Responses to consultation ARM 83 on Pirinase Hayfever Relief for Adults 0.05% Nasal Spray P to GSL reclassification

Copies of responses to ARM 83 consultation are attached and can be found at the page numbers listed below. Responses with no comment are not included.

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From The Registrar
[redacted]

[redacted]
Reclassification Unit
MHRA
3-M
151 Buckingham Palace Road
London
SW1W 9SZ
By email: reclassification@mhra.gsi.gov.uk

1 February 2013

Dear [redacted]

Re: ARM 83 Pirinase hayfever relief for adults 0.05% nasal spray

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 27,500 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The RCP is grateful for the opportunity to comment on the above consultation. Overall, our experts believe that the reclassification is uncontroversial. However, there are some concerns that the name of the product might cause confusion amongst some members of the public. This is because it is very similar to an anti-histamine product. We therefore raise this from a patient safety perspective.

Yours sincerely

[redacted]
Registrar

[redacted]

From: [redacted]
Sent: 22 January 2013 09:28
To: [redacted]
Cc: 'UKCPA Administration'
Subject: RE: REQUEST TO RECLASSIFY A PRODUCT FROM P TO GSL - PIRINASE HAYFEVER RELIEF FOR ADULT 0.05% NASAL SPRAY

To whom it may concern

The UKCPA Respiratory Group have considered this reclassification and would like to make the following comments:

We have no major comment regarding this deregulation from P to GSL. One minor point is that we would like to think that by purchasing through a pharmacy the person would get appropriate advice re length of use and technique on how to use the device. Beconase has been on the GSL list since 2003 and therefore this seems fairly reasonable.

Please excuse the fact that this response is not on your form, as specified as being included in the ARM 83 letter, because it was not attached.

I trust you can accept this response as is. However, if this is not the case, please get in touch.

Kind regards

[redacted]
UKCPA
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Mobile: [redacted]
Fax: 0116 2776272
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Website: http://www.ukcpa.org

[redacted]

From: [redacted]
Sent: 09 January 2013 10:00
To: Reclassification
Subject: FW: REQUEST TO RECLASSIFY A PRODUCT FROM P TO GSL - PIRINASE HAYFEVER RELIEF FOR ADULT 0.05% NASAL SPRAY

From: [redacted]
Sent: 09 January 2013 09:53
To: [redacted]
Subject: RE: REQUEST TO RECLASSIFY A PRODUCT FROM P TO GSL - PIRINASE HAYFEVER RELIEF FOR ADULT 0.05% NASAL SPRAY

[redacted]

Content. No comments on this proposal.

Regards

[redacted]
Pharmacy and Medicines Division
9 January 2013

[redacted]

From: OnlineFeedbackToConsultationDocument@mhra.gov.uk
Sent: 07 January 2013 16:05
To: Reclassification
Subject: Consultation Feedback <ARM><83> Mon Jan 07 16:04:58 GMT 2013

Consultation type:
ARM

Reference Number:
83

Consultation Document Title:
Public consultation: (ARM 83): Request to reclassify Pirinase Hayfever Relief for Adults 0.05% Nasal Spray (fluticasone propionate) from Pharmacy (P) to General Sales List (GSL)

Name:
[redacted]

E-mail:
[redacted]

Address:

Comment on proposal:
My comments on the proposals in the document are below

My comments on the proposal :
GSK seem to have adressed all the concerns and this is represented in the label so I have no objections to the changes

Confidentiality :
My reply may be made freely available

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[redacted]
MHRA
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1st February 2013

Dear [redacted]

Re: ARM 83 Pirinase Hayfever Relief for Adults 0.05% Nasal Spray request to reclassify a product from P to GSL

We write on behalf of the Royal Pharmaceutical Society (RPS) to respond to the above consultation.

The RPS is the professional body for pharmacists in Great Britain. We represent all sectors of pharmacy in Great Britain and we lead and support the development of the pharmacy profession including the advancement of science, practice, education and knowledge in pharmacy. In addition, we promote the profession's policies and views to a range of external stakeholders in a number of different forums.

The RPS does not support the reclassification of Pirinase Hayfever Relief for Adults 0.05% Nasal Spray from P to GSL.

The patient information leaflet consistently advises patients to seek advice from a doctor or pharmacist. In non-pharmacy outlets where GSL medicines are sold, professional advice is not available. Pharmacy sale of GSL medicines have shown to be safe, as pharmacists and trained healthcare advisors are on hand to counsel the patient on their medicines.

In addition, we request that the following points be taken into consideration:

Patient Information Leaflet

Section 2: Check before you use Pirinase Hayfever Relief

In this section the patient is advised to talk to their pharmacist or doctor before using Pirinase Hayfever Relief if the following applies to them:
- They have an infection in their nose or sinuses, or have recently had surgery, an injury or ulcers in their nose
- Their symptoms do not improve or are not well controlled after 7 days
- They are taking any other medicines

Appropriate advice on the use of this product cannot be given to individuals at non pharmacy outlets, whereas in a pharmacy, pharmacists and trained staff could ensure that patients are given appropriate advice and directed, where necessary to a health professional.

Section 3: How to use Pirinase Hayfever Relief

This section provides the patients with information on how to use the Pirinase Hayfever Relief Nasal Spray. Pharmacies will have trained staff ready to advise and counsel patients on using this device, which will not be available from non pharmacy outlets.

We hope these comments are useful. Our reply may be made freely available.

Thank you for contacting the Royal Pharmaceutical Society.

Yours Sincerely

[redacted]

[redacted]
Professional Support Pharmacist

Response to the proposal to reclassify Pirinase (fluticasone) nasal spray from P to GSL

1. This paper is a joint response from the British HIV Association (BHIVA) and the HIV Pharmacy Association (HIVPA) to the proposed reclassification of fluticasone nasal spray (Pirinase).

2. We strongly recommend that Pirinase should not be reclassified from P to GSL, but should remain a Pharmacy medicine

3. The British HIV Association (BHIVA) is the leading UK professional association representing professionals in HIV care. BHIVA acts as a national advisory body to professions and other organisations on all aspects of HIV care, producing the only national NHS accredited treatment guidelines for HIV. The current membership of the association is over 1,000 across a wide range of healthcare professionals and other HIV healthcare workers.

4. The UK HIV Pharmacy Association (HIVPA) is the national professional organisation for pharmacists and pharmacy technicians working in the HIV speciality. HIVPA promotes excellence in the pharmaceutical care of people living with HIV and is recognised by the Royal Pharmaceutical Society and BHIVA as the expert opinion provider on HIV medicines. HIVPA is represented on the BHIVA guidelines writing committees and is a key stakeholder in national pharmacy consultations.

5. BHIVA and HIVPA have profound concerns about the proposed deregulation of fluticasone nasal spray, due to the extensive experience of our members in diagnosing and treating patients who have developed Cushing's syndrome following co-administration of fluticasone nasal spray or inhaler with ritonavir. We list a selection of relevant references, though we are aware of many more cases (including some that have been presented at conferences as case reports).

6. We wish to make the following specific points in response to the request:

a) Section 3.1 (Hazard to health)

- 'the risks associated with fluticasone use are small'

  Although this statement may be true at a population level, for specific groups - eg those taking medicines that are potent inhibitors of the isoenzyme cytochrome P450 3A4 (CYP3A4) - the risks of significant morbidity are high (even after coadministration for less than one month).

- 'there are few clinically significant drug interactions, with appropriate advice provided in the SmPC and patient information leaflet'

  Although the number of clinically significant drug interactions may be small, the effect of those interactions is highly significant and potentially extremely dangerous for the affected patients. Ritonavir is widely used by people with HIV infection (many of whom also suffer from allergic rhinitis) and cobicistat (another potent CYP 3A4 inhibitor which has the same potentiating effect on fluticasone) is due to be launched in the UK early in 2013. There is recent evidence to demonstrate that the ritonavir/fluticasone interaction may be underdiagnosed in practice, resulting in preventable morbidity (Okasaki-Gutierrez et al, 2012).

  The patient information leaflet advises purchasers to seek advice from their doctor or pharmacist if they are taking ritonavir, but our experience is that most patients either do not read or do not heed the information leaflet. It is a common perception that if a product can be purchased from any retail outlet then it must be safe; furthermore, nasal sprays are often not considered as medicines that may be implicated in drug interactions.

People living with HIV still report significant stigma associated with the condition and are thus often reluctant to disclose the names of their antiretrovirals to those outside their specialist centre. Disclosure, when it does occur, is more likely to be in the context of an encounter with an appropriately trained health care professional. A GSL classification would mean that even within community pharmacies the vast majority of sales would be carried out by counter assistants, who would be even less likely to counsel prospective purchasers about potential drug interactions.

- 'Beconase Hay Fever Relief (beclometasone) has been available as a GSL product since 2003'

This is true, but beclometasone does not interact significantly with ritonavir (and other potent CYP3A4 inhibitors) whereas fluticasone does - see paragraphs below from the Liverpool HIV Drug Interactions website www.hiv-druginteractions.org (accessed 22/02/13); similar information also available in the SmPCs for beclometasone and fluticasone.

> Beclometasone with ritonavir:
>
> Beclometasone is a pro-drug which is not metabolised by CYP450, but is hydrolysed via esterase enzymes to the highly active metabolite beclometasone -17-monopropionate. Coadministration of ritonavir (100 mg twice daily) increased the AUC and Cmax of beclomethasone-17-monoproprionate by 108% and 67%, respectively. However, coadministration of a boosted PI (darunavir/ritonavir, 600/100 mg twice daily) decreased the AUC and Cmax of the active metabolite by 11% and 19%, respectively. No significant effect on adrenal function was seen with either ritonavir or darunavir/ritonavir. Although statistically significant, the 2-fold increase in AUC of the active metabolite seen with ritonavir is unlikely to be of clinical significance.
>
> Fluticasone with ritonavir:
>
> Coadministration is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. Coadministration of fluticasone nasal spray (200 µg once daily) and ritonavir (100 mg twice daily) increased fluticasone AUC by ~350-fold and Cmax by ~25-fold. The significant increase in fluticasone exposure resulted in a significant decrease (86%) in plasma cortisol AUC. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression have been reported. A dose reduction of fluticasone should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.

b) Section 3.4 (Convenience to the purchaser)

As beclometasone (Beconase) is already widely available as a GSL medicine, prospective purchasers do have a treatment that they can obtain from many outlets without restriction. For people who wish to try fluticasone as it is currently licensed (as a P medicine) there are '100 hour pharmacies' situated within easy reach of the vast majority of the population (many of which are co-located with supermarkets), thus facilitating access to the product and the appropriate advice from a pharmacist during the evenings and at weekends.

c) Section 6 (Safety profile)

This section does not address our key concern, which is the increased risk of hypothalamic-pituitary-adrenal (HPA) axis suppression when fluticasone is co-administered with a potent inhibitor of CYP3A4 (such as ritonavir). The SmPC for Pirinase includes a summary of this information:

> In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects.

Many HIV specialist clinicians have seen patients with HPA axis suppression due to inadvertent co-administration of fluticasone nasal spray with ritonavir. Some HIV centres have made great efforts to educate patients, hospital doctors and general practitioners about this interaction, despite which new cases continue to be observed with alarming regularity. Long-term consequences of the interaction that have been observed in practice include:

osteoporosis, bilateral avascular necrosis, diabetes mellitus, psychosis and a need for chronic oral steroid replacement therapy.

7. In summary, BHIVA and HIVPA strongly recommend that to reduce the risk of serious sequelae of drug interactions with fluticasone, people wishing to use this medicine should always have the opportunity to receive appropriate advice from a pharmacist or doctor at the point of sale, dispensing or prescribing. **We therefore recommend that Pirinase should not be reclassified from P to GSL, but should remain a Pharmacy (P) medicine.**

References:

Chen F, Kearney T, Robinson S, Daley-Yates PT, Waldron S, Churchill DR. Cushing's syndrome and severe adrenal suppression in patients treated with ritonavir and inhaled nasal fluticasone. *Sex Transm Infect*. 1999;75:274.

Clevenbergh P, Corcostegui M, Gerard D, et al. Iatrogenic Cushing's syndrome in an HIV-infected patient treated with inhaled corticosteroids (fluticasone propionate) and low dose ritonavir enhanced PI containing regimen. *J Infect*. 2002;44:194 –195.

Foisy MM, Yakiwchuk EMK, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Medicine (2008), 9, 389–396.

Gupta SK, Dube´ MP. Exogenous Cushing syndrome mimicking human immunodeficiency virus lipodystrophy. *Clin Infect Dis*. 2002;35:e69–e71.

Hillebrand-Haverkort ME, Prummel MF, ten Veen JH. Ritonavir-induced Cushing's syndrome in a patient treated with inhaled fluticasone. *AIDS*. 1999;13:1803.

Johnson SR, Marion AA, Vrchoticky T, et al. Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr*. 2006;148:386 –388.

Okasaki-Gutierrez R, Poole P, Troia-Concio P, Asmuth DM. Prevalence of subclinical iatrogenic Cushing's syndrome (ics) in patients being co-administered ritonavir and corticosteroids via inhaled, intranasal and/or topical route. *XIX International AIDS Conference, Washington, 2012, Poster MOPE103.*

Rouanet I. Peyrie`re H, Mauboussin JM, Vincent D. Cushing's syndrome in a patient treated by ritonavir/lopinavir and inhaled fluticasone *HIV Medicine*. 2003;4:149 –150.

Soldatos G, Sztal-Mazer S, Woolley I, Stockigt J. Exogenous glucocorticoid excess as a result of ritonavir–fluticasone interaction. *Intern Med J*. 2005;35:67– 68.

Response submitted on behalf of BHIVA and HIVPA by:

[redacted] BHIVA Chair

[redacted] HIVPA Co-Chairs

[redacted] Consultant HIV/Sexual Health Pharmacist

GHP Guild of Healthcare Pharmacists

unite theUNION

31st January 2013

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ARM 83: Pirinase Hayfever Relief for Adults 0.05% Nasal Spray – Request to Reclassify from P to GSL

Response from the Guild of Healthcare Pharmacists

Thank you for the opportunity to respond to this consultation. The Guild of Healthcare Pharmacists represents UK wide around 4,000 pharmacists including the majority of hospital pharmacists, pharmacists employed by NHS Primary Care organisations and pharmacists employed by other public bodies such as Prisons and the Care Quality Commission. The Guild is part of the health sector of the union Unite.

We do not support the reclassification request for the following reasons. Our views are supported by the Royal Pharmaceutical Society of Great Britain:

We acknowledge that GSL status would provide greater convenience for the purchaser and enable patients to manage their hay fever immediately when it commences, and that fluticasone propionate 0.05% nasal spray has a well-established safety profile. However, the active ingredient is a synthetic corticosteroid and has special warnings and precautions for use which in our view requires appropriate controls –

- Patients who are allergic to fluticasone propionate
- People with local infections (such conditions should be treated first)
- Higher than recommended doses must not be used as this could give clinically significant adrenal suppression
- Possible interactions with other medicines e.g. risk of systemic side effects when used in combination with potent CYP3A inhibitors such as itraconazole; similarly care is advised when co-administering potent cytochrome p450 3A4 inhibitors such as ketoconazole as there is a risk of increased systemic exposure to fluticasone propionate.

GlaxoSmith Kline Consumer Healthcare has acknowledged in their 'request' for the reclassification that "post-marketing experience has shown that the wider public availability of the product through

pharmacies has not significantly changed the safety profile of the product" – we would argue that it is because the product has only been available through pharmacies that the safety profile has been maintained i.e. the intervention of pharmacists in sales transactions to the public has ensured the necessary professional oversight to safeguard patients to date against the potential problems highlighted above. In the absence of this professional oversight the current safety profile would be completely different.

We hope these comments are of assistance. Our reply may be made freely available.

Yours faithfully

[redacted]
Professional Secretary
Guild of Healthcare Pharmacists

[redacted]
Chair of Practice
Guild of Healthcare Pharmacists