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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
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Dear Sir or Madam:

CITIZEN PETITION

The undersigned submits this Petition on behalf of GlaxoSmithKline, which markets the inhaled corticosteroids FLOVENT[®] (fluticasone propionate), BECLOVENT[®] (beclomethasone dipropionate) and the combination drug product ADVAIR[™] (fluticasone propionate and salmeterol), under 21 C.F.R. § 10.30, to request that the Food and Drug Administration take specified action.

A. Action Requested

Petitioner requests that FDA remove the "Black box" surrounding the warning information in the prescribing information for inhaled corticosteroids but retain the warning information contained within the "box."^{*}

* For example, contained within the "black box" warning for FLOVENT Inhalation Aerosol it states: "Particular care is needed for patients who are transferred from systemically active corticosteroids to FLOVENT Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone propionate inhalation aerosol may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack."

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B. Statement of Grounds

GlaxoSmithKline holds approved New Drug Applications (NDAs) for the inhaled corticosteroids, FLOVENT[®] Inhalation Aerosol, FLOVENT[®] ROTADISK[®], FLOVENT[®] DISKUS[®], BECLOVENT[®] Inhalation Aerosol and the combination drug product ADVAIR[™] DISKUS[®] (fluticasone propionate and salmeterol). Current national and international guidelines recommend inhaled corticosteroids as the most effective medication for the long-term control of persistent asthma. This recommendation stems in part from clinical data that substantiates their effectiveness in pulmonary function and symptom control. In addition, epidemiological data have demonstrated their ability to impact asthma morbidity, for example, with associated decreases in emergency room visits and hospitalizations, and perhaps more importantly, decreases in mortality. It is therefore plausible that these recognized beneficial effects of inhaled steroids have played, in part, a role in their widespread acceptance as first line asthma therapy in the United States, as well as many European countries and Canada.

However, since the introduction in 1979 of the first inhaled corticosteroid (ICS) in the United States, beclomethasone dipropionate (BDP) inhalation aerosol, labeling for the marketed products, Beclovent[®] (Glaxo) and Vanceril[®] (Schering), has carried a boxed warning. The intent of this warning was to alert physicians to take particular care when transferring patients from systemically active corticosteroids to BDP by inhalation, i.e. to a product with less systemically bioavailable corticosteroid. The warning further pointed out that after withdrawal from systemic corticosteroids, a number of months are required for functional recovery of the hypothalamic-pituitary-adrenal (HPA) axis. The warning also stressed that patients on high doses of oral corticosteroids, e.g. 20mg or more per day of prednisone, were at particular risk of adrenal insufficiency when exposed to markedly stressful situations e.g. trauma, surgery. Although recognizing the intent and need for a warning label, many health care providers and consumers have attached inappropriate negative connotations to the mere presence of the "Black box," and either do not prescribe or are reluctant to accept any drug bearing a "Black Box." This reluctance persists despite guidelines from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), which advocate inhaled steroids as the most effective treatment for persistent asthma.

As an analogy that exemplifies the unintentional adverse impact of labeling, three years ago the FDA convened jointly the Pulmonary/Allergy and Endocrine Drug Advisory Committees to discuss growth effects of inhaled and intranasal corticosteroids, and proposed class labeling. Although the overarching intent was to inform the public of their potential risks, and encourage physicians who used these agents in children to monitor growth, the Agency expressed concern that the revised labeling might unintentionally create an unnecessary degree of reluctance and fear among health care providers in using these effective therapies. Just as importantly, there was the concern that a "steroid phobia" might develop in parents of asthmatics, so as to not readily accept this form of therapy for their children. It is our concern that an excessive amount of fear is attached to the presence of the "Black box," rather than the warning it contains. It is our belief that more physicians would be willing to prescribe and more patients willing to accept this form of therapy were the "Black box" to be removed. We however, do agree that the warning contained therein is appropriate so as to remind prescribers of the

potential risks that may occur when transitioning patients from systemic to inhaled steroids. We believe that the "Black box" can be safely removed, as physicians are familiar with the role and use of inhaled steroids in asthma, and generally recognize that oral steroid tapering is required when instituting the inhaled drug. This familiarity and recognition of the requirement for systemic steroid tapering becomes evident as exemplified in the evolution of asthma treatment, such as described in medical textbooks.

The treatment of asthma has significantly evolved since the 1970's, which is particularly pertinent to this petition. First, no oral corticosteroid-sparing medications were available during this early period. Cromolyn sodium had not been demonstrated (nor has it ever been demonstrated) to possess oral steroid-sparing properties; and data indicating that theophylline could be of some usefulness in reducing systemic corticosteroids were not available. For these reasons, far more patients were likely to be maintained on regular therapy with prednisone (or its equivalent) than is the case today. However, even during this period, the impact of systemic steroids on the HPA axis was clearly recognized, and recommendations for their use in asthma management were well delineated. For example, in the 18th edition of Harvey's *Principles and Practice of Medicine*, which was published in 1972, maintenance therapy with prednisone was suggested, if necessary, for patients with "incomplete remissions...[and] manifestations of airway obstruction."¹ A copy of the relevant pages (p.409-416) are attached hereto as Appendix A. Doses of 7.5 to 15 mg per day were felt to be adequate. However, as was also stated, "Prednisone should be used no longer than necessary, and full precautions should be taken to detect and control its side effects."¹ Thus, even in 1972, recommendations for the chronic treatment of asthma emphasized a reduction in the dose and duration of oral corticosteroids because of potential side effects. It can therefore be presumed that those recommendations represented the current teaching in asthma management to medical trainees and practicing physicians.

At the time of BDP's introduction in the USA in 1979 with its boxed warning, physicians may not have been universally aware of the fact that inhaled drug was associated with a markedly reduced systemic load of the corticosteroid, when compared to an oral preparation. However, by 1983 a slight shift in the management of chronic asthma had occurred. For example, in the 10th edition of *Harrison's Principles of Internal Medicine*, which was published in 1983, an alternate-day schedule with oral steroids was advocated to minimize side effects.² A copy of the relevant pages (p.1512-19) are attached hereto in Appendix A. The use of inhaled beclomethasone was also described in this 1983 textbook, but not for any steroid-sparing potential. Nevertheless, at that time, i.e. 1979-1980, the general medical opinion and teaching was that inhaled corticosteroids at prescribed dosages have little if any systemic impact and that systemic side effects were extremely rare. Moreover, during this period, when discussed at medical forums, some medical opinion leaders posited the use of inhaled BDP as a means to minimize the dosages of required oral corticosteroid.

This medical viewpoint apparently became much more commonplace as was exemplified with the printing of the 12th edition of *Harrison's Principles of Internal Medicine* in 1991. Inhaled corticosteroids were viewed as a way "...to greatly facilitate the withdrawal of oral agents" and as an "...alternative to corticosteroids in situations where asthma symptoms are escalating."³ A copy of the relevant pages (p.1047-53) are attached hereto in Appendix A. The current viewpoint held at that time, regarding the

effects of inhaled corticosteroids on the HPA axis was that "Hyperadrenal corticism and adrenal suppression are not major issues."³

Only in the mid to late 1980's and the 1990's did papers begin to appear in the literature indicating that systemic adverse effects from ICS could occur in some patients at higher dosages, and that some body systems (e.g. growth) were more susceptible to those effects than others. Medical education had long acknowledged and emphasized the risks of systemic corticosteroids in asthma management and thus, had consequently evolved. This evolution occurred first, with the recommendation of alternate-day steroid use and, during the last two decades, supplanting oral steroids with the inhaled product. Moreover, warnings in the package insert of inhaled corticosteroids, present since their initial introduction into the US marketplace, have also emphasized the requirement to not abruptly transfer patients from maintenance systemic steroids to an inhaled corticosteroid. In addition, a study by Noonan et al., from which portions of the data were included in the prescribing information for Flovent[®], demonstrated that patients receiving chronic oral steroid therapy, were able to tolerate small (2.5 mg), weekly tapering of prednisone without sustaining episodes of adrenal crisis.⁴ A copy of the relevant pages are attached hereto in Appendix B. Hence, the published medical literature also emphasized the importance of the slow taper when supplanting the oral with the inhaled product.

Current market research data also indicates that physicians today are aware of the need to minimize the use of systemic steroids in chronic asthma management, and to taper oral steroids gradually when either initiating inhaled corticosteroid (ICS) therapy or when the patient is already on an ICS. GlaxoSmithKline recently commissioned a marketing research and consulting firm, Vendanta Associates, Inc., to conduct a survey in order to assess current physician knowledge and practices with regard to the discontinuation of oral steroid medication among patients with respiratory disorders. The specific objectives of the survey were: 1) to assess current physician practices with respect to the transition of asthma patients from oral steroid medications to inhaled corticosteroids, 2) to determine if differences in treatment practices exist among key physician specialties, and 3) to understand how treatment practices may vary by patient type or level of asthma severity. Two hundred ninety-one physicians were surveyed, of whom one-fifth were asthma specialists (allergists and pulmonologists), and the remainder were primary-care physicians (PCPs) or pediatricians (PEDs). Their medical practices spanned urban, suburban, and rural geographical regions. A report of the research is attached hereto as Appendix C.

The physicians reported that of the patients they see in an average month for "respiratory or breathing problems" an average of 5.3% were taking an oral corticosteroid (OCS); the specialists saw twice as many patients on an OCS as did the PCPs or PEDs. This infrequent use of OCS is in keeping with current national asthma guidelines, which reserve the use of OCS only for patients with severe-persistent asthma or for short courses when treating asthma exacerbations. When queried as to "What risks, if any, are associated with discontinuing the use of oral steroid medications," over half (56.7%) the physicians cited HPA-axis suppression as a risk; 8.5% indicated "none/no risk." On the other hand, when physicians were specifically asked how often they worry about the risk of HPA-axis suppression when using OCS, nearly 3 out of 4 physicians surveyed reported "sometimes" or "always" worrying about this risk. However, the physicians who indicated "none/no risk" with discontinuing an OCS tended to be pediatricians, who

predominantly prescribe/use short burst OCS regimens seasonally to control asthma exacerbations (84.9% of OCS use).

This high use by pediatricians of short bursts is also supported by the Scott-Levin Physician Drug and Diagnosis Audit (PDDA) market research data. This audit is a monthly survey of approximately 3400 physicians from 29 specialties, in which they describe various aspects that include diagnoses, drugs prescribed, and switching behaviors. A portion of this research is attached hereto as Appendix D. In fact, of all the physicians surveyed by Vendanta Associates, Inc., oral steroids were used as short bursts in 69.4% of their patients (Appendix C). These observations are supported by the Scott-Levin market research data. For example, in an analysis of the PDDA data from December, 1999 through September, 2000, regarding the relationship of long-term concomitant use of ICS and oral steroids, it was reported that 5.8% of all steroid use was in combination with an ICS medication. Conversely, 7.5% of ICS use was with an oral steroid (Appendix D). When these data were analyzed over a longer timeframe, that is, from December, 1997 through September, 2000, the findings were similar; 4.8% of all steroid use was in combination with an ICS, whereas 6.5% of ICS use was with an oral steroid (Appendix D). This suggests that long-term concomitant usage of oral and inhaled steroids appears to be fairly rare.

In patients who were receiving a short course (15-28 days) of an OCS, administered at a low dose (<20 mg/day), and were either already taking or were being initiated on an ICS, when the physician decided to discontinue the OCS, he/she tapered the OCS over 1-2 weeks. In contrast, similar patients (i.e. already taking or being initiated on an ICS) currently on a long course (>28 days) of an OCS at a high dose (≥ 20 mg/day) were tapered off the OCS (when clinically warranted) over 3 to 4 weeks, or longer (See Appendix C). "Across all specialties sampled and all locations, physicians consistently reported the need to taper oral steroid use when discontinuing therapy. This was particularly true when high doses were used over long time periods." This awareness by the physicians probably explained in part, the relatively infrequent occurrence of clinically significant adrenal insufficiency following OCS withdrawal. Episodes of adrenal insufficiency that were reported did not appear to be related to ignorance on the part of the physician regarding their association with systemic steroid withdrawal. It is arguable that physicians may need more education on how to taper systemic steroids when used for extended periods. However, the data seems clear that physicians are aware of the need to taper the steroids following their prolonged use.

Physician awareness of the role of inhaled corticosteroids, and the decreasing use of oral steroids in the long-term treatment of asthmatics, possibly explain why current medical textbooks devote little discussion to the topic of oral steroid use in chronic asthma management.

For example, as stated in the latest, 14th edition of *Harrison's Principles of Internal Medicine* (McGraw-Hill, 1998), where the role of glucocorticoids in asthma was described, "Systemic or oral steroids are most beneficial in acute illness...and in chronic disease when there has been failure of a previously optimal regimen with frequent recurrences of symptoms of increasing severity."⁵ A copy of the relevant pages (p.1419-26) are attached hereto in Appendix A. In this chapter on asthma, mention is also made that; "Several inhaled steroids... are available [which] greatly facilitate the withdrawal of oral agents"⁵ (Appendix A)

Regarding the pharmacological approach to the chronic treatment of asthma, the textbook described the addition of inhaled steroids for those patients in whom "as needed" inhaled sympathomimetics were insufficient. This regimen is in turn followed by the addition of "... long-acting inhaled beta₂ agonists, sustained-release theophylline, and/or parasympatholytics. In patients with recurrent or perennial symptoms and unstable lung function, oral steroids in a single daily dose are added to the regimen. Once control is reached and sustained for several weeks, a step-down reduction in therapy should be undertaken, beginning with the most toxic drug, to find the minimum amount of medication required to keep the patient well. During this process, the PEFR should be monitored and medication adjustments should be based on objective changes in lung function as well as on the patient's symptoms." Thus, current medical textbooks emphasize the need for close patient monitoring during the withdrawal of systemic steroids.

In an even more recent textbook, Murray JF and Nadel JA's *Textbook of Respiratory Medicine*, 3rd Edition (W.B. Sanders 2000, page 1278) the subject of tapering high dose oral corticosteroids is not included, and the only relevant advice given is: "And pharmacologic therapy must be adjusted periodically to maintain optimal control with minimal risk of toxicity" ⁶. A copy of the relevant pages (p.1247, 1274-78) are attached hereto in Appendix A. Likewise, in the chapter on Asthma by Wenzel SE, in Kelley's *Textbook of Internal Medicine*, 4th Edition (Lippincott Williams and Wilkins [2000, page 2432]), systemic corticosteroids are described as "Quick-relief medications", rather than for chronic therapy⁷. A copy of the relevant pages (p.2427-33) are attached hereto in Appendix A.

In summary, although in none of the recent textbooks of medicine or respiratory medicine that were reviewed was there any explicit discussion of the risk of adrenal crisis when transferring patients from a long term oral to inhaled corticosteroid therapy, the need to withdraw the oral agent was implied.

Current asthma treatment guidelines, both national (e.g. NHLBI's Expert Panel Report 2 (EPR2), 1997) and international (e.g. NHLBI/WHO Workshop report: Global Initiative for Asthma, 1995) appear not to perceive the transfer of patients from oral to inhaled corticosteroids as an area for significant further education. Little or no space is devoted to this topic, especially in the U.S. guidelines. As described in the Expert Panel Report II (p.59), "Corticosteroids: Most potent and effective antiinflammatory medication currently available. Inhaled form is used in the long-term control of asthma. Systemic corticosteroids are often used to gain prompt control of the disease when initiating long-term therapy". A copy of the relevant pages (p.58-62, 82-92) is attached hereto as Appendix E. It is of note that this situation is strikingly different from the pharmacologic therapy that prevailed in 1979, when oral corticosteroids were widely used for long-term treatment of severe asthma. The EPR2 continues (p.82), "Maintaining Control of Asthma: Once control is achieved and sustained for several weeks or months, a reduction in pharmacologic therapy – a step down – is appropriate and helpful to identify the minimum therapy for maintaining control. Reduction in therapy should be gradual because asthma can deteriorate at a highly variable rate and intensity." (Appendix E) It is of interest that no guidance was given for the rate of reduction of oral corticosteroids. However, recommendations are given for reducing the dose of inhaled corticosteroids, perhaps a reflection of the change in therapeutic strategies that have occurred over the last 20 years (Appendix E).

In the Global Initiative for Asthma (GINA) Guidelines, NIH 1995, there is only a brief mention relative to reduction of oral corticosteroid dosages (p.80): "Although it is rare, adrenal failure may occur when a patient is withdrawn from long-term suppressive doses of oral corticosteroids. Any such withdrawal should thus be observed for clinical and laboratory evidence of adrenal insufficiency" (Appendix E). In addition, GINA guidelines recommend that when stepping down any asthma therapy (p.90): "Review treatment every 3-6 months. If control is sustained for at least three months, a gradual stepwise reduction in treatment may be possible. (Appendix E). Elsewhere it states (p.96): "Long-term oral corticosteroids should be used in the lowest possible dose (alternate or single daily dose after a 3 to 7 day burst). Persistent trials of high doses of inhaled corticosteroids administered with a spacer device should be made in an attempt to reduce oral corticosteroids. When patients are transferred from oral corticosteroids to high-dose inhaled corticosteroids, they should be monitored closely for evidence of adrenal insufficiency." (Appendix E)

The most recent U.S. published pediatric guidelines, Pediatric Asthma: Promoting Best Practice Guide for Managing Asthma in Children AAAAI/NHLBI/AAP, 1999, does not include warning language or advice on oral steroid dosage reduction when transferring patients from oral to inhaled corticosteroid therapy. It gives some recommendations regarding stepping down asthma therapy in general, the most detailed of which is as follows (p.78):

"Reduce therapy gradually.

How much to reduce therapy is based on evaluation of the child's asthma severity and any special considerations.

- Asthma can deteriorate at a highly variable rate and intensity.
- For inhaled corticosteroids, some physicians suggest decreasing the dose by 25% every 2-3 months to the lowest possible dose to maintain control.
- Carefully follow up." (Appendix E)

Furthermore, in a stepwise approach diagram for treating asthma in children older than 5 years of age with acute or chronic symptoms (p.68): "Corticosteroid tablets or syrup long-term (2mg/kg/day, generally not to exceed 60mg per day); make repeated attempts to reduce systemic corticosteroids and maintain control with high dose inhaled corticosteroids" (Appendix E). The potential for systemic effects with oral steroids is noted. It is therefore suggested (p.72), "Use at lowest effective dose either daily or on alternate days (which may lessen adrenal suppression)."

Summary

We believe that the "Black box" surrounding the warning information about the risks of adrenal insufficiency should be removed from the prescribing information for all inhaled corticosteroids, but that the current text should remain because it provides useful information for physicians that is pertinent to those occasions when asthmatics may be switched from chronic oral corticosteroid to inhaled corticosteroid therapy.

The salient arguments are:

- (i) few asthmatics are currently maintained on chronic OCS therapy;

- (ii) the situation today, in terms of asthma therapy in the USA, is dramatically different from what pertained in 1979-1980;
- (iii) physicians today appear to have a high level of awareness of the need to taper oral corticosteroids gradually, following long-term therapy;
- (iv) current textbooks of medicine and recent national asthma treatment guidelines do not appear to perceive this issue as a significant problem and devote little discussion to it;
- (v) the presence of a Black box may work as a deterrent in the acceptance and appropriate use of the most strongly recommended long-term controller medication; and
- (vi) The use of a Black box may distract the attention away from other statements in the full prescribing information, which may be possibly of greater importance given current therapeutic practices and available data today.

C. Environmental Impact

This petition simply requests that FDA provide for a modest reformatting of prescription drug labeling for a particular class of asthma medications, in line with current medical science and understandings. Because the effect should be to bring the prominence of certain warning information in line with consensus views, with the availability of the drugs remaining unchanged, the action requested qualifies for a categorical exclusion, pursuant to 21C.F.R. § 25.31 (a); to the petitioner's knowledge, no extraordinary circumstances exist.

D. Economic Impact

Information on the economic impact of the requested action will be submitted upon request of the Commissioner of the Food and Drug Administration.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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