200μg/day and triamcinolone acetonide 220μg/day.

In one study, the twice daily regimen of FP appeared to confer some significant benefits over twice daily beclomethasone on patient-rated symptom scores for nasal obstruction and rhinorrhoea. Both treatments were significantly better than placebo.

In a two-centre placebo-controlled study comparing FP 200μg once daily with intranasal budesonide 128 and 250μg once daily, all regimens were shown to be significantly better than placebo at improving nasal symptoms.

2. Local data and special considerations relating to New Zealand

Local adverse events to fluticasone as reported to CARM are included in Appendix 9. During the period Dec 2000 - Jan 2003, only 12 adverse events were received with only 1 serious case. This reinforces the excellent tolerability and safety profile of this product and supports its suitability as a Pharmacy Medicine in New Zealand.

3. Safety profile of fluticasone propionate

FPANS has a very low potential to cause systemic side effects.

The safety of intranasal FP in clinical pharmacology studies was assessed by routine haematology, biochemistry and urinalysis screening tests, by monitoring HPA function and by incidence of adverse events. In studies performed to date, no clinically significant effects on laboratory safety parameters have been observed. In addition, single and repeated intranasal doses up to 4mg showed no clinically significant suppressive effect on HPA function.

Intranasal FP has been well tolerated in healthy volunteers and the overall incidence of adverse events was similar during treatment with FP, BDP and placebo. In addition, the nature of adverse events in volunteers receiving BDP and FP were consistent with adverse events reported with other nasal corticosteroids (e.g., nasal burning, nasal dryness and sneezing).

As with other nasal sprays, dryness and irritation of the nose and throat, unpleasant taste and smell, and epistaxis have been reported. Hypersensitivity reactions including skin rashes and oedema of the face or tongue have also been reported. There have also been rare reports of anaphylaxis/anaphylactic reactions and bronchospasm. Extremely rare cases of nasal septal perforation have been reported following the use of intranasal corticosteroids (Please refer to Product Information Leaflet, Appendix 6).

FP has similar properties to other topically active steroids, but in contrast to other corticosteroids, FP has extremely low oral bioavailability (<1.0%) and thus an improved therapeutic ratio.

FPANS was considered for marketing approval at the Australian Drug Evaluation Committee (ADEC) meeting dated 7–8 October 1999. The ADEC's view was that "fluticasone nasal spray was not different from the other intranasal steroids and possessed the same safety profile."
This conclusion was based on information presented from both clinical trials and post-marketing surveillance. Clinical trials showed that local effects, including nasal

irritation, throat irritation and epistaxis occurred in a small proportion of patients treated with FP nasal spray, and there were several reports of unpleasant taste or smell. There was no significant difference in the incidence of these adverse events in patients treated with FP nasal spray compared to BDP nasal spray.

Post-marketing experience in Australia and New Zealand has confirmed that intranasal FP does not pose any safety concerns different to those corticosteroids currently included as Pharmacy Medicine products.

The most frequently reported adverse reactions (>1% in any treatment group) considered by the investigator to be potentially related to FPANS or placebo in trials of seasonal AR are listed below. These studies were conducted in 948 adults and in 499 children and evaluated 14–28 days of treatment with recommended doses of FPANS compared with placebo.

Table 2. Adverse reactions reported most frequently in clinical trials of seasonal AR.

	Adults (age ≥12 years)			**Children (age 4–11 years)**		
	FPANS 100μg b.i.d. (n=312) (%)	FPANS 200μg once daily (n=322) (%)	Placebo (n=314) (%)	FPANS 100 μg once daily (n=167) (%)	FPANS 200 μg od (n=164) (%)	Placebo (n=168) (%)
Nasal burning	2.2	3.4	2.5	1.8	2.4	1.2
Pharyngitis	1.3	1.6	<1	<1	0	0
Runny nose	<1	1.6	<1	<1	<1	<1
Blood in nasal mucus	0	1.6	<1	0	<1	0
Epistaxis	1.6	2.8	2.2	3.0	3.7	3.6
Sneezing	<1	1.2	2.2	0	<1	0
Crusting in nostrils	0	0	0	1.2	0	0
Nasal congestion	0	0	0	0	1.2	0
Nasal ulcer	<1	0	0	1.2	1.2	1.2
Headache	1.3	2.5	1.9	1.2	1.2	1.2

In two 6-month trials involving 831 patients with perennial AR aged 12–75 years, the adverse reactions reported by patients treated with FPANS were similar in type and incidence to those reported in seasonal trials, with the exception of epistaxis (≤13.3%) and blood in nasal mucous (≤8.3%). In addition to the events reported most frequently in the seasonal trials, patients receiving FPANS in the 6-month trials reported nasal soreness (≤2.5%), nasal excoriation (≤2.0%), sinusitis (≤1.6%) and nasal dryness (≤1.3%).

Infrequent adverse reactions (incidence of 0.1%–1% and >placebo) reported by patients receiving FPANS at the recommended daily dose of 200μg (or 100μg per day for children 4–11 years of age) in the aforementioned clinical trials included pharyngeal irritation, nasal stinging, nausea and vomiting, unpleasant smell and

taste, and sinus headache (0.3%); lacrimation, eye irritation, xerostomia, cough, urticaria, and rash (0.2%); and nasal septum perforation (0.1%).

Post-marketing surveillance

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of FP in clinical practice.

- General: Hypersensitivity reactions, including angioedema, skin rash, oedema of the face or tongue, pruritus, wheezing, dyspnea, and rarely, bronchospasm and anaphylaxis/anaphylactic reactions.
- Ear, nose and throat: Alteration or loss in sense of taste and/or smell, sore throat, throat irritation and dryness, hoarseness, and voice changes.
- Eye: Dryness and irritation of the eyes, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.

Contraindications

FPANS is contraindicated in patients with a history of hypersensitivity to any of its components.

Infections of the nasal passages and paranasal sinuses should be appropriately treated but do not constitute a specific contraindication to treatment with intranasal FP.

4. Risk of misuse

Potential for abuse or misuse

Up to 31 December 2002, there were no reported cases of abuse, or of symptoms suggestive of recreational use (e.g., euphoria and hallucinations), with intranasal FP. It has a low potential for harm from inappropriate use because of the inherent characteristics of the active ingredient combined with the dosage form and administration method of the product.

FP has a low oral bioavailability, therefore the swallowed portion of an intranasal dose does not produce detectable systemic levels or unwanted interactions with oral antihistamines and intranasal decongestants.

Overdosage

There are no data available on the effects of acute or chronic overdosage with FPANS. There have been a small number of reports of overdose with intranasal FP, mainly from consumers, but these reports do not give any cause for concern.

Drug interactions

Up to 31 December 2002, eleven reports were received of possible drug interactions with intranasal or unknown formulations of FP.

FP is metabolised by the cytochrome P450 isoenzyme CYP3A4 to an inactive carboxylic acid (GR36264, the major metabolite) and 6-hydroxy-FP (a minor metabolite). Investigations into potential drug interactions of FP with known inhibitors or substrates of CYP3A4 (terfenadine, erythromycin, ketoconazole and ritonavir) have been reported.

Potential for development of drug resistance

Nil.

PART B2: BDPANS — Reasons for requesting classification change

1. Product overview

Pharmacological properties

The exact mechanism of action of corticosteroids is not well understood but probably involves reductions in the numbers of mediator cells, such as mast cells, and reduction in the sensitivity of sensory nerve cells to mechanical stimuli. Other mechanisms may involve inhibition of capillary dilation and permeability, the stabilisation of lysosomal enzymes and the subsequent prevention of release of proteolytic enzymes. In addition, topical steroids, such as BDP, have been shown to suppress the production of pro-inflammatory cytokines, such as interleukin (IL)-1β anf granulocyte/macrophage colony stimulating factor (GM-CSF).[43]

After topical application to the nasal mucosa, BDP produces potent anti-inflammatory and vasoconstrictor effects. The anti-inflammatory effect of topical BDP, as measured by vasoconstrictor assay test, is about 5000 times greater than that of hydrocortisone, 500 times greater than beclomethasone, betamethasone or dexamethasone, and about five times greater than fluocinolone.[43]

Pharmacokinetics

Absorption

BDP is readily absorbed from the respiratory and gastrointestinal tracts. Following nasal administration, a portion of the drug is swallowed. Orally administered BDP is readily absorbed and undergoes extensive first-pass metabolism in the liver and the gastrointestinal tract. In addition, a portion of the drug that enters the bronchial tree may undergo hydrolysis in the respiratory tract. Attempts have been made to determine the rate of absorption following nasal administration of BDP. After a 200μg dose, BDP could not be detected in plasma samples up to 8 hours after dosing at an assay LLOQ of 200 pg/mL. These samples did not contain quantifiable amounts of total monopropionates (LLOQ: 200 pg/mL) although a semi-quantitative estimate for

monopropionates (17-BMP and 21-BMP combined) was possible in some subjects shortly after dosing. This was in the range of 100-200pg/mL.[43]

These data demonstrate that the extent of absorption of BDP is low. A correlation between plasma BDP concentrations and therapeutic effects has not been described for BDP; it is thought that systemically absorbed drug contributes little to the effect of the drug on the nasal mucosa. High lipophilicity has important implications for the way in which corticosteroids are taken up and retained in lung tissue. A clear correlation between lipophilicity and binding to lung tissue has been observed, with the more lipophilic compounds (such as BDP) exhibiting more rapid and greater binding activity than more hydrophilic compounds such as budesonide, flunisolide and hydrocortisone.[43] The findings suggest that the more lipophilic corticosteroids, such as BDP, may be deposited at 'micro-depots' on the airway mucosa, thereby prolonging the duration of action of their local anti-inflammatory effects.

When administered by the oral route, the bioavailability of BDP has been reported as less than 20%.[43] When given by the inhaled route, BDP has approximately the same degree of bioavailability (<20%) as when administered orally. No studies have been undertaken to assess the bioavailability of BDP following intranasal administration.

Distribution

BDP is not widely distributed into tissues following intramuscular or subcutaneous administration, and distribution of BDP following intranasal administration has not been described. However, the distribution of 1mg of inhaled FP, a similar glucocorticoid to BDP, at up to 6.5 hours after administration showed high concentrations in lung tissue and low concentrations in plasma; indeed the lung: plasma FP ratios ranged from 70:1 to 165:1.[43]

It is not known whether BDP crosses the placenta in humans. Teratogenic and embryocidal effects have been seen in animals following subcutaneous administration, but not after oral administration or inhalation. It is not known if BDP is distributed into milk; however, other corticosteroids are.

Metabolism

Recent work suggests that BDP should be regarded as a prodrug since it is hydrolysed in the lung to the much more active 17-monopropionate ester (17-BMP). The monopropionate ester (17-BMP) is then transesterified to the inactive 21-monopropionate ester (21-BMP), which is in turn hydrolysed to beclomethasone.

Excretion

The plasma half-life of BDP following nasal administration cannot be determined because of the lack of sufficiently sensitive assay methods. In a volunteer study of intranasal BDP 200μg,[43] BDP was not detectable in either plasma (assay sensitivity: 100pg/mL) or urine (assay sensitivity: 1ng/mL). Following intravenous administration of 1mg BDP, the plasma half-life of BDP was found to be 30 minutes. BDP monopropionates were present at a much higher concentration than BDP following intravenous dosing but were eliminated at a similar rate to the parent compound.

The excretory fate of BDP and its metabolites following intranasal administration have not been described. However, following intravenous or oral administration, the drug and its metabolites are excreted mainly in the faeces via biliary elimination and to a lesser extent in urine. Following oral administration, approximately 12–15% of a 4mg dose of BDP is excreted as free and unconjugated metabolites.

There is no evidence of tissue storage of BDP or its metabolites.

Clinical experience

Considerable data supporting the efficacy of BDP in the treatment of SAR and PR are available. BDP has been available for the treatment of SAR as a metered-dose pressurized aerosol (nasal spray) since 1974 and as an aqueous nasal spray since 1983. BDPANS was the first formulation of BDP approved for the treatment of SAR and PR. A 400μg daily dose (50μg/spray, two sprays in each nostril twice daily) from the nasal spray has been shown to provide significantly better control of seasonal rhinitis than placebo.[43]

In addition to these studies, BDPANS has also been evaluated over the past 20 years in 79 published clinical trials involving over 5400 patients with either SAR or PR. These trials varied in length from 1 week to 6 years. Between 52–100% of all patients achieved good to excellent control of nasal symptoms with 336–400μg/day.[43]

Comparative studies of the inhalation aerosol (nasal spray) and aqueous preparation in SAR in adults and children have shown equivalent efficacy of the two formulations.[43] One or two doses (50μg or 100μg) of either BDPANS or inhalation aerosol (nasal spray) used in each nostril twice daily for the management of SAR and PR are well tolerated in patients ≥6 years of age. Although both dosage forms are equally effective, most patients prefer the aqueous spray, because the force of the inhalation aerosol (nasal spray) may be uncomfortable, irritating and dry to the nasal mucosa.[43]

BDPANS has also been evaluated in 15 published clinical trials involving over 1500 patients with either seasonal AR or perennial rhinitis. BDPANS has proven to be superior in efficacy to placebo, and has shown equivalent efficacy to Beconase Nasal Spray in these published studies.

Global analysis of efficacy

The nature of rhinitis is such that no reproducible, objective measurement of efficacy can be made. Assessment of efficacy relies more on subjective methods and usually involves some kind of symptom scoring. In the studies presented in this submission, two methods of symptom scoring have been used. The four- or five-point symptom score and the visual analogue scale have both been well tested and widely accepted as reasonable methods of assessing disease severity and treatment efficacy in seasonal rhinitis. In the studies in this submission, the two methods gave similar trends of results.

Results

The results of clinical studies in over 1900 patients with seasonal AR and an additional 1500 patients with perennial rhinitis have demonstrated that BDPANS is significantly superior to placebo in terms of effectiveness. BDP has also been shown to provide equivalent efficacy to other intranasal corticosteroids in the treatment of the symptoms of rhinitis, which include nasal itching, sneezing, nasal obstruction,

and rhinorrhoea. Ocular symptoms have also been shown to correlate well with objective nasal cytology findings and nasal rhinomanometry measurements. The wealth of data from clinical trials and the published literature, as well as the availability of the prescription product for over 20 years is supportive of the efficacy of the product.

Dosage justification

In the majority of clinical trials, BDPANS was given at a dosage of 336μg daily in the US and 400μg daily in the rest of the world. In Australia and New Zealand, the product has been approved since 1974 as a prescription-only medication at a dosage of 400μg daily. This same dosage has also been reclassified to a general sales classification in New Zealand since 1997 and to a Pharmacy Medicine in Australia since 1999. Based on the ample safety and efficacy data of the prescription product, the recommended dosage for over-the-counter use is 400μg daily, administered as two 50μg sprays in each nostril twice daily.

Comparisons with other intranasal corticosteroids

In large double-blind randomised studies, the efficacy of FP 200μg/day in relieving nasal symptoms was found to be similar to that of intranasal beclomethasone 336–400μg/day. In addition, FP 200μg/day showed similar efficacy to flunisolide 200μg/day and triamcinolone acetonide 220μg/day.

In one study the twice daily regimen of FP appeared to confer some significant benefits over twice daily beclomethasone on patient-rated symptom scores for nasal obstruction and rhinorrhoea. Both treatments were significantly better than placebo.

2. Local data and special considerations relating to New Zealand

Beclomethasone Nasal Spray has been available in New Zealand for over a 25 years. Local adverse events to beclomethasone as reported to CARM are included in Appendix 9. During the period Mar 1990 - Jan 2003, only 12 adverse events were received with 1 reported death.

3. Safety profile of beclomethasone dipropionate

Since first launch in 1974 and 1983, respectively, there have been 29 years of post-marketing experience with BDP nasal inhaler and 20 years of experience with BDPANS. During this time, approximately 1763 spontaneous adverse event reports have been received worldwide by GlaxoSmithKline. Comprehensive review of these data has confirmed the safety profile and has not identified any new potential safety signals. From the sales figures for the last 6 years, the market exposure to intranasal BDP can be estimated to be over 8 million patient years and hence the total patient exposure is probably in the region of 20 to 30 million patient years. Thus, with a conservative estimate of 20 million patient years of exposure and a total of 1763 adverse events, the reporting rate has been in the region of 1 in 11,000 patient years.

Two international BDP safety updates covering the periods from launch to January 1995 and from February 1995 to January 1998 are enclosed as Appendix 3. This low incidence of spontaneous adverse event reporting is reflected in the local Australian market and is verified by the ADRAC report for BDP covering the last 16 years. (Please refer to Appendix 8 for the ADRAC report.)

Summary of spontaneous adverse event reports

The majority of events reported with intranasal BDP were not clinically serious and were reversible on discontinuing therapy.[43] The most common events were:

- local nasal symptoms such as epistaxis, irritation, itching, sneezing, burning, congestion and dryness
- mild hypersensitivity-type reactions, mainly skin rash and oedema of the eyes, face and lips
- headache
- dizziness
- disorders of taste and smell.

A maximum (depending on the criteria used) of 140 of the 1763 reports (8%) were regarded as serious; 40 reports (2%) fulfilled CIOMS I criteria for expedited reporting to regulatory authorities.[43] Only four patients died. One death occurred following an overdose of approximately 200 doses of BDP nasal inhaler and 100 doses of

salbutamol inhaler (given via the nose); post-mortem concluded that salbutamol-induced acute circulatory collapse was the most likely cause of death and that BDP did not contribute. The second death involved a patient who suddenly developed *Haemophilus influenzae* meningitis; there was, however, no record of whether she had actually taken BDP. In the third case, the patient developed a duodenal ulcer and later died; cause of death was not stated although the patient had a history of cirrhosis, oesophageal varices and hepatitis. The cause of death in the final report was stated as myocardial infarction (MI); this case involved a patient with a 19-year history of diabetes who was awaiting heart transplant following an earlier MI. Thus there appears to be no causal relationship between BDP use and any of the four fatal events.

Other clinically serious events of interest with respect to non-prescription use of a drug are severe hypersensitivity reactions and, in the case of a corticosteroid, systemic effects. Intranasal BDP is contra-indicated in patients with a history of hypersensitivity to any of its components. Approximately 10% of all spontaneously reported adverse events are suggestive of hypersensitivity reactions. The majority of these are skin reactions, although in some cases oedema or puffiness of the lips, eyes or face were also noted. However, the relationship of all of these reactions to use of intranasal BDP is difficult to assess in a population that is typically atopic and prone to conditions such as AR, asthma, eczema, and food or environmental allergies.

In a number of cases, concomitant medications appear to be a more likely cause of the reaction, or the time to onset is inappropriately long (months or years) for a causal relationship.[43] Allergic reactions to the preservatives in the aqueous nasal spray (phenylethyl alcohol and benzalkonium chloride) may occur very rarely. More severe hypersensitivity reactions with systemic manifestations are extremely rare and no fatal anaphylactic-type reactions have been reported. Thus, true allergic reactions to BDPANS are likely to be rare and usually mild and transient.

There are many known effects that occur following systemic exposure to corticosteroids. However, in view of the minimal absorption of BDP into the systemic circulation following intranasal administration the potential for these side effects is very low when the product is taken in recommended doses. However, as stated in the data sheet for BDP, systemic effects may occur in cases of excessive dosage, in sensitive individuals, or in patients who have recently received systemic

corticosteroids. These statements are supported by review of spontaneous data. Specifically, review of all possible cases of Cushing's syndrome or of HPA-axis suppression found that in every instance a causal association with intranasal BDP could not be established for one or more of the following reasons:

- atypical or inadequately described symptoms
- concurrent administration of inhaled or oral corticosteroids
- lack of endocrine studies to support diagnosis
- reporter considered that events were unrelated to BDP
- alternative diagnosis
- limited data.

There was also a tendency for symptoms to occur after using intranasal BDP for a period of months or years. Thus, only isolated cases provide possible evidence for occurrence of adrenal suppression or Cushing's syndrome following sole treatment with intranasal BDP.

In addition to the above cases, there are reports which describe single events that might be associated with systemic exposure to BDP.[43] These include reports of cataract, glaucoma, hyperglycaemia, weight gain, skin thinning, bruising, acne, hirsutism, menstrual disturbances, psychosis, aseptic necrosis of bone, osteoporosis, myopathy and infections. For all of these events, there are only occasional cases which are not confounded by one or more of the factors described above in the discussion of Cushing's syndrome and HPA suppression. Again, these effects tend to occur following long-term use of the drug. Only 4 reports of growth suppression in children have been received; these also provide little evidence for an effect of intranasal BDP.[43] The Boston Collaborative Drug Surveillance Program has recently conducted two studies using data from the General Practice Research Database (GPRD) in the UK. In the first study, which was primarily one of drug utilisation patterns, the frequency of physician-recorded diagnoses of growth retardation before and after treatment with intranasal BDP was compared and no signal for growth suppression identified. In conclusion, intranasal BDP is unlikely to result in systemic effects if administered in recommended doses for relatively short periods.

The low potential for serious adverse events noted in spontaneous reporting was confirmed in the second Boston Collaborative Drug Surveillance Program study,

which analysed data on over 70,000 non-asthmatic patients who had received a prescription for intranasal BDP. No difference was found in the frequency of hospitalisations or referrals to consultant specialists for certain specified disorders (gastrointestinal, neuropsychiatric, blood, skin, liver and renal conditions, or infectious diseases) before and after use of BDP.

Potentially serious local effects such as nasal septal perforation (NSP) and mucosal atrophy are more commonly associated with aerosol than aqueous spray formulations of corticosteroids, possibly due to the higher speed of drug delivery with the nasal spray. Spontaneous data reveals a low reporting rate of NSP with BDPANS.

Administration of intranasal BDP in large enough doses can theoretically result in HPA-axis suppression, but no unexpected effects have been observed. Data from the American Association of Poison Control Centres (AAPCC), the Drug Abuse Warning Network (DAWN) and the first of the Boston Collaborative Drug Surveillance Program studies also confirm low potential for BDP to be abused or taken in intentional overdose. Other types of misuse of intranasal BDP are very rare and include occasional accidental or intentional administration to the eye, ear or mouth.

Although BDP is not intended for use in children under 12 years of age, its safety in this population is of importance in the context of accidental or intentional overdose by children. Review of events reported in children reveals no safety issues specific to this group of patients. Similarly, there is no evidence of any difference in safety profile between patients over 65 years of age and younger adults.

As with all drugs, administration of intranasal BDP during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. However, in the context of OTC use, it is inevitable that the product will be administered to women of child-bearing potential who unexpectedly become pregnant. For this reason, safety following inadvertent first-trimester exposure is of considerable importance. Information on safety during pregnancy is anecdotal, but the spontaneous cases received do not suggest that intranasal BDP is associated with congenital abnormalities. In most of the reports there were alternative causes for the anomaly or the period of BDP administration appeared inappropriate for a drug-induced effect. Systemic exposure is minimal after intranasal administration of BDP,

hence there is only a very low risk of effects following administration to pregnant or lactating females.

BDPANS has been available for OTC use in the UK since February 1994 as Beconase Hayfever. The Company has received only 16 spontaneous adverse event reports specifically with the OTC presentation and sales of the product represent approximately 98,000 patient years of exposure. Thus the reporting rate is in the region of 1 in 6,000 patient years. BDPANS has been available as an OTC product in Australia for 3 years and New Zealand for 6 years. During this time, adverse events have been minor events, which resolved on reduction of dose or withdrawal of the medication. The events were mainly lack of efficacy or known local side-effects such as nasal irritation, taste and smell disorders, or epistaxis. Some of the other non-specific symptoms reported such as dizziness, drowsiness and pain may also be due to underlying medical conditions or to concomitant drugs. Thus the experience to date with OTC preparations of intranasal BDP does not highlight any new or unexpected side effects.

In conclusion, the safety profile of BDP aqueous nasal spray fulfils all the criteria for a product suitable for classification as a Pharmacist Medicine. The majority of adverse reactions are mild, transient local effects, minimal systemic absorption ensuring a low incidence of more serious events. There is a low potential for abuse or for interactions with concomitant medications and no interference with tasks such as driving or operating machinery.

Summary of adverse events from published literature

The incidence of adverse events with nasally inhaled corticosteroids has been shown to be lower than that experienced by patients on oral systemic steroid therapy. However, systemic effects with nasally inhaled corticosteroids have been reported. Because of the possibility of systemic absorption of nasally inhaled corticosteroids, symptoms of systemic effects of corticosteroids are important in a population of patients on inhaled corticosteroid therapy. A list of specific systemic events noted in patients on systemic steroid therapy is presented here:

Cardiovascular: hypertension
Psychiatric, and central and peripheral nervous system: CNS stimulation, psychoses
Gastrointestinal: blood in stools
Musculoskeletal: myalgia, bone fractures

Metabolic/nutritional: hyperglycaemia, weight gain, Cushingoid findings, hyperlipidaemia, Addison's disease
Vision: eye pain, cataracts, increased intraocular pressure
Reproductive (female): intermenstrual bleeding
Urogenital: glycosuria

A total of 185 references investigating BDP in the treatment of seasonal rhinitis were reviewed, with special emphasis on the events listed above. Seventy-eight (42.2%) contained specific information related to adverse events and BDP use.[43]

Cardiovascular disorders
No adverse events describing cardiovascular problems were reported.

Central and peripheral nervous system disorders
No adverse events describing psychiatric, or central or peripheral nervous system problems were reported.

Gastrointestinal disorders
No adverse events describing gastrointestinal problems were reported.

Haematological/biochemical disorders
One placebo-controlled trial in 30 adult patients treated with 400μg/day intranasal BDP for 3 weeks showed no change in the levels of circulating blood eosinophils. Two placebo-controlled trials and one comparator trial reported no significant change in haematological or biochemical laboratory analyses during the course of the studies. In these trials, 30 and 148 patients, respectively, received treatment with intranasal aqueous or aerosolized BDP in doses of 336–400μg/day over a period of 2–4 weeks.

Musculoskeletal disorders
One comparator trial in 39 paediatric patients revealed that a 2-month course of BDP aerosol with doses of 200–400μg/day exerted no effect on serum markers of bone metabolism.

Metabolic/nutritional disorders

Ten randomized, placebo-controlled studies of 18 to 351 patients treated with intranasal aqueous or aerosolized BDP at doses ≤800μg/day (most patients received 336–400μg/day) for up to 9 weeks showed no effect on the HPA axis as measured by serum cortisol and adrenocorticotropic hormone (ACTH) stimulation testing.
In addition, two uncontrolled studies reported no evidence of adrenal suppression at doses similar to those used in the studies described immediately above.
Available review articles did not comment on significant HPA-axis suppression.

Visual disorders

No adverse events describing visual problems were reported.

Reproductive disorders

No adverse events describing female reproductive problems were reported.

Urogenital Disorders

No adverse events describing urogenital problems were reported.

Long-term use

A comprehensive review of more than 200 studies revealed that even during prolonged treatment, no significant systemic side effects have occurred with the use of therapeutic dosages of BDP.[44] Safety for long-term use has been demonstrated in studies in PAR where patients have used BDP up to 400μg daily for durations of 9 months to 6 years.

This review[44] stated that one of the most comprehensive follow-up studies of intranasal BDP involved 87 patients treated for perennial rhinitis over periods of 1–6 years (mean: 5 years). During the course of this study, 23 randomly selected patients underwent mucosal biopsies and 16 received plasma cortisol tests to determine if any changes had occurred in these two parameters as a result of long-term BDP therapy. The investigators reported that no mucosal atrophy was seen in any of the patients' biopsies. No suppression of plasma cortisol level occurred. These findings are of particular significance, as patients suffering from rhinitis are likely to remain on extended therapy in order to obtain long-term relief of their symptoms. The authors noted that "mucosal changes revealed by the biopsies were of the same order before

and after beclomethasone therapy and they were apparently due to prolonged chronic rhinitis."

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 reported occasionally. There have been rare reports of headache and rare cases of raised intraocular pressure or glaucoma. Hypersensitivity reactions including rashes, urticaria, pruritus, erythema, and oedema of the eyes, face, lips and throat have also been reported.

During the three-year period from 1 February 1995 to 31 January 1998, GlaxoSmithKline received a total of 481 spontaneous adverse event reports from worldwide sources in association with intranasal formulations of BDP. There have been no serious, attributable adverse reports from clinical trials during this period.

In summary, the spontaneous reports received in the last 3 years confirm the known safety profile of intranasal BDP and reveal no new safety signals.

Contraindications

BECONASE Hayfever™ is contraindicated in patients with a history of hypersensitivity to any of its components. Infections of the nasal passages and paranasal sinuses should be appropriately treated but do not constitute a specific contraindication to treatment with intranasal BDP.

4. Risk of misuse

Potential for abuse or misuse

Up to January 1998, one report was received in which abuse of BDP was considered as an adverse event. However, the physician, who described the events as worsening of allergies unrelated to BDP, did not confirm the report. BDP has a low potential for harm from inappropriate use because of a combination of the inherent characteristics of the active ingredient and the dosage form and administration method of the product.

BDP has low oral bioavailability, so the swallowed portion of an intranasal dose does not produce detectable systemic levels or any unwanted interactions with oral antihistamines or intranasal decongestants.

Overdose

There have been 14 spontaneous cases of overdose associated with intranasal formulations of BDP, representing less than 1% of all reports. Review of these cases reveals no consistency or trend in terms of dose–response affecting a particular body system or specific adverse events following the administration of higher doses. The most common event reported in association with overdose was headache, which was reported on three occasions. Epistaxis was reported on two occasions and both cases resolved uneventfully following discontinuation of BDP. One report of mania was received; however, this patient was diagnosed with a cerebral infarct. An additional report of psychosis was received in a patient with pre-existing schizophrenia.

A 12-year old male reportedly self-administered 200 doses of BDP and 100 doses of salbutamol over a 10-minute period and died. The reporting physician considered the overdose of salbutamol as the cause of death.

Consideration of the remaining adverse events reported in association with overdose (i.e., hyperactivity, lack of efficacy, local burning, hypothyroidism [unrelated to BDP], conjunctival scarring [patient inadvertently sprayed the nasal inhaler formulation into the eye], and throat constriction) confirm the lack of a dose–response relating to any body system or specific event. Additionally, review of these events reveals no differences in comparison with the overall spontaneous adverse-event database.

Drug interactions

There have been 11 reports of drug interaction in association with intranasal BDP. Alcohol was the most commonly implicated interacting substance, occurring in five separate reports. Three of these reports were received during legal proceedings following arrest for operating a motor vehicle under the influence of alcohol. Another report involved a male who had ingested alcohol and marijuana concomitantly with

BDP and experienced syncope. The final such case occurred in a patient who experienced chest pain after the ingestion of alcohol. There is no pharmacological basis for an interaction between BDP and alcohol.

Two events were reported as interactions with antibiotics. One patient reported tongue discolouration after administering either erythromycin or penicillin and the second patient reported urticaria following four doses of penicillin.

The remaining four cases were as follows: changes in menstrual cycle in a patient receiving concomitant oral contraceptive; myopathy in a patient receiving concomitant prednisone 20mg/day; muscle pain in a patient receiving concomitant ranitidine; and a patient with a history of seizures and non-compliance with medication, concomitantly receiving valproate, carbamazepine and trimipramine, who experienced increased seizure activity.

Review of these data fails to reveal evidence of a drug interaction between BDP and concomitant prescription medications, including other formulations of corticosteroids and other anti-allergy preparations.

Potential for development of drug resistance

Nil.

Conclusions

Allergic rhinitis is much more than just having a blocked or runny nose. It is associated with impairments in how people function in their everyday lives and can create difficulties at work or school.[24] Effective management of AR can therefore have a significant effect on quality of life and work performance.[24]

AR (seasonal and non-seasonal) is a common condition, affecting an estimated 10% to 15% of the population. 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. It is a recurring yet self-limiting disorder, which requires no special investigations, and is unlikely to mask a more serious underlying disease.

In the management of AR allergen avoidance is clearly the best strategy, but this is rarely practical. If avoidance fails then pharmacotherapy is the next step. It is now widely established that intranasal corticosteroids provide more complete symptom control than do any other class of medications.[1,2] Moreover, because intranasal corticosteroids have lower average wholesale prices than non-sedating antihistamines, they offer clinical superiority in conjunction with a lower cost per treatment day.[13]

1. Fluticasone propionate

FPANS has been available as a Restricted Medicine in New Zealand since June 2000. It was approved for registration in Australia on 13th January 2000, as a Schedule 4 product, it was rescheduled to Restricted Medicine status in November of 2000 and launched as a Pharmacist Only Medicine in July 2002.

The safety of FP in the treatment of AR has been assessed by studying adverse events and laboratory data from over 4000 patients who have received the nasal spray during studies in rhinitis. In addition, data are available from over 100 healthy volunteers who received the nasal spray in clinical pharmacology studies. There were no clinically significant trends in laboratory data and no evidence of HPA axis

suppression even at high doses. Animal studies and adverse-event reporting from studies with FP in other indications support this impression of overall safety.

Comparative data from controlled studies suggested that minor events such as headache, which was reported relatively frequently, were of similar incidence in all treatment groups. Epistaxis was reported at a higher rate in both steroid treatment groups (FP and BDP) compared with placebo. It is known to be a symptom of rhinitis and is more common when treatment with intranasal steroids is given. However, the incidence of new cases was constant throughout the long-term studies. A warning of the possible occurrence of epistaxis with use of intranasal FP is contained in the Product Information Leaflet. Other adverse reactions such as slight irritation or stinging, mainly related to the use of a nasal spray, are also identified in the Product Information Leaflet.

The only definitive contraindication is that of hypersensitivity to corticosteroids or any excipient contained in the spray. Warnings and precautions relate to care when replacing a systemic corticosteroid therapy with a nasal spray without systemic effects, which may result in adrenal insufficiency if the HPA axis had been suppressed previously.

There have been several reports of possible overdosage, but these did not give rise to serious consequences. High intranasal doses given to volunteers for seven days were well tolerated, as were oral doses of up to 20mg. It is possible that extremely high doses could suppress HPA axis function and care would then be required until this had returned to normal.

Use during pregnancy and lactation has generally been avoided. However, systemic exposure after intranasal administration is negligible and therefore adverse effects during pregnancy are unlikely. Nevertheless, as with all drugs, use during pregnancy should be avoided whenever possible and should be dictated by the needs of the patient versus the risk of the foetus. There is no information on excretion via breast milk but in view of its pharmacokinetic profile, transfer of FP in milk is unlikely.

One report has been received of a possible drug interaction with a selective serotonin re-uptake inhibitor (SSRI). There have also been ten reports of possible drug interactions with isolated drugs such as alcohol, naphazoline, sumatriptan and bendrofluazide; however, none of these reports gave cause for concern. The

theoretical potential for an interaction between high-dose FP and certain other drugs metabolised through the same liver enzyme system is addressed under "Pharmacokinetics" (Page 34).

Assuming a dose of 200μg/day, it can be estimated from worldwide volume sales that there have been at least 16.3 million patient years of exposure to intranasal FPANS from launch in 1991 until 31 December 2002. During this time, approximately 1628 spontaneous reports have been received involving intranasal or unknown formulations of FP, suggesting a favourable safety profile for FPANS. Moreover, intranasal FP lacks the important adverse effects and/or drug interactions commonly found with the oral antihistamines and intranasal decongestants that are currently marketed as Pharmacy Medicines for the prevention and treatment of AR. The safety data collated from exposure to intranasal FP worldwide (16.3 million patient years), coupled with local experience, provides sufficient product exposure to support rescheduling to Pharmacy Medicine.

Rescheduling of FPANS to Pharmacy Medicine status would offer the consumer another choice of a safe, effective, once-daily medicine for the prevention and treatment of AR. FPANS would be more accessible to the general community, but its Pharmacy Medicine status would allow appropriate counselling to ensure its proper use.

The other intranasal corticosteroids currently available on the Australian market, such as beclomethasone, budesonide and mometasone have recently been recommended for rescheduling to Pharmacy Medicine status. Given the similarity in safety and efficacy profiles to the other intranasal corticosteroids, it is appropriate that FP is also considered for rescheduling to Pharmacy Medicine status.

2. Beclomethasone dipropionate

BDP 400μg/day is efficacious in the treatment of seasonal AR and is well tolerated by patients.

Efficacy has been proven in controlled clinical trials described in this report, as well as a large number of other trials reported in the literature. BDP has been available for

the treatment of seasonal rhinitis as a metered-dose pressurized aerosol since 1974 and as an aqueous nasal spray since 1983. A 400μg daily dose (50μg/spray, two sprays in each nostril twice daily) has been shown to provide significantly better control of seasonal rhinitis than placebo, and this dosage has shown equivalent or superior efficacy to other comparator regimens.

The safety of the aqueous nasal spray has been assessed by studying the adverse events and laboratory data from a large number of patients in clinical trials as well as a review of the spontaneous adverse event data reported from world-wide usage of the prescription product and a review of the medical literature. Controlled clinical trials with BDPANS have shown that it was well-tolerated and safe to use in the treatment of seasonal AR.

The most common adverse events have been primarily associated with minor irritation of the nasal mucous membranes, expected events that are commonplace with the use of nasal sprays. There were no clinically important trends in the laboratory data and no evidence of HPA-axis suppression at the dosage recommended for OTC usage. The spontaneous adverse event data as well as the medical literature support the adverse event profile elucidated from clinical trials.

The recommended dosage of over-the counter BDPANS is 400μg daily, given as two 50μg sprays per nostril twice daily. This dosage is recommended for all patients 12 years of age or older. The efficacy and safety of this dosage has been supported by controlled clinical trials and in general clinical practice over the past two decades. This dosage is the same as that currently recommended for the prescription product.

It is essential that any therapy for AR have a very low risk since the disease itself cannot generally be considered serious or life threatening. In this respect, BDPANS compares favourably with other topical corticosteroids and with alternatives such as decongestants, antihistamines and sodium cromoglycate. BDP administered intranasally has the advantage of dosing directly at the site of therapeutic action. Its efficacy has been clearly demonstrated and the risk of systemic activity at the recommended dosage is negligible.

From world-wide sales figures for the last 6 years, the market exposure to intranasal BDP can be estimated to be over 8 million patient years and hence the total patient

exposure is probably in the region of 20 to 30 million patient years. Thus, with a conservative estimate of 20 million patient years of exposure and a total of 1763 adverse events, the reporting rate has been in the region of 1 in 11,000 patient years. Over the past 21 years, BDPANS has been widely utilised in over 30 countries with over 10 million patient years exposure. During this time, BDPANS has been shown to be extremely safe for use in the treatment of seasonal and perennial rhinitis.

Allergic rhinitis is easily self-diagnosed by its characteristic nasal symptoms and its recurring nature. While there are periods of acute exacerbation, AR is a self-limiting disorder, which does not require special investigation and is unlikely to mask a more sinister underlying disease. Indeed, it can be argued that the extensive range of antihistamines and decongestants which have been freely marketed direct to consumers for many years worldwide reinforce the opinion that the condition is appropriate for self-diagnosis.

Beclomethasone dipropionate and fluticasone propionate aqueous nasal sprays satisfy all the MCC criteria for classification as Pharmacy Medicines.

With appropriate labelling amendments, and the option of professional intervention, the approval of BDP as a Pharmacy Medicine will allow sufferers easier access to this efficacious, safe, cost-effective product for prevention and treatment of their symptoms. Limiting supply to pharmacies will allow counseling to ensure appropriate use.

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Appendices

1. Draft performance-based labelling for fluticasone propionate and beclomethasone dipropionate

2. Extract from the minutes of the November 2000 meeting of the New Zealand Medicines Classification Committee

3. International Safety Updates for intranasal beclomethasone dipropionate. 01 February 1995 – 31 January 1998

4. This Appendix is Intentionally Blank.

5. Patient Information leaflets for fluticasone propionate and beclomethasone dipropionate

6. Approved Product Information for fluticasone propionate

7. Periodic Safety Update for Intranasal fluticasone propionate Aqueous Nasal Spray (1990-2003)

8. ADRAC report for beclomethasone dipropionate (1974–2002)

9. CARM report for fluticasone propionate and beclomethasone dipropionate (1990–2003)