TEVA UK Limited

Ms Alana Miller
National Institute for Health and Clinical Excellence
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14 May 2007

Dear Alana,

Re: Health Technology Appraisal: Corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over.

Thank you for sending us the Appraisal Consultation Document for the Technology Appraisal of corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over. Firstly we would like to put on record that our previous comments on the Assessment Report were overlooked due to misdirection to Andrea Sutcliffe. We understand that they have now been forwarded and will be considered during the next Committee meeting. A copy is attached for reference (Appendix 1) and contains a number of points that have not been addressed by the ACD.

In general, we are comfortable with the overall conclusions of the ACD, although there are a number of points we would wish you to consider. These are as listed below. As many of these issues relate to several sections in the ACD, it may be of value to include them in an additional paragraph in section 1. This would also ensure that for anyone reading the summary these issues would be highlighted.

1. CFC-beclometasone Phase Out in the UK

In October 2006, GSK advised the NHS that, in line with the requirements of the Montreal protocol under which the manufacture of CFCs is gradually being phased out, they would be discontinuing Becotide/Becloforte metered dose beclometasone inhalers during the second half of 2007 (attached GSK communications to UK Healthcare Professionals October 2006 & March 2007).

GSK currently supplies approximately 43% of the CFC- beclometasone metered dose inhalers (pMDIs) prescribed in the UK, and Teva UK Ltd, as the second largest supplier, cannot guarantee to supply beclometasone in a CFC pMDI for more than one year. Currently there are approximately 2 million patients that are receiving metered dose inhalers of CFC- beclometasone to control their asthma symptoms.

In view of the above, the remaining preparations of CFC- beclometasone should not be included in any cost analysis or subsequent guidance as their supplies will be limited by the time the guidance is finalised.

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Conclusion

The phase out of CFC containing beclometasone should be clearly communicated in the guidance as by the time it is published Becotide and Becloforte will no longer be available. The few remaining suppliers of CFC containing beclometasone, of which Teva UK Ltd is the largest, will have limited stocks remaining and this should be reflected clearly in the guidance.

2. CFC free Beclometasone - Guidance Summary Section 1

The current use of beclometasone in the UK accounts for around 77% of single inhaled corticosteroid usage (IMS March 2007). The BTS/SIGN guidelines currently recommend beclometasone based on its established safety and efficacy profile. As the mainstay of asthma management prescribers are likely to continue to prescribe beclometasone in a CFC free preparation.

The guidance should therefore reflect the properties relating to the two CFC free beclometasone preparations and should clearly define the different potencies of the two products, Qvar being more potent than Clenil. The MHRA thought this important enough to issue recommendations in August 2006 to prescribe CFC-Free beclomethasone by brand (MHRA guidance August 2006 included)

Conclusion

The different potencies of the two currently available CFC-free beclometasone products should be defined in the summary section of the NICE guidance.

3. Breath Actuated Devices

In the ACD section 3.2 there is some discussion of the use of breath actuated inhalers and it is stated that they cannot be used with spacer devices. This is incorrect as Beclazone Easi-Breathe (containing CFC-beclometasone) is only available in the UK in a pack that contains a dose optimiser (small volume spacer).

The statement made in section 3.5 that breath actuated inhalers are more expensive than pMDI versions is incorrect. The breath actuated Qvar Autohaler is the same price as the Qvar pMDI version. The Qvar Easi-Breathe breath actuated device is less expensive than the pMDI.

Conclusion

Beclazone Easi-Breathe is supplied with a small volume spacer for use with the product. Although Qvar Autohaler and Qvar Easi-Breathe can be used with an Aerochamber spacer device, they are rarely used together as no additional benefit in lung deposition is seen with a spacer.

4. Cost Effectiveness of Qvar and Fluticasone

Whilst this conclusion is supported in part in the Assessment Report by the comparison of CFC-free Inhaled Corticosteroid alternatives in the cost effectiveness section, we believe that several of the calculations are inaccurate and lead to false assumptions of the most appropriate treatment choice. The cost comparisons within the Assessment Report have been based on mean weighted and unweighted annual

costs for each ICS. At the lower starting dose of 400ug/day, excluding CFC-beclometasone products, CFC-free beclometasone was confirmed as the most cost effective option (most clinically effective at lowest cost). However, at the higher 800µg/day beclometasone equivalent dose, the Assessment Report showed fluticasone to be the cheapest option. We have reviewed the data, based on the PCA 2005, and wish to make the following observations:

- Fluticasone Low Dose: Approximately 70% of fluticasone prescriptions are for the pMDI, in order to receive a 400µg CFC- beclometasone equivalent, the patient must take 4 doses of 50µg of fluticasone (the cheapest fluticasone preparation) at an annual cost of £66.19. This is more expensive than Qvar at an annual cost of £62.82 for a 400µg CFC- beclometasone equivalent dose. In addition, fluticasone 50µg pMDI accounts for only 15% of all fluticasone prescriptions.
- Fluticasone High Dose: At a CFC- beclometasone equivalent dose of 1600µg, the only scenario where FP would be cheaper than Qvar would be if the patient were to take 16 doses of 50µg. The weighted and unweighted means presented in the Assessment Report do not allow for the impracticality of this regimen, and since the most commonly prescribed fluticasone dose is 250µg. It seems more likely that the patient would be prescribed 4 doses of fluticasone 250µg at an annual cost of £439.70, compared with £251.27 for Qvar 800 (1600µg CFC- beclometasone equivalents).

Conclusion

We therefore contend that after the phase out of CFC containing beclometasone, CFC-free beclometasone will be the most cost effective ICS over the whole dose range. We believe that the cost comparisons should reflect commonly prescribed and practically used dosage regimens.

5. Use of Weighted averages

Beclometasone is available in a number of different presentations, which have widely differing costs as recognised in the ACD. Currently 97% are prescribed as aerosol and 3% prescribed as the higher cost Dry Powder Inhalers (IMS March 2007). The use of weighted averages in the Assessment Report is misleading as it includes all devices without considering the difference in usages of the various devices. This assumption skews the analysis in favour of fluticasone, when CFC- beclometasone is clearly the more cost effective option. This is particularly evident when CFC beclometasone is removed as the current market shares (PCA 2005) of DPI and HFA are applied to the whole market – thus increasing the mean & median cost due to the higher price of the DPIs.

We also question the calculation of mean weighted and unweighted annual costs as these are based on the extent of beclometasone DPI prescribing after the CFC phase out. The calculation assumes that DPIs will represent 8% of the ICS usage rather than the current 3%, this is because the calculations relates to the quantities of DPI shown in the PCA 2005 are based on dose and not units prescribed.

Conclusion

We therefore conclude that Fluticasone is often not the lowest cost inhaled corticosteroid, and therefore the ACD conclusion is misleading.

A more detailed assessment of these concerns is included in Appendix 1.

We hope that these comments will be helpful to you in your consideration of the ACD. If you would like any further assistance or clarification from Teva Pharmaceuticals in this matter, please do not hesitate to contact us.

Yours sincerely,

Appendix 1

TEVA UK Limited

Ms Andrea Sutcliffe
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

28 February 2007

Dear Andrea

Re: Health Technology Appraisal: Corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over.

Thank you for sending us the Assessment Report for the Technology Appraisal of corticosteroids in adults. We assume that NICE have been informed that Teva, and not IVAX, now market Qvar and are the appropriate consultees in this process?

Overall, we consider this Assessment Report to be well written and effectively presented. A large amount of data has been reviewed in order to answer the questions posed and therefore provide evidence for the technology appraisal conducted by the National Institute for Health and Clinical Excellence (NICE).

Nevertheless, we do have some concerns with regards to this review and these largely relate to the positioning of HFA-BDP in general, and of Qvar in particular.

1. In October 2006, GSK advised the NHS that, in line with the requirements of the Montreal protocol under which the manufacture of CFCs is gradually being phased out, they would be discontinuing Becotide/Becloforte metered dose BDP inhalers during the second half of 2007 (copy letter attached). Since GSK currently supply some 43% of the CFC-BDP metered dose inhalers (MDIs) prescribed in the UK, as the second largest supplier, Teva is presented with a difficult ethical situation: in view of the imminent phasing out of CFC propellants, we cannot guarantee to supply BDP in a CFC pMDI for more than one more year. Since some 2 million patients are currently prescribed BDP to control their asthma symptoms, Teva is therefore committed to helping the transition from CFC containing BDP to the CFC-free BDP, Qvar.

2. Accordingly, Teva contend that comparisons of HFA BDP with CFC-BDP and other steroids should be the main focus of the Technology Appraisal. We also suggest that, in view of their imminent discontinuation, Becotide/Becloforte should not be included in any cost analysis or subsequent Guidance.

3. Teva wish to remind NICE that the CFC phase out is genuine and will happen within the next few years. It is important that the transition to CFC-free BDP is carefully managed to ensure consistency of asthma treatment. We believe that Qvar is the best alternative to CFC-BDP, and should be the treatment of choice within the current BTS/SIGN guidelines. We feel that NICE has a critical role in supporting the CFC phase out as part of their Guidance.

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4. The use of BDP in the UK currently accounts for around 80% of over 8 million ICS prescriptions. As the mainstay of asthma management, we believe that prescribers will wish to continue to prescribe BDP according to the BTS/SIGN guidelines, because of its consistent and established safety and efficacy profile.

5. The Assessment Report thus appears to be incomplete and inconsistent in terms of the assessment of HFA-BDP. In the clinical section, HFA-BDP is not compared with CFC-BDP, BUD or low dose FP, despite the availability of appropriate clinical trials. Our submission showed that CFC-free Qvar offers clinical benefits over CFC-BDP in terms of increased number of symptom free days and an improved quality of life. Moreover, its unique formulation using HFA as a propellant produces extra fine particles that are one quarter the size of CFC-BDP particles resulting in a higher proportion of the dose being deposited in the lungs, such that Qvar has an equivalent therapeutic effect at half the equivalent CFC-BDP dose. This is particularly important as of the discontinuation of Becotide/Becloforte will occur before Guidance is issued, and the need to reduce the BDP dose when prescribing Qvar due to its greater potency was highlighted in a recent letter to prescribers by the MHRA (copy letter attached).

6. Whilst this conclusion is supported in part in the Assessment Report by the comparison of CFC-free ICS alternatives in the cost effectiveness section, we believe that several of the calculations are inaccurate and lead to false assumptions of the most appropriate treatment choice. The cost comparisons within the Assessment Report have been based on mean weighted and unweighted annual costs for each ICS. At the lower starting dose of 400ug/day, excluding CFC-BDP products, HFA-BDP was confirmed as the most cost effective option (most clinically effective at lowest cost). However, at the higher 800µg/day BDP equivalent dose, the Assessment Report showed FP to be the cheapest option. We have reviewed the data, based on the PCA 2005, and wish to make the following observations:

   - To achieve a daily dose of 400µg BDP equivalent, the patient has a number of options: 8 doses of 50µg, 4 doses of 100µg, or 2 doses of 200 µg, for which the annual costs would be £64.82, £44.17, and £29.71 respectively (the most commonly prescribed regimen is 4 doses of 100µg).

   - For FP, for which around 70% of prescriptions are for the MDI, in order to receive a 400 µg BDP equivalent, the patient must take 4 doses of 50 µg (the cheapest FP form) at an annual cost of £66.19 which is more expensive than Qvar at an annual cost of £62.82 for a 400µg BDP equivalent dose. In addition, FP 50µg MDI accounts for only 15% of all FP prescriptions, and higher doses are relatively more expensive: for example, to deliver 500µg/day, using FP 125µg MDI has an annual cost of £129.33.

   - A similar corollary applies to higher doses: at a 1600-2000µg BDP equivalent dose, the only scenario where FP would be cheaper than Qvar, would be if the patient were to take 16 doses of 50µg. The weighted and unweighted means presented in the Assessment Report do not allow for the impracticality of this regimen, and since the most commonly prescribed FP dose is 250 µg, it seems more likely that the patient would be prescribed 4 doses of 250ug at an annual cost of £439.70 (compared with £198.41 for generic 2000µg CFC-BDP equivalents and £251.27 for Qvar 1600µg CFC-BDP equivalents). We therefore contend that after the CFC phase out, HFA-BDP will remain the most cost effective ICS over the whole dose range. Moreover, we feel that the cost comparisons should reflect dosage regimens used in current clinical practice rather than being based on theoretical possibilities.

7. The use of weighted averages in the Assessment Report also includes BDP administered by DPI. Since the DPIs are more expensive than their MDI equivalents, this assumption skews the analysis in favour of FP, when CFC-BDP is clearly the more cost effective option. We also believe that the calculation of mean weighted and unweighted annual costs has made an erroneous assumption around the extent of DPI prescribing after the CFC phase out, that the DPIs will represent 8% of the ICS usage rather than the current 3% of prescriptions, due to the fact that the quantities of DPI shown in the PCA 2005 are based on dose and not units prescribed.

The attached table includes a more detailed summary of our areas of concern.

We therefore suggest that, in view of the imminent phasing out of CFCs, HFA-BDP should be consistently included in the NICE Appraisal, including a thorough explanation of:

- The current situation relating to CFC use in MDIs, and the imminent discontinuation of Becotide/Becloforte.
- A review of all available data comparing currently available HFA-BDP products with the alternatives, according to the protocol.
- An explanation of comparable doses across all of the available ICS, to ensure that they are prescribed appropriately. It is particularly important that the different dosing of the two available HFA-BDPs is made clear.
- Guidance on prescribing of BDP that is appropriate, given the international attempts to reduce use of CFC and the likelihood that CFC-MDIs will be unavailable after 2010, if not sooner.

As it currently stands, we consider the information pertaining to HFA-BDP to be confusing and inconsistent. While the cost-effectiveness section highlights the impact of the phasing out of CFCs, the background and clinical sections do not provide the reader with the information required to understand the reasons behind this or make judgements on the clinical impact of the withdrawal of CFCs. It is therefore difficult to see how conclusions can be drawn, or what recommendations NICE will be able to make, on the evidence presented.

In summary, Teva believe that NICE has a responsibility to recommend HFA-BDP as the preferred ICS choice in the phase out of CFC-BDP, since it represents the best value for money for the NHS without compromising clinical outcomes.

We hope that these comments will be helpful to you in your consideration of the Assessment Report. If you would like any further assistance or clarification from Teva Pharmaceuticals in this matter, please do not hesitate to contact us.

Yours sincerely

Table. Summary of specific comments on the Assessment Report

Location	Text / Issue	Comment
Page xvi	Q1. Which is the most clinically and cost-effective of the three ICS when used in low doses (400–800µg BDP per day or equivalent) at Step 2 of the guidelines? Q2. Which is the most clinically and cost-effective of the three ICS when used in high doses (800-2000µg BDP per day or equivalent), at Step 4 of the guidelines?	The Executive Summary, page xv, cites the 5 ICS products available, either as monotherapy or combination formulations (FP and BUD), while the research questions listed under 2.3 *Methods* relate to only 3 of the 5 (although the results actually report 5). Further, Q1 refers to low dose as 400–800µg BDP equivalents and not 200-800µg BDP as per the BTS/SIGN guidelines. This question is correctly formulated in section 4.2 *Definition of the decision problems* (page 38): *Q1. At low doses (200–800µg BDP per day or equivalent), which is the most clinically and cost-effective of the five ICS? (Step 2 of the guidelines)*
Page 15 Section 3.4.1.2	"HFA propellants were phased in to replace CFC propellants when it was realised that the latter have ozone depleting properties. Studies show that HFA propellants deliver a greater proportion of fine particles than CFC propellants in the same device resulting in a greater proportion of the drug begin deposited in the small airways."	While it is accurate to state that HFA propellants were developed to replace CFC propellants, we feel that it is important that the Assessment Committee are fully aware that CFCs are being phased out. The Technology and Assessment Panel (TEAP) Committee have stated that CFC-MDIs can be phased out by 2010. Therefore, HFA-BDP will be the only BDP formulation available. Moreover, the fine particles formulation is unique to Qvar and not Clenil, and despite the HFA propellant in Clenil, these two products are not equipotent owing to the smaller particle size and greater lung deposition of Qvar. As the NICE guidance is unlikely to be updated before 2010, we feel that this change needs to be taken into consideration in the AR and in the guidance issued so that recommendations can include provision for a time when CFC-BDP is not available. Otherwise, the guidance will be out of date soon after it is issued.
38	Similarly, the effect of the propellant (CFC versus HFA) used in the MDIs is not considered.	While comparisons of devices have not been made, we suggest that, given the imminent phasing out of CFCs, it would be pertinent for the propellant to be considered in this review. Indeed, in the protocol, it states "similarly, comparisons of ICS where a CFC-propelled pMDI is used may be grouped separately to those where the propellant is HFA, given suggested differences in potency."

Location	Text / Issue	Comment
40	"Within the context of the BTS/SIGN Guidelines, it is generally accepted that the following are clinically equivalent doses: BDP 400µg, BUD 400µg, FP 200µg, CIC 200µg and MF 200µg. Studies which compare these drugs at these drug ratios, delivered through the same device, are thus the most appropriate method for testing this hypothesis."	In line with our previous comments, we suggest that it is important to make clear that this is CFC-BDP, with the equivalent dose of HFA-BDP (QVAR) being 200µg due to higher lung deposition and fine particles previously mentioned.
Page 57 / section 5.2.2	No studies of HFA-BDP vs HFA-FP are included under Question 1 (low dose)	It is unclear why Fairfax et al 2001, cited in our submission, has not been included under this comparison. Fairfax et al report a double-blind, double-dummy, parallel group 6-week study in adult patients. 400µg daily HFA-BDP is compared with 400µg daily FP. As the reasons for exclusion of particular trials are not presented we can not tell if this is an oversight, or if there are valid reasons for exclusion. It is possible that the exclusion from this AR is due to its inclusion in a Cochrane review that is discussed (Lasserson et al 2005). However, Aubier et al 2001, which is reviewed under question 2, is also included in Lasserson et al 2005.
Section 5	It is unclear why Molimard et al 2005 is included in comparisons of FP and BUD but not HFA-BDP with either FP or BUD.	One study (Molimard et al 2005) that includes FP, BUD and HFA-BDP is included in the comparison of FP and BUD under Question 2 (high dose) (page 176-182) but not as evidence for HFA-BDP versus either FP or BUD. The reasons for this are unclear. It is possible that the exclusion from this section of the AR is due its inclusion in a Cochrane review comparing HFA-BDP with FP that is discussed (Lasserson et al 2005). However, Aubier et al 2001, which is reviewed, is also included in Lasserson et al 2005.
Section 5	Comparisons of HFA-BDP and BUD are not made.	We suggest that a comparison of HFA-BDP versus BUD should be made. This would include 3 relevant RCTs included in our submission: Reichel et al 2001; Molimard et al 2005 and Worth et al 2001.

Location	Text / Issue	Comment
354	Adams and colleagues[54] – BDP versus BUD for chronic asthma	Ref 54 refers to Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma (update of Cochrane Database Syst Rev 2000; (4): CD002738. Cochrane Database of Systematic Reviews 2005; (1): CD002738. We believe that it should refer to Adams NP, Bestall JM, Jones PW. Beclomethasone versus budesonide for chronic asthma. Cochrane Database of Systematic Reviews 2000: CD003530, which does not appear to be cited.
377	Section 6.3.7 *Summary of the cost-effectiveness submissions made by manufacturers* states that the submission by Ivax Pharmaceuticals Ltd "*...was limited to a presentation of the costs of their BDP product, Qvar*".	This is not strictly true since the analysis included costs of BDP, HFA-FP and BUD-TH as comparators. Moreover, the budget impact analysis covered a wide range of available ICS products currently prescribed in the UK (not including CIC or MF).
382	Section 6.5.1 *Rationale for cost comparisons* stated that "given the likely withdrawal of CFC-containing products in the near future, we have calculated these cost estimates both including and excluding currently available CFC-containing products (this is an issue for BDP and BUD preparations only). During the period when CFC-containing products are withdrawn from sale in the UK, it is likely that the relative market shares of different named preparations will also alter, because many patients will need to switch between products, new products may simultaneously enter the market, and pack prices may also change".	Our submission assumed that CFC-BDP will no longer be available in the UK as a result of enactment of the Montreal protocol, and showed that it can be satisfactorily replaced with the CFC-free Qvar at little extra cost, and with superior efficacy in terms of symptom-free days and quality of life. The budget impact analysis included consideration of the need to switch to non-CFC containing ICS formulations based on current prescribing patterns (ie cost per prescription assuming dose equivalence) rather than just a direct cost comparison. Moreover, the analysis showed that, since BUD and FP cost significantly more than BDP equivalents, were Qvar to be substituted for these products, it would result in a substantial cost saving to the NHS.
387	In Section 6.5.3.1 Research question 1 *Cost comparison: What is the cheapest ICS drug at treatment Step 2?*, line 5 of paragraph 1 states: "Following the tables, *Table 59* and *Table 60* also plot the weighted and unweighted mean annual cost, and the estimated annual cost of using the cheapest and the most expensive product for each drug"	This should read "Following the tables, *Figures 25 and 26* also plot the weighted and unweighted mean annual cost....".

Location	Text / Issue	Comment
387	"Overall BDP appears to be the current cheapest ICS drug at starting low doses (400µg BDP-CFC equivalent per day).... If CFC-propelled products are excluded from the available products, BDP is still the cheapest but at a slightly higher annual cost. Excluding CFC-propelled products, and using current prices, causes a significant increase in the mean annual cost of taking BDP at this dose level since CFC-propelled products still account for over half of the product types and quantities of BDP sold. In contrast, for FP, MF and CIC no currently available products are CFC-propelled, so their exclusion does not alter the calculated mean annual cost. FP and MF are consistently the two most expensive drugs - at almost twice to three times the annual cost of taking BDP".	This analysis is consistent with the Teva submission in that the AR concludes that, for 400µg CFC-BDP equivalence, FP and MF (but does not mention BUD) are consistently the most expensive drugs. Here it is not explicit that the BDP options are currently only Qvar and Clenil Modulite. At higher doses of 800µg CFC-BDP equivalence (at the upper end of step 2), FP is stated to be marginally cheaper than BDP (although it is not clear why this might be).
408	Section 6.6 *Summary of the economic analysis* states that "At low ICS doses at Step 2 of the Guidelines the weighted mean annual cost of taking an ICS drug at 400µg BDP-CFC (or equivalent) varies over three-fold from £53 for BUD to £170 for MF".	The actual range of costs (according to Table 60) is £62 for BDP to £162 for MF.

Location	Text / Issue	Comment
409	"What these weighted averages conceal, however, is very wide variations in the cost of individual preparations for each drug. For example, currently the cheapest way of obtaining 800µg of BDP per day is with Becotide® 200µg four times daily (4.07p per dose = £59.42 per year)".	A recent communication from the MHRA (August 06, letter attached) after the launch of the second BDH HFA product Clenil Modulite informed prescribers that there are two BDP CFC-free pressurised MDIs available on the market in the UK: Qvar and Clenil Modulite. In their letter, the MHRA advised that: - Qvar and Clenil Modulite are not equipotent with each other. - Qvar is not equipotent with CFC-containing products. It has 2 to 2.5 fold greater potency than currently available products. - Clenil Modulite was formulated specifically to be equipotent with the existing beclometasone generic and branded CFC-containing products, such as Becotide. If prescriptions are written using the generic term 'beclometasone dipropionate CFC-free inhaler', either Qvar or Clenil Modulite could be dispensed. The MHRA letter therefore directs that "when the prescriber wishes a patient to have a CFC-free formulation of beclometasone dipropionate that the intention should be made clear by prescribing by brand name." Subsequent to this communication from the MHRA in August 06, GSK announced their discontinuation of CFC Becotide and Becloforte in October 06. This discontinuation will be effective from July 07.
422-423 Discussion	In the discussion of FP and BDP at higher doses, it is stated "Based on these studies high doses of CFC pMDI FP appear to result in comparable control to BDP at half the dose. If using an HFA pMDI, similar doses of the two drugs can achieve comparable control.	We agree that Qvar (HFA-MDI) results in comparable control at a similar dose to FP, (this sentence should state HFA pMDI FP and not CFC pMDI) and feel that this reduced dose should be emphasised in the guidance issued by NICE, to ensure prescribing is appropriate and patient safety maintained. However, it is important to note that two HFA-MDIs are available, and only Qvar is comparable at a reduced daily dose compared with BDP (ie a dose equivalent to that of FP); Clenil Modulite is approximately comparable to the equivalent dose of CFC-BDP. For this reason, the MHRA has advised (August 2006) that CFC-free BDP inhalers should be prescribed by brand name (see above comment). Therefore, we suggest that this sentence should read "if using Qvar, similar doses of the two drugs can achieve comparable control."

MHRA Press Release and Letter

August 2006

From the Chief Executive Officer of Medicines and Healthcare products Regulatory Agency

August 2006

Dear Colleague,

BECLOMETASONE DIPROPIONATE PRESSURISED METERED DOSE INHALER

IMPORTANT INFORMATION

Under the terms of the Montreal Protocol, production and supply of chlorofluorocarbons (CFCs) is being phased out worldwide. As a result pressurised metered dose inhalers (pMDIs) for use in asthma and chronic obstructive pulmonary disease (COPD) previously formulated with CFCs are now being formulated with hydrofluoroalkane (HFA) propellants and are CFC-free. These reformulated CFC-free pMDIs have been gradually introduced onto the UK market over the last ten years.

There are two beclometasone dipropionate CFC-free pMDIs available on the market in the UK: Qvar marketed by Ivax Pharmaceuticals Limited has been available for a number of years and Clenil Modulite marketed by Trinity-Chiesi Pharmaceuticals Limited has been introduced to the market recently. **These two CFC-free products, both containing the active substance beclometasone dipropionate are NOT equipotent and this could have safety implications.** The purpose of this letter is to alert healthcare professionals to this and help ensure the intended product is prescribed and dispensed.

PRESCRIBING AND DISPENSING INFORMATION

- **Prescribers** should be aware:

  - that prescriptions written using the generic name *beclometasone dipropionate* do not distinguish between CFC-containing and CFC-free formulations of beclometasone dipropionate, and pharmacists can dispense either. When prescriptions are written using the generic term *beclometasone dipropionate CFC-free inhaler*, there are two products that can be dispensed, Qvar and Clenil Modulite, **and these two products are not equipotent;**

  therefore

  - when the prescriber wishes a patient to have a CFC-free formulation of beclometasone dipropionate that intention should be made clear by **prescribing the product by brand name.**

- **Pharmacists** receiving a generic prescription for a beclometasone dipropionate pMDI **must establish** whether a CFC-free product is required, and if so, which of the two available branded products should be dispensed.

NEW PATIENTS OR PATIENTS BEING SWITCHED

- For new patients or patients being switched from one beclometasone dipropionate inhaler to another, advice on dosing is as follows:

1. **Clenil Modulite (Trinity-Chiesi Pharmaceuticals Limited) should be prescribed at the same dose as the currently available CFC-containing beclometasone dipropionate pMDIs.**

2. **Qvar (Ivax Pharmaceuticals Limited) has a 2 to 2.5 fold greater potency than the currently available CFC-containing beclometasone dipropionate pMDIs and therefore should be prescribed at a lower dose than the currently available CFC-containing beclometasone dipropionate pMDIs. Further information is available in the Summary of Product Characteristics.**

3. **Clenil Modulite is authorised for use in children; Qvar is not authorised for use in children (12 years of age and younger).**

4. **For all inhaled corticosteroids and in line with accepted clinical practice, when control of asthma is achieved the dose of the inhaled corticosteroid should be titrated to the lowest dose at which effective control of asthma is maintained.**

When a prescriber transfers a patient to a beclometasone dipropionate pMDI which is not equipotent with the patient's existing therapy, the importance of this should be discussed with the patient and titration of the dose of the inhaled steroid managed carefully in order to avoid confusion and loss of disease control.

Conversion table for dosing with CFC-containing beclometasone dipropionate (CFC-BDP), Clenil Modulite or Qvar

	Total Daily Dose (micrograms/day)			
CFC-BDP	200-250	300	400 - 500	600-750
Clenil Modulite	200-250	300	400 - 500	600-750
Qvar	100	150	200	300

	Total Daily Dose (micrograms/day)			
CFC-BDP	800 - 1000	1100	1200 - 1500	1600 - 2000
Clenil Modulite	800 - 1000	1100	1200 - 1500	1600 - 2000
Qvar	400	500	600	800

A questions and answers document will be placed on the website of the Medicines and Healthcare products Regulatory Agency www.mhra.gov.uk and on the website of the Department of Health www.dh.gov.uk.

For further information please call the MHRA on 0207 084 2000 or Isabelle Izzard (Dept of Health) on 0207 972 2913.

Yours sincerely,

Professor Kent Woods
CEO/MHRA.

Safeguarding public health

MHRA

Press release

Date: 8 August 2006
Time: 10.45am
Subject: CFC-free inhalers

Contact: Press Office 020 7084 3535 / 3564 press.office@mhra.gsi.gov.uk
Out of hours 07770 446 189

Medicines regulator informs healthcare professionals about prescribing UK beclometasone dipropionate CFC-free inhalers for asthma

The Chief Executive of the Medicines and Healthcare products Regulatory Agency (MHRA) has written to healthcare professionals today about the prescribing of CFC-free inhalers to treat asthma. There are two CFC-free inhalers available on the UK market which contain the active substance beclometasone dipropionate, called Clenil Modulite and Qvar. However these two inhalers have been designed differently and provide different quantities of the active drug to the lungs. Qvar is approximately twice as potent as Clenil Modulite.

It is important that this is taken into account, and doses adjusted accordingly, to ensure that patients receive an appropriately effective dose and to prevent potential safety concerns arising if patients are either switched from a CFC containing inhaler to a CFC–free inhaler, particularly the more potent Qvar, or if patients are switched from one CFC-free inhaler to the other CFC-free inhaler.

For this reason, the MHRA is alerting healthcare professionals to this and to help ensure that the intended inhaler is prescribed and dispensed. The MHRA is asking doctors and any other prescribers of inhalers for asthma to state clearly on the prescription which product should be dispensed by using the brand name (Clenil Modulite or Qvar) rather than prescribing the inhaler by using the generic name, beclometasone dipropionate CFC-free inhaler. If a pharmacist receives a generic prescription for a beclometasone dipropionate inhaler, they should establish whether a CFC-free product is required, and if so, which of the two available branded products should be dispensed.

Notes to Editors:

1. Further information for healthcare professionals, including a Q&A document, can be viewed on the MHRA website (www.mhra.gov.uk) or on the Department of Health website (www.dh.gov.uk).

2. The MHRA is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe. The MHRA keeps watch over medicines and devices, and takes any necessary action to protect the public promptly if problems arise. No product is risk-free. Underpinning all of their work lie robust and fact-based judgements to ensure that the benefits to patients and the public justify the risks.

Ends

MHRA Questions and Answers

August 2006

MHRA

BECLOMETASONE DIPROPIONATE PRESSURISED METERED DOSE INHALER QUESTIONS AND ANSWERS

1. What is the potential safety issue concerning beclometasone dipropionate pressurised metered dose inhaler?

CFC-free beclometasone dipropionate metered dose inhalers (pMDIs) are safe but there are now two CFC-free beclometasone dipropionate pressurised metered dose inhalers (pMDIs) available on the market in the UK: Qvar marketed by Ivax Pharmaceuticals Limited has been available for a number of years and Clenil Modulite marketed by Trinity-Chiesi Pharmaceuticals Limited has been introduced to the market recently. These two CFC-free products, both containing the same active substance beclometasone dipropionate are **not** equipotent and this could have safety implications if the patient receives the wrong product.

2. What other beclometasone dipropionate inhalers are available on the market?

CFC-containing beclometasone dipropionate inhalers have been available on the UK market for many years and are still available. Dry powder formulations of beclometasone dipropionate for inhalation are also available.

3. What are CFCs and why are they being removed from pressurised metered dose inhalers?

CFCs are chlorofluorocarbons. In the past all metered dose inhalers were formulated with CFCs which are inert propellants. The low boiling point of CFCs propels the drug to aerosolise it for inhalation when the inhaler is actuated.

CFCs are harmful to the environment and under the terms of the Montreal Protocol, production and supply of CFCs is being phased out worldwide. As a result pressurised metered dose inhalers for use in asthma and chronic obstructive pulmonary disease (COPD) previously formulated with CFC propellants are now being reformulated with non-CFC hydrofluoroalkane (HFA) propellants. These reformulated CFC-free pMDIs have been gradually introduced onto the UK market over the last ten years.

4. What is the difference between Clenil Modulite and Qvar?

Both of these CFC-free products contain the same active ingredient, but they are not equipotent because the formulation of Qvar results in smaller particles and greater lung deposition when compared with Clenil Modulite

Medicines and Healthcare products Regulatory Agency
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Clenil Modulite should be prescribed at the same dose as the currently available CFC-containing beclometasone dipropionate pMDIs.

Qvar has a 2 to 2.5 fold greater potency than the currently available CFC-containing beclometasone dipropionate pMDIs and therefore is prescribed at a lower dose than the currently available CFC-containing beclometasone dipropionate pMDIs.

Clenil Modulite is authorised for use in children; Qvar is not authorised for use in children.

5. Why are Clenil Modulite and Qvar inhalers not interchangeable?

Although both Clenil Modulite and Qvar are CFC-free metered dose inhalers they are not interchangeable for the reasons discussed in Question 4, above.

6. Which inhalers are CFC-containing and which are CFC-Free?

With the exception of Clenil Modulite and Qvar, all other beclometasone dipropionate pressurised metered dose inhalers contain CFCs. Clenil Modulite and Qvar are the only CFC-free pressurised metered dose inhalers containing beclometasone dipropionate available on the market in the UK.

7. Can patients just switch from one beclometasone dipropionate inhaler to another?

Once a patient has been changed from a CFC-containing beclometasone dipropionate inhaler to a CFC-free beclometasone dipropionate inhaler **the patient should not switch from one CFC-free inhaler to the other unless advised to do so by their doctor** as the two CFC-free inhalers, Clenil Modulite and Qvar are **not equipotent** and Qvar and the original CFC-containing formulations of beclometasone dipropionate are **not equipotent.**

If a patient switches to a beclometasone dipropionate inhaler which is less potent or more potent than the inhaler they have been using previously and their dose is not changed appropriately to take into account the change in the potency of the new inhaler, the patient may notice that the symptoms of their asthma return or their asthma becomes less well controlled or they develop side effects and begin to feel generally unwell.

See also the answer to Question 8, below.

All of the CFC-containing beclometasone dipropionate pressurised metered dose inhalers are equipotent and patients can be switched from one CFC-containing formulation to another CFC-containing formulation without alteration of their dose regimen.

8. What could be the consequences of switching from one beclometasone dipropionate metered dose inhaler to another?

If one beclometasone dipropionate inhaler is less or more potent than another and a patient is switched from one inhaler to another, the patient may notice that the symptoms of their asthma return, they may become more wheezy and/or short of breath, their cough may return, they may notice that they require more of their *reliever* inhaler (their short-acting bronchodilator) than usual or that their *reliever* inhaler is not providing as much relief as usual and their asthma becomes generally less well controlled or they may develop side effects and begin to feel generally unwell.

9. What are prescribers and pharmacists being advised to do?

Prescribers are being advised that they should state clearly on the prescription whether they wish that a CFC-free formulation of beclometasone dipropionate be dispensed or an original CFC-containing formulation of beclometasone dipropionate be dispensed.

If prescribers wish that a CFC-free formulation of beclometasone dipropionate be dispensed then they should state clearly which of the two available products, Clenil Modulite or Qvar is to be dispensed by prescribing the product by brand name. **Clenil Modulite and Qvar are not equipotent and therefore it is extremely important that the intended product is prescribed by brand name.**

When a prescriber transfers a patient to a beclometasone dipropionate pMDI which is not equipotent with the patient's existing therapy, this should be discussed with the patient and titration of the dose to the appropriate dose to maintain control of disease will require the utmost care.

For all inhaled corticosteroids and in line with accepted clinical practice, when control of asthma is achieved the dose of the inhaled corticosteroid should be titrated to the lowest dose at which effective control of asthma is maintained.

Pharmacists receiving a generic prescription for a beclometasone dipropionate pMDI **must establish** whether a CFC-free product is required, and if so, which of the two available branded products should be dispensed.

10. Why is the potential safety issue of beclometasone dipropionate pressurised metered dose inhaler being raised now?

There is now a second CFC-free beclometasone dipropionate pMDI on the UK market, Clenil Modulite, which is not equipotent with Qvar, the first available CFC-free beclometasone dipropionate pMDI. Therefore it is felt appropriate to raise the potential safety issue which might ensue if the potency differences between these two CFC-free inhalers and between Qvar and the original CFC-containing formulations of beclometasone dipropionate are not understood fully by prescribers, dispensers and patients.

11. How are healthcare professionals and patients being informed about the potential safety issue with CFC-free beclometasone dipropionate pressurised metered dose inhalers?

All healthcare professionals, including all doctors, pharmacists and asthma nurses will receive a communication from the Chief Executive Officer of the Medicines and Healthcare products Regulatory Agency.

Further information can be obtained by contacting either the Medicines and Healthcare products Regulatory Agency on telephone number 0207 084 2000 or the Department of Health via their website – www.dh.gov.uk – or by telephone to Isabelle Izzard at the Department of Health on 0207 972 2913.

Patients will be informed about all of the above issues by their general practitioner, their hospital chest consultant their asthma nurse or their pharmacist.

GSK Communications

October 2006

GlaxoSmithKline

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October 2006

Dear Healthcare Professional,

Discontinuation of 50mcg, 100mcg and 200mcg *Becotide™* and 250mcg *Becloforte™* (beclometasone dipropionate) Metered Dose Inhalers (MDIs)

We are writing to inform you that Allen & Hanburys will cease supply of all strengths of *Becotide / Becloforte* MDIs from its respiratory portfolio from Quarter 3 2007 and patients will need to be transferred to alternative products over the next year.

Becotide / Becloforte MDIs are inhaled corticosteroids for use in the prophylactic management of mild, moderate, or severe asthma. Beclometasone will still be available from GlaxoSmithKline in the form of *Becodisks™*, which is a dry powder inhaler.

This discontinuation should not compromise patients' asthma management as a range of alternatives are available. Health care professionals will need to make sure that patients on *Becotide / Becloforte* MDIs are transferred to an alternative device and/or treatment that suits the patient. This may require an adjustment to the dose for certain beclometasone products. Patients who are switched to a different device or medicine should be monitored frequently in the normal way for the emergence or worsening of symptoms, or adverse events.

GlaxoSmithKline made a public commitment to phase out the manufacture of all CFC-containing MDIs globally in line with the requirements of the Montreal Protocol, by 2006. We have been committed to making the transition from CFC-containing inhalers as easy as possible for prescribers, pharmacists and patients. We have invested heavily over the past 10 years in the development of dose-equivalent CFC-free MDIs which has led to the introduction of dose-equivalent CFC-free *Ventolin™, Serevent™* and *Flixotide™* MDIs. However, in the case of *Becotide / Becloforte* MDIs, we have been unsuccessful in our attempts to secure licences for dose-equivalent CFC-free MDIs. We will not therefore be introducing CFC-free *Becotide / Becloforte* MDIs in the UK.

We recognise the important role played by *Becotide/ Becloforte* MDIs in the management of asthma and want to ensure as smooth a transition as possible over the coming months. In this pack, there is a patient letter that can be signed and photocopied, as well as a list of alternative treatments available that has been compiled in consultation with, professional and patient bodies. We will also provide patient information tear off sheets for pharmacists and telephone support.

Healthcare Professionals wishing further information and guidance on transferring patients to alternative products can call the GlaxoSmithKline Customer Contact Centre on 0800 221 441.

Yours Sincerely

istered in England & Wales
4310159

istered office
Great West Road
tford, Middlesex. TW8 9GS

Alternatives for Becotide™ MDI and Becloforte™ (beclometasone dipropionate) Metered Dose Inhalers (MDIs)

Becotide / Becloforte MDIs are inhaled corticosteroids for use in the prophylactic management of mild, moderate, or severe asthma.

As you are aware, Allen and Hanburys will cease supply of all strengths of *Becotide / Becloforte* MDIs from its respiratory portfolio from Quarter 3 2007.

This discontinuation should not compromise patients' asthma management as a range of alternatives are available. Health care professionals will need to make sure that patients on *Becotide / Becloforte* MDIs are transferred to an alternative device and/or treatment that suits the patient. This may require an adjustment to the dose for certain beclometasone products. Patients who are switched to a different device or medicine should be monitored frequently in the normal way for the emergence or worsening of symptoms, or adverse events.

Beclometasone CFC MDIs	**Manufacturer**
*+Filair	3M (IVAX/TEVA)
*+Beclazone	IVAX (TEVA)
Beclometasone Neohaler	Neolabs
*+Unbranded generic	IVAX (TEVA)
*+Unbranded generic	Neolabs

Beclometasone CFC-free MDIs	**Manufacturer**
* Qvar Autohaler	IVAX (TEVA)
* Qvar Easibreathe	IVAX (TEVA)
* Qvar	IVAX (TEVA)
*+Clenil Modulite	Trinity Chiesi

Beclometasone Alternate device	**Manufacturer**
* Aerobec Autohaler	3M (IVAX/TEVA)
* Beclazone EasiBreathe	IVAX (TEVA)
* Pulvinal Beclometasone	Trinity Chiesi
* Becodisks™ Diskhaler™	GlaxoSmithKline
* Easyhaler Beclometasone	Ranbaxy
* Cyclohaler Becometasone	TEVA (IVAX)
* Asmabec Clickhaler	UCB

GlaxoSmithKline

Alternatives for Becotide™ MDI and Becloforte™ (beclometasone dipropionate) Metered Dose Inhalers (MDIs) continued

Alternate Corticosteroid	Manufacturer
*+Pulmicort MDI	AstraZeneca
* Pulmicort Turbohaler	AstraZeneca
* Novoliser Budesonide	Meda (Viatris)
* Easyhaler Budesonide	Ranbaxy
* Cyclohaler Budesonide	TEVA (IVAX)
* Alvesco MDI	Altanta
* Asmanex Twisthaler	Schering Plough
*+Flixotide™ Diskhaler™	GlaxoSmithKline
*+Flixotide™ Accuhaler™	GlaxoSmithKline
*+Flixotide™ Evohaler™	GlaxoSmithKline

* One or more pack is indicated for children aged 12 years and under

+ One or more pack is indicated for children aged 5 years and under

Please note: This is not an exhaustive list of alternatives.

You may need to ensure that you have supplies of placebo devices to support this transition. These are available from the manufacturers. You can order Allen & Hanburys placebo devices by calling 0800 221 441. Please note it is necessary for a GMC-registered physician to countersign the request for placebo devices.

Healthcare Professionals wishing further information and guidance on transferring patients to alternative products can call the GlaxoSmithKline Customer Contact Centre on 0800 221 441.

BCT/LTR/06/26816/1 July 2006

GlaxoSmithKline

GSK Communications

March 2007

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March 2007

Dear Healthcare Professional,

REMINDER: Discontinuation of 50mcg, 100mcg and 200mcg *Becotide™* and 250mcg *Becloforte™* (beclometasone dipropionate) Metered Dose Inhalers (MDIs)

You will have previously received a communication from GlaxoSmithKline regarding the discontinuation of *Becotide* and *Becloforte*. This is to remind you that we anticipate stocks will cease to be available **from** the following dates:

- *Becotide 50 mcg - June 2007*
- *Becotide 100, 200 mcg - July 2007*
- *Becloforte - October 2007*

To ensure that patients' asthma management is not compromised, please make sure that patients on *Becotide/Becloforte MDI* are transferred to an alternative device and/or treatment that allows appropriate control of the patient's respiratory condition. This may require an adjustment to the dose for certain beclometasone products. Patients who are switched to a different device or medicine should be monitored frequently in the normal way for the emergence or worsening of symptoms, or adverse events.

Please find attached the list of alternatives for *Becotide* and *Becloforte* to help you with this process.

Healthcare Professionals wishing further information and guidance on transferring patients to alternative products can call the GlaxoSmithKline Customer Contact Centre on 0800 221 441.

Yours faithfully

Alternatives for Becotide™ and Becloforte™ (beclometasone dipropionate) Metered Dose Inhalers (MDIs) continued

Alternate Corticosteroid	Manufacturer
Pulmicort MDI	AstraZeneca
Pulmicort Turbohaler	AstraZeneca
Novoliser Budesonide	Meda (Viatris)
Easyhaler Budesonide	Ranbaxy
Cyclohaler Budesonide	TEVA (IVAX)
Alvesco MDI	Altana
Asmanex Twisthaler	Schering Plough
Flixotide™ Diskhaler™	GlaxoSmithKline
Flixotide™ Accuhaler™	GlaxoSmithKline
Flixotide™ Evohaler™	GlaxoSmithKline

Please note: This is not an exhaustive list of alternatives, please consult individual SPCs for detailed prescribing guidance on indications, age ranges and dosage information of suggested alternatives.

You may need to ensure that you have supplies of placebo devices to support this transition. These are available from the manufacturers. You can order Allen & Hanburys placebo devices by calling 0800 221 441. Please note it is necessary for a GMC-registered physician to countersign the request for placebo devices from GSK.

Healthcare Professionals wishing further information and guidance on transferring patients to alternative products can call the GlaxoSmithKline Customer Contact Centre on 0800 221 441.

BCT/LTR/07/30074/1 March 2007

GlaxoSmithKline

Alternatives for Becotide™ and Becloforte™ (beclometasone dipropionate) Metered Dose Inhalers (MDIs)

Becotide / Becloforte MDIs are inhaled corticosteroids for use in the prophylactic management of mild, moderate, or severe asthma.

As you are aware, Allen and Hanburys will cease supply of all strengths of *Becotide / Becloforte* MDIs from its respiratory portfolio from the second half of 2007.

This discontinuation should not compromise patients' asthma management as a range of alternatives are available. Health care professionals will need to make sure that patients on *Becotide / Becloforte* MDIs are transferred to an alternative device and/or treatment that allows control of the patient's respiratory condition. This may require an adjustment to the dose for certain beclometasone products. Patients who are switched to a different device or medicine should be monitored frequently in the normal way for the emergence or worsening of symptoms, or adverse events. Please find below a list of possible alternatives to consider when switching patients from *Becotide / Becloforte* MDIs.

Please consult individual SPCs for detailed prescribing guidance on indications, age ranges and dosage information of suggested alternatives.

Beclometasone CFC MDIs	**Manufacturer**
Filair	3M (IVAX/TEVA)
Beclazone	IVAX (TEVA)
Beclometasone Neohaler	Neolabs
Unbranded generic	Various

Beclometasone CFC-free MDIs	**Manufacturer**
Qvar Autohaler	IVAX (TEVA)
Qvar Easibreathe	IVAX (TEVA)
Qvar	IVAX (TEVA)
Clenil Modulite	Trinity Chiesi

Beclometasone Alternate device	**Manufacturer**
Aerobec Autohaler	3M (IVAX/TEVA)
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