

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**21-077/S017**

***Trade Name:*** Advair Diskus 100/50

***Generic Name:*** fluticasone propionate and salmeterol

***Sponsor:*** GlaxoSmithKline

***Approval Date:*** 4/21/2004

***Indication:*** For the long-term, twice-daily, maintenance treatment of asthma in patients 4 years of age and older.

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21-077/S017**

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*APPLICATION NUMBER:*

**21-077/S017**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-077/S-017

GlaxoSmithKline  
P. O. Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Attention: Lorna C. Wilson  
Director, US Regulatory Affairs

Dear Ms. Wilson:

Please refer to your supplemental new drug application dated June 26, 2003, received June 27, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair Diskus 100/50 (fluticasone propionate 100 and salmeterol 50 mcg inhalation powder).

We acknowledge receipt of your submissions dated October 24, 2003, and March 9, 11, and 30, and April 1, 2004, and 16, 2004.

This supplemental new drug application provides for the use of Advair Diskus 100/50 mcg in children 4 to 11 years of age with asthma.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, as submitted on April 1, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-077/S-017." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for children under the age of 4 years, since this formulation is not appropriate for this age group.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Pulmonary & Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure (Package insert)

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Badrul Chowdhury  
4/21/04 04:03:00 PM

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RESEARCH**

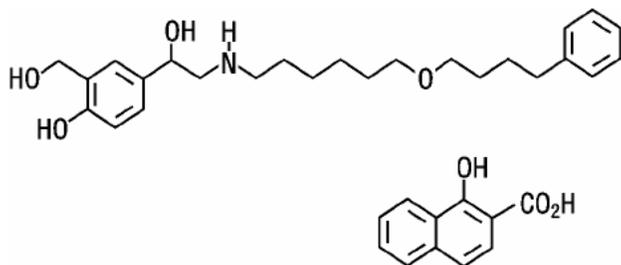
*APPLICATION NUMBER:*

**21-077/S017**

**LABELING**



35 of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- $\alpha^1$ -[[[6-(4-phenylbutoxy)  
36 hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has  
37 the following chemical structure:  
38



39  
40  
41 Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the  
42 empirical formula is  $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ . It is freely soluble in methanol; slightly soluble in  
43 ethanol, chloroform, and isopropanol; and sparingly soluble in water.

44 ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are  
45 specially designed plastic devices containing a double-foil blister strip of a powder formulation  
46 of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister  
47 on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone  
48 propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of  
49 salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins).  
50 Each blister contains 1 complete dose of both medications. After a blister containing medication  
51 is opened by activating the device, the medication is dispersed into the airstream created by the  
52 patient inhaling through the mouthpiece.

53 Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg  
54 of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS  
55 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.  
56 In adult patients with obstructive lung disease and severely compromised lung function (mean  
57 forced expiratory volume in 1 second [FEV<sub>1</sub>] 20% to 30% of predicted), mean peak inspiratory  
58 flow (PIF) through a DISKUS<sup>®</sup> inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

59 Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to  
60 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF  
61 of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with  
62 asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range,  
63 49.0 to 104.8 L/min) for the 4-year-old patient set (N = 20) and 107.3 L/min (range, 82.8 to  
64 125.6 L/min) for the 8-year-old patient set (N = 20).

65 The actual amount of drug delivered to the lung will depend on patient factors, such as  
66 inspiratory flow profile.

67 **CLINICAL PHARMACOLOGY**

68 **Mechanism of Action: ADVAIR DISKUS:** Since ADVAIR DISKUS contains both  
69 fluticasone propionate and salmeterol, the mechanisms of action described below for the  
70 individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of  
71 medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor  
72 agonist) that have different effects on clinical and physiological indices.

73 **Fluticasone Propionate:** Fluticasone propionate is a synthetic trifluorinated corticosteroid  
74 with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations  
75 have established fluticasone propionate as a human glucocorticoid receptor agonist with an  
76 affinity 18 times greater than dexamethasone, almost twice that of  
77 beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone  
78 dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor  
79 assay in man are consistent with these results.

80 Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have  
81 been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes,  
82 macrophages, and neutrophils) and mediator production or secretion (e.g., histamine,  
83 eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These  
84 anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

85 Inflammation is also a component in the pathogenesis of chronic obstructive pulmonary  
86 disease (COPD). In contrast to asthma, however, the predominant inflammatory cells in COPD  
87 include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in  
88 the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone  
89 propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of  
90 COPD.

91 **Salmeterol Xinafoate:** Salmeterol is a long-acting beta<sub>2</sub>-adrenergic agonist. In vitro studies  
92 and in vivo pharmacologic studies demonstrate that salmeterol is selective for  
93 beta<sub>2</sub>-adrenoceptors compared with isoproterenol, which has approximately equal agonist  
94 activity on beta<sub>1</sub>- and beta<sub>2</sub>-adrenoceptors. In vitro studies show salmeterol to be at least 50 times  
95 more selective for beta<sub>2</sub>-adrenoceptors than albuterol. Although beta<sub>2</sub>-adrenoceptors are the  
96 predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-adrenoceptors are the  
97 predominant receptors in the heart, there are also beta<sub>2</sub>-adrenoceptors in the human heart  
98 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors  
99 has not been established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists  
100 may have cardiac effects.

101 The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including salmeterol, are at  
102 least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes  
103 the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic  
104 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition  
105 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

106 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast  
107 cell mediators, such as histamine, leukotrienes, and prostaglandin D<sub>2</sub>, from human lung.  
108 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits  
109 platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when  
110 administered by the inhaled route. In humans, single doses of salmeterol administered via  
111 inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

112 **Pharmacokinetics: ADVAIR DISKUS: Adult and Adolescent Patients 12 Years of**  
113 **Age and Older:** Following administration of ADVAIR DISKUS to healthy adult subjects, peak  
114 plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours and those of  
115 salmeterol were achieved in about 5 minutes.

116 In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was  
117 administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were  
118 administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol  
119 powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean  
120 peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL,  
121 respectively, and of salmeterol averaged 200 and 150 pg/mL, respectively, indicating no  
122 significant changes in systemic exposures of fluticasone propionate and salmeterol.

123 In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was  
124 administered to 45 adolescent and adult patients with asthma. One (1) inhalation twice daily of  
125 the following treatments was administered: ADVAIR DISKUS 500/50, fluticasone propionate  
126 powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate  
127 powder 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate  
128 averaged 57, 73, and 70 pg/mL, respectively, indicating no significant changes in systemic  
129 exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in  
130 this repeat-dose study.

131 No significant changes in excretion of fluticasone propionate or salmeterol were observed.  
132 The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR  
133 DISKUS was administered, which is similar to that reported when fluticasone propionate was  
134 given concurrently with salmeterol or when fluticasone propionate was given alone (average,  
135 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of  
136 ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

137 **Pediatric Patients:** In a clinical study conducted in patients with asthma aged 4 to  
138 11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes  
139 after dosing with 50 and 100 mcg of fluticasone propionate inhalation powder twice daily using  
140 the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the  
141 plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma concentrations at the  
142 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

143 **Special Populations:** Formal pharmacokinetic studies using ADVAIR DISKUS have  
144 not been conducted to examine gender differences or in special populations, such as elderly  
145 patients or patients with hepatic or renal impairment.

146 **Drug Interactions:** In the repeat- and single-dose studies, there was no evidence of  
147 significant drug interaction in systemic exposure between fluticasone propionate and salmeterol  
148 when given as ADVAIR DISKUS.

149 **Fluticasone Propionate: Absorption:** Fluticasone propionate acts locally in the lung;  
150 therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled  
151 and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone  
152 propionate is negligible (<1%), primarily due to incomplete absorption and presystemic  
153 metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered  
154 to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from  
155 the DISKUS device in healthy volunteers averages 18%.

156 Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma  
157 (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone  
158 propionate inhalation powder using the DISKUS device. The mean fluticasone propionate  
159 plasma concentration was 110 pg/mL.

160 Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD  
161 averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily  
162 (N = 30) via the DISKUS device.

163 **Distribution:** Following intravenous administration, the initial disposition phase for  
164 fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding.  
165 The volume of distribution averaged 4.2 L/kg.

166 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.  
167 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly  
168 bound to human transcortin.

169 **Metabolism:** The total clearance of fluticasone propionate is high (average,  
170 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only  
171 circulating metabolite detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone  
172 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had  
173 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of  
174 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other  
175 metabolites detected in vitro using cultured human hepatoma cells have not been detected in  
176 man.

177 **Elimination:** Following intravenous dosing, fluticasone propionate showed  
178 polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours.  
179 Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the  
180 remainder excreted in the feces as parent drug and metabolites.

181 **Special Populations: Hepatic Impairment:** Since fluticasone propionate is  
182 predominantly cleared by hepatic metabolism, impairment of liver function may lead to  
183 accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease  
184 should be closely monitored.

185 **Gender:** Full pharmacokinetic profiles were obtained from 9 female and 16 male  
186 patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using  
187 the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg  
188 twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

189 **Age:** No relationship between fluticasone propionate systemic exposure and age was  
190 observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

191 **Other:** Formal pharmacokinetic studies using fluticasone propionate have not been  
192 conducted in other special populations.

193 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.  
194 Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor  
195 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18  
196 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was  
197 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate  
198 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable  
199 (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels ( $C_{max}$   
200 averaged 11.9 pg/mL [range, 10.8 to 14.1 pg/mL] and  $AUC_{(0-\tau)}$  averaged 8.43 pg•hr/mL [range,  
201 4.2 to 18.8 pg•hr/mL]). Fluticasone propionate  $C_{max}$  and  $AUC_{(0-\tau)}$  increased to 318 pg/mL (range,  
202 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,  
203 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This  
204 significant increase in plasma fluticasone propionate exposure resulted in a significant decrease  
205 (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

206 Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are  
207 coadministered with fluticasone propionate. In a drug interaction study, coadministration of  
208 orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted  
209 in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had  
210 no effect on urinary excretion of cortisol.

211 In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone  
212 propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect  
213 fluticasone propionate pharmacokinetics.

214 **Salmeterol Xinafoate:** Salmeterol xinafoate, an ionic salt, dissociates in solution so that the  
215 salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed,  
216 metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma  
217 levels do not predict therapeutic effect.

218 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low  
219 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder  
220 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol  
221 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7  
222 patients with asthma; plasma concentrations were very low, with mean peak concentrations of  
223 167 pg/mL at 20 minutes and no accumulation with repeated doses.

224 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages  
225 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much  
226 higher concentrations than those achieved following therapeutic doses of salmeterol.

227 **Metabolism:** Salmeterol base is extensively metabolized by hydroxylation, with  
228 subsequent elimination predominantly in the feces. No significant amount of unchanged  
229 salmeterol base was detected in either urine or feces.

230 **Elimination:** In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as  
231 salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was  
232 eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination  
233 half-life was about 5.5 hours (1 volunteer only).

234 The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly  
235 protein bound (>99%) and has a long elimination half-life of 11 days.

236 **Special Populations: Hepatic Impairment:** Since salmeterol is predominantly  
237 cleared by hepatic metabolism, impairment of liver function may lead to accumulation of  
238 salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

239 **Other:** Formal pharmacokinetic studies using salmeterol base have not been conducted  
240 in other special populations.

241 **Pharmacodynamics: ADVAIR DISKUS: Adult and Adolescent Patients:** Since  
242 systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose,  
243 higher doses were used to produce measurable effects. Four (4) studies were conducted in  
244 healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR  
245 DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given  
246 concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study  
247 using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a  
248 repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50,  
249 fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose  
250 study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg  
251 alone, or placebo. In these studies no significant differences were observed in the  
252 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and  
253 glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone  
254 propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic  
255 effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR  
256 DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the  
257 hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. No significant  
258 differences across treatments were observed in 24-hour urinary cortisol excretion and, where  
259 measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone  
260 propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy  
261 subjects.

262 **Asthma:** In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12  
263 years of age and older with asthma, no significant differences were observed in the systemic

264 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and  
265 glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and  
266 adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS  
267 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose  
268 and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

269 In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50  
270 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone  
271 propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg  
272 alone. No significant differences across treatments were observed in plasma cortisol AUC after  
273 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

274 In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50  
275 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder  
276 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in  
277 response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with  
278 ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal  
279 response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who  
280 received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients  
281 who received salmeterol.

282 **Chronic Obstructive Pulmonary Disease:** In clinical studies with ADVAIR  
283 DISKUS in patients with COPD associated with chronic bronchitis, no significant differences  
284 were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the  
285 individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS  
286 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the  
287 fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the  
288 placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5)  
289 of these 8 subjects had a prolonged QTc interval at baseline.

290 In a 24-week study, 130 patients with COPD associated with chronic bronchitis received  
291 continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of  
292 twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder  
293 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or  
294 supraventricular arrhythmias and heart rate were observed among the groups treated with  
295 ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the  
296 fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the  
297 group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of  
298 nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone  
299 propionate 500 mcg treatment groups).

300 Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in  
301 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate  
302 powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to  
303 increase cortisol production in response to stress, as assessed by short cosyntropin stimulation,

304 remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR  
305 DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL  
306 assessed by high-performance liquid chromatography) after dosing, compared with 2 patients  
307 (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol  
308 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early  
309 discontinuation from study.

310 **Pediatric Patients:** In a 12-week study in patients with asthma aged 4 to 11 years who  
311 were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was  
312 compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via  
313 the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks  
314 of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol  
315 excretion was also similar between the 2 groups.

316 **Fluticasone Propionate: Asthma:** In clinical trials with fluticasone propionate inhalation  
317 powder using doses up to and including 250 mcg twice daily, occasional abnormal short  
318 cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted  
319 both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence  
320 of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out  
321 with the DISKHALER<sup>®</sup> inhalation device in 64 patients with mild, persistent asthma (mean  
322 FEV<sub>1</sub> 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo,  
323 no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin  
324 infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1  
325 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing  
326 at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had  
327 an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or  
328 2 years.

329 **Chronic Obstructive Pulmonary Disease:** In a 24-week study, the steady-state  
330 fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of  
331 patients with COPD associated with chronic bronchitis (N = 86) randomized to twice-daily  
332 fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate  
333 inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured  
334 across a 12-hour dosing interval following at least 4 weeks of dosing. Serum cortisol  
335 concentrations following 250 and 500 mcg twice-daily dosing were 10% and 21% lower than  
336 placebo, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

337 **Salmeterol Xinafoate:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can  
338 produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium  
339 (see PRECAUTIONS: General). The cardiovascular effects (heart rate, blood pressure)  
340 associated with salmeterol occur with similar frequency, and are of similar type and severity, as  
341 those noted following albuterol administration.

342 **Asthma:** The effects of rising doses of salmeterol and standard inhaled doses of albuterol  
343 were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg

344 administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the  
345 same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and  
346 adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent  
347 continuous electrocardiographic monitoring during two 12-hour periods after the first dose and  
348 after 1 month of therapy, and no clinically significant dysrhythmias were noted.

349 **Chronic Obstructive Pulmonary Disease:** In 24-week clinical studies in patients  
350 with COPD associated with chronic bronchitis, the incidence of clinically significant  
351 electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically  
352 significant conduction abnormalities, clinically significant arrhythmias) was lower for patients  
353 who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or  
354 ADVAIR DISKUS) compared with placebo (3%, 10 of 370 subjects).

355 No significant differences with salmeterol 50 mcg alone or in combination with fluticasone  
356 propionate as ADVAIR DISKUS 500/50 was observed on pulse rate and systolic and diastolic  
357 blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign  
358 measurements after the first dose (N = 183) and after 12 weeks of therapy (N = 149). Median  
359 changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to  
360 those seen with placebo (see ADVERSE REACTIONS: Chronic Obstructive Pulmonary Disease  
361 Associated With Chronic Bronchitis).

362 Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence  
363 of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when  
364 beta-agonists and methylxanthines are administered concurrently. The clinical significance of  
365 these findings is unknown.

## 366 **CLINICAL TRIALS**

367 **Asthma: Adult and Adolescent Patients 12 Years of Age and Older:** In clinical trials  
368 comparing ADVAIR DISKUS with the individual components, improvements in most efficacy  
369 endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate  
370 or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS  
371 and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from  
372 separate inhalers.

373 **Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or**  
374 **Salmeterol Alone:** Three (3) double-blind, parallel-group clinical trials were conducted with  
375 ADVAIR DISKUS in 1,208 adolescent and adult patients ( $\geq 12$  years, baseline FEV<sub>1</sub> 63% to 72%  
376 of predicted normal) with asthma that was not optimally controlled on their current therapy. All  
377 treatments were inhalation powders, given as 1 inhalation from the DISKUS device twice daily,  
378 and other maintenance therapies were discontinued.

379 **Study 1: Clinical Trial With ADVAIR DISKUS 100/50:** This placebo-controlled,  
380 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,  
381 fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to  
382 baseline asthma maintenance therapy; patients were using either inhaled corticosteroids

383 (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;  
 384 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)  
 385 or salmeterol (N = 106). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR  
 386 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and  
 387 placebo, 2.15 L.

388 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were  
 389 utilized for this placebo-controlled study. Worsening asthma was defined as a clinically  
 390 important decrease in FEV<sub>1</sub> or peak expiratory flow (PEF), increase in use of VENTOLIN<sup>®</sup>  
 391 (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency  
 392 intervention or hospitalization due to asthma, or requirement for asthma medication not allowed  
 393 by the protocol. As shown in Table 1, statistically significantly fewer patients receiving  
 394 ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone  
 395 propionate, salmeterol, and placebo.

396

397 **Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**  
 398 **Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

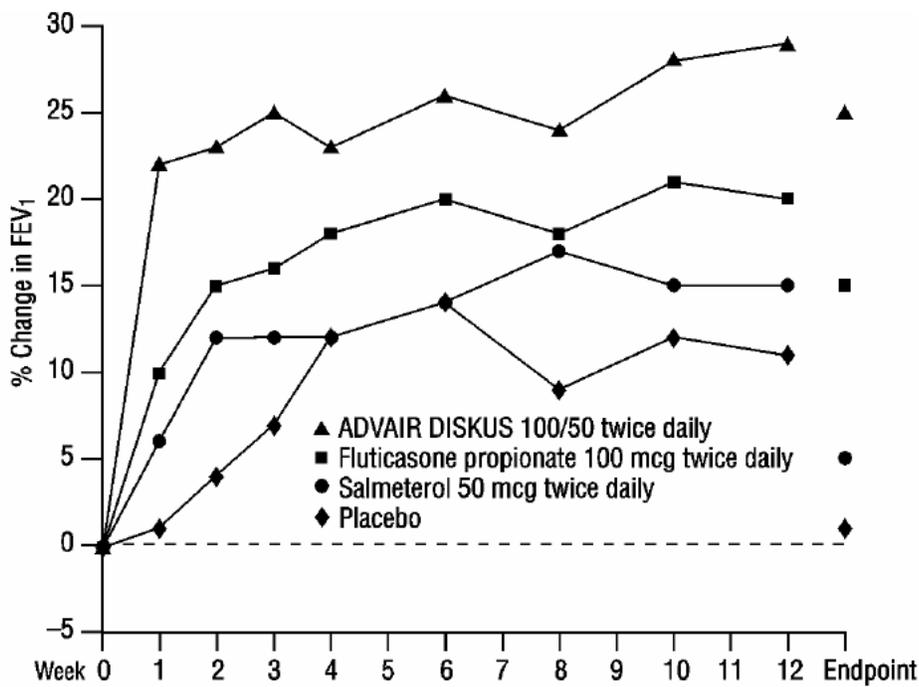
ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

399

400 The FEV<sub>1</sub> results are displayed in Figure 1. Because this trial used predetermined criteria for  
 401 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV<sub>1</sub>  
 402 results at Endpoint (last available FEV<sub>1</sub> result) are also provided. Patients receiving ADVAIR  
 403 DISKUS 100/50 had significantly greater improvements in FEV<sub>1</sub> (0.51 L, 25%) compared with  
 404 fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,  
 405 1%). These improvements in FEV<sub>1</sub> with ADVAIR DISKUS were achieved regardless of baseline  
 406 asthma maintenance therapy (inhaled corticosteroids or salmeterol).

407

408 **Figure 1. Mean Percent Change From Baseline in FEV<sub>1</sub> in Patients With Asthma**  
 409 **Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**  
 410



	Week 0	Week 6	Week 12	Endpoint
	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 100/50	87	79	73	86
Fluticasone propionate 100 mcg	85	71	65	85
Salmeterol 50 mcg	86	59	51	86
Placebo	77	34	27	74

411  
 412  
 413 The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in  
 414 Table 2.  
 415

416 **Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With**  
 417 **Either Inhaled Corticosteroids or Salmeterol (Study 1)**

Efficacy Variable*	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

418 \*Change from baseline = change from baseline at Endpoint (last available data).

419

420 The subjective impact of asthma on patients' perception of health was evaluated through use  
421 of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point  
422 scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS  
423 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as  
424 defined by a difference between groups of  $\geq 0.5$  points in change from baseline AQLQ scores  
425 (difference in AQLQ score of 1.25 compared to placebo).

426 **Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled,  
427 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components,  
428 fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled  
429 corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to  
430 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100  
431 to 1,600 mcg). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR DISKUS  
432 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

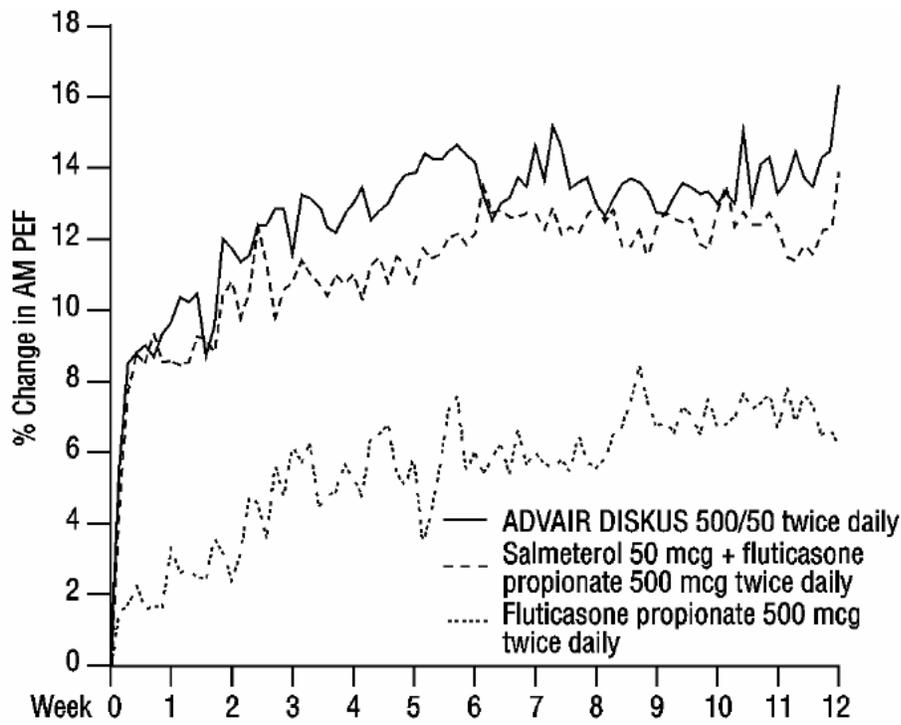
433 Efficacy results in this study were similar to those observed in Study 1. Patients receiving  
434 ADVAIR DISKUS 250/50 had significantly greater improvements in FEV<sub>1</sub> (0.48 L, 23%)  
435 compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and  
436 placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving  
437 ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%)  
438 compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition,  
439 ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for  
440 improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also  
441 had clinically meaningful improvements in overall asthma-specific quality of life as described in  
442 Study 1 (difference in AQLQ score of 1.29 compared to placebo).

443 **Study 3: Clinical Trial With ADVAIR DISKUS 500/50:** This 28-week, non-US  
444 study compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and  
445 concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from  
446 separate inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily  
447 doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg;  
448 flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750  
449 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected  
450 daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect  
451 safety data.

452 Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,  
453 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As  
454 shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50  
455 compared with fluticasone propionate 500 mcg over the 12-week treatment period.  
456 Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to  
457 improvements observed with concurrent therapy.

458

459 **Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory**  
 460 **Flow in Patients With Asthma Previously Treated With Inhaled Corticosteroids**  
 461 **(Study 3)**  
 462



	Week 0	Week 6	Week 12
	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 500/50	167	159	149
Salmeterol 50 mcg + fluticasone propionate 500 mcg	170	160	147
Fluticasone propionate 500 mcg	164	148	136

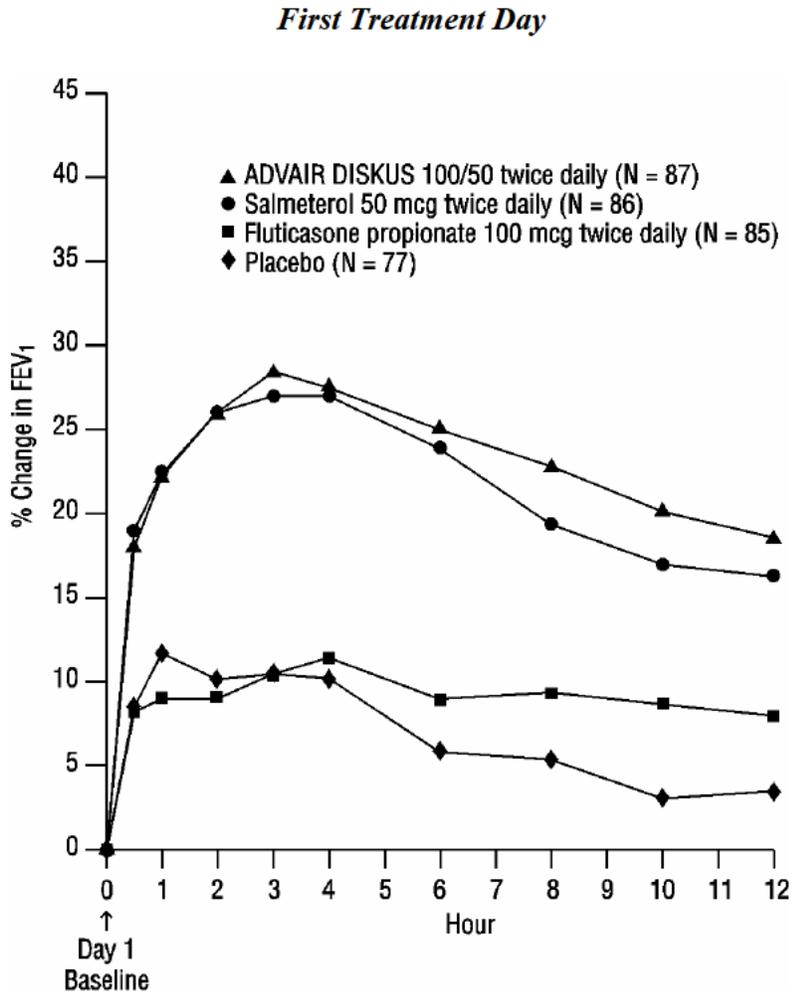
463  
 464  
 465 **Onset of Action and Progression of Improvement in Asthma Control:** The  
 466 onset of action and progression of improvement in asthma control were evaluated in the 2  
 467 placebo-controlled US trials. Following the first dose, the median time to onset of clinically  
 468 significant bronchodilatation ( $\geq 15\%$  improvement in FEV<sub>1</sub>) in most patients was seen within 30  
 469 to 60 minutes. Maximum improvement in FEV<sub>1</sub> generally occurred within 3 hours, and clinically  
 470 significant improvement was maintained for 12 hours (see Figure 3).

471 Following the initial dose, predose FEV<sub>1</sub> relative to Day 1 baseline improved markedly over  
 472 the first week of treatment and continued to improve over the 12 weeks of treatment in both  
 473 studies.

474 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR  
 475 DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV<sub>1</sub> following  
 476 12 weeks of therapy.  
 477

478 **Figure 3. Percent Change in Serial 12-hour FEV<sub>1</sub>**  
479 **in Patients With Asthma Previously Using Either Inhaled**  
480 **Corticosteroids or Salmeterol (Study 1)**

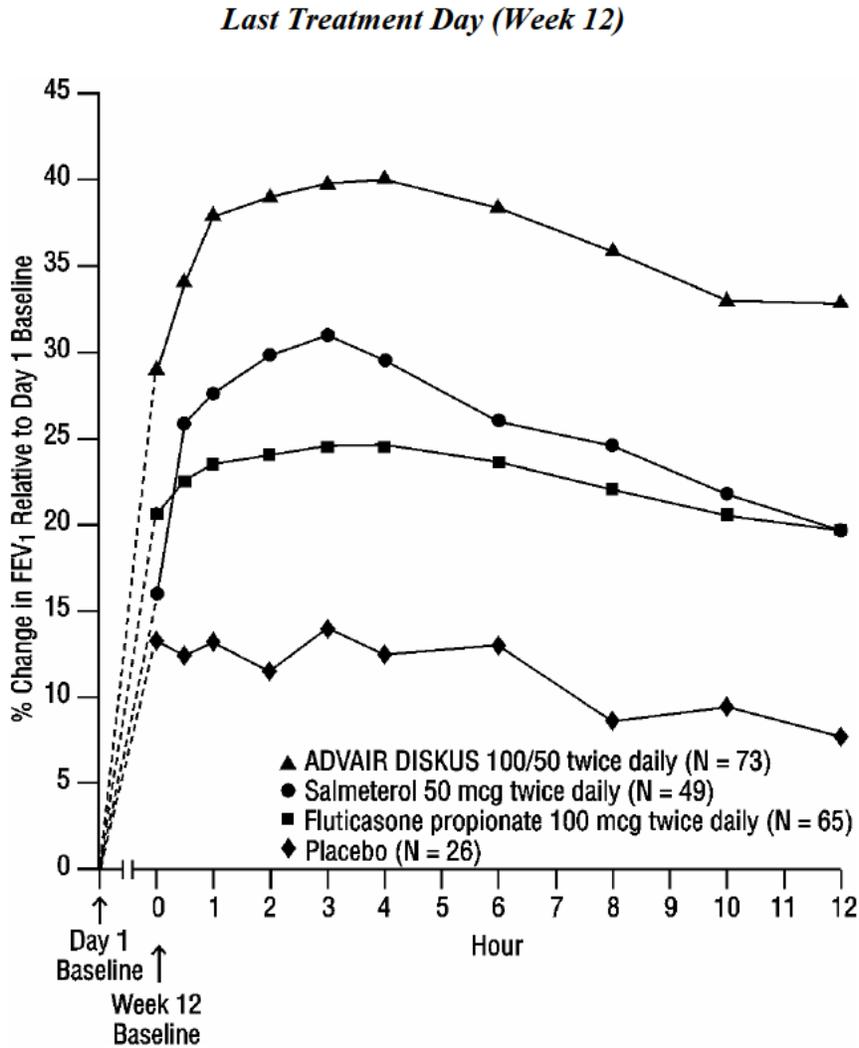
481  
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484  
485

486 **Figure 4. Percent Change in Serial 12-hour FEV<sub>1</sub>**  
 487 **in Patients With Asthma Previously Using Either Inhaled**  
 488 **Corticosteroids or Salmeterol (Study 1)**

489  
 490  
 491



492  
 493

494 Reduction in asthma symptoms, use of rescue VENTOLIN Inhalation Aerosol, and  
 495 improvement in morning and evening PEF also occurred within the first day of treatment with  
 496 ADVAIR DISKUS, and continued to improve over the 12 weeks of therapy in both studies.

497 **Pediatric Patients:** In a 12-week US study, ADVAIR DISKUS 100/50 twice daily was  
 498 compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children  
 499 with asthma aged 4 to 11 years. At study entry, the children were symptomatic on low doses of  
 500 inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to  
 501 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or  
 502 fluticasone propionate 88 to 250 mcg/day). The primary objective of this study was to determine  
 503 the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder

504 100 mcg in this age-group; however, the study also included secondary efficacy measures of  
505 pulmonary function. Morning predose FEV<sub>1</sub> was obtained at baseline and Endpoint (last  
506 available FEV<sub>1</sub> result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS  
507 100/50, FEV<sub>1</sub> increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69)  
508 compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in  
509 patients receiving fluticasone propionate 100 mcg.

510 The findings of this study, along with extrapolation of efficacy data from patients 12 years of  
511 age and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the  
512 maintenance treatment of asthma in patients aged 4 to 11 years.

513 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** In a  
514 clinical trial evaluating twice-daily treatment with ADVAIR DISKUS 250/50 in patients with  
515 COPD associated with chronic bronchitis, improvements in lung function (as defined by predose  
516 and postdose FEV<sub>1</sub>) were significantly greater with ADVAIR DISKUS than with fluticasone  
517 propionate 250 mcg, salmeterol 50 mcg, or placebo. The study was a randomized, double-blind,  
518 parallel-group, 24-week trial. All patients had a history of cough productive of sputum that was  
519 not attributable to another disease process on most days for at least 3 months of the year for at  
520 least 2 years. Study treatments were inhalation powders given as 1 inhalation from the DISKUS  
521 device twice daily. Maintenance COPD therapies were discontinued, with the exception of  
522 theophylline.

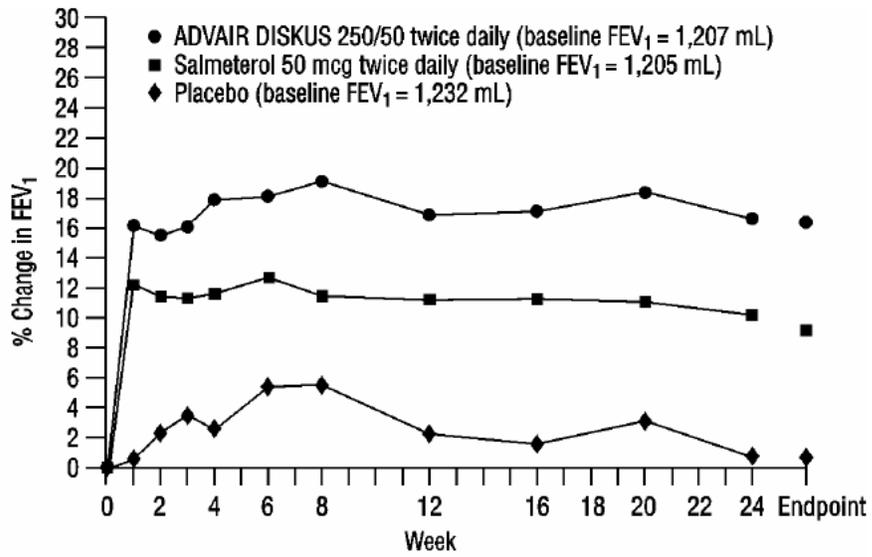
523 Figures 5 and 6 display predose and 2-hour postdose FEV<sub>1</sub> results. To account for patient  
524 withdrawals during the study, FEV<sub>1</sub> at Endpoint (last evaluable FEV<sub>1</sub>) was evaluated. Patients  
525 receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV<sub>1</sub> at  
526 Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL,  
527 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung  
528 function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had  
529 significantly greater improvements in postdose FEV<sub>1</sub> at Endpoint (281 mL, 27%) compared with  
530 fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the  
531 contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS  
532 (Figure 6).

533 A similar degree of improvement in lung function was also observed with ADVAIR DISKUS  
534 500/50 twice daily.

535

536 **Figure 5. Predose FEV<sub>1</sub>: Mean Percent Change From Baseline in Patients**  
 537 **With COPD Associated With Chronic Bronchitis**

538

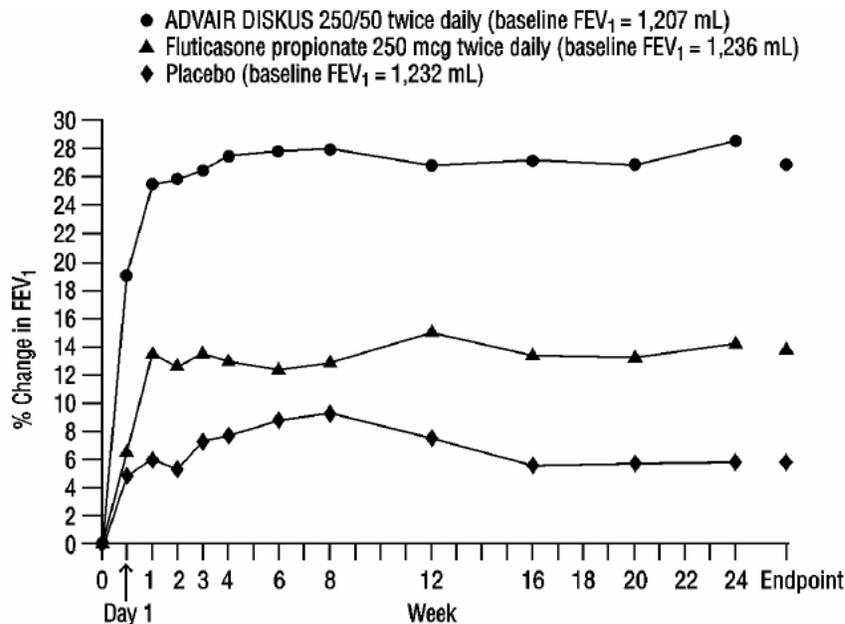


	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

539

540

541 **Figure 6. Two-Hour Postdose FEV<sub>1</sub>: Mean Percent Changes From Baseline**  
 542 **Over Time in Patients With COPD Associated With Chronic Bronchitis**  
 543



	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	117	171
Fluticasone propionate 250 mcg	183	147	130	175
Placebo	185	139	119	172

544  
 545  
 546 Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a  
 547 significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis  
 548 Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo  
 549 over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50  
 550 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of  
 551 more systemic exposure to fluticasone propionate from this higher dose and no documented  
 552 advantage for efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

553 The benefit of treatment of patients with COPD associated with chronic bronchitis with  
 554 ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated.

555 **INDICATIONS AND USAGE**

556 **Asthma:** ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment  
 557 of asthma in patients 4 years of age and older.

558 ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

559 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:**

560 ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow  
 561 obstruction in patients with COPD associated with chronic bronchitis.

562 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of  
 563 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,

564 are not recommended (see DOSAGE AND ADMINISTRATION: Chronic Obstructive  
565 Pulmonary Disease Associated With Chronic Bronchitis).

566 The benefit of treating patients with COPD associated with chronic bronchitis with ADVAIR  
567 DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are  
568 treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods  
569 longer than 6 months should be reevaluated periodically to assess the continuing benefits and  
570 potential risks of treatment.

571 ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

## 572 **CONTRAINDICATIONS**

573 ADVAIR DISKUS is contraindicated in the primary treatment of status asthmaticus or other  
574 acute episodes of asthma or COPD where intensive measures are required.

575 Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see  
576 DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site*  
577 *Specific*).

## 578 **WARNINGS**

579 DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS  
580 STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR  
581 DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR  
582 ASTHMA-RELATED DEATHS. The Salmeterol Multi-center Asthma Research Trial  
583 (SMART) enrolled long-acting beta<sub>2</sub>-agonist-naïve patients with asthma to assess the safety of  
584 salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to  
585 placebo, when added to usual asthma therapy. The primary endpoint was the combined number  
586 of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and  
587 mechanical ventilation). Other endpoints included combined asthma-related deaths or  
588 life-threatening experiences and asthma-related deaths

589 A planned interim analysis was conducted when approximately half of the intended number of  
590 patients had been enrolled (N = 26,353). The analysis showed no significant difference for the  
591 primary endpoint for the total population. However, a higher number of asthma-related deaths or  
592 life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4)  
593 occurred in the patients treated with SEREVENT Inhalation Aerosol. Post hoc subgroup analyses  
594 revealed no significant increase in respiratory- or asthma-related episodes, including deaths, in  
595 Caucasian patients. In African Americans, the study showed a small, though statistically  
596 significantly greater, number of primary events (20 vs. 7), asthma-related deaths or  
597 life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking  
598 SEREVENT Inhalation Aerosol compared to those taking placebo. Even though SMART did not  
599 reach predetermined stopping criteria for the total population, the study was stopped due to the  
600 findings in African American patients and difficulties in enrollment. The data from the SMART  
601 study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as  
602 fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk.

603 Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would  
604 apply to ADVAIR DISKUS.

605 Findings similar to the SMART study findings were reported in a prior 16-week clinical study  
606 performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the  
607 SNS study, the incidence of asthma-related death was numerically, though not statistically,  
608 greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol  
609 (180 mcg 4 times daily) added to usual asthma therapy.

610 Given the similar basic mechanisms of action of beta<sub>2</sub>-agonists, it is possible that the findings  
611 seen in the SMART study may be consistent with a class effect.

612 **1. ADVAIR DISKUS SHOULD NOT BE USED FOR TRANSFERRING PATIENTS**  
613 **FROM SYSTEMIC CORTICOSTEROID THERAPY.** Particular care is needed for patients  
614 who have been transferred from systemically active corticosteroids to inhaled corticosteroids  
615 because deaths due to adrenal insufficiency have occurred in patients with asthma during and  
616 after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.  
617 After withdrawal from systemic corticosteroids, a number of months are required for recovery of  
618 HPA function.

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

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

633 **2. ADVAIR DISKUS SHOULD NOT BE INITIATED IN PATIENTS DURING RAPIDLY**  
634 **DETERIORATING OR POTENTIALLY LIFE-THREATENING EPISODES OF**  
635 **ASTHMA. Serious acute respiratory events, including fatalities, have been reported both in**  
636 **the United States and worldwide when salmeterol, a component of ADVAIR DISKUS, has**  
637 **been initiated in patients with significantly worsening or acutely deteriorating asthma.** In  
638 most cases, these have occurred in patients with severe asthma (e.g., patients with a history of  
639 corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent  
640 hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients  
641 in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications;  
642 increasing need for inhaled, short-acting beta<sub>2</sub>-agonists; increasing need for systemic

643 corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or  
644 progressive deterioration in pulmonary function). However, they have occurred in a few patients  
645 with less severe asthma as well. It was not possible from these reports to determine whether  
646 salmeterol contributed to these events or simply failed to relieve the deteriorating asthma.

647 **3. Drug Interaction With Ritonavir:** A drug interaction study in healthy subjects has shown  
648 that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma  
649 fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations  
650 (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug*  
651 *Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During  
652 postmarketing use, there have been reports of clinically significant drug interactions in patients  
653 receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects  
654 including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone  
655 propionate and ritonavir is not recommended unless the potential benefit to the patient  
656 outweighs the risk of systemic corticosteroid side effects.

657 **4. Do Not Use ADVAIR DISKUS to Treat Acute Symptoms:** An inhaled, short-acting  
658 beta<sub>2</sub>-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of shortness of  
659 breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an  
660 inhaled, short-acting beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of shortness of breath that  
661 occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

662 When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or  
663 inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to  
664 discontinue the regular use of these drugs. For patients taking ADVAIR DISKUS, inhaled,  
665 short-acting beta<sub>2</sub>-agonists should only be used for symptomatic relief of acute symptoms of  
666 shortness of breath (see PRECAUTIONS: Information for Patients).

667 **5. Watch for Increasing Use of Inhaled, Short-Acting Beta<sub>2</sub>-Agonists, Which Is a Marker of**  
668 **Deteriorating Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over  
669 several days or longer. If the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective,  
670 the patient needs more inhalations than usual, or the patient develops a significant decrease in  
671 lung function, this may be a marker of destabilization of the disease. In this setting, the patient  
672 requires immediate reevaluation with reassessment of the treatment regimen, giving special  
673 consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a  
674 higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids.  
675 Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR  
676 DISKUS.

677 **6. Do Not Use an Inhaled, Long-Acting Beta<sub>2</sub>-Agonist in Conjunction With ADVAIR DISKUS:**  
678 Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol  
679 or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of exercise-induced  
680 bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of  
681 bronchospasm associated with COPD. Additional benefit would not be gained from using

682 supplemental salmeterol or formoterol for prevention of EIB since ADVAIR DISKUS already  
683 contains an inhaled, long-acting beta<sub>2</sub>-agonist.

684 7. Do Not Exceed Recommended Dosage: ADVAIR DISKUS should not be used more often or  
685 at higher doses than recommended. Fatalities have been reported in association with excessive  
686 use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times  
687 the recommended dose) have been associated with clinically significant prolongation of the QTc  
688 interval, which has the potential for producing ventricular arrhythmias.

689 8. Paradoxical Bronchospasm: As with other inhaled asthma and COPD medications, ADVAIR  
690 DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical  
691 bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated  
692 immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be  
693 discontinued immediately, and alternative therapy should be instituted.

694 9. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after  
695 administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash,  
696 and bronchospasm.

697 10. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as  
698 stridor and choking, have been reported in patients receiving fluticasone propionate and  
699 salmeterol, components of ADVAIR DISKUS.

700 11. Cardiovascular Disorders: ADVAIR DISKUS, like all products containing sympathomimetic  
701 amines, should be used with caution in patients with cardiovascular disorders, especially  
702 coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of  
703 ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as  
704 measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon  
705 after administration of salmeterol at recommended doses, if they occur, the drug may need to be  
706 discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as  
707 flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The  
708 clinical significance of these findings is unknown.

709 12. Discontinuation of Systemic Corticosteroids: Transfer of patients from systemic  
710 corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by  
711 the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and  
712 eosinophilic conditions.

713 13. Immunosuppression: Persons who are using drugs that suppress the immune system are more  
714 susceptible to infections than healthy individuals. Chickenpox and measles, for example, can  
715 have a more serious or even fatal course in susceptible children or adults using corticosteroids.  
716 In such children or adults who have not had these diseases or been properly immunized,  
717 particular care should be taken to avoid exposure. How the dose, route, and duration of  
718 corticosteroid administration affect the risk of developing a disseminated infection is not known.  
719 The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also  
720 not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)  
721 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular

722 immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG  
723 and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be  
724 considered.

## 725 **PRECAUTIONS**

726 **General: Cardiovascular Effects:** Cardiovascular and central nervous system effects seen  
727 with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can  
728 occur after use of salmeterol, a component of ADVAIR DISKUS, and may require  
729 discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all medications containing  
730 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,  
731 especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with  
732 convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to  
733 sympathomimetic amines.

734 As has been described with other beta-adrenergic agonist bronchodilators, clinically  
735 significant changes in electrocardiograms (ECGs) have been seen infrequently in individual  
736 patients in controlled clinical studies with ADVAIR DISKUS and salmeterol. Clinically  
737 significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen  
738 infrequently in individual patients in controlled clinical studies with salmeterol, a component of  
739 ADVAIR DISKUS.

740 **Metabolic and Other Effects:** Long-term use of orally inhaled corticosteroids may affect  
741 normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of  
742 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving  
743 chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice  
744 daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and  
745 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar  
746 region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the  
747 COPD population have not been studied.

748 In patients with major risk factors for decreased bone mineral content, such as tobacco use,  
749 advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of  
750 drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR DISKUS  
751 may pose an additional risk. Since patients with COPD often have multiple risk factors for  
752 reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR  
753 DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and  
754 ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD  
755 therapy, use of medication to treat or prevent osteoporosis should be strongly considered.  
756 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of  
757 COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS  
758 500/50, are not recommended.

759 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with  
760 asthma and COPD following the long-term administration of inhaled corticosteroids, including

761 fluticasone propionate, a component of ADVAIR DISKUS; therefore, regular eye examinations  
762 should be considered.

763 Lower respiratory tract infections, including pneumonia, have been reported following the  
764 inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR  
765 DISKUS.

766 Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously,  
767 have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic  
768 agonist medications may produce significant hypokalemia in some patients, possibly through  
769 intracellular shunting, which has the potential to produce adverse cardiovascular effects. The  
770 decrease in serum potassium is usually transient, not requiring supplementation.

771 Clinically significant changes in blood glucose and/or serum potassium were seen  
772 infrequently during clinical studies with ADVAIR DISKUS at recommended doses.

773 During withdrawal from oral corticosteroids, some patients may experience symptoms of  
774 systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and  
775 depression, despite maintenance or even improvement of respiratory function.

776 Fluticasone propionate, a component of ADVAIR DISKUS, will often help control asthma  
777 symptoms with less suppression of HPA function than therapeutically equivalent oral doses of  
778 prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically  
779 active at higher doses, the beneficial effects of ADVAIR DISKUS in minimizing HPA  
780 dysfunction may be expected only when recommended dosages are not exceeded and individual  
781 patients are titrated to the lowest effective dose. A relationship between plasma levels of  
782 fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown  
783 after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual  
784 sensitivity to effects on cortisol production exists, physicians should consider this information  
785 when prescribing ADVAIR DISKUS.

786 Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated  
787 with ADVAIR DISKUS should be observed carefully for any evidence of systemic  
788 corticosteroid effects. Particular care should be taken in observing patients postoperatively or  
789 during periods of stress for evidence of inadequate adrenal response.

790 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal  
791 suppression (including adrenal crisis) may appear in a small number of patients, particularly  
792 when fluticasone propionate is administered at higher than recommended doses over prolonged  
793 periods of time. If such effects occur, the dosage of ADVAIR DISKUS should be reduced  
794 slowly, consistent with accepted procedures for reducing systemic corticosteroids and for  
795 management of asthma symptoms.

796 A reduction of growth velocity in children and adolescents may occur as a result of poorly  
797 controlled asthma or from the therapeutic use of corticosteroids, including inhaled  
798 corticosteroids. The effects of long-term treatment of children and adolescents with inhaled  
799 corticosteroids, including fluticasone propionate, on final adult height are not known.

800 A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone  
801 propionate inhalation powder (FLOVENT<sup>®</sup> ROTADISK<sup>®</sup>) at 50 and 100 mcg twice daily was  
802 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to  
803 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were  
804 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and  
805 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering  
806 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled  
807 asthma may be confounding factors in interpreting these data. A separate subset analysis of  
808 children who remained prepubertal during the study revealed growth rates at 52 weeks of  
809 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and  
810 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of  
811 children in this study, the range for expected growth velocity is: boys – 3<sup>rd</sup>  
812 percentile = 3.8 cm/year, 50<sup>th</sup> percentile = 5.4 cm/year, and 97<sup>th</sup> percentile = 7.0 cm/year; girls –  
813 3<sup>rd</sup> percentile = 4.2 cm/year, 50<sup>th</sup> percentile = 5.7 cm/year, and 97<sup>th</sup> percentile = 7.3 cm/year.

814 The clinical significance of these growth data is not certain. Physicians should closely follow  
815 the growth of children and adolescents taking corticosteroids by any route, and weigh the  
816 benefits of corticosteroid therapy against the possibility of growth suppression if growth appears  
817 slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that  
818 effectively controls their asthma.

819 The long-term effects of ADVAIR DISKUS in human subjects are not fully known. In  
820 particular, the effects resulting from chronic use of fluticasone propionate on developmental or  
821 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients  
822 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or  
823 longer. In clinical studies in patients with asthma treated for 2 years with inhaled fluticasone  
824 propionate, no apparent differences in the type or severity of adverse reactions were observed  
825 after long- versus short-term treatment.

826 In clinical studies with ADVAIR DISKUS, the development of localized infections of the  
827 pharynx with *Candida albicans* has occurred. When such an infection develops, it should be  
828 treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on  
829 treatment with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be  
830 interrupted.

831 Inhaled corticosteroids should be used with caution, if at all, in patients with active or  
832 quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial,  
833 viral, or parasitic infections; or ocular herpes simplex.

834 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
835 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some  
836 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
837 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
838 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
839 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions

840 have also been reported with other inhaled corticosteroids in this clinical setting. Physicians  
841 should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac  
842 complications, and/or neuropathy presenting in their patients. A causal relationship between  
843 fluticasone propionate and these underlying conditions has not been established (see ADVERSE  
844 REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

845 **Chronic Obstructive Pulmonary Disease:** ADVAIR DISKUS 250/50 twice daily is the  
846 only dosage recommended for the treatment of airflow obstruction in patients with COPD  
847 associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not  
848 recommended, as no additional improvement in lung function (defined by predose and postdose  
849 FEV<sub>1</sub>) was observed in clinical trials and higher doses of corticosteroids increase the risk of  
850 systemic effects.

851 The benefit of treatment of patients with COPD associated with chronic bronchitis with  
852 ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients  
853 who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis  
854 for periods longer than 6 months should be reevaluated periodically to assess the continuing  
855 benefits and potential risks of treatment.

856 **Information for Patients:** Patients being treated with ADVAIR DISKUS should receive the  
857 following information and instructions. This information is intended to aid them in the safe and  
858 effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

859 It is important that patients understand how to use the DISKUS inhalation device  
860 appropriately and how it should be used in relation to other asthma or COPD medications they  
861 are taking. Patients should be given the following information:

- 862 1. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical  
863 trials indicate significant improvement may occur within the first 30 minutes of taking the  
864 first dose; however, the full benefit may not be achieved until treatment has been  
865 administered for 1 week or longer. The patient should not use more than the prescribed  
866 dosage but should contact the physician if symptoms do not improve or if the condition  
867 worsens.
- 868 2. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However,  
869 whether or not patients are able to sense delivery of a dose, you should instruct them not to  
870 exceed the recommended dose of 1 inhalation each morning and evening, approximately 12  
871 hours apart. You should instruct them to contact you or the pharmacist if they have questions.
- 872 3. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or  
873 longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not  
874 be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use  
875 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of  
876 EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in  
877 COPD.
- 878 4. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should  
879 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting

- 880 beta<sub>2</sub>-agonist such as albuterol (the physician should provide the patient with such  
881 medication and instruct the patient in how it should be used). ADVAIR DISKUS is not  
882 meant to relieve acute asthma symptoms or exacerbations of COPD.
- 883 5. Patients should not stop therapy with ADVAIR DISKUS without physician/provider  
884 guidance since symptoms may recur after discontinuation.
- 885 6. The physician should be notified immediately if any of the following situations occur, which  
886 may be a sign of seriously worsening asthma:
- 887 • decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 888 • need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 889 • significant decrease in lung function as outlined by the physician.
- 890 7. Patients should be cautioned regarding common adverse effects associated with  
891 beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 892 8. Patients who are at an increased risk for decreased BMD should be advised that the use of  
893 corticosteroids may pose an additional risk and should be told to monitor and, where  
894 appropriate, seek treatment for this condition.
- 895 9. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of  
896 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).  
897 Regular eye examinations should be considered.
- 898 10. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD  
899 should be used only as directed by their physicians.
- 900 11. ADVAIR DISKUS should not be used with a spacer device.
- 901 12. Patients who are pregnant or nursing should contact their physicians about the use of  
902 ADVAIR DISKUS.
- 903 13. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it  
904 should be used:
- 905 • Never exhale into the DISKUS.
  - 906 • Never attempt to take the DISKUS apart.
  - 907 • Always activate and use the DISKUS in a level, horizontal position.
  - 908 • After inhalation, rinse the mouth with water without swallowing.
  - 909 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
  - 910 • Always keep the DISKUS in a dry place.
  - 911 • Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after  
912 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
- 913 14. Patients should be warned to avoid exposure to chickenpox or measles and, if they are  
914 exposed, to consult their physicians without delay.
- 915 15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient  
916 should read and carefully follow the Patient’s Instructions for Use accompanying the  
917 product.
- 918 **Drug Interactions:** ADVAIR DISKUS has been used concomitantly with other drugs,  
919 including short-acting beta<sub>2</sub>-agonists, methylxanthines, and intranasal corticosteroids, commonly

920 used in patients with asthma or COPD, without adverse drug reactions. No formal drug  
921 interaction studies have been performed with ADVAIR DISKUS.

922 **Short-Acting Beta<sub>2</sub>-Agonists:** In clinical trials with patients with asthma, the mean daily  
923 need for albuterol by 166 adult and adolescent patients 12 years of age and older using ADVAIR  
924 DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five  
925 percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations  
926 per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse  
927 reactions was observed among patients who averaged 6 or more inhalations per day.

928 In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR  
929 DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR  
930 DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No  
931 increase in frequency of cardiovascular adverse reactions was observed among patients who  
932 averaged 6 or more inhalations of albuterol per day.

933 **Methylxanthines:** The concurrent use of intravenously or orally administered  
934 methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of  
935 age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials  
936 with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50  
937 twice daily concurrently with a theophylline product had adverse event rates similar to those in  
938 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in  
939 patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily  
940 concurrently with a theophylline product (N = 39) or without theophylline (N = 132).

941 In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily  
942 concurrently with a theophylline product had adverse event rates similar to those in 161 patients  
943 receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant  
944 administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse  
945 event profile.

946 **Fluticasone Propionate Nasal Spray:** In adult and adolescent patients 12 years of age  
947 and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse  
948 events or HPA axis effects was noted between patients taking FLONASE<sup>®</sup> (fluticasone  
949 propionate) Nasal Spray, 50 mcg concurrently (N = 46) and those who were not (N = 130).

950 **Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:** ADVAIR DISKUS  
951 should be administered with extreme caution to patients being treated with monoamine oxidase  
952 inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents,  
953 because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system  
954 may be potentiated by these agents.

955 **Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the  
956 pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but  
957 may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma  
958 should not normally be treated with beta-blockers. However, under certain circumstances, there  
959 may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with

960 asthma. In this setting, cardioselective beta-blockers could be considered, although they should  
961 be administered with caution.

962 **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of  
963 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by  
964 beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although  
965 the clinical significance of these effects is not known, caution is advised in the coadministration  
966 of beta-agonists with nonpotassium-sparing diuretics.

967 **Inhibitors of Cytochrome P450:** Fluticasone propionate is a substrate of cytochrome  
968 P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy  
969 subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can  
970 significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced  
971 serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics:  
972 *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports  
973 of clinically significant drug interactions in patients receiving fluticasone propionate and  
974 ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal  
975 suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not  
976 recommended unless the potential benefit to the patient outweighs the risk of systemic  
977 corticosteroid side effects.

978 In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a  
979 single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of  
980 ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate  
981 exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.  
982 Caution should be exercised when ADVAIR DISKUS is coadministered with ketoconazole and  
983 other known potent cytochrome P450 3A4 inhibitors.

984 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**  
985 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to  
986 1,000 mcg/kg (approximately 4 and 10 times, respectively, the maximum recommended daily  
987 inhalation dose in adults and children on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation  
988 doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum  
989 recommended daily inhalation dose in adults and children on a mcg/m<sup>2</sup> basis) for 104 weeks.

990 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in  
991 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in  
992 vitro or in the mouse micronucleus test.

993 No evidence of impairment of fertility was observed in reproductive studies conducted in  
994 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum  
995 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis). Prostate weight was  
996 significantly reduced at a subcutaneous dose of 50 mcg/kg.

997 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of  
998 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose  
999 in adults and children based on comparison of the plasma area under the curves [AUCs]) caused

1000 a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular  
1001 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of  
1002 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg  
1003 (approximately 3 times the maximum recommended daily inhalation doses in adults and children  
1004 based on comparison of the AUCs).

1005 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol  
1006 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at  
1007 doses of 0.68 mg/kg and above (approximately 55 and 25 times, respectively, the maximum  
1008 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). No tumors were  
1009 seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended  
1010 daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). These findings in rodents are  
1011 similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of  
1012 these findings to human use is unknown.

1013 Salmeterol produced no detectable or reproducible increases in microbial and mammalian  
1014 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo  
1015 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated  
1016 with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum  
1017 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

1018 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the  
1019 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using  
1020 combinations of fluticasone propionate and salmeterol compared to toxicity data from the  
1021 components administered separately. In mice combining 150 mcg/kg subcutaneously of  
1022 fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a  
1023 mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum  
1024 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis) was teratogenic. Cleft palate,  
1025 fetal death, increased implantation loss and delayed ossification were seen. These observations  
1026 are characteristic of glucocorticoids. No developmental toxicity was observed at combination  
1027 doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum  
1028 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) and up to 1.4 mg/kg orally of  
1029 salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults  
1030 on a mg/m<sup>2</sup> basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg  
1031 subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation  
1032 dose in adults on a mcg/m<sup>2</sup> basis) and up to 1 mg/kg of salmeterol (approximately 80 times the  
1033 maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Combining  
1034 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended  
1035 daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol  
1036 (approximately 810 times the maximum recommended daily inhalation dose in adults on a  
1037 mg/m<sup>2</sup> basis) produced maternal toxicity, decreased placental weight, decreased fetal weight,  
1038 umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate  
1039 and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS

1040 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
1041 fetus.

1042 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse  
1043 and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily  
1044 inhalation dose in adults on a mcg/m<sup>2</sup> basis), respectively, revealed fetal toxicity characteristic of  
1045 potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft  
1046 palate, and retarded cranial ossification.

1047 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
1048 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
1049 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg  
1050 (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
1051 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this  
1052 study, consistent with the established low bioavailability following oral administration (see  
1053 CLINICAL PHARMACOLOGY).

1054 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose  
1055 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a  
1056 mcg/m<sup>2</sup> basis), administration of a subcutaneous or an oral dose of 100 mcg/kg to rats  
1057 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a  
1058 mcg/m<sup>2</sup> basis), and administration of an oral dose of 300 mcg/kg to rabbits (approximately 5  
1059 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

1060 There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate  
1061 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
1062 fetus.

1063 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to  
1064 physiologic, doses suggests that rodents are more prone to teratogenic effects from  
1065 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid  
1066 production during pregnancy, most women will require a lower exogenous corticosteroid dose  
1067 and many will not need corticosteroid treatment during pregnancy.

1068 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses  
1069 up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in  
1070 adults on a mg/m<sup>2</sup> basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and  
1071 above (approximately 50 times the maximum recommended daily inhalation dose in adults based  
1072 on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting  
1073 from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,  
1074 sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.  
1075 No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the  
1076 maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

1077 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal  
1078 bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum  
1079 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Extensive use of other

1080 beta-agonists has provided no evidence that these class effects in animals are relevant to their use  
1081 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant  
1082 women. Salmeterol should be used during pregnancy only if the potential benefit justifies the  
1083 potential risk to the fetus.

1084 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice  
1085 and rats (approximately 410 and 810 times, respectively, the maximum recommended daily  
1086 inhalation dose in adults on a mg/m<sup>2</sup> basis).

1087 **Use in Labor and Delivery:** There are no well-controlled human studies that have  
1088 investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the  
1089 potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during  
1090 labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

1091 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR DISKUS, after  
1092 inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There  
1093 are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known  
1094 whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast  
1095 milk. However, other corticosteroids have been detected in human milk. Subcutaneous  
1096 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the  
1097 maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) resulted in  
1098 measurable radioactivity in milk.

1099 Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing  
1100 mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR  
1101 DISKUS, taking into account the importance of ADVAIR DISKUS to the mother.

1102 Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

1103 **Pediatric Use:** Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported  
1104 by extrapolation of efficacy data from older patients and by safety and efficacy data from a study  
1105 of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years (see CLINICAL  
1106 TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric*  
1107 *Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under  
1108 4 years of age have not been established.

1109 Controlled clinical studies have shown that orally inhaled corticosteroids may cause a  
1110 reduction in growth velocity in pediatric patients. This effect has been observed in the absence of  
1111 laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive  
1112 indicator of systemic corticosteroid exposure in pediatric patients than some commonly used  
1113 tests of HPA axis function. The long-term effects of this reduction in growth velocity associated  
1114 with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The  
1115 potential for “catch-up” growth following discontinuation of treatment with orally inhaled  
1116 corticosteroids has not been adequately studied.

1117 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS,  
1118 may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS:  
1119 General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled

1120 corticosteroids, including ADVAIR DISKUS, should be monitored. If a child or adolescent on  
1121 any corticosteroid appears to have growth suppression, the possibility that he/she is particularly  
1122 sensitive to this effect of corticosteroids should be considered. The potential growth effects of  
1123 prolonged treatment should be weighed against the clinical benefits obtained. To minimize the  
1124 systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient  
1125 should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE  
1126 AND ADMINISTRATION: Asthma).

1127 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS for  
1128 asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total  
1129 number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years  
1130 of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in  
1131 safety were observed between these patients and younger patients, and other reported clinical  
1132 experience, including studies of the individual components, has not identified differences in  
1133 responses between the elderly and younger patients, but greater sensitivity of some older  
1134 individuals cannot be ruled out. As with other products containing beta<sub>2</sub>-agonists, special caution  
1135 should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant  
1136 cardiovascular disease that could be adversely affected by beta<sub>2</sub>-agonists. Based on available  
1137 data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR  
1138 DISKUS in geriatric patients is warranted.

### 1139 **ADVERSE REACTIONS**

1140 **Asthma: *Adult and Adolescent Patients 12 Years of Age and Older:*** The incidence of  
1141 common adverse events in Table 3 is based upon 2 placebo-controlled, 12-week, US clinical  
1142 studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356  
1143 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with  
1144 ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder  
1145 (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.

1146

1147 **Table 3. Overall Adverse Events With  $\geq 3\%$  Incidence in US Controlled Clinical Trials**  
 1148 **With ADVAIR DISKUS in Patients With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, & throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea & vomiting	4	6	3	4	1	1
Gastrointestinal discomfort & pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal Infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3
Average duration of exposure (days)	77.3	78.7	72.4	70.1	60.1	42.3

1149  
 1150 Table 3 includes all events (whether considered drug-related or nondrug-related by the  
 1151 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR  
 1152 DISKUS and were more common than in the placebo group. In considering these data,  
 1153 differences in average duration of exposure should be taken into account. Rare cases of

1154 immediate and delayed hypersensitivity reactions, including rash and other rare events of  
1155 angioedema and bronchospasm, have been reported.

1156 These adverse reactions were mostly mild to moderate in severity.

1157 Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies  
1158 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1159 **Blood and Lymphatic:** Lymphatic signs and symptoms.

1160 **Cardiovascular:** Palpitations.

1161 **Drug Interaction, Overdose, and Trauma:** Muscle injuries, fractures, wounds and  
1162 lacerations, contusions and hematomas, burns.

1163 **Ear, Nose, and Throat:** Rhinorrhea/postnasal drip; ear, nose and throat infections; ear  
1164 signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal  
1165 irritation; blood in nasal mucosa.

1166 **Eye:** Keratitis and conjunctivitis, viral eye infections, eye redness.

1167 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,  
1168 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral  
1169 erythema and rashes, constipation, appendicitis, oral discomfort and pain.

1170 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1171 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower respiratory  
1172 infections.

1173 **Musculoskeletal:** Arthralgia and articular rheumatism; muscle stiffness, tightness, and  
1174 rigidity; bone and cartilage disorders.

1175 **Neurology:** Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

1176 **Non-Site Specific:** Allergies and allergic reactions, congestion, viral infections, pain, chest  
1177 symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

1178 **Skin:** Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of  
1179 sweat and sebum, sweating.

1180 The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical  
1181 study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily  
1182 with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and  
1183 salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation  
1184 powder 500 mcg was similar to the incidences reported in Table 3.

1185 **Pediatric Patients: Pediatric Study:** ADVAIR DISKUS 100/50 was well tolerated in  
1186 clinical trials conducted in children with asthma aged 4 to 11 years. The incidence of common  
1187 adverse events in Table 4 is based upon a 12-week US study in 203 patients with asthma aged 4  
1188 to 11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry  
1189 and were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation  
1190 powder 100 mcg twice daily.

1191

1192 **Table 4. Overall Adverse Events With  $\geq 3\%$  Incidence With ADVAIR DISKUS 100/50**  
 1193 **in Patients 4 to 11 Years of Age With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (N = 101) %	Fluticasone Propionate 100 mcg (N = 102) %
Ear, nose, & throat		
Upper respiratory tract infection	10	17
Throat irritation	8	7
Ear, nose, & throat infections	4	<1
Epistaxis	4	<1
Pharyngitis/throat infection	3	2
Ear signs & symptoms	3	<1
Sinusitis	3	0
Neurology		
Headache	20	20
Gastrointestinal		
Gastrointestinal discomfort & pain	7	5
Nausea & vomiting	5	3
Candidiasis mouth/throat	4	<1
Non-site specific		
Fever	5	13
Chest symptoms	3	<1
Average duration of exposure (days)	74.8	78.8

1194  
 1195 Table 4 includes all events (whether considered drug-related or nondrug-related by the  
 1196 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS  
 1197 100/50.

1198 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The  
 1199 incidence of common adverse events in Table 5 is based upon 1 placebo-controlled, 24-week, US  
 1200 clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult  
 1201 patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50,  
 1202 fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or  
 1203 placebo.  
 1204

1205 **Table 5. Overall Adverse Events With  $\geq 3\%$  Incidence With ADVAIR DISKUS 250/50**  
 1206 **in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic**  
 1207 **Bronchitis**

Adverse Event	ADVAIR DISKUS 250/50 (N = 178) %	Fluticasone Propionate 250 mcg (N = 183) %	Salmeterol 50 mcg (N = 177) %	Placebo (N = 185) %
Ear, nose, & throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise & fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps & spasms	3	3	1	1
Average duration of exposure (days)	141.3	138.5	136.1	131.6

1208  
 1209 Table 5 includes all events (whether considered drug-related or nondrug-related by the  
 1210 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS  
 1211 250/50 and were more common than in the placebo group.

1212 These adverse reactions were mostly mild to moderate in severity.

1213 Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an  
 1214 incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1215 **Cardiovascular:** Syncope.

1216 **Drug Interaction, Overdose, and Trauma:** Postoperative complications.

1217 **Ear, Nose, and Throat:** Ear, nose, and throat infections; ear signs and symptoms;  
 1218 laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

1219 **Endocrine and Metabolic:** Hypothyroidism.

1220 **Eye:** Dry eyes, eye infections.

1221 **Gastrointestinal:** Constipation, gastrointestinal signs and symptoms, oral lesions.

1222 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1223 **Lower Respiratory:** Breathing disorders, lower respiratory signs and symptoms.  
1224 **Non-Site Specific:** Bacterial infections, candidiasis unspecified site, edema and swelling,  
1225 nonspecific conditions, viral infections.  
1226 **Psychiatry:** Situational disorders.  
1227 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
1228 trials, the following events have been identified during worldwide use of any formulation of  
1229 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are  
1230 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.  
1231 These events have been chosen for inclusion due to either their seriousness, frequency of  
1232 reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol  
1233 or a combination of these factors.  
1234 In extensive US and worldwide postmarketing experience with salmeterol, a component of  
1235 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have  
1236 been reported. In most cases, these have occurred in patients with severe asthma and/or in some  
1237 patients in whom asthma has been acutely deteriorating (see WARNINGS no. 2), but they have  
1238 also occurred in a few patients with less severe asthma. It was not possible from these reports to  
1239 determine whether salmeterol contributed to these events or simply failed to relieve the  
1240 deteriorating asthma.  
1241 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular  
1242 tachycardia), ventricular tachycardia.  
1243 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus  
1244 pain, throat soreness.  
1245 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity  
1246 reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.  
1247 **Eye:** Cataracts, glaucoma.  
1248 **Gastrointestinal:** Abdominal pain, dyspepsia, xerostomia.  
1249 **Musculoskeletal:** Back pain, cramps, muscle spasm, myositis.  
1250 **Neurology:** Paresthesia, restlessness.  
1251 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction (including very rare  
1252 anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk  
1253 protein allergy.  
1254 **Psychiatry:** Agitation, aggression, depression.  
1255 **Respiratory:** Chest congestion; chest tightness; dyspnea; immediate bronchospasm;  
1256 influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory  
1257 symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.  
1258 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis.  
1259 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal  
1260 candidiasis, vaginitis, vulvovaginitis.  
1261 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
1262 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some

1263 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
1264 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
1265 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
1266 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions  
1267 have also been reported with other inhaled corticosteroids in this clinical setting. While  
1268 ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid  
1269 therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary  
1270 symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal  
1271 relationship between fluticasone propionate and these underlying conditions has not been  
1272 established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

### 1273 **OVERDOSAGE**

1274 **ADVAIR DISKUS:** No deaths occurred in rats given an inhaled single-dose combination of  
1275 salmeterol 3.6 mg/kg (approximately 290 and 140 times, respectively, the maximum  
1276 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and 1.9 mg/kg of  
1277 fluticasone propionate (approximately 15 and 35 times, respectively, the maximum  
1278 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis).

1279 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in  
1280 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other*  
1281 *Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate  
1282 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation  
1283 aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of  
1284 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.  
1285 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to  
1286 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or  
1287 moderate severity, and incidences were similar in active and placebo treatment groups. In mice,  
1288 the oral median lethal dose was >1,000 mg/kg (>4,100 and >9,600 times, respectively, the  
1289 maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). In rats  
1290 the subcutaneous median lethal dose was >1,000 mg/kg (>8,100 and >19,200 times,  
1291 respectively, the maximum recommended daily inhalation dose in adults and children on a  
1292 mg/m<sup>2</sup> basis).

1293 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of  
1294 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and  
1295 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or  
1296 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,  
1297 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and  
1298 insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the  
1299 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia  
1300 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead

1301 to clinically significant prolongation of the QTc interval, which can produce ventricular  
1302 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.  
1303 As with all sympathomimetic medications, cardiac arrest and even death may be associated  
1304 with abuse of salmeterol.

1305 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic  
1306 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing  
1307 in mind that such medication can produce bronchospasm. There is insufficient evidence to  
1308 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is  
1309 recommended in cases of overdosage.

1310 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg  
1311 (approximately 240 times and 110 times, respectively, the maximum recommended daily  
1312 inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and in dogs at an inhalation dose of  
1313 0.7 mg/kg (approximately 190 and 90 times, respectively, the maximum recommended daily  
1314 inhalation dose in adults and children on a mg/m<sup>2</sup> basis). By the oral route, no deaths occurred in  
1315 mice at 150 mg/kg (approximately 6,100 and 2,900 times, respectively, the maximum  
1316 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and in rats at  
1317 1,000 mg/kg (approximately 81,000 and 38,000 times, respectively, the maximum recommended  
1318 daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis).

## 1319 **DOSAGE AND ADMINISTRATION**

1320 ADVAIR DISKUS should be administered by the orally inhaled route only (see Patient's  
1321 Instructions For Use). After inhalation, the patient should rinse the mouth with water without  
1322 swallowing. ADVAIR DISKUS should not be used for transferring patients from systemic  
1323 corticosteroid therapy.

1324 **Asthma:** ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR  
1325 DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of  
1326 fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

1327 ADVAIR DISKUS should be administered twice daily every day. More frequent  
1328 administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation  
1329 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some  
1330 patients are more likely to experience adverse effects with higher doses of salmeterol. The safety  
1331 and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not  
1332 been established.

1333 If symptoms arise in the period between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should  
1334 be taken for immediate relief.

1335 Patients who are receiving ADVAIR DISKUS twice daily should not use additional  
1336 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of EIB,  
1337 or for any other reason.

1338 **Adult and Adolescent Patients 12 Years of Age and Older:** For patients 12 years of  
 1339 age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately  
 1340 12 hours apart).

1341 The recommended starting dosages for ADVAIR DISKUS for patients 12 years of age and  
 1342 older are based upon patients' current asthma therapy.

- 1343 • For patients who are not currently on an inhaled corticosteroid, whose disease severity  
 1344 warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid  
 1345 maintenance therapy, the recommended starting dosage is ADVAIR DISKUS 100/50 twice  
 1346 daily.
- 1347 • For patients on an inhaled corticosteroid, Table 6 provides the recommended starting dosage.  
 1348 The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

1349 **For all patients it is desirable to titrate to the lowest effective strength after adequate**  
 1350 **asthma stability is achieved.**

1351

1352 **Table 6. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Aged 12**  
 1353 **Years and Older Taking Inhaled Corticosteroids**

Current <b>Daily Dose</b> of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate	≤420 mcg	100/50 twice daily
	462-840 mcg	250/50 twice daily
Budesonide	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Fluticasone propionate inhalation aerosol	≤176 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	660-880 mcg*	500/50 twice daily
Fluticasone propionate inhalation powder	≤200 mcg	100/50 twice daily
	500 mcg	250/50 twice daily
	1,000 mcg*	500/50 twice daily
Triamcinolone acetonide	≤1,000 mcg	100/50 twice daily
	1,100-1,600 mcg	250/50 twice daily

\* ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy.

1354

1355 Improvement in asthma control following inhaled administration of ADVAIR DISKUS can  
 1356 occur within 30 minutes of beginning treatment, although maximum benefit may not be

1357 achieved for 1 week or longer after starting treatment. Individual patients will experience a  
1358 variable time to onset and degree of symptom relief.

1359 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,  
1360 replacing the current strength of ADVAIR DISKUS with a higher strength may provide  
1361 additional improvement in asthma control.

1362 If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate  
1363 improvement in asthma control, the therapeutic regimen should be reevaluated and additional  
1364 therapeutic options, e.g., replacing the current strength of ADVAIR DISKUS with a higher  
1365 strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be  
1366 considered.

1367 **Pediatric Patients:** For patients aged 4 to 11 years who are symptomatic on an inhaled  
1368 corticosteroid the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and  
1369 evening, approximately 12 hours apart).

1370 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The  
1371 dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately  
1372 12 hours apart).

1373 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of  
1374 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,  
1375 are not recommended, as no additional improvement in lung function was observed in clinical  
1376 trials and higher doses of corticosteroids increase the risk of systemic effects.

1377 If shortness of breath occurs in the period between doses, an inhaled, short-acting  
1378 beta<sub>2</sub>-agonist should be taken for immediate relief.

1379 Patients who are receiving ADVAIR DISKUS twice daily should not use additional  
1380 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for the maintenance  
1381 treatment of COPD or for any other reason.

1382 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see  
1383 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR DISKUS, efficacy and safety  
1384 did not differ from that in younger patients. Based on available data for ADVAIR DISKUS and  
1385 its active components, no dosage adjustment is recommended.

1386 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of  
1387 ADVAIR DISKUS.

## 1388 **HOW SUPPLIED**

1389 ADVAIR DISKUS 100/50 is supplied as a disposable, purple device containing 60 blisters.  
1390 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1391 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional  
1392 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS  
1393 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1394 (NDC 0173-0695-02).

1395 ADVAIR DISKUS 250/50 is supplied as a disposable, purple device containing 60 blisters.  
1396 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1397 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional  
1398 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS  
1399 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1400 (NDC 0173-0696-02).

1401 ADVAIR DISKUS 500/50 is supplied as a disposable, purple device containing 60 blisters.  
1402 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1403 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional  
1404 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS  
1405 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1406 (NDC 0173-0697-02).

1407 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place**  
1408 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**  
1409 **device is not reusable. The device should be discarded 1 month after removal from the**  
1410 **moisture-protective foil overwrap pouch or after all blisters have been used (when the dose**  
1411 **indicator reads “0”), whichever comes first. Do not attempt to take the device apart.**  
1412  
1413



1414 GlaxoSmithKline  
1415 GlaxoSmithKline  
1416 Research Triangle Park, NC 27709  
1417

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1419

1420 April 2004

RL-2085

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-077/S017**

**OFFICE DIRECTOR MEMO**

## **DIVISION DIRECTOR'S MEMORANDUM**

Date: April 20, 2004

To: NDA 21-077/S-017

From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Advair Diskus 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

Applicant: GlaxoSmithKline

### **Administrative and Introduction**

GlaxoSmithKline (GSK) submitted a 505(b)(1) supplemental new drug application (NDA 21-077/S-017) on June 26, 2003, for use of Advair Diskus 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder) in children ages 4 to 11 years. The CDER stamp date on the application is June 27, 2003, and the PDUFA due date is April 27, 2004. Advair Diskus is marketed in the United States in three strengths, 100/50, 250/50, and 500/50, containing 100, 250, and 500 mcg of fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation. Advair Diskus is approved for the long-term maintenance treatment of asthma in patients 12 years of age and older. The dosage is one inhalation twice daily. The recommended starting dosages are based on patients' current asthma therapy and disease severity. Advair Diskus 250/50 at a dosage of one inhalation twice daily is also approved as a maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease associated with chronic bronchitis. The current application is to seek approval of Advair Diskus 100/50 for asthma in patients 4 to 11 years of age at a dose of one inhalation twice daily. GSK conducted one study in North America and three studies internationally to support this application. The submitted clinical data support approval of this application. There are no outstanding issues from other disciplines.

### **Chemistry, Manufacturing, and Controls, and Establishment Evaluation**

There are no CMC and manufacturing issues because Advair Diskus 100/50 is an approved marketed product in the United States. All manufacturing sites related to this drug product have acceptable evaluation status.

GSK is proposing to update the product description section with flow rate data from young children. In a study on 4 year old patients with asthma (n=20) inhaling maximally through the Diskus device the mean peak inspiratory flow rate was 75.5 L/min (range, 49.0 to 104.8 L/min); in another study on 8 year old patients with asthma (n=29) the mean inspiratory flow rate was 107.3 L/min (range 82.8 to 125.6 L/min). The data show that young children can generate acceptable flow rates through the Diskus device.

### **Clinical and Statistical**

The development program was designed to primarily support safety of Advair Diskus 100/50 in the 4 to 11 year age group. This is reasonable as efficacy can be extrapolated from the adults because asthma in the pediatric population is the same disease as in adults, and the response to therapy to Advair is expected to be similar. The proposed dose of the Advair Diskus in the 4 to 11 year age group is also reasonable because both fluticasone and salmeterol at the same doses in Diskus formulations are approved for treatment of asthma down to 4 years of age. The dose for Flovent Diskus (fluticasone) in patients 4 to 11 years is 50 mcg or 100 mcg twice daily, and the dose of Serevent Diskus (salmeterol) in patients 4 years of age and older is 50 mcg twice daily. Therefore, the combination of fluticasone at 100 mcg and salmeterol at 50 mcg in Advair Diskus 100/50 is reasonable. The applicant was not required to show contribution of the individual components in the Advair Diskus (21 CFR 300.50, the Combination Drugs Regulation) in the 4 to 11 year age group because that was already demonstrated in adults for the same formulation.

The clinical program submitted in support of this application consisted of one study conducted in the United States and Canada (Study SAS 30031) and three studies conducted in Europe and South Africa (Studies SFCB 3020, SAM 40012, and RPS 3001). Study 30031 enrolled patients primarily from the United States. The applicant has designated Study 30031 as the pivotal study and the rest as supporting studies. All studies are reviewed in detail in Dr. Carol Bosken's medical review. Brief comments on the studies are made in the following sections.

SAS 30031 was a 12 week, double-blind, parallel group safety study in patients 4 to 11 years of age with persistent asthma who were on inhaled corticosteroids for at least one month before study entry. The study had a 2-week run-in period and 12-week treatment period where patients were treated with either Advair Diskus 100/50 or Flovent Diskus 100. All patients were allowed albuterol MDI as rescue medication. Safety evaluations included routine physical examination, routine laboratory tests, recording of adverse events, and 24-hour urine cortisol. Efficacy evaluation included pulmonary function test in children 6 years of age and older, PEFr in children 4 years of age and older, symptom score, and rescue albuterol use. A total of 203 patients were randomized into the study, divided approximately equally between the two treatment groups. Approximately 80% of patients in both treatment groups completed the study. Advair Diskus 100/50 was well tolerated in the study. Frequent adverse events (>3% frequency) that were more common in Advair Diskus 100/50 compared to Flovent Diskus 100 included throat irritation (8% vs 7%), ear nose and throat infection (4% vs <1%), epistaxis (4% vs <1%), throat infection (3% vs 2%), ear discomfort (3% vs <1%), sinusitis (3% vs 0%), gastrointestinal discomfort (7% vs 5%), nausea and vomiting (5% vs 3%), oral candidiasis (4% vs <1%), and non-specific chest discomfort (3% vs <1%). The values of 24-hour urinary cortisol excretion at study entry and after 12 weeks of treatment were similar between the treatment groups. Efficacy measures favored Advair Diskus 100/50 over Flovent Diskus 50. In patients receiving Advair Diskus 100/50 morning pre-dose FEV1 increased from 1.70 L at baseline (n=79) to 1.88 L at endpoint (n=69) compared to an increase from 1.65

at baseline (n=83) to 1.77 at endpoint (n=75) for patients receiving Flovent Diskus 100. Morning PEFr, symptom score, number of symptom free days, and rescue albuterol use also favored Advair 100/50 over Flovent 100.

Study 3020 was a 12 week, double-blind, parallel group study in patients 4 to 11 years of age with persistent asthma who were on inhaled corticosteroids on study entry. The stated objective of the study was to show equivalence based on morning PEFr between fluticasone and salmeterol given together as a combination product (a non-US formulation called Seretide Diskus 100/50) and the two components given together at the same doses by two different Diskus inhalers. As in the previous study, this study also had a 2-week run-in period and 12-week treatment period. Design and conduct of the study was also similar to the previous study. A total of 257 patients were randomized in the study. A total of 91 patients (35%) were considered to have protocol violations and were excluded from efficacy analysis. The study drugs were well tolerated by the subjects. Efficacy measures tended to be comparable in the two treatment groups. Morning PEFr increased by 32 L/min in the combination treatment group, and by 26 L/min in the group given the two components given together.

Study 40012 was a 24 week, double-blind, parallel group study in patients 4 to 11 years of age with persistent asthma on inhaled corticosteroids. The study had a 2-week run-in period and 24-week treatment period. The objective of the study was to demonstrate superiority of Seretide Diskus 100/50 (a non-US fluticasone and salmeterol combination product) over two doses of fluticasone (100 mcg twice daily and 200 mcg twice daily) delivered by Diskus device. A total of 548 patients were randomized approximately equally among the three treatment groups. Primary efficacy variable was symptom free days and nights. Other efficacy variables included PEFr recording. Safety evaluations were similar to the previous two studies. The primary efficacy variable recording was unreliable due to malfunctioning of the electronic device that was used to record the data. Therefore, no efficacy conclusion can be drawn from this study. Adverse event profile suggested a higher incidence of respiratory infection in the high dose fluticasone group, a finding which has been seen in similar previous studies.

Study RPS 3001 was a 12 week double-blind, parallel group study in patients 4-11 years of age with persistent asthma. The study had a 2-week run-in period and 12-week treatment period. The objective of the study was to show clinical equivalence between Seretide Diskus 100/50 (a non-US fluticasone and salmeterol combination product) to another fluticasone and salmeterol combination product device called Reservoir Powder Inhalation Device. A total of 176 patients were randomized approximately equally between the two treatment groups. The combination product delivered by both the devices was well tolerated by the patients.

The clinical program as described above to support the use of Advair 100/50 in children was relatively large. The pivotal US study SAS 30031 and the supporting non-US studies as discussed above support the safety of Advair 100/50 in children 4 to 11 years of age with asthma. Findings from study SAS 30031 are described in the Clinical Trials section and Adverse Reactions sections of the label. Findings from the three non-US

studies are not described in the label because they do not provide any added information and they had various other problems. In Study 3020 the primary efficacy variable was not available from about one-third of the patients. In Study 40012 recording of the primary efficacy variable was problematic because of malfunctioning of the electronic data recording device, and reliable data was available from about two-third of the patients. Study 3001 compared two non-US formulations. (b) (4)

(b) (4) but later, on my suggestion, agreed to replace that with the FEV1 data from Study 30031. FEV1 data from Study 30031 is complete and more informative and gives a better sense of efficacy than (b) (4).

### **Clinical Pharmacology and Biopharmaceutics**

GSK did not submit any pharmacokinetic data with this application. Pharmacokinetic evaluation of Advair in the 4 to 11 year old patient is ongoing and will be submitted at a later date. This is acceptable because pharmacokinetic data for each of the individual components of Advair are available, and both fluticasone and salmeterol are approved as single ingredient Diskus products down to 4 years of age. Furthermore, in adults the exposure to fluticasone is lower with Advair Diskus than with fluticasone alone and it is anticipated that the same would hold true for children 4 to 11 years of age.

### **Pharmacology and Toxicology**

The applicant did not conduct any new preclinical study for this application because Advair is currently an approved and marketed product.

### **Data Quality, Integrity, and Financial Disclosure**

No DSI audit of clinical study sites was request or conducted for this supplement. The components of Advair are not new molecular entities and each of the two components in Diskus formulations is already approved for marketing in the United States down to the age of 4 years. During review of the studies no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted an acceptable financial disclosure statement. Three investigators had significant financial conflict of interest with GSK. These were not considered to be of concern because the three investigators in total contributed 15 patients to the pivotal study.

### **Pediatric Considerations**

The applicant is proposing use of Advair Diskus in patients down to the age of 4 years. The lower age bound for Advair Diskus would stay at 4 years because the delivery device is not suitable for use in younger children. (b) (4)

(b) (4)

(b) (4)

Linear growth suppression in children is an important marker for systemic effect of corticosteroids including orally inhaled corticosteroids. GSK did not conduct a linear growth study with Advair and is not proposing to conduct one post-approval. This is acceptable because a linear growth study has already been conducted with Flovent Rotadisk (fluticasone propionate inhalation powder). There is no reason to believe that the combination of fluticasone and salmeterol would have a different effect on growth in children than fluticasone alone. Pharmacokinetic data from adults suggest that systemic exposure to fluticasone is lower with Advair compared to fluticasone alone.

**Product Name**

There is no nomenclature issue with this application. The proprietary name of Advair is approved and is being used by GSK for the combination product containing fluticasone and salmeterol. The suffix Diskus 100/50 is appropriate for this dosage form.

**Labeling**

GSK submitted a product label containing various new sections and addition to existing sections relevant to the new age group for the asthma indication. The notable additions were in the Description section describing the inhalation profile in the pediatric patients, Clinical Pharmacology section describing the 24 hour urinary cortisol data, Clinical Trials section describing the pivotal US study, Pediatric Use subsection under Precautions section describing the basis of approval, and Adverse Reactions section describing the safety findings from the pivotal US study. The labeling has been reviewed by all relevant disciplines and updated as appropriate. The Division and GSK have agreed on a final labeling text that adequately reflects the new pediatric data.

**Action**

GSK has submitted adequate safety data and supportive efficacy data to support the use of Advair Diskus 100/50 for asthma in patients 4 to 11 years of age at a dose of one inhalation twice daily. The action on this application will be APPROVAL.

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Badrul Chowdhury  
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MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-077/S017**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Medical Team Leader Memorandum

**Memorandum to:** NDA 21-077\S\_017

**Product:** Advair Diskus (fluticasone propionate/salmeterol inhalation powder)

**Applicant:** GlaxoSmithkline (GSK)

**Date:** April 8, 2004

**From:** Lydia I. Gilbert-McClain, MD, Medical Team Leader

### Background/Administrative

Advair Diskus (fluticasone propionate/salmeterol inhalation powder) was approved on August 24, 2000, under NDA 21-077 for the maintenance treatment of asthma in adults and adolescents 12 years of age and older. Three strengths of the product were approved: 100/50, 250/50 and 500/50 mcg per actuation of fluticasone/salmeterol. The sponsor submitted an efficacy supplement (NDA 21-077\S\_017) on June 26, 2003, seeking approval of the 100/50 mcg product for the maintenance treatment of asthma in patients 4 -11 years of age.

When Advair Diskus was originally approved, the sponsor had to establish that both individual components contributed to the efficacy of the combination (*21CFR 300.50*). However, for the pediatric development program the Division agreed that it was not necessary to repeat that requirement. The Division also agreed that based on the pediatric rule [*21CFR 201.57 (f)(9)(iv)*], the efficacy of Advair Diskus for the maintenance treatment of asthma in pediatric patients 4 -11 years of age could be extrapolated from the established efficacy in adults and adolescents because the disease course and the drug effects are similar in both populations. The Division further stated that efficacy of Advair Diskus for patients younger than 4 years of age could not be extrapolated from the adult patients because it was felt that the effect of a dry powder formulation via the Diskus in patients less than 4 years of age would be different from that of adults and older children. The Division's thinking also was that the combination product was an inappropriate formulation for patients < 4 years of age.

The Development program for the 4-11 year old patients was primarily focused on safety and included a growth study. Although a growth study was already conducted with fluticasone propionate (Flovent Rotadisk) there was the concern that the combination of salmeterol and fluticasone could potentially result in a higher systemic exposure of fluticasone because of the concomitant bronchodilatory effect of salmeterol in the combination. Pharmacokinetic data in adults however, showed that the exposure to fluticasone propionate is lower with Advair Diskus than with fluticasone alone. The Division decided that a growth study with Advair [Diskus] was not necessary since a growth study had already been conducted with fluticasone propionate (Flovent Rotadisk), and there was no clear scientific rationale to suggest that the combination of fluticasone and salmeterol would have a worse effect on growth than fluticasone alone.

A brief description of the development program and relevant findings is presented below. For more details please refer to Dr. Carol Bosken's excellent Medical Officer Review.

### **Overview of Development program**

The development program consisted of one pivotal safety study conducted in the U.S. and three (3) supporting studies conducted in Europe. All the studies were double-blind and randomized with active controls. The patients enrolled in the study were asthmatics who were symptomatic on inhaled corticosteroids (beclomethasone dipropionate, budesonide, or flunisolide 400 to 500 mcg/day or fluticasone propionate 200 to 250 mcg/day). In the pivotal study (SAS30013), Advair Diskus 100/50 was compared to Flovent Diskus 100 and in the supporting studies, (SAM40012, SFCB3020 and RPS30001) Advair was compared to fluticasone propionate 100 mcg BID, 200 mcg BID, or fluticasone 100 mcg and salmeterol 50 mcg given concomitantly via two individual inhalers BID.

In the pivotal safety study, a total of 203 patients were treated. The adverse event profile was similar in the Advair group compared to the fluticasone group. The most common ( $\geq 3\%$ ) adverse events were reported in the upper and lower respiratory system and included throat irritation, ENT infections, epistaxis, pharyngitis/throat infection and sinusitis. Other commonly reported AEs were headache, candidiasis mouth/throat, fever and chest symptoms. There were no clinically significant changes in laboratory values or vital signs. Twenty-four hour urine cortisol were conducted at study entry and after 12 weeks of treatment in approximately 50% of the patients and there was no difference between the urine cortisol values of the subjects on Advair Diskus compared to the subjects on fluticasone. Additionally, the values for 24-hour urine cortisol after 12 weeks of treatment compared to the values at study entry were similar within each treatment group. As all the patients were on inhaled corticosteroids at study entry, the clinical utility of this information is questionable. In all the studies combined, a total of 553 patients were exposed to Advair Diskus for 12 to 24 weeks of treatment. The safety profile from all the safety data combined did not show meaningful differences from the safety profile of Advair 100/50 in the adult and adolescent studies.

Efficacy was assessed as a secondary objective using pre-dose FEV<sub>1</sub>, AM and PM PEF, and asthma symptom scores. Summary statistics for the efficacy endpoints demonstrated improvement in AM pre-dose FEV<sub>1</sub>, PEF and asthma symptom scores for both treatment groups. The Advair 100/50 treatment group had a numerically greater increase in pre-dose FEV<sub>1</sub> (mean change from Baseline) compared to the fluticasone 100 group [0.16 L vs. 0.10 L]. The efficacy data, support the efficacy of Advair Diskus 100/50 for the maintenance treatment of asthma in patients 4 – 11 years of age.

### **Interdisciplinary Issues**

The product used in the pivotal study is the approved U.S. marketed product, therefore there are no CMC, or pharm/tox issues to be addressed. From a biopharm perspective, the sponsor is conducting a complete pharmacokinetic evaluation of Advair in the 4 – 11 year old patients and plans to submit those data at a later date. Generally, for a pediatric

indication we would have required that these data be available at the time of the sNDA submission, however, an exception to this requirement was acceptable for this application for a number of reasons. Firstly, we have pharmacokinetic data in the 4 – 11 year old patients for each of the individual components of Advair (fluticasone and salmeterol) and both fluticasone propionate and salmeterol are approved as single-ingredient products in patients 4 years of age and older. Secondly, the exposure to fluticasone is lower with Advair Diskus than with fluticasone alone in adults and it is anticipated that the same would hold true for the 4 – 11 year olds. For these reasons, the Division concluded that the PK data for Advair Diskus in the 4 -11 year olds was not required to make a decision on approval and could be submitted post-approval of the sNDA.

### **Pediatric Issues**

[REDACTED] (b) (4)

Additionally, the Agency determined that the fixed dose combination is not an appropriate product for pediatric subjects < 4 years of age. Therefore the sponsor was granted a waiver for studies for pediatric subjects < 4 years of age.

### **Labeling**

Minor labeling changes were made to the proposed label in the Pediatric Use Section to state clearly that efficacy of Advair Diskus 100/50 in the 4 – 11 year old patients is based on extrapolation of efficacy data from adults. A new table has been added in the Adverse Reactions section to present the most common ( $\geq 3\%$ ) AEs seen in the pivotal safety study. Other minor revisions to different sections of the label needed to be made as a result of the addition of the new age group ( 4 – 11 year olds). The sponsor has accepted all the Division's labeling changes and with these changes the supplement can be approved.

### **Recommendation**

Approval

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/s/

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Lydia McClain  
4/8/04 03:34:05 PM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-077/S017**

**MEDICAL REVIEW(S)**

## MEDICAL OFFICER REVIEW

### Division Of Pulmonary and Allergy Drug Products (HFD-570)

<b>APPLICATION:</b> NDA # 21-077\S_017	<b>TRADE NAME:</b> Advair® Diskus
<b>APPLICANT:</b> GlaxoSmithKline	<b>USAN NAME:</b> Fluticasone propionate + Salmeterol Xinafoate
<b>MEDICAL OFFICER:</b> Carol H. Bosken, M.D.	
<b>TEAM LEADER:</b> Lydia I. Gilbert-McClain, M.D.	<b>CATEGORY:</b> Corticosteroid + $\beta_2$ -adrenergic agonist
<b>DUE DATE:</b> April 17,2004	<b>ROUTE:</b> Oral Inhalation

#### SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
June 26, 2003	Electronic	SE5_017	Original Pediatric Supplement
October 24, 2003	Electronic	SE5_017 (SU)	120-Day Safety Update

#### RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
August 24, 2000	NDA 21-077	Original NDA for Advair in the adult population

**REVIEW SUMMARY:** This is an efficacy supplement to broaden the indication for the use of Advair (fluticasone propionate/salmeterol) 100/50 mcg BID for maintenance treatment of asthma to include patients 4-11 years of age. The efficacy of Advair in the pediatric population is extrapolated from efficacy demonstrated in the adult population with the understanding that asthma in the pediatric population is clinically comparable to the adult disease. Therefore, the primary objective of the pivotal study and the focus of this review was safety. Four randomized and blinded 12 or 24 week trials were submitted. The subjects in all of these trials were 4 – 11 years of age and they were all taking maintenance inhaled corticosteroids at the time of screening and enrollment. None was treated with placebo. In the pivotal trial (SAS30013) 203 patients (evenly divided) were treated for 12 weeks with either Advair 100/50 BID or Fluticasone propionate 100 mg BID (FP100). In the supporting trials (SAM40012, SFCB3020, RPS30001) Advair was compared with FP100, fluticasone propionate 200 mcg BID (FP200), and fluticasone 100 mcg and salmeterol 50 mcg given concomitantly via two individual inhalers BID (FP100+S). In all, 553 patients were exposed to Advair for a mean of 109 days. Of these, 55% reported adverse events as compared with 60%, 61%, and 59% of those treated with FP100, FP200, and FP100+S respectively. The most common site of complaints was the ear, nose, and throat (ENT) area with 33%, 34%, 33%, and 39% of the patients treated with Advair, FP100, FP200, FP100+S affected respectively. The most common complaints in the ENT area were upper respiratory infection, rhinitis, throat irritation, pharyngitis, tonsillitis, ENT infection, and sinusitis. The next most frequently involved area was the lower respiratory tract with 17%, 22%, 35%, and 24% of the patients treated with Advair, FP100, FP200, FP100+S affected respectively. The frequency and distribution of AEs seen with Advair in 4-11 year olds closely resembled the AEs seen in the adult population. The HPA axis was evaluated in the pivotal study with 24-hour urine collections for cortisol in 105 of the subjects. There was no evidence of HPA axis suppression when comparing the baseline values obtained while the patient was taking only inhaled corticosteroids to the value obtained at the end of the study. Pulmonary function measurements showed increases in FEV<sub>1</sub> and PEF that were comparable in all of the treatment groups. The studies submitted support the approval of Advair for use in patients 4-11 years of age as adverse events do not appear to be elevated in this population. The label will contain the same warnings about potential HPA suppression and growth retardation that appear on the label for fluticasone propionate.

**OUTSTANDING ISSUES:** None

#### RECOMMENDED REGULATORY ACTION

<b>NDA/SUPPLEMENTS:</b>	<input type="checkbox"/> FILEABLE	<input type="checkbox"/> NOT FILEABLE	
	<input checked="" type="checkbox"/> APPROVAL	<input type="checkbox"/> APPROVABLE	<input type="checkbox"/> NOT APPROVABLE

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**ABBREVIATIONS**

<b>Abbreviation</b>	<b>Description</b>
AE	Adverse Event
BUN	Blood Urea Nitrogen
ECG	Electrocardiogram
ENT	Ear, Nose, and Throat
FEV <sub>1</sub>	Forced Expired Volume in one second
FP100	Fluticasone Propionate 100 mcg BID
FP200	Fluticasone Propionate 200 mcg BID
FSC	Fluticasone/Salmeterol Combination Product. Used when subjects treated with Advair or Serevent are included in the tally.
ICS	Inhaled corticosteroids
ITT	Intention to treat
LRI	Lower Respiratory Infection
LRT	Lower Respiratory Tract
OC	Oral corticosteroids
PEFR	Peak Expiratory Flow Rate
RBC	Red Blood Cells
WBC	White Blood Cells
URI	Upper Respiratory Infection

# **CLINICAL REVIEW**

## ***EXECUTIVE SUMMARY***

### **1. RECOMMENDATIONS**

#### **1.1. Recommendation on Approvability**

Advair 100/50 mcg BID is recommended for approval for the maintenance treatment of asthma in patients 4 – 11 years of age who are symptomatic on inhaled corticosteroids. The recommendation is made on the basis of demonstrated safety and extrapolation of efficacy from the adult population. Salmeterol and fluticasone, the two components of Advair are both approved for the maintenance treatment of asthma in patients 4 years of age and older. The clinical studies submitted with this application were designed primarily to assess the safety of the combination product (Advair = fluticasone/salmeterol) 100/50 mcg BID in patients in the 4 – 11 age range. The studies have demonstrated that the incidence and range of adverse events is similar to those seen during treatment with Flovent 100 mcg BID alone. HPA axis suppression was not detected in the 12 and 24-week studies when baseline samples, obtained while the patient was on maintenance ICS, were compared to samples obtained at the end of the studies.

#### **1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps**

No Phase 4 studies are recommended.

### **2. SUMMARY OF CLINICAL FINDINGS**

#### **2.1. Brief Overview of Clinical Program**

Advair Diskus® is a combination product of a synthetic corticosteroid (fluticasone propionate) and a long-acting  $\beta$ -adrenergic agonist (salmeterol xinafoate) and is approved for the maintenance treatment of asthma in patients twelve years of age and older. The approved doses are 100/50, 250/50, and 500/50 mcg BID of fluticasone/salmeterol. The recommended starting dose is dependent upon the asthma medication taken prior to beginning Advair and/or asthma severity. Fluticasone propionate Diskus inhaler (Flovent Diskus®), 50 and 100 mcg BID, is approved for the treatment of asthma in patients 4 – 11 years of age. Likewise, salmeterol (Serevent Diskus®), 50 mcg BID, is approved for the treatment of asthma in patients 4 years and older. This application consists of one 12-week pivotal randomized clinical trial designed to demonstrate the safety of Advair® 100/50 mcg BID compared to Flovent Diskus® 100 mcg BID (FP100) in asthmatics who are symptomatic on maintenance inhaled corticosteroids (ICS). Three supporting randomized

trials were conducted in which Seretide (50/100), a combination of salmeterol (50 mcg) and fluticasone (100 mcg) marketed in Europe, was compared to:

- (1) Fluticasone 100 mcg BID and Salmeterol 50 mcg BID given concurrently (Study SFCB3020)
- (2) FP100 and Fluticasone 200 mcg BID (Study SAM40012) and
- (3) Seretide delivered with a Reservoir Powder Inhalation Device (RPID) a device unique to the European market (Study RPS3001).

The results of an additional trial (study SAS30019), comparing Seretide Diskus to a fluticasone plus salmeterol aerosol delivered with an HFA-134 propellant, was submitted with the 120-day safety update.

## **2.2. Efficacy**

The efficacy of Advair in the pediatric population is being extrapolated from the demonstrated efficacy of Advair in the adult population with asthma because it is generally agreed that the disease is pathophysiologically similar in adults, adolescents and children and that the drug effects are expected to be the similar in pediatric patients (21CFR 201.57 (f)(9)(iv)). In addition, the component parts of Advair, namely fluticasone and salmeterol, have been approved for the treatment of asthma in patients 4 years of age and older. The sponsor assessed efficacy as a secondary endpoint in the pivotal safety study. There was an increase in FEV<sub>1</sub> and PEF<sub>R</sub> as well as a trend towards decreased use of rescue medication, and reduced symptoms after 12 weeks of treatment with Advair 100/50 compared to Baseline.

## **2.3. Safety**

The submitted studies showed that asthmatic subjects, 4 to 11 years of age and symptomatic on ICS at the time of enrollment, who were treated with a combination product (Advair or Seretide) 100/50 mcg BID (FSC100/50) had an incidence and spectrum of adverse events (AE) similar to that seen in patients treated with FP100 alone. The overall incidence of AEs was 55, 59, and 60% in the FSC100/50, FSC100+S, and FP100 treatment groups respectively. The most common events were reported in the ears, nose, and throat (ENT). They were reported for 33% of the patients treated with FSC100/50, 39% of patients treated with FP100+S, and in 34% of patients treated with FP100 alone. The most common AE in the ENT area were upper respiratory tract infection, rhinitis, throat irritation, pharyngitis, tonsillitis, ENT infection, and sinusitis. The next most frequent site of AEs was the lower respiratory tract (LRT) with 17, 24, and 22% of the patients treated with FSC100/50, FP100+S, and FP100 respectively reporting one or more event. The most common events in the LRT were viral infection, cough, and bronchitis. Headaches occurred in 8% of the FSC100/50-treated patients, and in 5% and 11% of those treated with FP100+S, and FP100 respectively. One of the supporting trials (SAM40012) used fluticasone 200 mcg BID (FP200) as one of the comparator drugs. The incidence of any adverse event was 61% in the 186 patients treated with FP200. The incidence of ENT involvement was 33% and LRT involvement was 35%. Of note, 22% of the FP200-treated patients reported LRT viral infection and 11% reported “other viral infections”. This compares to 8% and 12% LRT

viral infection in the FSC100/50 and FP100-treated patients respectively. Other viral infections were reported in 4% of both the FSC100/50 and FP100 – treated patients.

In the pivotal study (SAS30031) 24-hour urine for cortisol was collected on 105 children at baseline and at the end of the study. In three other studies either blood cortisol or 12-hour urine for cortisol was collected. In all cases the geometric mean cortisol levels in the FSC100/50-treated patients were higher at the end of the study than at the beginning, and they were higher than the geometric mean levels measured in the FP100-treated patients.

#### **2.4. Dosing**

The proposed dose is fluticasone propionate/salmeterol inhalation powder 100/50 mcg (1 puff) BID for the maintenance treatment of asthma in children 4 – 11 years of age who are symptomatic on inhaled corticosteroids.

## **CLINICAL REVIEW**

### **1. INTRODUCTION AND BACKGROUND**

#### **1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups**

Advair (fluticasone propionate + salmeterol xinafoate) is a combination product of a synthetic corticosteroid and a long-acting  $\beta$ -agonist. Advair Diskus® is an approved drug product for the maintenance treatment of asthma in patients 12 years of age and older. The product comes in three dosage strengths- 100/50, 250/50, 500/50. The recommended starting dose is dependent upon the asthma medication taken prior to beginning Advair and/or asthma severity. This sNDA is an efficacy supplement to broaden the indication to include the pediatric population down to 4 years of age. The proposal is to change the INDICATIONS and USAGE sections of the currently approved label to include asthmatic patients 4 – 11 years of age who are symptomatic on inhaled corticosteroids. Only the lowest dosage strength 100/50 administered BID is proposed for this indication.

#### **1.2. State of Armamentarium for Indication**

Inhaled corticosteroid (ICS), long-acting  $\beta$ -adrenergic agonists, leukotriene inhibitors, theophylline, cromolyn and cromolyn-like drugs (i.e. nedocromil) are the three classes of drugs approved for the maintenance treatment of asthma. ICS include flunisolide (Aerobid), triamcinolone (Azmacort), and budesonide (Pulmicort Turbuhaler) that are approved for use in subjects  $\geq 6$  years of age. Beclomethasone (QVAR) [approved in subjects,  $\geq 5$  years of age], fluticasone propionate (Flovent) [approved in subjects  $\geq 4$  year of age], and budesonide (Pulmicort Respules) [approved in subjects  $\geq 1$  year of age] are other ICS used in the treatment of asthma. All of the ICS are taken BID. In addition, Pulmicort Turbuhaler can be given once a day in patients previously stabilized on a BID regimen. Long-acting  $\beta$ -agonists approved for the treatment of asthma include salmeterol (Serevent MDI and Serevent Diskus, in subjects  $\geq 4$  years of age) and formoterol (Foradil Aerolizer, in subjects  $\geq 5$  years of age), both given BID. Of the leukotriene inhibitors, Zafirlukast (Accolate) is approved in subjects  $\geq 5$  years of age, and montelukast (Singulair) is approved in tablets, chewable tablets and granules for subjects  $\geq 15$ ,  $\geq 4$  and  $\geq 1$  year of age respectively. There is no other combination product other than Advair currently on the market for the treatment of asthma.

#### **1.3. Important Milestones in Product Development**

Advair Diskus® was approved for the treatment of adolescent and adult asthma on August 24, 2000. Flovent Diskus® was approved for the treatment of asthma in patients 4 years and older on September 9, 2000, and Salmeterol Diskus® was approved for treatment of patients 4 – 11 years of age on September 25, 1998.

During the pediatric development program, several meetings were held with the Agency and the applicant. At a meeting on April 26, 2001 it was agreed that to meet the regulatory requirements for combination drug products, efficacy for the pediatric population could be extrapolated from the adult data. This decision was based on the prior demonstration of efficacy for fluticasone and salmeterol in children 4 years and older and the recognition that asthma is similar enough in adults and children that the effects of the drug would be similar in adults and pediatric patients down to 4 years of age. Subsequently, it was agreed that a pediatric growth study with Advair® was not needed because one had already been completed for Flovent Rotadisk® 50 and 100 mcg (Feb 24, 2003 communication to the sponsor). Similarly, the PK data obtained from prior studies of inhaled fluticasone were thought to be sufficient to support approval of Advair Diskus® in the 4-11 age-group. The applicant indicated that they were planning a large population analysis of PK data at some time during development. (See biopharm review.) The Agency emphasized that safety was the primary objective of the clinical studies in the pediatric age group, and that adverse events and safety variables should be the primary outcomes for the studies for this program

## **2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS**

Only clinical data were submitted in support of this new indication. The sponsor used the approved product in the clinical studies and there are no preclinical or CMC reviews. The clinical program is primarily safety and therefore, a statistical review was not conducted.

## **3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS**

No new pharmacokinetic or pharmacodynamic data were submitted with this application. Based on prior data obtained with Advair and Flovent in adults and Flovent in children from previous submissions, it appears that the exposure to fluticasone propionate in Advair Diskus 100/50 is lower than with fluticasone propionate alone and, therefore, the dose of Advair 100/50 proposed for the 4 – 11 age group appears to be acceptable. However, the applicant has been advised that a complete pharmacokinetic characterization of Advair in the pediatric population 4 – 11 years of age is desirable. (See Biopharm Review.)

## **4. DESCRIPTION OF CLINICAL DATA AND SOURCES**

### **4.1. Sources of Clinical Data**

Four randomized clinical trials are submitted by the applicant with the sNDA. The 120-day safety update contains the clinical report for a fifth study in addition to a summary of a post-marketing survey performed in the UK.

### **4.2. Overview of Clinical Trials**

The primary objective of the clinical trials was to evaluate the safety of the combination product (Advair or Seretide) 100/50 BID in asthmatic patients 4 – 11 years of age symptomatic on ICS compared to the same nominal dose of fluticasone propionate. There was one 12-week pivotal study (SAS30031) conducted in the U.S. and four supporting trials conducted in Europe. The pivotal trial compared Advair 100/50 to FP100 . The supporting

trials compared the European-marketed (Seretide Diskus inhaler 50/100) to FP100, FP200, and to FP100 and salmeterol given concomitantly (FP100 +S). In this review the term “combination product” or FSC100/50 will refer to either Advair100/50 mcg BID or Seretide 100 mcg BID.

#### **4.2.1. Study SAS30031**

This was the pivotal safety trial. It was a randomized, double-blind study with a 12-week treatment period and a two-week run-in period. Pulmonary function (FEV<sub>1</sub> in subjects >5 years, and PEFr in 4-5 year-olds) was 50-95% predicted at enrollment. Patients were treated with either Advair 100/50 BID (n=101) or FP100 BID (n=102) with Ventolin provided for rescue to all patients. Symptoms, PEFr, and physical exam were monitored throughout the study. Urinalysis, blood for hematology and routine chemistries and a 24-hour urinary cortisol were obtained at baseline and at the end of the study. The other studies SAM40012, SFCB3020, RPS3001 and SAS30019 were the supporting studies.

#### **4.2.2. Study SAM40012**

This is a randomized, double-blind comparison of Seretide (salmeterol/fluticasone) 50/100 mcg BID (n=176), FP 100 mcg BID (n=175), and FP 200 mcg BID 180) all delivered via Diskus inhaler. There was a 2-week run in period and treatment continued for 24 weeks. The primary outcome variable was percentage symptom-free days and nights. PEFr was a secondary outcome. Safety was evaluated with adverse events, physical exam, routine blood and urines and a 12-hour overnight cortisol.

#### **4.2.3. Study SFCB3020**

This is a randomized, double-blind comparison of Seretide 50/100 BID (n=125) with salbutamol 50 mcg and fluticasone 100 mcg BID (n=132) delivered in two separate inhalers. This was a 12-week study with a 2-week run-in period. The primary outcome was AM PEFr taken from the patient’s diary. Safety was assessed with adverse events, and routine urinalysis and blood work, and an AM serum cortisol were obtained at baseline and at the end of the study.

#### **4.2.4. Study RPS3001**

This is a randomized, double-blind comparison of Seretide 50/100 BID (n=176) with salmeterol/fluticasone 50/100 (n=170) delivered via reservoir powder inhalation device (RPID), a device that is not in use in the US. There was a 2-week run-in period and treatment continued for 12 weeks. The primary outcome was AM PEFr taken from the patient’s diary. Safety was assessed with adverse events, and routine urinalysis and blood work, and an AM serum cortisol were obtained at baseline and at the end of the study.

#### **4.2.5. Study SAS30019**

This is a randomized, double-blind comparison of Seretide 50/100 BID (n=213) with fluticasone/salmeterol 50/100 delivered via HFA aerosol (n=215). There was a 2-week run-in period and treatment continued for 12 weeks. The primary outcome was AM PEFr taken from the patient’s diary. Safety was assessed with adverse events, and routine urinalysis and blood work, and an AM serum cortisol were obtained at baseline and at the end of the study.

### **4.3. Postmarketing Experience**

In the 120-day safety update the applicant submitted data from the applicant's post-marketing surveillance data-base collected through July 2003. In addition, a survey of the AERS database was performed by this reviewer.

### **4.4. Literature Review**

The applicant submitted a list of four recent articles. These articles were reviewed and an additional search of recent PubMed literature was performed by this reviewer.

## **5. CLINICAL REVIEW METHODS**

### **5.1. Conduct of the Review**

The safety data in the pivotal trial was reviewed in detail. Because of a prior agreement with the Agency that efficacy in the pediatric population could be extrapolated from the adult data, the efficacy data in this study was not reviewed in detail. The supportive studies were also reviewed primarily for an analysis of the safety results. In addition, study RPS3001 compared the to-be-marketed formulation to a formulation that is only available in Europe. Therefore, only the safety data for the to-be-marketed formulation were reviewed. In the 120-day safety update the applicant submitted brief summaries of numerous clinical trials involving Advair. Study SAS30019 was the only one that was completed and that enrolled children. It was reviewed briefly and compared to the results of the other four studies.

### **5.2. Materials Consulted and Documentation**

This is an electronic submission. The original application arrived on June 26, 2003 and the archival copy is stored at [\\CDSESUB1\N21077\S\\_017\2003-06-26](#). The 120-day safety update was submitted on October 24, 2003 and can be found at [\\CDSESUB1\N21077\S\\_017\2003-10-24](#). AERS Datamart was searched on January 15, 2003. The search was limited to the trade name "Advair" and to patients <13 years of age.

### **5.3. Data Quality and Integrity**

These studies were conducted by various components of the GSK clinical network. Several audits have been conducted recently and additional auditing was not requested.

### **5.4. Ethical Standards**

All of the studies were conducted according to ICH good clinical practices. This is attested to on the first page of each study report. The study reports are filed at *(\clinstat\pediacuse\study number)*

The following items were included in this submission:

- Form FDA 356h (\356h.pdf)
- Debarment certification (\other\debar.pdf)

- Statements that IRB approval and written patient consent had been obtained in all cases as described in 21 CFR Part 50 are found in the individual study reports, all of which are filed under *clinstat\pediatricuse\...* (*SAS30031, pg 12; SAM40012, pg 18; SFCB3020, pg 9; RPS30002, pg 14*)

## 5.5. Financial Disclosure

### 5.5.1. SAS30031

Three investigators meet the definition of having a potential financial conflict of interest. One investigator (b)(4) received other payments from GSK that exceeded \$25,000 and had an equity interest in GSK of greater than \$50,000. One investigator (b)(4) only received other payments greater than \$25,000, and another (b)(4) had an equity interest of greater than \$50,000 in GSK. However, the applicant claims exemption on the basis that this was not an efficacy trial. In addition, enrollment by these three investigators was low. Investigator (b)(4) enrolled 2 patients, investigator (b)(4) enrolled 6, and investigator (b)(4) enrolled 7.

### 5.5.2. Supportive studies

None of the investigators participating in these trials reported a financial conflict of interest. (*Other\financial.pdf, pg 3-4*)

## 6. INTEGRATED REVIEW OF EFFICACY

Pulmonary function increased to a similar degree in all of the treatment groups. In the pivotal trial (SAS30031) pre-dose FEV<sub>1</sub> was measured in the clinic in the 6 – 11 year-olds. In the Advair treated subjects the FEV<sub>1</sub> increased from a baseline value of 1.70 L/sec to 1.88 L/sec at the end of the study. In the FP100 treated subjects the values were 1.65 and 1.77 L/sec respectively. Peak expiratory flow was taken from the symptom diaries in all of the subjects (including the 4-5 year-olds). There was an increase of 21.5 L/min in the subjects treated with Advair and an increase of 16.9 L/min in the subjects treated with FP100. Symptom scores and albuterol use decreased to a similar degree in both treatment groups over the course of the trial.

## 7. INTEGRATED REVIEW OF SAFETY

### 7.1. Brief Statement of Findings

A total of 553 asthmatics 4 – 11 years of age on maintenance ICS were treated with the combination product (FSC100/50) for a mean of 109 days in four double-blind, randomized controlled trials (SAS30031, SAM40012, RPS3001, SFCB3020). The pivotal trial (SAS30031) enrolled 101 asthmatics who were treated with Advair 100/50 and 102 who were treated with FP100. In all of the trials the patients had to have been symptomatic on maintenance ICS.

In all of the trials the incidence of most adverse events was less after treatment with the combination product than after treatment with the comparator drug. In all of the studies, the

most common adverse events were in the upper respiratory tract, occurring in slightly greater than 33% of each treatment group. Lower respiratory tract disease was the next most common with 17% of the FSC100/50 patients reporting an event compared with 24% of those treated with FP100+S, 22% of those treated with FP100, and 35% of those treated with FP200. Headache occurred in 8%, 5%, 11%, and 10% of those treated with FSC100/50, FP100+S, FP100, and FP200 respectively. Patients less than six years of age had more AEs (62.7%) compared with patients 6-11 years of age (55.4%), and females had more AEs (62.2%) than males (55.4%) (... \clinstat\iss\iss.pdf, pg 36-41).

The HPA axis was evaluated in three of the studies (SAS30031, SFCB3020, and SAM40012) but only the pivotal study (SAS30031) collected 24-hour urines. In the other two studies 12-hour urines (SAM40012) and AM blood (SFCB3020) were collected for cortisol. A total of 391 patients who had received FSC100/50 had one of these tests. The changes in urinary cortisol measurements from the baseline period when patients were receiving only ICS and the end of the study, were comparable in the various treatment groups.

A study submitted with the 120-day safety update (SAS30019) comparing Serevent to a fluticasone/Salmeterol aerosol showed a range of AEs that was the same as seen with the studies submitted with the original application.

An observational study of Seretide in the UK showed a similar incidence and spectrum of adverse events as was found in the clinical trials. Comparing adverse events pre and post introduction of Seretide in patients 1 – 11 years of age, it was noted that the incidence of adverse events decreased in patients classified as having moderate and severe disease. However, the incidence went from 28.9% pre-treatment to 34.7% post-treatment in patients with mild disease.

Between May 8, 2001 and December 10, 2003, 62 events reported in 4 – 11 years olds with Advair as the suspect drug were sent to the AERSMART database. Twenty-four of the events were classified as serious. There were no reports of adrenal insufficiency, decreased cortisol, or growth retardation.

## **7.2. Description of Patient Exposure**

In the pivotal study (SAS30031) 101 subjects were treated with Advair 100/50 BID for a median of 84 days. When all five of the submitted studies are combined, there were 766 patients randomized and the median exposure was 102 days. All of the studies were planned for 12 weeks except for SAM40012 which was a 24-week trial.

## **7.3. Safety Findings from Clinical Studies**

### **7.4.1. Patient Demographics and Exposure**

When the patients treated in studies SAS30031, SAM40012, SFCB3020, and RPS30001 are combined there were 553 patients treated with the combination product (FSC100/50), 132 were treated with concurrent FP100 and salmeterol (FP100 + S), 283 treated with FP100 alone and 186 with FP200 alone. The demographic characteristics of the population are presented in Table 1 and the duration of exposure in Table 2.

**Table 1. Demographic Characteristics of the Combined Study Population\* (Studies SAS30031, SAM40012, SFCB3020, RPS30001)**

		FSC100/50 (n=553)	FP100 + S (n=132)	FP100 (n=283)	FP200 (n=186)
Male (%)		68	54	64	71
Age	Mean years	7.7	7.6	8.0	7.7
	4-5 years, n(%)	116 (21)	26 (20)	54 (19)	40 (22)
	6-11 years, n(%)	437 (79)	106 (80)	229 (81)	146 (78)
Ethnic Origin	White (%)	90	90	91	100
	Black (%)	6	2	4	0
	Other (%)	4	8	6	0
Height (mean cm)		129	128	132	131

\* Excludes the patients in ROS30001 who were treated with the RIPD device.

A large majority of the subjects were Caucasian and most were 6 years of age or older.

**Table 2. Summary of Combined Exposure to Fluticasone (Studies SAS30031, SAM40012, SFCB3020, RPS30001)**

	FSC100/50 (n=553)	FP100 + S (n=132)	FP100 (n=283)	FP200 (n=186)
Completed	513	127	257	181
Withdrawn	40	5	26	5
Exposure (days)				
Mean (SD)	109 (43)	83 (13)	133 (47)	166 (22)
Median	88	85	168	169
Range	6-185	3-99	1-184	9-193
Number of Days, n(%)				
<57	31 (6)	5 (4)	14 (5)	4 (2)
57-84	120 (22)	43 (33)	36 (13)	0
84-112	219 (40)	84 (64)	57 (20)	1 (<1)
>112	180 (32)	0	173 (62)	178 (96)

### 7.3.1. Adverse Events

The adverse event experience of the entire population is summarized in Table 3. A smaller percentage of patients in the combination product group complained of adverse events than in any of the other treatment groups. The incidence of viral lower respiratory tract infections was particularly high in the FP200 group (22%) compared with 8% in both the FSC100/50 and FP100+S treated patients (*clinstat\iss\iss.pdf pg 36*).

**Table 3. Adverse Events occurring in > 3% of Patients in the Combined Population Stratified by Drug Product (Studies SAS30031, SAM40012, SFCB3020, RPS30001)**

	FSC100/50 (n=553)	FP100 + S (n=132)	FP100 (n=283)	FP200 (n=186)
Mean exposure (days)	109	83	133	166
% with any event	55	59	60	61
<b>ENT*</b>	<b>33</b>	<b>39</b>	<b>34</b>	<b>33</b>
URI**	10	19	11	7
Rhinitis	7	7	5	11
Throat irritation	4	5	6	1
Pharyngitis	3	3	7	6
Tonsillitis	3	4	2	5
ENT infection	3	6	2	2
Sinusitis	3	<1	2	3
<b>LRI***</b>	<b>17</b>	<b>24</b>	<b>22</b>	<b>35</b>
Viral infection	8	8	12	22
Cough	4	8	7	8
Bronchitis	3	2	1	5
Fever	6	7	8	7
Other viral infections	4	2	4	11
Headache	8	5	11	10

\* Ear, Nose, and Throat, \*\* Upper Respiratory Infection, \*\*\*Lower Respiratory Infection,  
† All numbers are percentage of patients.

Events are stratified by age in Table 4. Adverse events were more common in the patients <6 years of age (62.7%) compared with patients 6-11 years-of age (55.4%). The distribution was similar in the 553 patients treated with FSC100/50 (61% of the patients < 6 years of age reported adverse events and 53% of the patients 6-11 years of age reported adverse events). For all events other than gastrointestinal, the FSC100/50 treated patients had fewer adverse events than patients in the other treatment groups. Fifteen (13%) of the 4-5 year-olds treated with FSC had gastrointestinal complaints compared to 3 (12%) of the 4-5 year olds treated with FP100+S, and 4 (7%) of the 4-5 year-olds treated with FP100 (*^clinstat\iss\iss.pdf pg 39*).

**Table 4. Adverse Events by Age in Patients Treated with fluticasone propionate, 100 mcg BID by Inhalation. (Studies SAS30031, SAM40012, SFCB3020, RPS30001)**

	< 6 Years Old n=196		6-11 Years Old n=772	
	N	%	n	%
<b>All</b>	<b>123</b>	<b>62.7</b>	<b>428</b>	<b>55.4</b>
<b>ENT</b>	<b>77</b>	<b>39.3</b>	<b>254</b>	<b>32.9</b>
<b>LRI†</b>	<b>46</b>	<b>23.5</b>	<b>144</b>	<b>18.7</b>
<b>Non-Site specific</b>	<b>35</b>	<b>17.9</b>	<b>101</b>	<b>13.1</b>
<b>GI††</b>	<b>22</b>	<b>11.2</b>	<b>75</b>	<b>9.7</b>
<b>Headache</b>	<b>15</b>	<b>7.7</b>	<b>66</b>	<b>8.5</b>

\* Includes all patients taking 100 mcg fluticasone except those using the RIPD device. † Lower Respiratory Infection. †† Gastrointestinal

Adverse events stratified by gender are shown in Table 5 (\clinstat\iss\iss.pdf, pg 41). Females made up 34.4% of the subjects treated with 100 mcg fluticasone BID. Of these, 62% described adverse events compared to 54.1% of the males. Females treated with the combination product had a 60% incidence of adverse events compared to 70% of the females treated with FP100+S 60% of the females treated with FP100.

**Table 5. Adverse Events Stratified by Gender in patients treated with FSC (Studies SAS30031, SAM40012, SFCB3020, RPS30001)**

	Males N=629		Females N=339	
	n	%	n	%
<b>ANY EVENT</b>	340	54.1	211	62.2
<b>ENT (all)*</b>	202	32.1	129	38.1
<b>LRI (all)**</b>	114	18.1	76	22.4
<b>Fever</b>	52	8.3	29	8.6
<b>Viral infection</b>	24	3.8	10	2.9
<b>GI (all)†</b>	58	9.2	39	11.5
<b>N&amp;V††</b>	14	2.2	10	2.9
<b>Headache</b>	51	8.1	30	8.8

\* Ear, Nose, and Throat, \*\* Lower Respiratory Infection, † Gastrointestinal, †† Nausea and Vomiting

Caucasians made up 89.7% of the study population. Adverse events were noted in 58.8% of the Caucasians and 41.0% of the non-Caucasians. The non-Caucasians had somewhat fewer respiratory infections than the Caucasians. Upper respiratory tract infection occurred in 12.1% and 7.0% and lower respiratory tract infection occurred in 20.7% and 10% Caucasians and non-Caucasians respectively (\clinstat\iss\iss.pdf, pg 42).

The spectrum of adverse events seen in both the pivotal and supportive studies is similar to the adverse events seen with Flovent Diskus. A comparison of the events in the pivotal

pediatric study (SAS30031) and the current approved label is displayed in table 6. The asthma studies used to construct the Adverse Event table in the label enrolled patients 12 years of age and above. Compared to the adult/adolescent population treated with Advair 100/50, the patients 4-11 years of age had fewer adverse events (71% compared with 59% for Advair).

**Table 6. Percent of patients with selected adverse events. (Studies SAS30031, SAM40012, SFCB3020, RPS30001)**

	SAS30031 (4-11 years)		Approved Label (Subjects ≥ 12 years)		
	Advair100/50	FP100	FP100	Advair100/50	Placebo
<b>N</b>	101	102	90	92	175
<b>Any Event (%)</b>	59	57	N/A	71	N/A
<b>Headache</b>	20	20	14	12	7
<b>URI</b>	10	17	29	27	16
<b>Hoarsness</b>			6	5	4
<b>Throat Irritation/ pharyngitis</b>	8	7	7	13	8
<b>GI distress</b>	7	5	0	4	1
<b>N &amp; V</b>	5	3	3	4	4
<b>Diarrhea</b>			2	4	1
<b>Fever</b>	5	13	7		4
<b>Candidiasis</b>	4	<1	9	1	7
<b>ENT Infection/sinusitis</b>	4	<1	10	7	6
<b>Epistaxis</b>	4	<1			
<b>Cough</b>	2	3	5	3	4
<b>Viral infection</b>	<1	3	10	7	7
<b>Upper Respiratory inflammation</b>			5	7	3
<b>Rhinitis</b>			3		2
<b>Bronchitis</b>			3	2	1
<b>Musculoskeletal pain</b>			1	0	3

As reported by the investigators, the incidence of drug-related adverse events was low (FSC100/50 = 6%, FP100+S = 5%, FP100=4%, and FP200 = 1%). The incidence of

adverse events that were considered predictable as a corticosteroid and/or  $\beta$ -adrenergic class effect (Table 7.) was also low.

**Table 7. Events Expected as Corticosteroid or Adrenergic Class Effects Occurring in More than 1% of Subjects. (Studies SAS30031, SAM40012, SFCB3020, RPS30001)**

	From NDA21-077\s_017 *			
	FSC100/50 (n=553)	FP100 + S (n=132)	FP100 (n=283)	FP200 (n=186)
Mean exposure (days)	109	83	133	166
Headaches	8	5	11	5
Cough	4	8	7	8
Throat Irritation	4	5	6	1
Pharyngitis	3	3	7	6
Oral Candidiasis	1	2	<1	<1

\* All numbers are percentages

Metabolic events occurred rarely. There was one case each of “full face”, increased thirst, hypoglycemia, and decreased appetite in the 553 patients treated with FSC100/50. In addition there were 2 cases of increased appetite in 139 patients treated with FP100 and one case of obesity in the 186 patients treated with FP200. There were 6 patients who had cardiovascular events. There was one case of angina (*clinstat\iss\iss.pdf, pg 47*) in each of the FSC100/50, FP100 and FP200 treatment-groups. In addition, one patient in the FP100 group developed hypertension and one patient each in the FSC100/50 group with coronary sinus arrhythmia and tachycardia.

Eighteen patients had ophthalmic complaints. There were 8 (1.4%) in the FSC100/50 group, 5 (3.8%) in the FP100+S group, 1 (<1%) in the FP100 group and 4 (2.1%) in the FP 200 group. All of the complaints were related to some form of conjunctivitis or ocular infection. There was no case of cataract or glaucoma.

Six fractures, mostly of small bones were described. There were 4 (0.7%) in the FSC100/50-treated patients, 1 (0.3%) in the FP100-treated patients and 1 (0.05) in the FP200-treated patients.

*Reviewer: The reporting of three cases of “angina” in subjects 5 – 10 years of age is unusual. However, all of these cases lived in Eastern Europe or Russia and were enrolled in SAM40012, a study when the procedures were so irregular that even the applicant dismissed the efficacy results. The adverse events were described as mild or moderate in severity and they resolved after 7-11 days. One additional child was said to have had “angina” 4 days prior to enrollment. She was enrolled despite the fact that the angina supposedly lasted 5 days. All of these subjects completed the study without further episodes. It is unlikely that these events represent episodes of coronary artery disease.*

### 7.3.2. Serious/Severe Adverse events

No patient died in any of the studies and there were no serious adverse events in the pivotal trial. There were six serious adverse events in patients taking the combination product in two of the supportive trials (SAM40012 & SFCB3020), however none of them was thought to be drug-related (one each of trauma, celiac disease, appendicitis, enlargement of tonsils, coxitis fugax [transient hip joint inflammation], and asthma exacerbation).

Six patients (1%) in the FSC100/50 group had severe adverse events during treatment and one additional patient had an asthma exacerbation during follow-up. This compares with no SAEs in the FP100+S-treated group, <1% in the FP100-treated group and 2% in the FP200-treated patients. Nine (2%) of 553 patients treated with FSC100/50 were withdrawn from the study as compared with 2 of 132 (2%) withdrawn from the FP100+S group, 2 of 283 (<1%) withdrawn from the FP100 group and none withdrawn from the FP200-treated patients. Conditions associated with withdrawal of patients from the FSC group are listed in Table 8.

**Table 8. Adverse Events leading to withdrawal of patients from studies SAS30031, SAM40012, SFCB3020, and RPS30001**

	FSC100/50 (n=553)	FP100 + S (n=132)	FP100 (n=282)	FP200 (n=186)
<b>N (%) with any event</b>	<b>9 (2)</b>	<b>2 (2)</b>	<b>2 (&lt;1)</b>	<b>0</b>
<b>Lower Respiratory (any event )</b>	<b>3 (&lt;1)</b>	<b>1(&lt;1)</b>	<b>2 (&lt;1)</b>	<b>0</b>
Asthma	2 (<1)	1(<1)		
Breathing Disorders	1 (<1)		1 (<1)	
Cough				
Infection	1 (<1)		1 (<1)	
Pneumonia				
<b>Gastrointestinal (any)</b>	<b>1 (&lt;1)</b>	<b>1 (&lt;1)</b>	<b>0</b>	<b>0</b>
Abdominal pain	1 (<1)			
Oral inflammation		1 (<1)		
<b>Neurology (any)</b>	<b>2 (&lt;1)</b>	<b>0</b>	<b>0</b>	<b>0</b>
Migraines	1 (<1)			
Sleep Disorders	1(<1)			
<b>Non-site Specific (any)</b>	<b>2 (&lt;1)</b>	<b>0</b>	<b>0</b>	<b>0</b>
Angioedema	1 (<1)			
Chest symptoms	1 (<1)			
Urticaria	1 (<1)	0	0	0
Abnormal heart rhythm	1 (<1)	0	0	0
Drug Overdose	1 (<1)	0	0	0
Upper Respiratory Infection	0	1 (<1)	0	0

### 7.3.3. Laboratory Abnormalities

Changes in routine hematology, chemistries and vital signs were mild, infrequent, and similar in frequency in all of the treatment groups

Three of the studies included an assessment of the hypothalamic-pituitary-adrenal (HPA) axis. In SAS30031, 24-hour urines were collected, in SFCB3020 serum cortisol was measured and in SAM40012, 12-hour urines were collected for cortisol measurement. Measurements were made at baseline when the patients were taking only ICS and at the end of the study after treatment with study drug. In all cases the ratio of baseline geometric mean to follow-up geometric mean cortisol in the FSC100/50-treated patients was greater than one. In addition, the ratio of (FSC100/50)/FP100 cortisol at the follow-up was greater than one.

**Table 9. HPA Axis Evaluation**

Study	N* (SFC/FP100)	Type of Test	Follow-up	FSC† Base/End	FSC/FP100† at end of study
SAS30031	48/57	Timed 24-hour Urine	12 weeks	1.26	1.40
SFCB3020 (95% CI)	117/122	AM serum cortisol	12 weeks	1.23	1.05 (0.93-1.19)
SAM40012 (95% CI)	49/53	12-hour overnight Urine	24 weeks	1.1	1.01 (0.81-1.26)

\* Number of subjects with technically acceptable baseline and follow-up measurements

† All values are ratios of geometric mean cortisol levels.

#### 7.4. Literature Review of Safety

The applicant included a list of four articles published between February 2003 and July 2003. One is a meta-analysis, one is an opinion piece, and two are reports of new clinical studies. All of the reports support the use of an inhaled long-acting  $\beta$ -agonist with an inhaled corticosteroid. Both clinical trials were funded by the applicant. They were both conducted in adult patients who were symptomatic on ICS therapy and do not provide additional information for or against the use of Advair 100/50 in pediatric patients 4 – 11 years of age.

#### 7.5. Postmarketing Surveillance

Post-marketing experience obtained from the GSK database was summarized for the period 5/02 – 7/03. (data for the period 5/02-1/03 were contained in original submission and data for the period 2/03-7/03 was submitted in the 120 day safety update). For the entire period there were 14 spontaneous reports of serious adverse events (8 US, 3 Europe, 3 S. America and Australia) in patients <12 years old. The reports included 2 cases of adrenal insufficiency, 2 cases of asthma exacerbations, and 1 case of Henoch-Schonlein purpura. No deaths were reported.

In the same time period (5/02 – 7/03) the AERS database (US PHS) received 12 adverse event reports in patients 4-11 years old where Advair is reported as the primary suspect drug. Seven of these are also contained in the GSK database. The AERS database records 62 adverse events in patients 4 -11 years of age between May 8, 2001 and December 10, 2003, 24 of which are classified as severe. The events span a large number of allergic and

non-specific reactions. Of note, there is no report of adrenal insufficiency, decreased cortisol, growth or bone abnormality.

An observational study was conducted in England to evaluate the safety of Seretide (salmeterol/fluticasone 25/50, 25/125, and 25/250 mcg delivered via HFA-aerosol inhaler).

The study was conducted by the [REDACTED] (b) (4).

Patients were identified through pharmacy records and clinical information was obtained via questionnaire sent both to the general practitioner and the patient six months after the initiation of therapy. A total of 13,464 patients were enrolled of whom 826 were < 12 years of age. Most of the patients had moderately severe disease (71.07%) and 28.9% required at least one course of high-dose oral corticosteroid treatment during the six-month surveillance period.

The use of oral corticosteroids pre and post exposure was similar in the 277 subjects for whom data was available. Pre-exposure, 1.13% of the subjects were treated with oral corticosteroids for greater than 14 days while post-exposure, 2.38% of the subjects were treated with oral corticosteroids for greater than 14 days. Pre-exposure the subjects were treated with 1.149 courses of oral corticosteroids/subject while post-exposure the number of courses/patient was 1.145. The number of subjects reporting adverse events decreased slightly in the post treatment period (297 (35.96%) events vs 288 (34.8%) events in the pre and post exposure periods respectively). The decrease was greatest in the subjects with severe disease (52% with events pre-exposure and 45.6% post-exposure) and less in patients with moderate disease. In patients with mild disease the relationship was actually reversed. Pre-exposure 28.9% of subjects reported events compared with 34.7% post-exposure. As in the controlled trials, respiratory and ENT infections were the most frequently reported events.

## 7.6. Safety Update

In the 120-day safety update the applicant described the results of study SAS 30019, a comparison between Seretide Diskus 100/50 and a combination fluticasone/salmeterol HFA-aerosol 100/50 BID in children 4-11 years old. The subjects were symptomatic on maintenance ICS and they had a stable AM PEF of > 50% predicted prior to enrollment. The primary endpoint was mean morning PEF over a 12 week period. The safety evaluation included 12-hour, over-night urine collections for cortisol as well as routine hematology and chemistry, physical exam, and adverse events. There were 213 patients entered into the Seretide Diskus arm and 199 completed the study. The mean age was 7.5 years with 50 (23%) <6 years of age. There were 78 (37%) females; 98% of the subjects were Caucasian. The baseline PEFR %predicted was 95.1, and the mean increase in FEV<sub>1</sub> after albuterol was 12%.

The median exposure to the study medication was 82.4 days in the Diskus-treated patients. Adverse events were reported by 91 (43%) of the subjects and the spectrum of events was similar to that reported in the pivotal trials for sNDA 21-077\S\_017. Nasopharyngitis was the most common, occurring in 16 (8%) of the subjects followed by cough (6%), rhinitis (6%), headache (6%), pyrexia (3%), upper respiratory tract infection (3%) and allergic rhinitis (3%). There were no deaths in the study but 2 patients suffered serious adverse events. One had a concussion and the other an exacerbation of asthma. The patient with asthma was withdrawn from the study as was one patient each with headache, psychomotor

hyperactivity, and a low urinary cortisol. Looking at the group as a whole, the geometric mean urinary cortisol did not change over the treatment period (Ratio week12/baseline = 1.01). When the adverse events from SAS30019 were combined with that of the clinical studies submitted with sNDA21077\S\_017 the percentages were practically identical to those seen in the primary studies.

### **7.7. Adequacy of Safety Testing**

The current submission includes studies of 12 and 24 weeks duration. Therefore, they do not provide information about the long term effects such as growth retardation that might result from the ingestion of Advair during childhood. Given the established effects of corticosteroids on linear growth velocity and the results of the Flovent Rotodisk growth study, we can conclude that decrease in linear growth velocity is a possible adverse effect of using Advair in childhood, and the Division concluded that a separate growth study with Advair was not warranted. The label carries appropriate warnings about the effect of inhaled corticosteroids on growth.

### **7.8. Labeling Safety Issues and Postmarketing Commitments**

The label will contain the standard warning about the possible effects on growth and the HPA axis due to long-term use of corticosteroids in children. No post-marketing commitments are being requested of the Applicant.

## **8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES**

The proposed dose of Advair Diskus is 100/50 mcg BID. This is a higher starting dose of FP than the current recommendation for Flovent Rotadisk (i.e. starting dose of 50 mcg BID) for patients > 4years of age. In the dosage and administration portion of the proposed label the dosage is said to be for (b) (4)

The pivotal as well as supportive trials for this application were all conducted in patients who were symptomatic on inhaled corticosteroids. There was no provision for patients on (b) (4). Therefore, the indication should be limited to patients who have previously been maintained on ICS and are still symptomatic. In addition, there are references throughout the label to the demonstration of safety of Advair in patients 4 to 11 years. These statements should include the fact that the patients were all on maintenance ICS before being enrolled in the referenced studies. (*See Appendix, Detailed Labeling Changes*)

## **9. CONCLUSIONS AND RECOMMENDATIONS**

### **9.1. Conclusions Regarding Safety and Efficacy**

Advair 100/50 mcg BID used to treat asthma in patients 4 to 11 years of age who are symptomatic on ICS has a similar safety profile as Flovent Diskus 100 mcg BID which is an approved drug for the treatment of asthmatics 4 – 11 years of age. There was no evidence of HPA axis suppression after 24 weeks of treatment. Efficacy in patients 4 – 11 years of age is extrapolated from the adult efficacy data. A growth study with Advair is not required given that one has already been completed with Flovent Rotadisk.

The recommended dose of Advair is 100/50 mcg BID while the starting dose of Flovent Rotadisk is 50 mcg BID in patients 4 – 11 years of age. The higher dose of Advair is approvable because the product is only recommended for patients who are symptomatic on inhaled corticosteroids. The elevated rate of respiratory infections seen with FP200 is a reminder that inhaled corticosteroids carry the potential for an increased susceptibility to a variety of infections and that the lowest possible dose should be used at all times. The observational study of Seretide that was conducted in the UK is also supportive of this conclusion. In that experience only patients who were classified as having moderate to severe disease were less symptomatic after taking Seretide than before they started the medication. Subjects with mild disease were actually more symptomatic after starting Seretide.

With label warnings appropriate for the chronic use of corticosteroids in children, Advair 100/50 mcg BID use for the maintenance treatment of asthma in children 4-11 years of age is recommended for approval.

## **APPENDIX**

### **1. DETAILED STUDY REVIEWS**

#### **1.1. Study # SAS30031.**

**A randomized, double-blind, 12-Week Trial Evaluating the Safety of the Fluticasone Propionate/Salmeterol DISKUS<sup>†</sup> Combination Product 100/50 mcg BID Versus Fluticasone Propionate DISKUS 100 mcg BID in Symptomatic Pediatric Subjects (4-11 Years) With Asthma**

##### **1.1.1. Protocol**

###### **1.1.1.1. Administrative**

Study Dates: April 9, 2002 – January 20, 2003

Clinical Centers: 66 sites, 44 United States, 13 in Canada (3 enrolled patients)

Medical Officer: Kathleen Rickard, MD

###### **1.1.1.2 Objective/Rationale**

The objective of the current study is to evaluate the safety of the fluticasone propionate/salmeterol **DISKUS** combination product 100/50 mcg BID (**DISKUS** combination product) compared with fluticasone propionate **DISKUS** 100 mcg BID (FP 100 mcg **DISKUS**) in symptomatic pediatric subjects ages 4 to 11 years of age with asthma.

###### **1.1.1.3 Overall Design**

This was a 12-week, randomized, double-blind, parallel-group trial in pediatric subjects 4-11 years of age with asthma. Subjects were provided with albuterol inhalation aerosol and Flonase® as needed throughout the trial. Subjects who met the entry criteria entered a 2-week run-in period during which their baseline asthma therapy was continued. At the end of the 2-week run-in period subjects who met all randomization criteria were randomly assigned to one of the following treatments for 12 weeks:

- Fluticasone propionate/salmeterol 100/50mcg **DISKUS** BID (**DISKUS** Combination Product)
- Fluticasone propionate 100mcg **DISKUS** BID (FP 100mcg **DISKUS**)

Subjects returned to the clinic during the double-blind treatment period at Weeks 1, 2, 4, 8, and 12 for evaluation. Each subject's parent/guardian was also contacted 3-5 days following the final visit for assessment of post-treatment adverse events.

###### **1.1.1.4 Study Population**

###### **1.1.1.4.1 Inclusion Criteria**

- Subjects must have been treatable on an outpatient basis.
- 4-11 years of age
- Male or premenarchal female.

- Asthma, which had required physician prescribed treatment for at least 2 months, as defined by the American Thoracic Society [*American Thoracic Society, 1987*].
- Screening Visit: subjects 6-11 years of age had to have a baseline best morning (AM) pre-albuterol FEV1 performed in the clinic of 50-95% of the Polgar predicted value, after withholding asthma medications. Subjects 4 and 5 years of age had to have a baseline best AM pre-albuterol PEF performed in the clinic of 50-95% of the Polgar predicted value [*Polgar, 1971*].
- Reversibility as demonstrated by an increase in FEV1 (6-11 years of age) or AM PEF (4 and 5 years of age) of  $\geq 12\%$  over baseline within 30 minutes following inhalation of 2-4 actuations of albuterol, with or without a spacer, or one nebulized albuterol treatment. Each subject had to demonstrate the ability to use a metered-dose inhaler (MDI) with or without a spacer since rescue albuterol was administered on an as needed basis via an MDI throughout the trial.
- Subjects must have been using inhaled corticosteroids (ICS) for at least 1 month prior to Screening at any one of the following consistent daily doses:

**Table 10. Requirement for Maintenance ICS prior to enrollment (Study SAS30031)**

Inhaled Corticosteroid	Dose (mcg/day)
Beclomethasone dipropionate	252-336
Triamcinolone acetonide	600-1000
Flunisolide	1000
Fluticasone propionate	88-250
Budesonide	200-400

Each subject had to be judged by the investigator as able to withhold their ICS the morning of the Screening and Randomization visits and then discontinue its use for the remainder of the study.

- All subjects had to be able to replace short-acting beta2-agonists with albuterol inhalation aerosol at the Screening Visit to use as needed with or without the Aerochamber plus spacer for the duration of the study. The use or non-use of the spacer had to be consistent throughout the study. Subjects had to be able to withhold all inhaled albuterol for at least 6 hours prior to study visits when FEV1 was performed (Screening, Randomization, and Week 12). Albuterol nebules were only permitted for reversibility testing at Screening.
- Subjects 6-11 years of age had to be able to adequately perform the spirometry maneuver defined as producing FEV1 values that varied by  $\leq 10\%$  (based on the highest two values) and maintain the effort for at least 3 seconds.

**1.1.1.4.2 Randomization Criteria**

- Randomization Visit (Treatment Day 1): subjects 6-11 years of age had to demonstrate an AM FEV1 of 50-95% of the Polgar predicted value. Subjects 4 and 5 years of age had to demonstrate a clinic AM PEF of 50-95% of the Polgar predicted value.
- A daily asthma symptom score of  $\geq 1$  on 3 or more days during the 7 days prior to the Randomization Visit,

**OR**

Use albuterol on 3 or more days during the 7 days prior to the randomization Visit.

- Adequate compliance, defined as  $\geq 70\%$  compliance with the diary card completion at the Randomization Visit, to continue in the study. Subjects who were 70-100% compliant with the completion of the diary card were re-educated on diary card completion.

**1.1.1.4.3 Exclusion Criteria**

- History of significant asthma episode(s) that required intubation, associated with hypercapnia, respiratory arrest or hypoxic seizures, or asthma-related syncopal episode(s). A subject must not have been hospitalized two or more times in the prior year due to asthma.
- Medications listed below must not have been used for the intervals indicated below prior to Screening, and not taken during the study.

**Table 11. Forbidden Medications (Study (SAS30031))**

<b>Prohibited Asthma Medication</b>	<b>Withheld prior to Screening</b>
Oral short-acting beta-agonists	12 hours
Nebulized short-acting beta-agonists (unless used for reversibility testing at Screening)	6 hours
Inhaled anticholinergics	24 hours
Theophylline	
Short acting forms of theophylline	12 hours
Twice-daily forms of theophylline	24 hours
Once-a-day controlled-release forms of theophylline	36 hours
Any inhaled long-acting beta-agonist alone, or in combination with an ICS	48 hours
Oral corticosteroids <sup>a</sup>	1 month
Parenteral corticosteroids	1 month
5-lipoxygenase inhibitors	1 month
Any leukotriene antagonist/modifier alone, or in combination with an ICS	1 week
Nedocromil	1 month
Cromolyn	1 month

<sup>a</sup> Any subject receiving daily oral corticosteroid treatment for 2 months or longer must have discontinued this medication at least 6 months prior to the Screening Visit

- Historical or current evidence of clinically significant uncontrolled disease including, but not limited to, those listed below.

- Active chickenpox or exposure to chickenpox within the 3 weeks prior to Screening in a non-immune subject.
- Hypersensitivity to any beta2-agonist, sympathomimetic drug, any intranasal, inhaled, or systemic corticosteroid therapy.
- ENT or respiratory tract infections within the 2 weeks immediately preceding screening requiring the use of an antibiotic or accompanied by symptoms of worsening asthma.
- Past or present use of tobacco products.
- Clinically significant abnormal laboratory tests during screening which were still abnormal upon repeat analysis and were not believed to be due to disease(s) present by each investigator.
- History or presence of glaucoma and/or posterior, subcapsular cataracts.
- Any investigational drug use within 30 days prior to the Screening Visit
- Subject or his/her parent/guardian had any infirmity, disability, or geographical location which seemed likely (in the opinion of the investigator) to impair compliance with study procedures.
- The subject or subject's parent/guardian had a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions (e.g., inability to read, comprehend and write) which would limit the validity of informed consent to participate in this study.
- Immediate family members of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator were not eligible.
- Subject had an abnormal, clinically significant ECG at the Screening Visit Section

*Reviewer: The above inclusions and exclusion criteria were finalized with Amendment #4 after 12% of the patients had been enrolled. As can be seen in the chart below, the criteria were liberalized due in part to the elimination of efficacy as a primary endpoint. Amendments 1-3 were instituted prior to patient enrollment.*

**Table 12. Amendments to Protocol SAS30031**

	<i>Amendment #2</i>	<i>Amendment #4</i>
<i>Criteria for 4-5 yr olds</i>	<i>FEV1</i>	<i>PEF</i>
<i>FEV1 (% predicted)</i>	<i>50-85</i>	<i>50-95</i>
<i>Reversibility</i>	<i>No historical data</i>	<i>Allows data within 1 yr</i>
<i>PFT reproducibility</i>	<i>Required</i>	<i>Not required</i>
<i>Symptom score within 7 days</i>	<i>≥ 2 on at least 4 days</i>	<i>≥ 1 on at least 3 days</i>
<i>Albuterol within 7 days</i>	<i>≥ 4 days</i>	<i>≥ 3 days</i>
<i>Withhold leukotriene modifiers</i>	<i>1 month</i>	<i>1 week</i>
<i>Withhold inhaled steroids</i>	<i>3 months</i>	<i>1 month</i>

#### 1.1.1.4.4 Subject withdrawal from the study

A subject who received double-blind study drug, but either did not complete the 12-week treatment period or did not complete the Week 12 Visit evaluations was defined as prematurely discontinued. Premature discontinuation was required when:

- A subject experienced an asthma exacerbation/worsening of asthma (*see Section 1.1.5.1.2.*)
- A subject was significantly non-compliant
- A female subject began menses
- A subject had an adverse event (AE) that would, in the investigator's judgment, make continued participation in the study an unacceptable risk
- Exposure to chickenpox
- The treatment blind was broken for a subject
- GlaxoSmithKline discontinued the study.

#### 1.1.1.5 Study Procedures

##### 1.1.1.5.1 Treatment

Patients were randomized to Advair Diskus or FP100 DISKUS by calling RAMOS, GSK's Interactive Voice Response System. Blinded medication was provided by GSK in identical numbered treatment packs. Albuterol sulfate inhalation aerosol (VENTOLIN HFA in Canada) 90 mcg/spray was provided for rescue therapy and FLONASE was provided for treatment of allergic rhinitis as described in the label.

Patients took either Advair Diskus or FP100 BID for 84±2 days. Compliance was assessed by counting the number of doses left in the DISKUS at clinic visits.

##### 1.1.1.5.1.1 Allowed concomitant medication

- **Short-acting antihistamines**, decongestants or combination products
- **Long-acting antihistamines, decongestants, or** combination products provided they were started before Screening and continued unchanged throughout the study.
- **Guaifenesin** if used without a cough suppressant (e.g., dextromethorphan, codeine).
- **Central Nervous System Stimulants:** Medications used to treat Attention Deficit/Hyperactivity Disorder, including Ritalin., provided they were started before Screening and were continued unchanged throughout the study.
- **Immunotherapy:** Regularly scheduled immunotherapy provided the subject had received immunotherapy for 1 month prior to Screening, and the regimen did not change significantly during the study. Immunotherapy should not have been administered prior to any study visit procedures.
- **Immunizations** such as flu shots and childhood immunization.

##### 1.1.1.5.1.2 Prohibited Medications

Except where otherwise stated, concurrent use of any prescription or over-the-counter medication, which could affect the course of asthma or interact with any concomitant

medication required for the study, was not allowed during the study. Specifically, the following medications were prohibited:

- anticholinergic agents (atropine and ipratropium bromide)
- anticonvulsants (barbiturates, hydantoins, and carbamazepine)
- polycyclic antidepressants
- beta-adrenergic blocking agents
- phenothiazines
- monoamine oxidase (MAO) inhibitors
- **Concurrent Topical or Intranasal Corticosteroid Therapy:** The use of any corticosteroid medication other than study medication was prohibited with the exception of low-dose ( $\leq 1\%$ ) topical hydrocortisone cream or ointment and intranasal **FLONASE**.
- **Methotrexate, gold, cyclosporine, and azathioprine:** These medications must not have been used within the 12 months prior to Screening or at any time during the study.

#### 1.1.1.5.2. Safety Evaluations

- **Adverse Events** queried at each visit. Asthma-related signs and/or symptoms that caused a subject to withdraw from the study (and did not meet the definition of serious) were not considered AEs
- **Routine laboratory tests** were performed at Screening and at Week 12 or the discontinuation visit.
  - Hemoglobin, hematocrit, RBC, WBC, differential, and platelet count.  
Alkaline phosphatase, alanine amino-transferase, aspartate amino-transferase, total bilirubin, creatinine, glucose, calcium, potassium, sodium, BUN, total protein, and albumin.
- **24-hour urine collection for cortisol** excretion and creatinine was performed within 7 days prior to the Randomization Visit and within 7 days prior to the Week 12 Visit.
  - **12-lead ECG** at Screening, Randomization (prior to the first dose of medication), and Week 12 or Subject Discontinuation. An independent cardiologist reviewed the 12-week ECG to determine if there had been a significant change.
  - **Physical examination**, including blood pressure, were determined at Screening and Week 12.
  - **An oropharyngeal examination** for evidence of infection (e.g., *Candida albicans*) was performed at all visits. Positive findings should have been

followed up with cultures and antibiotic therapy while the patients remained in the study.

- **Worsening asthma** either for a clinical exacerbation or at the investigator's discretion: A clinical exacerbation was defined as worsening asthma requiring emergency intervention, hospitalization, or treatment with excluded asthma medication. The following criteria were used to aid the investigator in determining asthma stability, but did not necessarily cause a subject to be withdrawn:
  - During the 7 days immediately preceding the visit the subject experienced:
    - more than 3 days in which the AM or PM PEF had fallen below the PEF Stability Limit calculated at the Randomization Visit
    - and/or
    - more than 2 days in which  $\geq 12$  puffs/day of albuterol were used
- PEF Stability Limit: Calculated for all subjects (4-11 years of age) using the mean AM PEF from the 7 days preceding the Randomization Visit, where the AM PEF from the day of the Randomization Visit was used as Day 7. A 20% decrease in this mean was calculated and used for the duration of the study.
- FEV<sub>1</sub> Stability Limit: Calculated for subjects 6-11 years of age by taking a 20% decrease in the best FEV<sub>1</sub> obtained at the Randomization Visit (0 timepoint). This value was used for the remainder of the study.

#### 1.1.1.7. Efficacy Evaluation

The efficacy measures were all secondary outcomes

- AM PEF for patient 4 & 5 years old at visit 1 & 2
- FEV<sub>1</sub> at Visits 1, 2, 7, or Discontinuation by subjects 6-11 years of age.
- Reversibility at visit 1
- At visit 1, PEF or FEV<sub>1</sub> pre-dose, 30, 60, and 120 min post-dose
- AM & PM Peak expiratory flow was measured via study-issued Mini-Wright peak flow meter and recorded in the diary.
- Asthma symptom score

##### **Asthma Symptom Score**

0 = No symptoms during the day

1 = Symptoms for one short period during the day

2 = Symptoms for two or more short periods during the day

3 = Symptoms for most of the day which did not affect the child's normal daily activities.

4 = Symptoms for most of the day which did affect the child's normal daily activities.

5 = Symptoms so severe that the child could not go to school or perform normal daily activities.

### 1.1.1.8. Statistical Plan

#### 1.1.1.8.1 Power

The size of the study population was negotiated with the Division to be 100 patients in each arm. There is no independent power analysis.

#### 1.1.1.8.2 Populations analyzed

**Intent-to-Treat (ITT) population** included all subjects who were randomized and received at least one dose of study drug. This was the primary population used for all demographic, safety, and other measures.

**Cortisol population** was defined as the ITT population excluding subjects with any one or more of the following:

- Urine volumes of <300mL (age 4 and 5 years), <400mL (age 6-11 years) and 24 hour creatinine excretion below the lower limit of threshold range ( $\pm 2.5$  SD)
- Collection time intervals outside  $24 \pm 4$  hours
- Was off study drug for more than one day at the start time of the post-baseline urine collection
- Used oral, ophthalmic, injectable, intranasal, or topical corticosteroids (except **FLONASE** nasal spray or 0.1% hydrocortisone cream) within 30 days of the Screening Visit or during the treatment period
- Used inhaled corticosteroids during the treatment period (other than the study drug)
- Missing Baseline and/or Treatment Week 12 urine collection.

#### 1.1.1.8.3 Analysis

There is no efficacy analysis. Summary statistics are provided for efficacy and safety outcomes.

**1.1.2. Results**

**1.1.2.1. Subjects**

1.1.2.1.1. Screen Failures

Of the 421 patients screened, 203 were enrolled. The rate of exclusion was 78.3% in the patients screened under amendment #2 and 41.8% of those screened under amendment #4. As would be expected from the change in entry criteria, more of the patients in the early enrollment group were excluded due to lack of reversibility (24% vs 16%), FEV<sub>1</sub> out of range (34% vs 16%), and unable to perform spirometry (10 vs <1%) than were excluded under Amendment #4. Of the patients included in the intention to treat (ITT) analysis 25 were enrolled under the provisions of Amendment #2 and 178 were enrolled under Amendment #4.

The demographic characteristics of the screening failures were similar to that of the ITT population. The mean age of the screening failures was 7.6 years, 66% were male and 67% were White.

1.1.2.1.2 Baseline Characteristics of ITT Population

The treatment groups were similar in gender (68 and 59% male), mean age (8.0 and 8.1 years), and ethnic distribution (67 and 72% Caucasian) for Advair and FP100 respectively (Table 13). Similarly, the mean duration of asthma prior to entering the protocol (5.3 and 5.2 years) and baseline pulmonary function (80.9 and 80.0 % predicted FEV<sub>1</sub> and 83.9 and 89.4 % predicted PEF) were similar for Advair and FP100 (Table 14).

**Table 13. Population Demographics (SAS30031)**

Characteristic		<b>Advair100/50 N=101</b>	<b>FP100 n=102</b>
<b>Gender n(%)</b>	Male	69(68)	60(59)
	Female	32(32)	42(41)
<b>Age n(%)</b>	Mean (yrs)	8.0	8.1
	4-5 years	21(21)	19(19)
	6-11 years	80(79)	83(81)
<b>Ethnic Origin n(%)</b>	White	68(67)	73(72)
	Black	23(23)	16(16)
	Asian Hispanic	3(3)	1(<1)
	Other	7(7)	12(12)
		0	0

**Table 14. Disease Characteristics of the ITT population (SAS30031)**

<b>Patient Group</b>	<b>Characteristic</b>	<b>Advair 100/50</b>	<b>FP100</b>
<b>All ages</b>	Years of Asthma	5.3	5.1
<b>Age 6-11 years</b>	FEV1 (L)	1.70	1.65
	FEV1 % predicted	80.9	80.0

	% Reversibility	19.2	19.4
<b>Age 4 &amp; 5 years</b>	PEF (L/min)	140	145
	PEF % predicted	83.9	89.4
	% Reversibility	30.7	25.1

1.1.2.1.3. Subject Disposition - ITT Population

Similar proportions of patients completed the study in the two treatment groups (81% Advair and 84% FP100). Adverse events were more common in the Advair group (3) than in patients treated with FP100 (0). On the other hand, asthma exacerbations were more frequent in the FP100 group (5 in patients treated with FP100 compared to 3 in the Advair group).

**Table 15. Patient Disposition (SAS30031)**

	Advair N (%)	FP100 N (%)
Total Randomized (N)	101	102
Completed	82 (81)	86 (84)
Discontinued	19 (19)	16 (16)
Reason for Discontinuation		
Adverse event	3 (3)	0
Consent withdrawn	1 (<1)	2 (2)
Lost to follow-up	5 (5)	2 (2)
Protocol violation	4 (4)	3 (3)
Worsening of asthma	3 (3)	5 (5)
Clinical exacerbation	2 (2)	3 (3)
Investigator’s discretion	1 (<1)	3 (3)
Other	3 (3)	4 (4)

In addition, 9 (9%) patients in the Advair group and 5 (5%) in the FP100 group were non-compliant with the study medication.

1.1.2.2. Safety Outcomes

1.1.2.2.1 Duration of Exposure

The mean duration of exposure to the test products was similar in the two treatment groups. However slightly fewer patients in the Advair group were treated for 82 days (Table 16).

**Table 16. Duration of Exposure for the ITT population (SAS30031)**

	Advair 100/50 n = 101	FP100 n = 102
Exposure (days)		
Mean (sd)	74.8 (22.25)	78.8 (20.55)
Median	84	85
Range	6-95	1-103

Length of Exposure n %)		
≤ 14	4 (4)	5 (5)
15 – 28	4 (4)	1 (<1)
29 – 56	9 (9)	4(4)
57 – 81	6 (6)	5(5)
82 – 86	64 (63)	65 (64)
>86	14 (14)	22 (22)

*Reviewer: the study was planned for 12 weeks(84 days). In Table 3 it is indicated that 19 patients in the Advair group and 16 patients in the FP group did not complete the treatment period. However, Table 4 shows that 23 patients in the Advair group were treated for less than 82 days while only 15 patients in the FP group were treated for less than 82 days. Performing a survival analysis using data taken from the data sets submitted by the applicant and using time on study medication as the outcome variable, results in a difference between FP100 and Advair that is of borderline significance (p=0.065). The time on study was not related to age, gender, duration of asthma, or change in medication regimen prior to enrollment.*

**1.1.2.2.2 Adverse Events**

There were no fatalities and no serious adverse events in randomized patients.

Three patients (5 events) in the Advair group were withdrawn due to adverse events. Two of the events (sleeplessness and chest pain) were drug related according to the Investigators (Table 17).

**Table 17. Adverse Events Leading to Withdrawal (SAS30031)**

Subject	Adverse Event	Onset (Days)	Duration (Days)	Resolution
68408	Angioedema	32	1	Y
	Hives	32	1	Y
68198	Sleeplessness	1	38	Y
68347	Chest Pain	24	2	Y
	Shortness of Breath	25	1	Y

The overall incidence of adverse events was similar in the two treatment groups. There was a slight excess of upper respiratory infections and fevers in the FP100 group and more cases of oropharyngeal candidiasis in the patients treated with Advair (Table 18).

**Table 18. Adverse Events Occurring in > 3% of Patients (SAS30031)**

		Advair 100/50		FP100	
		All	Drug Related	All	Drug Related
Number of Subjects (%)		60 (59)	11	58 (57)	10
Ear, Nose & Throat	URI	10 (10)		<b>17 (17)</b>	
	Throat Irritation	8 (8)	3 (3)	7 (7)	2 (2)
	ENT Infection	4 (4)		1 (<1)	
	Epistaxis	4 (4)		1 (<1)	
	Throat infection	3 (3)		2 (2)	
	Ear abnormalities	3 (3)		1 (<1)	
	Sinusitis	3 (3)		0	
Neurology	Headache	20 (20)		1 (<1)	
Gastrointestinal	GI discomfort	7 (7)	0	5 (5)	1 (<1)
	N&V	5 (5)		3 (3)	
	Candidiasis (mouth)	<b>4 (4)</b>		1 (<1)	
	Diarrhea	1 (<1)		3 (3)	
Non-site specific	Fever	5 (5)	0	<b>13 (13)</b>	1 (<1)
	Allergic reactions	2 (2)	0	3 (3)	0
	Chest symptoms	3 (3)	1 (<1)	1 (<1)	
Musculoskeletal	Pain	2 (2)		3 (3)	
LRI	Cough	2 (2)		3 (3)	
	Viral Infection	1 (<1)		3 (3)	
Psychiatry	Mood disorders	1 (<1)	1 (<1)	3 (3)	2 (2)
Trauma	Contusion	0		3 (3)	

#### 1.1.2.2.1. Hematology and Chemistry

Vales beyond the laboratory normal range for the hematology and chemistry measurements were rare. One patient in the Combination Product group had a low neutrophil count and one patient in the FP Diskus group had a high eosinophil count. One patient each in the Combination Product and FP Diskus groups had an elevated glucose and one patient in the Combination Product had a high potassium.

#### 1.1.2.2.2. Urinary Cortisol

24-hour urine collections were adequate to perform the cortisol analysis on 57 of the patients treated with Advair and 48 patients treated with FP. The reasons for exclusion are shown in Table 19.

**Table 19. Exclusion from Cortisol Population (SAS30031)**

<b>Exclusion</b>	<b>Reason for</b>	<b>Advair100/50 n=101</b>	<b>FP100 n=102</b>
Number of subjects excluded (n,%)		53	45
No urine collection at Baseline and/or Week 12		23	21
Urine Volume <400 mL and 24-hour creatinine excretion below threshold range (subjects 6-11 years of age)		19	16
Corticosteroid use within 30 days of Visit 1 or during study		15	10
Urine Volume <300 mL and 24 hour creatinine excretion below threshold range (subjects 4 and 5 years of age)		2	1
Subject off study medication >1 day prior to start of urine collection		2	0
Urine collection not 20-28 hours in duration		3	5

Results of the cortisol measurements in those with adequate collections show a lower geometric mean value, but a higher variability in the FP100 patients. Over the 12-week treatment period cortisol excretion increased slightly in the Advair-treated patients and decreased in the FP100-treated patients (Table 20). Most of the values for cortisol excretion were within the normal limits of the laboratory both a baseline and at the end of the study (84.2% for FP and 87.5% for Advair). Low values were recorded in only 4 instances. Three of the FP patients had low values at entry to the study and normal values at the end. One patient in the Advair-treated group had a low value at baseline that was above the normal range at the end of the study. No low values were recorded at the end of the study.

**Table 20. Results of 24-hour Urinary Cortisol (SAS30031)**

<b>Timepoint/Parameter</b>	<b>Advair100/50 n=101</b>	<b>FP100 n=102</b>
N with Baseline & Week 12 Data	48	57
<b>Baseline</b>		
Geometric mean	8.15	7.82
N(%) with abnormal high values	4 (8)	7 (12)
N(%) with abnormal low values	2 (4)	3 (5)
<b>Week 12</b>		
Geometric mean	10.29	7.37
N(%) with abnormal high values	4 (8)	3 (5)
N(%) with abnormal low values	0	0
Mean change from baseline	1.31	-2.56
Geometric mean ratio (Week 12/Baseline)	1.26	0.94

*Reviewer: Looking at the characteristics of the subjects who had cortisol measurements and those who did not, there was no difference in gender, treatment group, duration of asthma or baseline pulmonary functions. The subjects with cortisol measurements were slightly older (8.2 vs 7.9 years respectively) but this was not significant. In a logistic regression of the determinants of an adequate cortisol collection, the only significant determinant was a change in steroid regimen within a month of run-in. (Odds ratio 0.3, p = 0.019)*

1.1.2.2.3. Vital Signs and ECG

There was no difference between treatment groups in the baseline heart rate or QTc interval and there was no significant change from baseline to week 12. Additionally, there was no difference between patients who completed the protocol and those who withdrew prematurely. Categorical increases and decreases in blood pressure were infrequent and similar in the two treatment groups and were not of clinical significance.

1.1.2.2.4. Other Safety Evaluations

Oropharyngeal examination was abnormal in 7 patients treated with Advair and in 2 patients in the FP100 group. Of these, 4 in the combination product group and one in the FP100 group were culture positive for *Candida albicans*. The one infection in the FP100 group occurred on the first day of treatment. In the combination product group three cultures were positive at the week-2 visit and one on the week-4 visit.

There were 11 exacerbations of asthma recorded during the study period, and all but three of the patients with exacerbations were withdrawn. There were 8 exacerbations and 5 withdrawals in the FP100-treated patients and 3 exacerbations with two withdrawals in the Advair-treated patients. The mean age of the patients with an exacerbation was 6.5 years and half (5 out of 11) were female (Table 21).

**Table 21. Asthma Exacerbations (Study SAS30031)**

	Advair 100/50 n=101	FP100 n=102
Number of subjects experiencing an asthma exacerbation	3 (3)	8 (8)
Severity of exacerbation:		
Mild	0	2 (25)
Moderate	1 (33)	5 (63)
Severe	2 (67)	1 (13)
Number of subjects withdrawn due to asthma exacerbation	2 (2)	5 (5)
Severity of exacerbation:		
Mild	0	1 (20)
Moderate	0	3 (60)
Severe	2 (100)	1 (20)

### 1.1.2.3 Efficacy Endpoint Outcomes

Pulmonary function evaluation is available for 197 patients (97 treated with Advair and 100 treated with FP). After 12 weeks of treatment the AM FEV1 in the 6 – 11 year-olds increased by 160 cc in the Advair treated group as compared to 100 cc in the FP treated children (Table 22).

**Table 22 Change in FEV1 with Treatment (SAS30031)**

	Advair100/50 N=101	FP100 N=102
AM Pre-Dose FEV1		
Baseline (n)	79	83
Mean L/sec (SE)	1.70 (0.49)	1.65 (0.44)
End of Study (n)	68	75
Mean L/sce (SE)	1.88 (0.056)	1.77 (0.047)
Mean change from Baseline (SE)	0.16 (0.029)	0.10 (0.25)

Peak expiratory flow was available from the symptom diaries in all of the subjects. The AM peak flow increased from 221 L/min at baseline to 246 L/min at the end of the study in the Advair treated subjects. The baseline and end-of-study values for the FP100 treated subjects were 215 L/min and 232 L/min respectively. The increase over the 12-week period for the Advair and FP-treated subjects was 21.5 and 16.9 L/min respectively.

Symptom scores were also taken from the diaries and showed a mean fall in the Advair group of -0.6 and a fall in the FP100 group of -0.5. The mean percentage of symptom-free days increased by 24.4% and 21.2% in the Advair and FP100 group respectively. Rescue albuterol use also decreased slightly in both groups: -0.5 puffs/day and -0.4 puffs/day in the Advair and FP100 groups respectively.

### 1.1.3. Discussion and Conclusions

This 12-week study comparing the effects of Advair Diskus100/50 mcg and FP Diskus 100 mcg BID was designed to evaluate safety as its primary objective. One hundred patients in each treatment group were treated for a mean of 74.8 days (Advair) and 78.8 days (FP100). The subjects were comparable in age, duration of asthma, and baseline pulmonary function. There was adequate follow-up in both groups, and while there was a suggestion of earlier drop-out in the Advair group compared to the FP100 group this did not reach statistical significance. Adverse events were uncommon and not severe. There was a slightly higher incidence of fever in the patients treated with FP100 (13% vs 5% in the Advair Diskus group) and a higher incidence of oropharyngeal candidiasis in the patients treated with Advair (4% vs < 1% in the FP100 group). Twenty four-hour urine collections were available for cortisol determination in approximately half of the subjects. Cortisol suppression, comparing treatment with Advair to treatment with ICS alone, was less in the patients treated with Advair than in those treated with fluticasone alone. Efficacy was evaluated as a secondary endpoint and although the studies were not powered for efficacy it

appeared that the objective endpoints (FEV<sub>1</sub> and PEF<sub>R</sub>) are suggestive of efficacy of Advair100/50 in the patient population studied. As expected, the FEV<sub>1</sub> measurements were numerically higher in the Advair group than in the FP100 group. Other endpoints such as symptom scores, and use of rescue medication (Albuterol) showed a trend that favored efficacy. In summary, Advair 100/50 mcg BID did not have an unfavorable safety profile in patients 4 – 11 years of age in this 12-week study. The reason for the higher incidence of candidiasis in the Advair-treated patients compared to the FP-treated patients is unclear since both patients groups received the same total dose of corticosteroid in Diskus formulations. Since a placebo group was not included in the study design and the patients were taking ICS during the baseline, the results of the HPA axis evaluation can not be used to conclude that Advair has no effect on the HPA axis function.

## **1.2. Study # SAM40012.**

**This is a multicenter, Randomised, Double-blind, Double-dummy, Parallel Group Comparison of Three Treatments: 1) SERETIDE (50/100 mcg Strength) BID via DISKUS/ACCUHALER Inhaler, 2) Fluticasone Propionate 200 mcg BID via DISKUS Inhaler, 3) Fluticasone Propionate 100 mcg BID via DISKUS/ACCUHALER Inhaler in Children Aged 4-11 Years with Asthma.**

### **1.2.1 Protocol**

#### **1.2.1.1 Investigators and Centers**

38 investigators in Russia, Poland, Bulgaria, Hungary, Israel, Spain and the UK. Enrollment ranged from 1-66 subjects/investigator with all but 2 investigators enrolling ≤ 24.

#### **1.2.1.2 Objectives.**

The primary objective is to demonstrate that Seretide50/100mcg (salmeterol 50 mcg/fluticasone 100 mcg) BID is a more effective treatment than either fluticasone propionate 100mcg BID or fluticasone propionate 200 mcg BID in subjects with asthma aged 4-11 years who are symptomatic on 400 to 500mcg budesonide (BUD), beclomethasone dipropionate (BDP), or equivalent daily, as demonstrated by an increase of symptom-free days and nights.

Secondary objectives

- To compare the impact of the different treatments on the functional status of the subjects and the quality of life of their parents/carers.
- To assess the safety and tolerability of Seretide 50/100mcg, fluticasone propionate 100mcg BID and fluticasone propionate 200mcg BID in children with asthma.

#### **1.2.1.3 Overall Design**

##### **1.2.1.3.1 Planned treatment schedule**

This was an international, multicenter, randomized, double-blind, double-dummy, parallel group study, consisting of a 2-week run-in period, a 24-week treatment period and a follow-up visit at 2 weeks after the end of study treatment. Subjects could repeat the 2-week

run-in period if they did not meet all of the inclusion/exclusion criteria at Visit 2. Subjects who completed the 2-week run-in period were randomized at Visit 2/2A to one of three treatment regimens:

**SERETIDE** (salmeterol/fluticasone 50/100mcg) **DISKUS** inhaler BID  
fluticasone propionate 100mcg **DISKUS** inhaler BID  
fluticasone propionate 2 x 100mcg **DISKUS** inhaler BID.

Subjects continued taking their current asthma medication (subject to the inclusion/exclusion criteria) during the run-in period. **VENTOLIN** (salbutamol) was supplied as rescue medication. Subjects attended the clinic after 4 weeks of treatment (Visits 3 and 4), and then at 8-weekly intervals until the end of the study (Visits 5 to 6). A follow-up visit was planned at 2 weeks post-treatment.

#### **1.2.1.4 Study Population**

##### **1.2.1.4.1 Inclusion Criteria for run-in**

- Clinical history of asthma.
- Healthy males and females 4-11 years of age
- Received BDP, BUD equivalent at a dose of 400-500 mcg/day or fluticasone propionate at a dose of 200-250 mcg/day for at least 4 weeks before Visit 1.
- Able to use Mini-Wright peak-flow meter and record PEF
- Written consent of parent or guardian.

##### **1.2.1.4.2 Inclusion Criteria for Randomization**

- Symptom score (24 hours)  $\geq 2$  on at least 3 of last 7 days of the run-in period.
- Mean (over last 7 days of run-in) AM PEF 50-85% of PEF 15 minutes after 400 mcg VENTOLIN.
- Ability to complete electronic diary entries
- Documented entries in diary of  $\geq 70\%$  required during the run-in period.

##### **1.2.1.4.3 Exclusion Criteria**

- Receiving (or received within 2 weeks of Visit 1) any of the following: salmeterol or any other long acting inhaled  $\beta_2$ -agonist, combination therapy (containing  $\beta_2$ -agonist and/or ICS for asthma), cromoglycate, oral  $\beta_2$ -agonists or slow-release bronchodilators.
- Receiving (or received within 4 weeks of Visit 1) any of the following: theophyllines, leukotriene antagonists or oral, depot or parenteral corticosteroids. Changed their medication for asthma (other than those in 1., above) within 4 weeks of Visit 1.
- Lower respiratory tract infection within 4 weeks of Visit 1.

- Acute exacerbation of reversible airway obstruction requiring hospitalization within 4 weeks of Visit 1.
- Females who had reached menarche.
- Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study.
- Received any investigational drugs within 4 weeks of Visit 1 or, for the UK only, participated in a clinical trial within 3 months of Visit 1 (Protocol Amendment 2, dated 10 May 2000).
- Known or suspected hypersensitivity to inhaled steroids,  $\beta_2$ -agonists or lactose.
- Previously randomized into this study.
- A child of a participating investigator or study co-ordinator.

**Exclusion criteria for entry into the randomized treatment period**

- Clinic peak expiratory flow rate <50% of predicted normal at Visit 2/2A

**1.2.1.4.4 Patient Withdrawal**

- Adverse Events
- Asthma exacerbation – Patients were withdrawn for a severe exacerbation or a moderate exacerbation requiring a second course of oral steroids. Asthma exacerbations were defined as mild, moderate or severe as defined below.

Mild – AM PEF > 20% below baseline (mean of last 10 days of run-in) OR > 3 additional inhalations/24 hours VENTOLIN for  $\geq 2$  consecutive days OR PM awakenings due to asthma for  $\geq 2$  nights.

Moderate – AM PEF > 30% below baseline on  $\geq 2$  consecutive days OR requirement for treatment with inhaled corticosteroid > study medication &/or oral corticosteroids.

Severe – Any exacerbation requiring treatment in the hospital or an emergency room.

- Non-compliance
- Lack of efficacy
- Social reasons

**1.2.1.5 Study Procedures**

**1.2.1.5.1 Treatment**

Patients were randomized using a computer generated list of treatment numbers supplied to each center. Each subject was give 2 inhalers and instructed to use one inhalation from each inhaler in the AM and PM. The subjects randomized to SERETIDE and fluticasone 100 mcg each received a placebo canister. The patients receiving fluticasone 200 mcg received 2 canisters of fluticasone.

Patients were treated for 24 weeks. During that time only VENTOLIN was allowed for rescue or a single course of oral corticosteroids for a moderate exacerbation.

#### **1.2.1.5.2 Measurements and evaluations**

- Demographic variables obtained at the screening visit
- PEF, oropharyngeal, and elicitation of AEs examination at each clinic visit
- Overnight urine for cortisol, and quality of life questionnaires at baseline and 24 weeks.
- Electronic diaries to record AM and PM PEF, symptom score, and ventolin use.

#### **1.2.1.6 Efficacy evaluation**

The primary efficacy endpoint, percentage of combined symptom-free days and nights, was calculated from the symptom scores reported twice daily by the patient in the electronic diary.

Day-time symptom scores were as follows:

- 0 = No symptoms during day-time
- 1 = Symptoms for a short period during day-time
- 2 = Symptoms for two or more short periods during day-time
- 3 = Symptoms for most of the day, which did not affect your normal daily activities
- 4 = Symptoms for most of the day, which affected your normal daily activities
- 5 = Symptoms so severe that you were unable to work or go to school or perform your normal daily activities.

Night-time symptom scores were as follows:

- 0 = No symptoms during the night
- 1 = Symptoms causing you to wake up once or wake early
- 2 = Symptoms causing you to wake up twice or more (include waking up early)
- 3 = Symptoms causing you to be awake for most of the night
- 4 = Symptoms so severe that you were unable to sleep at all.

Secondary efficacy endpoints included the following:

- Percentage of symptom-free days
- Percentage of symptom-free nights
- Percentage of day-time and night-time use of relief VENTOLIN (salbutamol).
- Morning and evening PEF
- Clinic PEF
- Incidence of mild, moderate and severe exacerbations
- Parental assessment of the functional status of subjects

- Quality of Life of parents of subjects with asthma (FSII-R & PACQLQ)
- Unscheduled asthma-related healthcare contacts

During the course of the study it was noted that either the data were being entered incorrectly or the electronic diaries were malfunctioning. In those cases, the patient was provided a new diary and the patient was designated as being in the “jump to treatment” (JTT) analysis group. When the efficacy data was finally analyzed it was found that the results were significantly different if the JTT patients were excluded. Therefore the applicant concluded that diary data were unreliable. In view of this reviewer will not review these data. Additionally, the objective of the clinical program for Advair 100/50 for the 4 - 11 year old asthmatic population is safety.

#### **1.2.1.7 Safety measures**

- Adverse Events
- Urinary Cortisol
- Oropharyngeal examinations
- Device incidents

#### **1.2.1.8. Populations for Safety Analysis**

- Cortisol Population – Excludes patients with incomplete urine collection (<150 ml age 4-5 and <200 ml age 6-11 or low creatinine excretion), collection interval outside  $12 \pm 2$  hours, off study drug for > one day, used steroids other than study medication during the treatment period.
- Safety Population – All randomized patients including 17 patients excluded from Center 26 due to protocol irregularities.

### **1.2.2 Results**

The review will focus on the safety results only. Although the stated primary objective of the study was efficacy, the major flaws in the conduct of the study render the efficacy data unreliable. Additionally, the primary endpoint chosen for efficacy – diary recorded symptoms scores would not be an acceptable primary endpoint for this age group. A more objective endpoint such as clinic-obtained PEFr for patients < 6 years of age, and FEV1 for patients > 6 years is a more reliable a measure of efficacy in asthma studies. Even worse is the fact that the electronic diaries used in this study malfunctioned during the study and had to be replaced in 190 (34%) of the randomized subjects. The sponsor noted that efficacy results for these patients differed significantly from the results for the rest of the randomized patients who presumably had well functioning electronic diaries. Another major problem with this study is the number of protocol violations (Table 23) and the number of patients who continued in the study in spite of these protocol violations. These major flaws aside, the study can still provide useful safety information since one of the treatment arms is FP 200 BID.

**Table 23. Protocol Violations (SAM40012)**

	Seretide50/100 N=181	FP100 N=181	FP200 N=186
Forbidden Medication	25	20	22
Low Symptom Score at randomization	10	12	14
PFTs not within range at randomization	0	2	1
Non-compliance	1	1	2
>1 exclusion	7	1	6
Patients with indications for exclusion	29	34	33

**1.2.2.1 Subjects****1.2.2.1.1 Disposition**

Of 887 subjects screened 548 were randomized and these patients constitute the analysis population for safety. There were 181 patients each in the Seretide100/50 and FP100 treatment groups and 186 patients in the FP200 treatment group. There were very few withdrawals due to adverse events. There were none in the Seretide100/50 group and only 2 (one each in the FP100, and FP200) in subjects treated without concomitant salmeterol. Two subjects (one each in the FP treatment groups) were withdrawn because of an asthma exacerbation.

*Reviewer: The entry criteria required that patients be on a stable dose of corticosteroids for one month prior to screening. This is documented in the datasets for approximately 2/3<sup>rd</sup> of the subjects (66.3% SFC 50/100, 68.0% FP100, 65.7% FP200). For the remaining 1/3<sup>rd</sup> of the subjects either a shorter duration is indicated in the dataset or there is no date of initiation of therapy. From other entries it appears that patients came for the screening visit 2-3 weeks prior to enrollment in the study. At that time forbidden medications were discontinued and it is highly likely that ICS were initiated at that time. These apparent protocol violations were balanced among the treatment groups and are not relevant to the safety evaluation.*

**1.2.2.1.2 Baseline Characteristics.**

The median age was 8 years and 70% of the subjects were male. The median height ranged from 130 -132 cm and the median weight ranged from 27.5 – 28.0 kg. Of the 531 subject in the ITT population, 92 were 4-5 years old. The prior duration of asthma was similar in all of the treatment groups as well as the prevalence of atopy and baseline pulmonary function was similar in all of the treatment groups.

### 1.2.2. Safety Outcomes

Overall, exposure to the study drug was similar among the treatment groups. The duration of exposure ranged from 113 -169 days for the majority (72 -76%) of the patients. Exposure of > 169 days was noted in 19 -24% of the subjects (Table 24).

**Table 24 Exposure to Study Drug (SAM40012)**

		SFC 50/100	FP100	FP200
Treatment exposure (days)	N	178	178	183
	Mean (SD)	167.1	164.1	165.6
	Range	29-185	29-184	9-193
Range of Exposure (days)	≤ 14	0	0	1 (<1%)
	15-28	0	0	1 (<1%)
	29-56	1 (<1%)	4 (2%)	2 (1%)
	57-112	1 (<1%)	1 (<1%)	1 (<1%)
	113-169	135 (75%)	138 (76%)	134 (72%)
	>169	41 (23%)	35 (19%)	44 (24%)

#### 1.2.2.1 Adverse Events

Of the 548 subjects in the safety population, 341 (62%) reported at least one adverse event. The total number of AEs reported in each treatment group was relatively high, ranging from 298 – 361. The number was highest in the FP200 treatment group where a total of 361 events were reported in 118 (63%) subjects. The most common events were reported in the respiratory system as had been previously reported in other studies. Headache and fever were also among the more common adverse events. A summary of the most common events are shown in the table 25.

**Table 25. Most Common Adverse Events (SAM40012)**

	Seretide 100/50 n=181	FP100 n=181	FP200 n=186
Number subjects (%) Any Event	99 (55)	111 (61)	112 (60)
Influenza	29 (16)	27 (15)	36 (19)
Cough	11 (6)	16 (9)	14 (8)
Fever	13 (7)	10 (6)	13 (7)
Headache	14 (8)	10 (6)	10 (5)
Common cold	11 (6)	11 (6)	9 (5)
Viral infection	8 (4)	5 (3)	14 (8)
Rhinitis	7 (4)	4 (2)	12 (5)
Acute nasopharyngitis	6 (3)	9 (5)	6 (3)
Pharyngitis	2 (1)	10 (6)	8 (4)

Overall, adverse events were higher in the two FP groups compared to the Seretide treatment group. Of note, influenza was reported more frequently in the FP200 group (19%) compared to the Seretide group (16%). Also viral infection was higher in the FP200 group (8%) compared to 3% and 4% in the FP100 and Seretide treatment groups respectively. There was a 4% report of acute nasopharyngitis/pharyngitis in the Seretide group compared to 11% in the FP100 group and 7% in the FP200 group.

There were only 2 cases of oropharyngeal candidiasis in the study, one in the Seretide group and one in the FP200 group. None of these patients was withdrawn from the study due to these events. The total number of respiratory infections was highest in the FP200 group (84) compared to the Seretide (70) and the FP100 (65) group. Likewise, the number of asthma exacerbations following respiratory infections were reported more frequently in the FP200 group (33) than in the Seretide group (22) and were least (15) in the FP100 group.

### **Deaths and Serious Adverse Events**

No patient died and there were 8 patients with serious adverse events, 7 of whom had SAEs that started during therapy. The other patient (in the FP100 group) had arthritis reported as a serious event which antedated treatment. There was a total of 10 SAEs in the 7 patients. Five of these events were related to trauma. There was one report each of pneumonia, salmonella, acute laryngitis, viral infection and hospitalization for celiac disease. None of these events appear to be drug-related although in the case of pneumonia and acute laryngitis, it is plausible that corticosteroid treatment may have played a role. Patient 4329, who had pneumonia, was withdrawn from the study as was one additional patient, also in the FP treatment group, because of a non-serious AE.

#### **1.1.2.2. HPA Axis Function**

Adequate 12-hour urine collections as pre-defined by the sponsor were available at baseline and 24 weeks in 153 patients (Seretide n = 49, FP100 n=53, and FP200 n= 51). There were no differences in the ratio of the geometric means of the cortisol at 24-weeks compared to the mean baseline values among the treatment groups (Seretide = 1.1, FP100 = 1.1, and FP 200 = 1.0). The mean values are displayed in Table 26.

**Table 26. Study SAM40012****Statistical analysis of overnight urinary cortisol uncorrected for creatinine at Week 24 (cortisol population)**

Urinary cortisol (nmol/12hours)	SFC50/100 (N=61)	FP100 (N=88)	FP200 (N=73)
Number of subjects	49	53	51
Baseline geometric mean (cv%)	50.4 (15.8)	47.9 (16.5)	44.9 (22.6)
Adjusted geometric mean	51.8	51.3	48.6
Ratio SFC50/100 / FP dose <sup>a</sup> [95% CI] p-value		1.01 [0.81, 1.26] 0.941	1.06 [0.85, 1.34] 0.588
Ratio FP200-FP100 <sup>a</sup> [95% CI] p-value		0.95 [0.76, 1.18] 0.629	

Source data: Table B4, Listing 29

a. ANCOVA adjusted for baseline, age, sex and country grouping

**1.2.3. Discussion and Conclusions**

This 24-week study of the efficacy and safety of Seretide, the combination product salmeterol/fluticasone 50/100 mcg BID, was conducted in 38 countries primary in Eastern Europe with a small contribution from England and Spain. There were numerous problems with patient enrollment and outcome measurements and the applicant concluded that the diary-recorded primary efficacy measure (PM PEF) was not reliable. From a safety standpoint, the adverse event profile seen in this study is similar to what was seen in other asthma studies with similar products. There was a higher incidence of respiratory infections, and asthma exacerbations in the FP200 treatment group compared to Serevent100/50 and FP100. Previous studies with inhaled corticosteroids have suggested that there might be an increase incidence of respiratory infections including pneumonias associated with ICS. The observation in this study underscores the importance of stressing the use of the lowest effective dose of ICS to control asthma. The 12-hour urinary cortisol was not suggestive of HPA axis suppression although these tests alone are insufficient to test for this.

**1.3. Study #SFCB3020**

**A multicentre, randomized, double-blind, double-dummy, parallel-group, comparison of the salmeterol/fluticasone propionate combination product (50/100 mcg strength) bd via one DISKUS/ACCUHALER inhaler with salmeterol 50 mcg bd via one DISKUS/ACCUHALER inhaler and fluticasone propionate 100 mcg bd via a second DISKUS/ACCUHALER inhaler in children age 4-11 years with reversible airways obstruction.**

**1.3.1 Protocol****1.3.1.1 Administrative**

Study dates: November 11, 1996 – September 10, 1997

Location: 35 Centers in nine countries: Estonia, Finland, Lithuania, Netherlands, Norway, Portugal, Spain, South Africa, and Sweden.

PI: Dr. Mair Jenkins

### **1.3.1.2. Objectives**

To demonstrate the equivalence of salmeterol/fluticasone combination (FSC) product (50/100 mcg) BID delivered via one DISKUS inhaler and fluticasone (FP) 100 mcg BID and salmeterol (S) 50 mcg BID delivered in two separate inhalers.

*Reviewer: Although this is the applicant's stated objective, from a statistical standpoint, this trial is not a true equivalence (non-inferiority) study (among other things one would need predefined non-inferiority margins a means of assessing "assay sensitivity" and a much larger n to determine this) and is being reviewed primarily as a supportive safety study.*

### **1.3.1.3 Overall Design.**

This was a multicentre, randomized, double-blind, double-dummy, parallel group design with a 2-week run-in period, 12-week treatment period, and 2-week follow-up. During the run-in the patients took their usual inhaled corticosteroid (ICS) and Ventolin as needed. During the treatment phase, patients were randomized to receive Seretide via Diskus or salmeterol and fluticasone via Diskus concomitantly (FP100 + S). All subjects received two inhalers to maintain the blind and Ventolin was used as rescue medication throughout the study. Outcome measures were pulmonary function, symptom scores, and Ventolin use. The primary endpoint for statistical analysis was AM PEFR measured by the patient. Safety measures included eliciting adverse events, vital signs, oropharyngeal examination, and blood work (hematology and biochemistry) In addition a morning serum cortisol was measured at the beginning and end of the study.

### **1.3.1.4 Population**

The patients were 4 – 11 year-old (n=166) asthmatics who were symptomatic on inhaled corticosteroids (equivalent to 200-250 mcg/day fluticasone). At the end of the run-in period the patients had to have had a symptom score of  $\geq 1$  on at least four of the previous 7 days and a mean morning PEFR of 50-85% of the PEFR measured after 400 mcg Ventolin. The PEFR also had to be  $<50\%$  predicted. Patients who had a respiratory infection, who had changed their medications, or who had taken a long-acting  $\beta$ -agonist or oral corticosteroids within four weeks of enrollment were excluded.

### **1.3.1.5. Analyses**

The sponsor stated that treatment equivalence was determined by using the 90% confidence limits of the difference between treatments. As stated before, this study design is not an equivalence trial and the efficacy data are reported here in the review in a numerical fashion only. No efficacy conclusions can be made from these results and none is warranted for the purposes of this development program which relies mainly on safety. The mean morning PEFR for weeks 1 through 12 was compared to the baseline. Subgroups based on prior ICS use were also analyzed

### 1.3.2. Results

#### 1.3.2.1 Patient Demographics and Disposition

A total of 402 patients were recruited and 257 were randomized (125 received Seretide and 132 received FP100 + S). Ten patients were withdrawn after randomization, 5 in each treatment group. A total of 91 of the remaining subjects were completely excluded from the per-protocol efficacy analysis due to protocol violations. The violations included inappropriate ICS prior to enrollment (11 Seretide, 7 FP100+S) pulmonary, function not within range (14 Seretide, 20 FP100+S), symptom score not within range (13 Seretide, 11 FP100), and non-compliance (15 Seretide, 11 FP100+S). Additional subjects were excluded from some part of the analyses. The Demographic characteristics of the ITT population are shown in Table 27. There were slightly more males in the Seretide group, but the ages, duration of asthma and PEFRs were similar.

**Table 27. Demographic and Clinical Characteristics of the Patient Population (SFCB3020)**

	<b>Seretide 100/50</b> N = 125	<b>FP100 + S</b> n=132
Gender (%male)	64	54
Caucasian (%)	90	90
Age (mean years, SD)	7.6 (2.1)	7.6 (2.1)
Age ranges, n(%)		
4-7 years old	62 (50)	60 (45)
8-11 years old	63 (50)	72 (55)
Duration of Asthma n(%)		
< 0.5 years	4 (3)	4 (3)
0.5- <1 years	7 (6)	6 (5)
1- <5 years	70 (56)	75 (57)
5 - <10 years	43 (34)	45 (34)
≥ 10 years	1 (<1)	2 (2)
Patients with atopy (%)	64	67
PEFR L/min (% predicted)	241 (100)	243 (100)

#### 1.3.2.2 Efficacy Outcome

FEV<sub>1</sub> was obtained on only 105 and 101 patients in the Seretide and FP100 + S patients respectively. Therefore, the efficacy analysis will focus on the PEFr. The AM PEFr increase by 32 L/min in the Seretide group and by 26 L/min in the FP100+S group.

**1.3.2.3 Safety Outcome**

1.3.2.3.1 Extent of exposure

As can be seen in Table 28, less than half of the patients in both treatment groups received treatment for the entire 84 days of the planned treatment period.

**Table 28. Exposure to Study Drug I Study SFCB3020**

	<b>Seretide100/50</b>	<b>FP100+S</b>
Range of Exposures		
≤ 14 days	0	2 (2)
15- 28 days	2 (2)	0
29 – 56 days	2 (2)	3 (2)
57- 84 days	47 (38)	43 (33)
85 – 112 days	73 (58)	84 (64)
113-182 days	1 (<1)	0
Exposure (days)		
Mean (SD)	84.0 (11.4)	82.6 (13.0)
Range	25 - 118	3 - 99

1.3.2.3.2. Adverse Events

There were no deaths in this study. There were, however, 4 serious AEs all in patients taking Seretide (Table 29). None of these events was thought to be related to the active drug and this reviewer concurs with this assessment.

**Table 29. Serious Advents Events in Subjects receiving Seretide Study SFCB3020**

<b>Summary of Serious Adverse Events</b>						
<b>Patient</b>	<b>Treatment</b>	<b>Treatment period</b>	<b>Adverse Event</b>	<b>Drug-related</b>	<b>Resolved</b>	<b>Withdrawn*</b>
3795	N/A N/A	Pre-treatment Pre-treatment	Fever Petechial exanthema	N/A N/A	Yes Yes	No No
3814	Combination	During	Asthmatic crisis	Unrelated	Yes	Yes
3922	Combination	During	Appendicitis	Unrelated	Yes	No
3983	Combination	During	Enlargement of the tonsils	Unrelated	Yes	No
4160	Combination	During	Coxitis fugax on the right side of the hip	Unrelated	Yes	No

During treatment a total of 162 patients described any AE (84 (67%) treated with Seretide and 78 (59%) treated with FP100 + S). Table 30 lists the six most common events. There were more reports of rhinitis in the Seretide group (14%) compared with FP100+S (7%) but the adverse event profile was generally similar in the two treatment groups and similar to the AE profile reported in other studies.

**Table 30. Most Common Adverse Events in Study SFCB3020\***

	Seretide100/50	FP100 +S
Upper respirator tract infection	25 (20)	25 (19)
Rhinitis	17 (14)	9 (7)
Fever	15 (12)	9 (7)
Viral respiratory infections	10 (8)	10 (8)
Cough	5 (4)	11 (8)
Headaches	8 (6)	7 (5)

\* number (percentage)

Adverse events that the investigators classified as drug-related were uncommon and occurred in similar frequency in the two treatment groups (Table 31).

**Table 31. Drug-Related Adverse Events in Study SFCB3020.**

Number (%) Of Patients Experiencing Drug-Related Adverse Events With An Incidence $\geq$ 2%		
Adverse Event	Combination product	Concurrent therapy
Candidiasis (mouth/throat)	2 (2%)	2 (2%)
Malaise and fatigue	1 (<1%)	2 (2%)
Candidiasis (unspecified site)	2 (2%)	0
Aggression and hostility	1 (<1%)	2 (2%)

### 1.3.2.3 HPA axis function

AM serum cortisol at both baseline and 12 weeks was obtained on 117 subjects in the Seretide group and 122 patients in the FP100 group. The ratio of geometric mean serum cortisol Baseline, while on ICS only to the geometric mean at 12 weeks was 1.23 in both treatment groups. The ratio of Seretide/FP100 +S follow-up geometric mean serum cortisol was 1.05 (95% CI = 0.93, 1.19)

### 1.3.3 Discussion and Conclusions

This study was planned to be a randomized, double-blind comparison of Seretide 100/50 to FP100+ S. Of the 257 subjects enrolled, 91 (35%) were serious protocol violations and more than half did not complete the prescribed 12-week treatment course. The incidence of adverse events was similar in the two treatment groups with upper respiratory infections being the most common event. There were more serious events in the Seretide group (4 vs 0 in the FP100+S group). Although none of these events appear to be drug-related, one of these events was an exacerbation of asthma. There were also no differences in the geometric mean urinary cortisol at the end of treatment in the two treatment groups.

## **1.4. Study # RPS3001**

### **A Multicentre, Randomised, Double-Blind, Double-Dummy, Parallel-Group Study to establish Equivalence of the Slameterol/Fluticasone Combination Product (50/100) via either the Reservoir Powder Inhalation Device (RPID) or via the *Diskus*<sup>™</sup> Inhaler over 12 Weeks in Children with Asthma.**

#### **1.4.1 Protocol**

##### **1.4.1.1 Administrative**

Study Dates: January 30, 1999 – March 15, 2000

Centers: 39 Centers in France, 7 in Norway, and 4 in Portugal.

Medical Officer: Jacques BONS, MD

##### **1.4.1.2. Study Objectives and Design**

The objective was to demonstrate the clinical equivalence of Seretide delivered with two different devices. The Diskus is the only product that is available in the United States, and only the safety results with this product will be reviewed. In this study 176 subjects were treated with Seretide 100/50 mcg BID for 12 weeks after a 2 week run-in period. The subjects were steroid dependent asthmatic, 4 – 14 years of age. They had an AM PEFR of 60-85% predicted and 20% reversibility. The primary efficacy measure was mean AM PEFR<sub>w1-12</sub>. Adverse events were recorded.

#### **1.4.2. Results**

##### **1.4.2.1. Subject Description and Disposition**

Of the 176 patients enrolled 160 completed the trial. Four were withdrawn due to an adverse event, 3 due to non-compliance, 5 because of a protocol violation and 4 for assorted other reasons. The patients in the Diskus-treated group had a mean age of 8.4 years (range 4-14) and 72 (41%) were less than 7. Thirty-five percent were female and 91% were Caucasian.

##### **1.4.2.2. Efficacy Results**

The mean AM PEFR increased by 42.1 L/min (16.8%) over the 12-week period.

##### **1.4.2.3. Safety Results**

There were no deaths or serious adverse events in the Diskus-treated patients. Five adverse events resulted in withdrawal of 4 of the patient from the protocol. An asthma exacerbation and lower respiratory tract infection in one patient were thought to be unrelated to the treatment and one case each of migraine, discomfort after inhalation of the study drug and abdominal pain were thought to be possibly related. In the 176 patients in the ITT population 63 (36%) described an adverse event. The only events that occurred in more than 3% of the subjects were ENT infections in 10 (6%), viral ENT infections in 8 (5%), bronchitis in 8 (5%), and asthma in 7 (4%).

### 1.4.3. Discussion and Conclusions

Because this study compared the to-be-marketed combination product to fluticasone/salmeterol delivered with an unapproved inhaler, only the adverse events seen with the to-be-marketed product were reviewed. ENT infections were the most common events as in the other studies.

## 2. DETAILED LABELING CHANGES OR REVISED DRUG LABEL

In the final label the reference to the (b) (4) will be removed since the subjects were all on ICS at baseline, the changes with further steroid treatment are not clinically useful. In addition, the wording in the “Pediatric Use” section will be changed to indicate that efficacy is being extrapolated from the adult data and safety from the results of the current clinical trials. We will add the percentage of subjects who reported the AEs that were more frequent than in the adult population.

## 3. OTHER RELEVANT MATERIALS

## 4. CITATIONS

[Polgar G](#), Promadhat V. Pulmonary Function Testing in Children, Techniques and Standards. Philadelphia: W.B. Saunder Co., 1971.

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Carol Bosken  
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MEDICAL OFFICER

Lydia McClain  
3/29/04 01:01:59 PM  
MEDICAL OFFICER

I concur. Based on DDMAC's labeling comments, we will  
not compare incidence of AEs in the pediatric  
population to the adults

**MEDICAL OFFICER 45-DAY Filing REVIEW**  
**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

<b>APPLICATION:</b>	NDA # 21,077	<b>TRADE NAME:</b>	Advair
<b>APPLICANT/SPONSOR:</b>	GlaxoSmithKline	<b>USAN NAME:</b>	Fluticasone 100 mcg + Salmeterol 50 mcg
<b>MEDICAL OFFICER:</b>	Carol H. Bosken, MD	<b>CATEGORY:</b>	Corticosteroid and long-acting $\beta_2$ agonist
<b>TEAM LEADER:</b>	Lydia Gilbert-McClain, MD	<b>ROUTE:</b>	Oral Inhalation
<b>DUE DATE:</b>	August 6, 2003		

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
6/26/03	6/27/03	SE5-017	Electronic submission

**RELATED APPLICATIONS**

<u>Stamp Date</u>	<u>Application #</u>	<u>Product</u>	<u>Application Type</u>	<u>Approval Date</u>
12/07/93	IND (b) (4)		Original IND	N/A
3/31/98	NDA 20,833	Flovent Diskus	Original NDA (Age $\geq$ 4 yrs)	9/29/00
8/8/90	IND (b) (4)		Original IND	N/A
6/19/96	NDA 20,692	Salmeterol Diskus	Original NDA (Age $\geq$ 12 yrs)	9/19/97
9/26/97	NDA 20,692 (S-002)	Salmeterol Diskus	Efficacy Supplement (Age 4-11 yrs)	9/25/98
10/23/98	IND 57,151	Advair Diskus	Original IND	N/A
3/25/99	NDA 21,077	Advair Diskus	Original NDA	8/24/00

**REVIEW SUMMARY:** This is a supplement to support approval of Advair (Fluticasone propionate/Salmeterol) Diskus® 100/50 for the maintenance treatment of asthma in children 4-11 years of age. The drug product is a fixed dose combination of 100 mcg fluticasone and 50 mcg salmeterol. By prior agreement with the Division, a determination of efficacy in the 4 – 11 year age group is based on the efficacy data in adult studies with Advair® and the pediatric studies with the individual components, fluticasone and salmeterol. The pivotal study in the drug development program for the 4- 11 year old was a safety study (SAS30031) that compared Advair® 100/50 to Flovent DISKUS® 100 (Fluticasone propionate) in 4-11 year olds with asthma. There were 100 patients in each arm of the study. The primary outcome was a comparison of AEs and 24-hour urinary cortisol between the treatment groups. Assessment of pulmonary function was a secondary outcome. Three supportive trials are submitted as part of the application. Each of these supportive trials compared Advair® 100/50 to fluticasone. In one study the comparator was Flovent® 100 mcg and salmeterol 50 mcg given by separate DISKUS inhalers; one study contained 3 arms – Advair® 100/50, fluticasone 100, and fluticasone 200, and one study compared Advair Diskus® 100/50 to fluticasone/salmeterol delivered by a RPID device. The supportive studies were all conducted in Europe.

This is an electronic submission with a complete index and cross references.

**OUTSTANDING ISSUES:** none

**RECOMMENDED REGULATORY ACTION**

<b>IND/NEW STUDIES:</b>	<input type="checkbox"/> SAFE TO PROCEED	<input type="checkbox"/> CLINICAL HOLD
<b>NDA/SUPPLEMENTS:</b>	<input checked="" type="checkbox"/> FILEABLE	<input type="checkbox"/> NOT FILEABLE
	<input type="checkbox"/> APPROVAL	<input type="checkbox"/> APPROVABLE
<b>OTHER ACTION:</b>		<input type="checkbox"/> NOT APPROVABLE

## **I. General Information**

Advair Diskus® is a combination product of salmeterol xinafoate and fluticasone propionate formulated as a dry-powder inhaler. The product is marketed in three strengths that depending on the dose of fluticasone propionate delivered from the actuator - 100, 250, or 500 mcg per inhalation. The dose of salmeterol is constant in all the three strengths at 50 mcg per inhalation measured at the actuator. Advair Diskus® is approved for twice daily administration in the treatment of chronic persistent asthma in patients over 12 years of age. This pediatric supplement contains safety data submitted to support an indication for Advair® 100/50 for the maintenance treatment of asthma in pediatric patients 4 – 11 years old.

## **II. Regulatory and Foreign Marketing History**

### **A. Regulatory History**

Advair Diskus® (fluticasone propionate/salmeterol inhalation powder) was approved in the United States for the maintenance treatment of asthma in patients 12 years of age and older on August 24, 2000. The product is approved in three strengths - 100/50 mcg, 250/50 mcg, and 500/50 mcg. The sponsor has submitted a supplemental NDA (sNDA) with safety data to support labeling changes to include treatment of patients 4 – 11 years of age with Advair® 100/50 mcg. Each of the individual components of Advair® has been approved for use in patients 4 – 11 years of age. The approved dose of salmeterol Diskus is 50 mcg BID for all age groups. The approved dose of fluticasone is 50 and 100 mcg BID in patients below the age of 12 years.

During discussions with the Agency it was agreed that to meet the regulatory requirements for combination drug products, it would be acceptable to extrapolate efficacy data of AdvairDiskus® given twice a day down to patients 4 years of age (Meeting with sponsor April 26, 2001). Subsequently, it was agreed that a pediatric growth study with Advair® was not needed because one had already been completed for Flovent Rotadisk® 50 and 100 mcg (Feb 24, 2003 communication to the sponsor). Similarly, the PK data obtained from prior studies of inhaled fluticasone were thought to be sufficient to support approval of Advair Diskus® in the 4-11 age group. The sponsor was advised that safety was the primary objective of the clinical studies in this age group, and adverse events and safety variables should be the primary outcome variables for the studies for this development program.

### **B. Foreign Marketing History**

Advair Diskus® was first approved for marketing on September 7, 1998 in Sweden. It has subsequently been approved for marketing in the following 93 countries:

Argentina, Armenia, Aruba, Australia, Austria, Azerbaijan, Bahrain, Bangladesh, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Georgia, Germany, Ghana, Greece, Guatemala, Guayana, Honduras, Hong Kong, Hungary, Iceland, India, Ireland, Israel, Italy, Jamaica, Jordan, Kazakhstan, Kenya, Kuwait, Latvia, Libya, Lithuania, Luxembourg, Malawi, Malaysia, Malta, Mauritius, Mexico, Morocco, Netherlands, Netherlands

Antilles, New Zealand, Nicaragua, Norway, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Saudi Arabia, Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Sri Lanka, Suriname, Sweden, Switzerland, Taiwan, Thailand, Trinidad & Tobago, Turkey, UAE, UK, Uruguay, Venezuela, Vietnam, Yugoslavia, Zambia, Zimbabwe.

Applications are pending in the following 9 countries:

[Redacted] (b) (4)

There have been no withdrawals from the market. As of October 31, 2002 the estimated exposure to Advair® worldwide was [Redacted] (b) (4) patient-years.

**III. Items Required for Filing and Reviewer Comments**

**A. Reviewer Comments**

This is an electronic NDA submission that includes a table of contents and adequate links.

Financial disclosure

1. [Redacted] (b) (4) investigators who enrolled patients into study [Redacted] (b) (4) meet the definition of having a potential financial conflict of interest. However, the sponsor claims exemption on the basis that this was not an efficacy trial.
  - [Redacted] (b) (4) investigators received other payments from GSK that exceeded \$25,000. The sponsor states that they each enrolled very few patients [Redacted] (b) (4)
  - [Redacted] (b) (4) investigators had an equity interest in GSK of greater than \$50,000. The sponsor states that they each enrolled very few patients ([Redacted] (b) (4))
2. There are statements of no conflict-of interest for studies RPS3001 and SAM40012
3. The sponsor states that study SFCB3020 was not covered because it was completed on September 10, 1997.

Indexes and references

References are listed starting on page 8 of the *Background and Overview of Clinical Studies* – clinstat\backgroundandove.pdf

Copies of selected articles are contained in clinstat\pubs\authorname.pdf and the titles are listed and cross-referenced in clinstat\clintoc.pdf

**B. Necessary Elements (21 CFR 314.50)**

**Table 1. Necessary Elements**

Item	Type	Status	Location (paper/electronic)
	Application Form (FDA 356h)	Present	\\CDSESUB1\N21077\S_0172003-06-26 356h.pdf

Item	Type	Status	Location (paper/electronic) \\CDSESUB1\N21077\S_0172003-06-26
	Formatting for Electronic Filing Format Table of Contents / Indexes Labeling	OK OK OK	
1	Index / Table of Contents	Present	Suppltoc.pdf
2	Samples and Labeling Proposed Package Insert Proposed Label Proposed Medication Guide	Present Present	Labeling\proposed.pdf
3	Summary Labeling Marketing History Chemistry, Manufacturing, & Controls (CMC) Nonclinical Pharmacology and Toxicology Human Pharmacokinetics and Bioavailability Clinical Benefits vs Risks	Present A. C. F. E. F. H. I.	Summary.pdf
4	CMC Environmental Impact statement	Present	cmc Cmcl\environ.pdf
5	Nonclinical Pharmacology and Toxicology	n/a	
6	Human Pharmacokinetics and Bioavailability	n/a	
8	Clinical		
8.5	Controlled studies	Present	Clintoc.pdf or Pediatricuse\sas30031 pediatricuse\sam40012 pdeiatricuse\sfc3020 pediatricuse\rps30001
8.7	Uncontrolled studies	Present	Clinstat\other\otherstudiesandi.pdf
8.8	Integrated Summary of Effectiveness (subsets for age, gender, and race)	Present	lse\ise.pdf
8.9	Integrated Summary of Safety Potential for Abuse	Present 19.2, pg 68	lss\iss.pdf lss\iss.pdf
8.11	Benefits vs Risks	Present	Riskben\riskben.pdf
8.12	Statements of Good Clinical Practice: Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures	Present Present	Stated in each study report Stated in each study report

Item	Type	Status	Location (paper/electronic) \\CDSESUB1\N21077\AS_017\2003-06-26
	Auditing information		SAS, SFCB
9	Safety Updates	Present	Other\otherstudiesandi.pdf
10	Statistics		Presented with study reports
11	Case Report Tabulations	Present	Crt
12	Case Report Forms (for patients who died or did not complete studies)	Present	Crf
13	Patent Information	Present	Other\patinfo.pdf
14	Patent Certification		
16	Investigator Debarment Certification	Present	Other\debar.pdf
17	Field copy certification (if applicable)		
18	User Fee Cover Sheet	Present	Other\userfee.pdf
19	Financial Disclosure	Present	Other\financial.pdf
20	Other Claimed Marketing Exclusivity Pediatric Use		Other\marketingexclusi.pdf Other\pediatricuseinfo.pdf

#### IV. Clinical Studies

Four studies are submitted in support of this application. SAS30031, conducted in the United States and Canada was designed primarily to look at the incidence of AEs in Advair® 100/50 as compared to Flovent® in asthmatics 4-11 years of age. Efficacy measures were secondary outcomes. Studies RPS30001, SAM40012, and SFCB3020 were conducted in Europe and are submitted as supporting data. They all compared Advair® 100/50 to other formulations of fluticasone. An integrated efficacy and safety analysis including these four studies is included in the application. Additionally, summaries are provided of the recent safety experience with Advair® used to treat adults with asthma.

In all the studies summarized below the test drug was the fixed combination product containing fluticasone 100 mcg + salmeterol 50 mcg delivered via Diskus DPI (Advair Diskus® 100/50). The subjects were all children with a clinical diagnosis of asthma who had been treated with a steady dose of inhaled steroids for the month prior to the study (see table).

**Table 2. Summary of Pivotal Studies**

Study	Design	Prior Inhaled Steroid Use	Dosage Of control treatment	Patients Exposed to Advair®	Age	Evaluations
SAS30031  USA	Randomized, double-blind comparison of Advair®100/50 and Flovent® 100 mcg BID  Duration: 12 weeks	252-336 mcg BDP or 200-400 mcg BUD or 600-1000 mcg TAA or 1000 mcg FLN or 88-250 mcg FP	100 mcg fluticasone BID  (n=101)	102	4-11	AEs and urine cortisol

**Table 3. Summary of Supporting Studies**

	Design	Prior Inhaled Steroid Use	Dosage Of control treatment	Patients Exposed to Advair®	Age	Evaluations
SFC3020 Non-US	Randomized, double-blind comparison of Advair®100/50 vs Fluticasone 100 mcg + salmeterol 50 mcg given concurrently BID  Duration: 12 weeks	400-500 mcg BDP or 400-500 mcg FLN or 200-250 mcg FP	100 mcg fluticasone 50 mcg salmeterol  Given BID concomitantly  (n=132)	125	4-11	Change in morning PEF
RPS3001 Non-US	Randomized, double-blind comparison of Advair Diskus® 100/50 and Advair 100/50 via RPID inhaler  Duration: 12 weeks	200-500 mcg BDP or 200-500 mcg BUD or 200-500 mcg FLN or 100-200 mcg FP	50 mcg salmetrol  100 mcg fluticasone together in a RPID inhaler  (n=176)	171	4-14	Change in morning PEF
SAM40012 Non-US	Randomized, double-blind comparison of Advair Diskus® 100/50 and Flovent® Diskus 100 mcg and Flovent® Diskus 200 mcg  Duration: 24 weeks	400-500 mcg BDP or 400-500 mcg BUD or 200-250 mcg FP	100 mcg fluticasone  (n=175)  200 mcg fluticasone  (n=180)	176	4-11	Symptom-free days

**C. Decision**

This application is fileable.

**V. DSI Review/ Audit Decision**

From a clinical standpoint, DSI consultation and audit are not necessary

**VI. Timeline for Review****Table 4. Timeline for Review**

Milestone	Target Date for Completion
Stamp Date	June 26, 2003
Study SAS30031	September 1, 2003
Study SFCB 3020	October 1, 2003
Study SAM 40012	October 1, 2003
Study RPS 30001	October 1, 2003
Integrated Efficacy Summary	November 1, 2003
Integrated Safety Summary	November 1, 2003
Draft Review	December 31, 2003
Label Review	January 31, 2003
Wrap-up Meeting	February 31, 2003
Due Date	April 17, 2004
PDUFA Date	April 27, 2004

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Carol Bosken  
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MEDICAL OFFICER

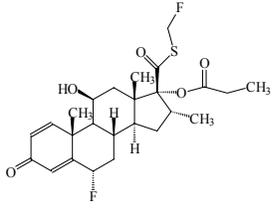
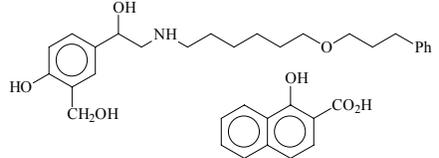
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MEDICAL OFFICER  
I concur

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-077/S017**

**CHEMISTRY REVIEW(S)**

CHEMIST'S REVIEW #1	1. ORGANIZATION HFD-570 DPADP (HFD-820)	2. NDA NUMBER 21-077
3. NAME AND ADDRESS OF APPLICANT (City and State) GlaxoSmithKline (GSK) Research Triangle Park, NC 27709	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER DATE SE5-017 26-Jun-2003 (assigned 10-Jul-2003)
6. NAME OF DRUG Advair® Diskus®	7. NONPROPRIETARY NAME fluticasone propionate/salmeterol xinafoate inhalation powder	
8. SUPPLEMENT PROVIDS FOR: expansion of the indication to include use of Advair Diskus 100/50 mcg for the long-term, twice-daily, maintenance treatment of asthma in patients 4-11 years of age.		9. AMENDMENT(S), REPORT(S), ETC.
10. PHARMACOLOGICAL CATEGORY glucocorticoid/beta-adrenergic agonist	11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC <input type="checkbox"/>	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) inhalation powders	14. POTENCY 100/50 mcg (per blister), 250/50 mcg, and 500/50 mcg (fluticasone/salmeterol)	
15. CHEMICAL NAME AND STRUCTURE S-(Fluoromethyl)6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxyandrost-1,4-diene-17-carbothioate;  (±)-4-hydroxy-α <sup>1</sup> -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate (salt) 		16. RECORDS AND REPORTS CURRENT YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> REVIEWED YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
17. COMMENTS: See review notes. cc: Orig. NDA #21-077 HFD-570/div. Files HFD-570/CBertha 8/15/03 HFD-570/GPoochikian HFD-570/LJafari R/D Init. by: _____ F/T by: C. Bertha/8/15/03 doc # 03-06-26.rev.doc		
18. CONCLUSIONS AND RECOMMENDATIONS: The supplemental application is recommended for <b>approval (AP)</b> , from a CMC perspective.		
19. REVIEWER NAME  Craig M. Bertha, Ph.D.	20. SIGNATURE	21. DATE COMPLETED  8/15/03

**Chemist's Review Notes**

This efficacy supplement is submitted to support the expansion of the age range into the 4-11 year age group for the use of the lowest strength (100 mcg fluticasone propionate/50 mcg salmeterol, metered) for the maintenance treatment of asthma. GSK states in the introduction to the CMC section that "There will be no change to the chemistry, manufacturing, and controls of the commercial drug product as a result of this supplement." In terms of the EA they state that:

"The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(b). GlaxoSmithKline has reviewed market forecasts, indications and dosage information and estimates that this action will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment. GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment."

Thus, the supplement is adequate from a CMC perspective and no further review is necessary.

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Craig Bertha  
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CHEMIST

Guiragos Poochikian  
8/20/03 09:31:41 AM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-077/S017**

**PHARMACOLOGY REVIEW(S)**

**DIVISION OF PULMONARY DRUG PRODUCTS**  
**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY**  
**Labeling Review**

**NDA No.:** 21-077, S-017

**Reviewer:** Lawrence F. Sancilio, Ph.D.

**Date of Submission:** 6/26/03

**Date Completed:** 7/15/03

**Sponsor:** GlaxoSmithKline  
5 Moore Drive  
Research Triangle Park, NC 27709

**Drug Name:** Advair Diskus (salmeterol xinafoate and fluticasone propionate)

**Chemical Names:**

Salmeterol xinaphoate: 4-Hydroxy- $\alpha$ <sup>1</sup>-[[[6-(4-phenylbutoxy) hexyl]] amino]-methyl]-1, 3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate

Fluticasone propionate: S-fluoromethyl 6, 9 -difluoro-11 -hydroxy-16- methyl-3- oxo- 17-propionyloxyandrosta-1, 4-diene-17 -carbothioate

**Class:** Salmeterol: B<sub>2</sub> Adrenoceptor agonist; fluticasone propionate: glucocorticoid.

**Indication:** Maintenance of asthma in children 4-11 years old and in children >12 years old and adults.

**Formulation:** Salmeterol xinafoate and fluticasone propionate powder with lactose in double-foil blister strip of powder formulations containing 100, 250 or 500 mcg of microfine fluticasone propionate with 50 mcg of salmeterol base equal to 72.5 mcg of salmeterol xinaphoate salt. Under standardized in vitro conditions, Advair Diskus delivers 93, 233 and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base. The human exposure is based on the labeled dose.

**Route of administration:** Inhalation.

**Maximum Daily Inhalation Dose:** The maximum daily delivered dose was 200 mcg of fluticasone propionate and 100 mcg of salmeterol base for children 4 to 11 years old (1 puff of the 100/50 formulation twice a day) and 1000 mcg of fluticasone propionate and 100 mcg of salmeterol base for children >12 years old and adults (1 puff of the 500/50 formulation twice a day).

## Labeling Review

The animal to human dose ratios based on  $\text{mg}/\text{m}^2$  utilizes the delivered human dose. Since this supplement will include children from 4-11 years old, the revised label will include the animal to human ratios for this age group; there is no difference in the ratios for children, >12 years old and adults.

The following changes in the portions of the label related to preclinical data are highlighted below are recommended.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (~~(approximately 4 and 10 times, respectively,~~ the maximum recommended daily inhalation dose in adults and children on a  $\text{mcg}/\text{m}^2$  basis)) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum recommended daily inhalation dose in adults and children on a  $\text{mcg}/\text{m}^2$  basis)) for 104 weeks. Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a  $\text{mcg}/\text{m}^2$  basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

**Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above [~~(approximately 20 times the maximum recommended daily inhalation dose in adults~~ <sup>(b) (4)</sup> ~~(~~ and children <sup>(b) (4)</sup> ~~)~~ based on comparison of the plasma area under the curves [AUCs] caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended daily inhalation doses in adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague-Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (~~(approximately 5555 and 25- times, respectively,~~ the maximum recommended daily inhalation dose in adults and children on a  $\text{mg}/\text{m}^2$  basis)). No tumors were seen at 0.21 mg/kg (approximately 15 <sup>(b) (4)</sup> and 8 times, respectively the maximum ~~r~~recommended daily inhalation dose in adults and children on a  $\text{mg}/\text{m}^2$  basis)). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with

salmeterol at oral doses up to 2 mg/kg (approximately 160<sup>(b)(4)</sup> times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

**Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol compared to toxicity data from the components administered separately. In mice combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol (approximately 410<sup>(b)(4)</sup> times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis) was teratogenic. Cleft palate, fetal death, increased implantation loss and delayed ossification were seen. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) and up to 1.4 mg/kg orally of salmeterol (approximately 5<sup>(b)(4)</sup> times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) and up to 1 mg/kg of salmeterol (approximately 8<sup>(b)(4)</sup> times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to <sup>(b)(4)</sup> - the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol (approximately 810<sup>(b)(4)</sup> times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis) produced maternal toxicity, decreased placental weight, decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis), respectively, revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see

## CLINICAL PHARMACOLOGY

Fluticasone propionate crossed the placenta following administration of a subcutaneous dose of 100 mcg/kg to mice (less than - the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis). administration of a subcutaneous or an oral dose of 100 mcg/kg to rats (approximately equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) and administration of an oral dose of 300 mcg/kg <sup>(b)(4)</sup> -to rabbits

(approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

 (b) (4)  
~~EE~~ Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

— **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 16<sup>(b)</sup>0 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,6<sup>(b)</sup>00 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with salmeterol in pregnant women. Salmeterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 41<sup>(b)</sup>0 and 810<sup>(b)</sup>(4) times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

~~**Use in Labor and Delivery:** There are no well-controlled human studies that have investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.~~

**Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR DISKUS, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast milk; however, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) resulted in measurable radioactivity in milk.

Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR DISKUS, taking into account the importance of ADVAIR DISKUS to the mother. Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

## OVERDOSAGE

**ADVAIR DISKUS:** No deaths occurred in rats given by inhalation a single dose combinations of 3.6 mg/kg of salmeterol (b) (4) (b) (4) (approximately 290 and 140 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and 1.9 mg/kg of fluticasone propionate (approximately 15 (b) (4) and 35 (b) (4) times, respectively the maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis).

**Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. In mice the oral median lethal dose was > 1,000 mg/kg (>4,100 and >9,600 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). In rats the subcutaneous median lethal dose was > 1,000 mg/kg (>8,100 and >19,200 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis).

(b) (4)

**Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of salmeterol.

Treatment consists of discontinuation of salmeterol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to

determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately (b) (4) 240 and 11<sup>(b)</sup>0 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately (b) (4) 190 and 90 times, respectively, the maximum recommended daily inhalation dose in adults and children, on a mg/m<sup>2</sup> basis). By the oral route, no deaths occurred in mice at 150 mg/kg ((approximately 6, 100<sup>(b) (4)</sup> and 2,900 times, respectively, the maximum recommended daily inhalation dose in adults and children- on a mg/m<sup>2</sup> basis)) and in rats at 1,000 mg/kg ((approximately 81,000<sup>(b) (4)</sup> and 38,000 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis)).

### Recommendation

From a preclinical standpoint, the labeling is approvable if the recommended changes are incorporated in the final label.

Reviewer's signature: \_\_\_\_\_

Supervisor's signature:

Concurrence - \_\_\_\_\_

Non-Concurrence - \_\_\_\_\_  
(see memo attached)

Drug:		Advair Fluticasone 4 yr/Adult							
	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m <sup>2</sup>	
Pediatric	4	0.1	2	0.2	16	0.0125	25	0.3125	
Adult	>12	0.5	2	1	50	0.02	37	0.74	
	route	mg/kg/d	conv. factor	mg/m <sup>2</sup>	Dose Ratio		Rounded Dose Ratio		
					Adults	Children	Adults	Children	
<b>Carcinogenicity:</b>									
rat			6	0	---	---	---	---	
rat	inh	0.057	6	0.342	0.46216	1.0944	< 1	1	
mouse	oral	1	3	3	4.05405	9.6	4	10	
dog			20	0	---	---	---	---	
mouse			3	0	---	---	---	---	
<b>Repro/Fertility:</b>									
rat	sc	0.05	6	0.3	0.40541	N/A	< 1	N/A	
rat	oral	0.1	6	0.6	0.81081	N/A	1	N/A	
rat	oral	2	6	12	16.2162	N/A	15	N/A	
rat	sc	0.03	6	0.18	0.24324	N/A	< 1	N/A	
<b>Teratogenicity:</b>									
rabbit	oral	0.004	12	0.048	0.06486	N/A	< 1	N/A	
rat	sc	0.1	6	0.6	0.81081	N/A	1	N/A	
rat	sc	0.01	6	0.06	0.08108	N/A	< 1	N/A	
rabbit	oral	0.3	12	3.6	4.86486	N/A	5	N/A	
mouse	sc	0.045	3	0.135	0.18243	N/A	< 1	N/A	
<b>Overdosage:</b>									
mouse	oral	1000	3	3000	4054.05	9600	4,100	9,600	
rat	sc	1000	6	6000	8108.11	19200	8,100	19,200	
dog			20	0	---	---	---	---	
rat	inh	1.9	6	11.4	15.4054	36.48	15	35	
<b>Other:</b> (Describe studies here)									
rat	oral	10	6	60	81.0811	192	80	190	
mouse	sc	0.04	3	0.12	0.16216	0.384	< 1	< 1	
mouse	sc	0.15	3	0.45	0.60811	1.44	< 1	1	
mouse	sc	0.1	3	0.3	0.40541	0.96	< 1	1	
extra			---	---	---	---	---	---	

Drug:		Advair Salmeterol, 4 yr/ Adult							
			# daily						
	age	mg/dose	doses	mg/day	kg	mg/kg	factor	mg/m <sup>2</sup>	
Pediatric	4	0.05	2	0.1	16	0.00625	25	0.15625	
Adult	>12	0.05	2	0.1	50	0.002	37	0.074	
			conv.	Dose Ratio		Rounded Dose Ratio			
	route	mg/kg/d	factor	mg/m <sup>2</sup>	Adults	Children	Adults	Children	
<u>Carcinogenicity:</u>									
rat	ihh/oral	0.68	6	4.08	55.1351	26.112	55	25	
rat	inh/oral	0.21	6	1.26	17.027	8.064	15	8	
mouse	oral	1.4	3	4.2	56.7568	26.88	55	25	
dog			20	0	---	---	---	---	
mouse	oral	0.2	3	0.6	8.10811	3.84	8	4	
<u>Repro/Fertility:</u>									
rat	oral	2	6	12	162.162	N/A	160	N/A	
rat	oral	10	6	60	810.811	N/A	810	N/A	
extra			---	---	---	N/A	---	N/A	
extra			---	---	---	N/A	---	N/A	
<u>Teratogenicity:</u>									
rabbit	oral	10	12	120	1621.62	N/A	1,600	N/A	
rat	oral	1	6	6	81.0811	N/A	80	N/A	
rat	oral	10	6	60	810.811	N/A	810	N/A	
rabbit	sc		12	0	---	N/A	---	N/A	
mouse	oral	10	3	30	405.405	N/A	410	N/A	
<u>Overdosage:</u>									
mouse			3	0	---	---	---	---	
rat	inh	2.9	6	17.4	235.135	111.36	240	110	
dog	inh	0.7	20	14	189.189	89.6	190	90	
rat	inh	3.6	6	21.6	291.892	138.24	290	140	
<u>Other:</u> (Describe studies here)									
rat	oral	1000	6	6000	81081.1	38400	81,000	38,000	
mouse	oral	150	3	450	6081.08	2880	6,100	2,900	
dog			20	0	---	---	---	---	
extra			---	---	---	---	---	---	
extra			---	---	---	---	---	---	

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/s/

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Lawrence Sancilio  
7/17/03 10:28:03 AM  
PHARMACOLOGIST

Joseph Sun  
7/24/03 09:45:21 AM  
PHARMACOLOGIST  
I concur.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-077/S017**

**STATISTICAL REVIEW(S)**

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCES  
OFFICE OF BIostatISTICS**

Date: December 17, 2003

From: James Gebert, HFD-715

Subject : Advair Diskus submission for the maintenance treatment of Asthma in Children  
4-11 years of age

To File: NDA 21-077/S-017

**ADVAIR DISKUS** (fluticasone propionate 100mcg and salmeterol 50mcg inhalation powder; New Drug Application 21-077) was approved by the Agency on 24 August 2000 for marketing in the United States. **ADVAIR DISKUS** is currently indicated for the long-term, twice daily, maintenance treatment of asthma in patients 12 years of age and older. The individual components are currently approved and marketed for use in children 4 to 11 years of age, as **FLOVENT ROTADISK** (50mcg and 100mcg BID) and **SEREVENT DISKUS** (50mcg BID). **FLOVENT DISKUS** (50mcg and 100mcg BID) is also approved in this age group but not yet marketed in the US.

During a meeting with GlaxoSmithKline on 26 April 2001, the Agency stated that to meet the regulatory requirements of the combination drug products, it would be acceptable to extrapolate efficacy data of **ADVAIR DISKUS** given twice daily down to the age of 4 years. At a follow-up meeting with the Agency on 19 February 2002, the Agency indicated that an additional study to evaluate the safety of the fluticasone propionate/salmeterol **DISKUS** Combination Product compared with fluticasone propionate **DISKUS** alone was necessary to provide adequate safety data for the label in subjects 4 to 11 years of age.

Given the demonstrated efficacy of **ADVAIR** in adolescents and adults, and the extrapolation of these efficacy data results to patients 4 to 11 years of age with asthma, the data in support of this supplement are the safety data from one well-controlled US study ([SAS30031](#)) and three well-controlled non-US studies ([SFCB3020](#), [RPS30001](#), and [SOM40012](#)). The **DISKUS** Combination Product was administered at the same dosage (100/50mcg BID) in all studies.

The safety data will be reviewed by Dr. Bosken. There will be no statistical review for this submission as there is minimal efficacy data and the pulmonary division conceded efficacy.

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this page is the manifestation of the electronic signature.**  
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/s/

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James Gebert  
12/17/03 11:28:37 AM  
BIOMETRICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-077/S017**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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<b>NDA:</b>	21-077 (SN017) (pediatric supplement)
<b>Proprietary Drug Name:</b>	ADVAIR DISKUS
<b>Generic Name:</b>	Fluticasone Propionate/Salmeterol
<b>Indication:</b>	Treatment of Asthma
<b>Dosage Form:</b>	DPI
<b>Strength:</b>	100/50, <span style="background-color: #cccccc; padding: 0 5px;">(b) (4)</span>
<b>Route of Administration:</b>	Oral Inhalation
<b>Applicant:</b>	GlaxoSmithKline
<b>Clinical Division:</b>	DPADP (HFD-570)
<b>Submission Dates:</b>	June 26 <sup>th</sup> , 2003
<b>Reviewer:</b>	Sandra Suarez-Sharp, Ph.D.
<b>Team Leader:</b>	Emmanuel O. Fadiran, Ph. D.

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## I. TABLE OF CONTENTS

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## 2. EXECUTIVE SUMMARY

Advair Diskus (NDA 21-077) was approved on 2000 for use in patients 12 years of age and older. The purpose of this supplemental NDA (21-077, SN017) is to gain approval of Advair Diskus for the maintenance treatment of asthma in children 4 to 11 years of age. The proposed dosage in patients 4 to 11 years of age is (b)(4)

The combination product contains two active ingredients, fluticasone propionate (FP) and salmeterol xinafoate (SAL). Both individual components are currently approved and marketed in a powder formulation for use in children 4 to 11 years of age with asthma as Flovent Rotadisk 50 mcg and 100 mcg BID and Serevent Diskus 50 mcg BID. Flovent Diskus 50 mcg and 100 mcg BID (NDA 20-833) are also approved in this age group, but not yet marketed in the United States.

Given the Agency's statement that it would be acceptable to extrapolate the efficacy data from adults and adolescents down to children 4 years of age, the primary basis for this supplement is safety data from 4 clinical studies: safety data in pediatric subjects from study SAS3003 and from three well-controlled non-US safety and efficacy studies (SFCB3020, RPS30001, and SAM40012).

GlaxoSmithKline agreed to collect pharmacokinetic data on fluticasone propionate and salmeterol in pediatrics 4- 11 years of age and also to perform a population PK analysis in adult patients to compare fluticasone propionate and salmeterol pharmacokinetics in these two populations. However, these data was not submitted during NDA filing because of difficulties in recruiting asthmatic children and because some PK studies are ongoing. The sponsor has proposed that the Population PK analysis will be finalized and submitted on April 2004.

After conducting a cross-study comparison analysis of the PK of FP and SAL in children and adults delivered from the Advair Diskus (adults only), Rotadisk and Flovent Diskus and following an internal discussion with the medical review team, the following conclusion was made:

- Since the systemic exposure (C<sub>max</sub>, AUC) of FP following administration of Advair Diskus was lower than that after the administration of FP from the Rotadisk or the Flovent Diskus devices in adult subjects, and there was not a significant difference between the exposure (C<sub>max</sub>) of FP in children and adults when dosed using the Rotadisk, then most likely the systemic exposure of FP in children from the Advair diskus device will be lower or similar to that from the Rotadisk and Flovent Diskus devices. Therefore, the safety data generated with the Flovent Diskus and Rotadisk may be used to make conclusions regarding the

safety profile of FP delivered to children 4 to 11 years of age from the Advair Diskus.

It is of importance to mention that this statement may be confirmed when the sponsor sends PK data of FP and SAL in asthmatic children receiving Advair Diskus 100/50 mcg. Meanwhile, this reviewer agrees with the sponsor's proposal for labeling the PK of Advair Diskus pediatric section:

*Pediatric Patients: In a clinical study conducted in patients with asthma aged 4 to 11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes after dosing with 50 and 100 mcg of fluticasone propionate inhalation powder twice daily using the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma concentrations at the 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.*

The above labeling recommendation made by the sponsor is the approved labeling for Flovent Diskus. This paragraph may be modified appropriately when the Advair Diskus PK data in pediatric children 4 to 11 years of age is submitted by the sponsor and reviewed.

Although the SAL PK data obtained from a single-dose study show that the combination product (Advair Diskus) had significantly higher mean  $C_{max}$  values for SAL as compared to the treatment where SAL was given concurrently with FP, these data should be viewed with caution since SAL plasma  $C_{max}$  values obtained were close to assay limits. In addition, no major differences were observed in PD between combination product (Advair Diskus) and individual component of SAL. The labeling recommendations in the pediatric section with respect to SAL systemic exposure will be updated when PK data on this drug substance is submitted as promised by the sponsor.

## **2.1 Recommendation**

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has conducted a cross-study comparison analysis of previously submitted data on the systemic exposure of fluticasone propionate and salmeterol delivered from different devices, since no PK data in children was included in this supplemental NDA (21-077 SN0417). The cross-study analysis comparison lead to the conclusion that the systemic exposure of FP in children from the Advair Diskus device may be lower than or similar to that from the Rotadisk or Flovent Diskus devices. Therefore, the safety data generated with the Flovent Diskus and Rotadisk may be used to make conclusions regarding the safety profile of FP delivered to children 4 to 11 years of age from the Advair Diskus. There are no comments to the sponsor at this time.

Reviewer

Sandra Suarez-Sharp, Ph.D.

Office of Clinical Pharmacology and Biopharmaceutics

Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader

cc: NDA 21-077 (SN 017): Division File  
HFD-870: Malinowski, Hunt  
HFD-570: Fadiran, Bosken, Gilbert-McClain, Jafari, Suarez-Sharp

### 3. BACKGROUND

Advair Diskus (NDA 21-077) was approved on 2000 for use in patients 12 years of age and older. Advair Diskus is currently indicated for the long-term, twice-daily maintenance treatment of asthma in patients 12 years of age and older and is not indicated for the relief of acute bronchospasm. The purpose of this supplemental NDA (21-077, SN017) is to gain approval of Advair Diskus for the maintenance treatment of asthma in children 4 to 11 years of age. The proposed dosage in patients 4 to 11 years of age is (b) (4)

The combination product contains two active ingredients, fluticasone propionate and salmeterol xinafoate. Both individual components are currently approved and marketed in a powder formulation for use in children 4 to 11 years of age with asthma as Flovent Rotadisk 50 mcg and 100 mcg BID (NDA 20-770) and Serevent Diskus 50 mcg BID (NDA 20-692). Flovent Diskus 50 mcg and 100 mcg BID (NDA 20-833) are also approved in this age group, but not yet marketed in the United States. Flovent Rotadisk was approved for use in children 4 to 11 years of age on November 1997. Flovent Diskus was approved for use in children 4 to 11 years of age on September 2000 based on data from 3 pivotal and 2 supporting pediatric studies. Serevent Diskus 50 mcg BID was approved for use in children 4 to 11 years of age on September 1998 based on data from 3 pivotal and 8 supporting pediatric studies.

An agreement (April 2001) was reached between the Agency and the sponsor that to meet the regulatory requirements of the combination drug products in the pediatric population (4-11 years of age), it would be acceptable to extrapolate the adult efficacy data of Advair Diskus given twice daily down to the age of 4 years. The Agency indicated however, that a US study to evaluate the safety of the fluticasone propionate/salmeterol Diskus Combination Product in patients 4 to 11 years of age with asthma was necessary to provide safety data for the label.

Given the Agency's statement that it would be acceptable to extrapolate the efficacy data in adults and adolescents down to children 4 years of age, the primary basis for this supplement is safety data from 4 well-controlled clinical studies: safety data in pediatric subjects from study SAS3003 and from three well-controlled non-US safety and efficacy studies (SFCB3020, RPS30001, and SAM40012). The efficacy data from these four studies were included and discussed in this supplement for completeness.

Following the April 2001 meeting, the sponsor revised their proposed clinical protocols and requested a meeting to review the changes and to obtain Agency's feedback on several questions. On November 18, 2001, the sponsor sent a package, which included a summary of the studies to support these applications. The proposed studies and the amendments sent were as follows:

**Protocol SAS30021:** A Stratified, Randomized, Double-Blind, Placebo-Controlled,

Parallel-Group, 12-Week Trial Evaluating the Safety and Efficacy of the Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50 mcg Once Daily Versus Fluticasone Propionate DISKUS 100 mcg Once Daily and Placebo in Symptomatic Pediatric Subjects (4 to 11 Years) With Asthma.

The OCPB team made the following recommendations to this protocol at a meeting that took place on February 19, 2002:

1. PK measurements for FP and salmeterol. The sponsor should apply the sparse blood sampling technique for PK analysis of the drugs. The number/timing of blood sampling should be optimized using an appropriate model applied to historical PK adult data. The data should be analyzed using a population PK approach
2. Urine for cortisol determination should be collected for 24hr instead of 12-hr overnight collection.
3. Statistical analysis of comparative PK and PD exposure (i.e. 90% CI)

**Protocol SAS30022:** A Randomized, Double-blind, Placebo-controlled Parallel-group, 12-week Trial Evaluating the Efficacy and Safety of the Fluticasone propionate/salmeterol DISKUS Combination Product 250/50mcg Once Daily versus Fluticasone propionate/salmeterol DISKUS Combination Product 100/50mcg Twice Daily versus Fluticasone propionate DISKUS 250 mcg Once Daily versus Placebo in Symptomatic Adolescent and Adult Subjects with Asthma That is Not Controlled on Short Acting Beta<sub>2</sub>-Agonists Alone

Recommendations made by the OCPB team at a meeting that took place on February 19, 2002:

- PK measurements for FP and salmeterol.
- Urine for cortisol determination should be collected for 24hr instead of 12-hr overnight collection.
- Statistical analysis of comparative PK and PD exposure (i.e. 90% CI)

(b) (4)



(b) (4)

(b) (4)

On a submission dated March 14, 2002, GlaxoSmithKline agreed to collect pharmacokinetic data on fluticasone propionate and salmeterol in pediatrics and also to perform a population PK analysis in adult patients to compare fluticasone propionate and salmeterol pharmacokinetics in these two populations. These analyses would define effects of age (from ages 4 to adult), device (DISKUS vs HFA MDI) and co-administered drug (salmeterol) on fluticasone propionate pharmacokinetics. The sponsor mentioned that to optimize the ability of these analyses to detect changes, fluticasone propionate pharmacokinetic data from four ongoing or planned studies (SAS30031, (b) (4) SAS30022, and SAS 10006) would be combined into a single analysis when all four studies are completed; these would include adolescents, adults and children 4-11 years of age. Data for this analysis would include PK data from dosing once daily and twice daily, with doses of FP from 200 to 250 mcg/day, with and without salmeterol (50 to 100 mcg/day). (b) (4)

With regards to salmeterol, a population pharmacokinetic approach would also be used to compare salmeterol pharmacokinetics in the 4-11 year old pediatric population from ADVAIR DISKUS and ADVAIR HFA (SAS30031, (b) (4) and also compare exposure from ADVAIR DISKUS in the pediatric and adult populations (SAS30031, (b) (4) SAS30022 and SAS 10006).

During the review of this supplemental NDA, the OCPB team requested that the sponsor submit the available PK data on children 4-11 years old taking Advair diskus, since not PK information was included in this submission. In December 2003, the sponsor sent the following response:

“In addition to the population PK analysis of the data from studies SAS30031, (b) (4) SAS30022, SAS10006, separate analyses and reports were planned for (b) (4) and SAS10006. Separate analyses and reports were not planned for SAS30031 and SAS30022 because it was felt that the limited data from these studies would be best utilized by incorporation into the proposed multi-center analysis. As described in the SAS30031 protocol, a minimum of 20 subjects (10/group) providing 3 - 5 serial PK samples would be needed to perform an adequate population PK analysis. Problems recruiting serial PK subjects in SAS30031 (only 4 Advair and 9 Flovent subjects) caused us to begin a separate PK study (SAS10016) to obtain enough serial PK data for an adequate population PK analysis in the pediatric population. SAS10016 uses the same population and serial sampling approach used for the PK sub-population in SAS30031. The study is ongoing with enrollment due to complete in January 2004. A separate population PK analysis of the combined data from SAS30031 and SAS10016 will be performed in order to provide an adequate assessment. The estimated timetable for this work is described below”.

**Table 1a.** Pediatric Pharmacokinetic Data Summary

Study No.	Number of Subjects with Serial PK		Number of Subjects with Single Sample Data		Data Available
	Advair	Flovent	Advair	Flovent	
SAS30031	4	9 <sup>b</sup>	Pre-dose 33 Post-dose 24	Pre-dose 37 Post-dose 34	Summary of individual concentrations December 2003
SAS10016	10	10	NA	NA	Individual concentrations available end- February 2004
Top-line results from combined Pop PK Analysis for SAS30031 and SAS10016 (Estimate 137 data points for Advair and 160 data points for Flovent.)					March 2004
Report for combined Pop PK Analysis for SAS30031 and SAS10016					April 2004

<sup>b</sup> Concentrations in one of the 9 subjects were all below the limit of detection

After reviewing the above response and following an internal discussion with the medical review team for this supplemental NDA, the following comment was sent to the sponsor:

- *We have reviewed your population pharmacokinetic plan for the Advair Diskus pediatric development program. You should submit the population pharmacokinetic report as soon as possible for Agency's review.*

This response was based on the assumption that the PK findings following administration of Advair diskus to adults in relation to the findings following administration of Flovent Diskus/Flovent Rotadisk could be extrapolated to children 4-11 years of age. The following summarizes the PK information in adults and children 4-11 years old after the administration of FP and salmeterol delivered from either the Advair Diskus (adult data only), Flovent Diskus, Flovent Rotadisk or Serevent Diskus.

On 03/24/99, GlaxoWellcome (GW) submitted an original NDA 21-077 (Advair Diskus) for review. The PK section included 4 PK studies (see Table 1) conducted in adults with the following objectives:

- 1) To determine whether the rate and extent of absorption of each active ingredient (or therapeutic moiety) in the combination drug product (SFC) is equivalent to that of each active ingredient administered concurrently in separate single-ingredient preparations (the requirements according to CFR 320.25 for combination products).
- 2) To assess drug-drug interaction (DDI) of SAL on FP mainly (Sal and FP administered concurrently vs. FP alone).

**Table 1. Descriptions of Individual Studies**

Study No. (Vol No.)	Comparison <sup>a</sup>	No. of Subjects (M/F)	Dosing Regimen	Strengths <sup>b</sup> (SAL/FP)	Total (or Daily) Dose (SAL/FP)	Assessments			
						FP		SAL	
						PK	PD <sup>c</sup>	PK	PD
<b>SFCB<sup>d</sup> 1002</b> (Vol 1.37)	<b>D vs. A</b>  Placebo	12M  Healthy Volunteers	Single Dose	<b>D:</b> 50/100  <b>A:</b> 100	50/100 x 5  100 x 5	√	√	--	--
<b>SFCB 1004</b> (Vol 1.38)	<b>D vs. A or B</b>  Placebo	13M+15F  Healthy Volunteers	Multiple Dose  (10 days)	<b>D:</b> 50/250  <b>A:</b> 250  <b>B:</b> 50	50/250 x2 BID  250 x 2 BID  50 x 2 BID	√	√	√	√
<b>SFCB 1005</b> (Vol 1.40)	<b>D vs. C vs. A</b>	8M+6F  Healthy Volunteers	Single Dose	<b>D:</b> 50/500  <b>C:</b> SAL 50 & FP 500  <b>A:</b> 500	50/500 x 2  SAL 50 x 2 & FP 500 x 2  500 x 2	√	√	√	√
<b>SFCB<sup>e</sup> 3019</b> (Vol 1.41)	<b>D vs. C vs. A</b>	31M+14F  Patients	Multiple Dose  (12 wks)	<b>D:</b> 50/500  <b>C:</b> SAL 50 & FP 500  <b>A:</b> 500	50/500 BID  SAL 50 BID & FP 500 BID  500 BID	√	√	--	--

<sup>a</sup>. **D** (SAL/FP combination product, **SFC**), **C** (SAL and FP given concurrently), **B** (SAL alone), and **A** (FP alone).

<sup>b</sup>. Combination products (**D**) are the to-be-marketed formulations.

<sup>c</sup>. PK and/or PD data analyzed.

<sup>d</sup>. Reviewed previously by OCPB.

<sup>e</sup>. A PK subset of a clinical trial.

Study No. **SFCB 1004** was a randomized, double-blind, placebo-controlled, four treatment, three-period, cross-over study, using an incomplete block design. Each study period lasted 12 days, with a washout of at least 9 days. Each subject received 3 of the 4 treatments: SFC (all subjects), SAL (all subjects), and then either FP (half the subjects) or placebo. A single dose of Sal which replaced the 19th placebo dose (Day 10) was given to half the subjects in the placebo group. On Day 10, after the 19th dose, PD effects of SAL were measured. PK of SAL (single- and multiple doses) and FP were investigated. Plasma and urinary cortisol levels were also monitored.

Study No. **SFCB 1005** was a single dose, randomized, double-blind, 3-way cross-over design, with a washout period of at least 7 days (dose to dose) between periods. Each study period lasted 48 hr. In addition to FP PK data, the PD effects of Sal were measured up to 4 hr post-dose. Plasma and urinary cortisol levels were also monitored.

Study No. **SFCB 3019** was a randomized, double-blind, double-dummy, parallel-group design consisting of three stages: run-in, treatment and follow-up. This is in fact a PK subset of a pivotal clinical trial. The study period was 32 or 34 weeks: run-in was two Weeks, treatment was 28 weeks, and follow-up was two weeks. In addition to clinical efficacy and safety data, the PK of FP, plasma and urinary cortisol levels were also monitored in the subset of patients.

Table 2 shows the mean (CV%) PK parameters of FP comparing the administration of D (Advair Diskus) versus C (FP + SAL) in studies 1005 and 3019.

**Table 2. Fluticasone PK (D vs. C)**

Study No.	Fluticasone PK Data				
	Total (Daily) Dose (µg)	Geo. LS Mean AUC (pg-hr/ml)	Geo. LS Mean C <sub>max</sub> (pg/ml)	Median T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)
SFCB1005  Single Dose	D (SFC): 100/1000	AUC <sub>0-∞</sub> 917 [CV 52%] <sup>a</sup> (78 – 131) <sup>b</sup>	107 [CV 41%] (95 – 113)	1.0	5.33
	C: SAL 100 & FP 1000	908 [CV 41%]	94.0 [CV 39%]	1.0	6.53
SFCB3019  Multiple Dose	D (SFC): 50/500 BID	AUC <sub>0-12, ss</sub> 389 [CV 58%] (53 - 104)	57.3 [CV 44%] (64 - 96)	2.0	-----
	C: SAL 50 BID & FP 500 BID	521 [CV 40%]	72.9 [CV 27%]	2.0	-----

The results of Study **SFCB 3019** showed that the highest recommended dose of the combination product, SFC given BID (**D**) had lower mean AUC and C<sub>max</sub> values when compared to Sal and FP given concurrently (**C**) to asthmatic patients.

Table 3 shows the mean (CV%) PK parameters of SAL comparing the administration of D (Advair Diskus) versus C (FP + SAL) in study 1005.

**Table 3. Salmeterol PK (D vs. C)**

Study No.	Salmeterol PK Data		
	Total (Daily) Dose (µg)	Geo. LS Mean C <sub>max</sub> (pg/ml)	Median T <sub>max</sub> (hr)
SFCB1005  Single Dose	D (SFC): 100/1000	200. (33% ↑)* [CV 42%]	0.1
	C: SAL 100 & FP 1000	150. [CV 22%]	0.1

The combination product (**SFC; D**) had significant increase in mean Sal C<sub>max</sub> value when compared to concurrent administration of Sal with FP (**C**) to healthy volunteers in this single-dose PK study. However, most of the C<sub>max</sub> values obtained were

close to LOQ and no AUC values were obtained for Sal due to assay limitations (LOQ being 100 pg/ml). Therefore, the differences in mean  $C_{max}$  values could not be further confirmed.

In general, the following conclusions were made by the CPB reviewer of this NDA at that time:

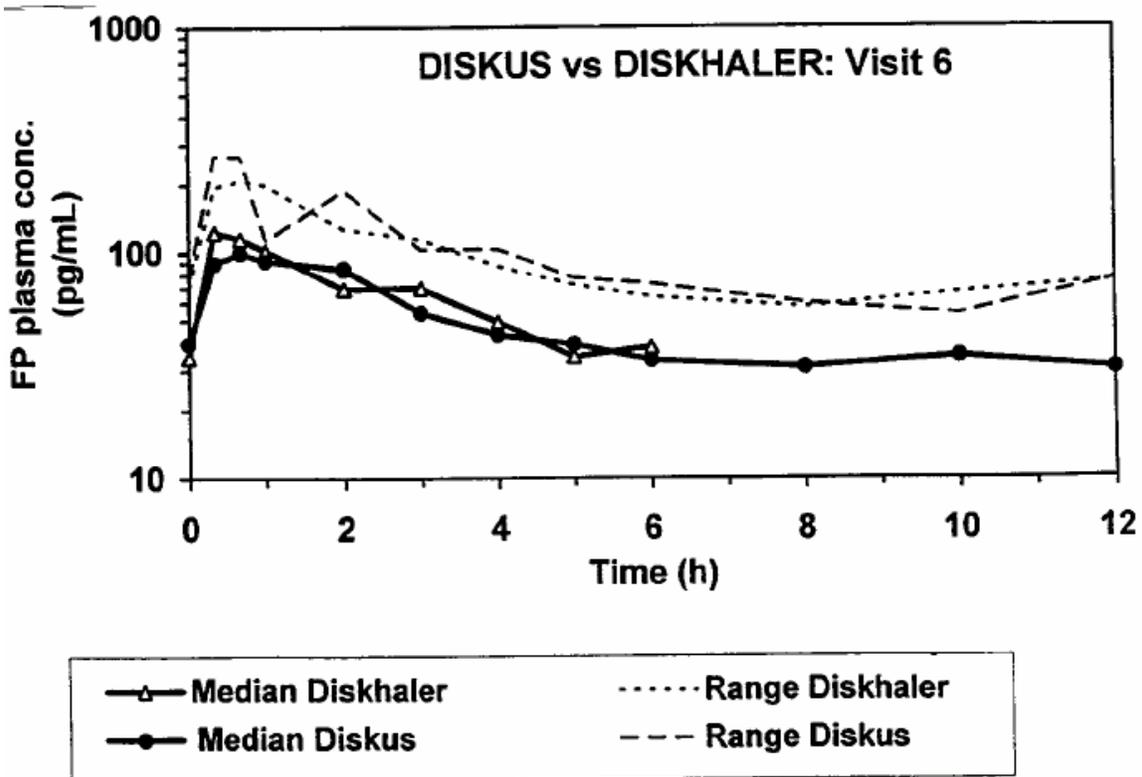
- The FP PK data obtained from Study **SFCB 3019** that was conducted in asthmatic patients (a PK subset of a clinical trial) show that the combination product (**SFC**) had lower (25%) mean AUC and  $C_{max}$  values for FP as compared to those when Sal and FP were given concurrently. Regarding drug interactions for Sal on FP (concurrent vs. FP alone), no major differences were observed since the magnitude of interactions were low.
- The FP PK data obtained from asthmatic patients (**SFCB 3019**) are lower than those obtained from healthy subjects (**SFCB 1002**, **1004**, and **1005**) which is seemingly perceivable due to disease status.
- When given to healthy volunteers as the combination product or given alone to healthy subjects (**SFCB 1004**) FP caused significant decrease in mean 24-hr urinary cortisol excretion but not in mean plasma cortisol levels. However, the above trend was not observed in asthmatic patients. Further, no major differences in patients were observed between baseline and FP when given alone, concurrently with Sal, or as the combination product.
- The Sal PK data obtained from a single-dose study **SFCB 1005** show that the combination product (**SFC**) had significantly higher mean  $C_{max}$  values for Sal as compared to the treatment where Sal was given concurrently with FP (**D** vs. **C**). However, the above data is inconsistent with those obtained from a multiple-dose study **SFCB 1004** (**D** vs. **B**). Furthermore, Study **SFCB 1004** show that Sal may accumulate after multiple dosing to healthy volunteers. However, no plasma Sal levels in asthmatic patients were obtained from study **SFCB 3019** to confirm the accumulation issue. It should be noted that the Sal plasma  $C_{max}$  values obtained were close to assay limits. Therefore, these data should be viewed with caution.
- No major differences were observed in PD between combination product (**D**) and individual component of Sal (**B**).

On 03/30/98, the sponsor submitted NDA 20-833 to support the approval of Flovent Diskus in adults and children 4 years and older. Submitted under NDA 20-833, were 6 human PK/Bio study reports. Three were pivotal and the other 3 were supportive. Two pivotal PK studies were parts of the clinical trials which tested Flovent Diskus, **1**) in adult patients employing 500  $\mu$ g BID as compared to Flovent Diskhaler 500  $\mu$ g BID and placebo (No. **FLTA2001**) and **2**) in pediatric patients employing 50 and 100  $\mu$ g BID as compared to Flovent Diskhaler 50 and 100  $\mu$ g BID and placebo (No. **FLTA2006**). The third pivotal one is a single-dose, drug-drug interaction study comparing Flovent Diskus 500  $\mu$ g with salmeterol/FP (250/500) and placebo in 12 healthy adults (No. **SFCB1002**).

Study No. **FLTA2001** was a randomized, placebo-controlled, parallel, double-dummy double-blind clinical trial in 213 adolescent and adult (M+F) patients with asthma (12-76 years old). The PK of FP 2x 250  $\mu$ g BID via the Diskus and Diskhaler for 84 days were compared. All patients had plasma levels of FP measured at 0, 20, and 40

min from Days, 1, 7, 28, and 84 post morning dosing. Complete 12-hr plasma profiles of FP were obtained from 41 patients (a subset of 3 clinical sites) at pre-dose, 20 min, 40 min, and 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr post dosing and for cortisol as well on Days 1, 7, and 28 for calculating PK and PD data/parameters. Patients co-administered with terfenadine in this clinical trial (7 in placebo group, 4 in Diskus group, and 6 in Diskhaler group) were also analyzed for D-D interaction. An RIA method (Report No. 2685-119) was used for plasma FP determination. The limit of quantitation (LOQ) was reported to be 0.025 ng/ml.

The PK results from this study are summarized in Figure 1 and Table 4. No statistically significant differences in PK between Diskus and Diskhaler were found.



**Figure 1.** Comparative median plasma FP concentrations over 12 hrs after dosing with the Diskhaler versus the Diskus at Day 28.

**Table 4.** Mean PK parameters of FP in adult patients following administration of FP from the Flovent Diskus and the Rotadisk via Diskhaler.

<b>PK Parameters<sup>a</sup></b>	<b>DISKUS (6M+5F)</b>	<b>DISKHALER (10M+4F)</b>
<b>C<sub>max</sub> Range (ng/ml)</b>	(BQL, 0.266)	(0.058, 0.208)
<b>C<sub>max</sub> Median (ng/ml)</b>	0.104	0.130
<b>Mean (± SD)<sup>b</sup> C<sub>max</sub> (ng/ml)</b>	0.110 ± 0.060	0.130 ± 0.051
<b>Geom. L.S. Mean<sup>c</sup> C<sub>max</sub> (ng/ml)</b>	0.092	0.120
<b>(95% CI)</b>	(0.064, 0.133)	(0.086, 0.166)
<b>Geom. L.S. Mean<sup>c</sup> T<sub>max</sub> (hr)</b>	0.50	0.67
<b>(95% CI)</b>	(0.33, 2.00)	(0.33, 10.00)
<b>Geom. L.S. Mean<sup>c</sup> AUC<sub>0-last</sub> (ng-hr/ml)</b>	0.474	0.412
<b>(95% CI)</b>	(0.298, 0.756)	(0.272, 0.622)

<sup>a</sup>. Data obtained from Day 28 (Visit 6).

<sup>b</sup>. Arithmetic mean ± standard deviation (SD).

<sup>c</sup>. Geometric least square mean with 95% confidence interval in parenthesis.

Study No. **FLTA2006** was a randomized, placebo-controlled, parallel, double-dummy double-blind clinical trial in pediatric (M+F) patients with asthma (4-11 years old, mean: 8.4). The PK of FP 50 and 100 mcg BID via the Diskus and Diskhaler for 84 days were compared. Plasma FP levels were measured at 20 and 40 min in a subgroup of patients on Day 84 (Visit 10 at 12<sup>th</sup> week) post morning dosing. Urine was also collected for a 24-hr period twice during the study, at baseline and prior to or on the Visit 10. An RIA method was used for plasma FP determination.

The mean plasma C<sub>max</sub> values of FP obtained from this study are summarized in the Table below:

**Table 5.** PK and PD parameters of FP in pediatric patients following administration of FP from the Flovent Diskus and the Rotadisk via Diskhaler

Flovent Device	Diskus		Diskhaler	
Dosing Regimen	50 µg BID	100 µg BID	50 µg BID	100 µg BID
No. of Subjects <sup>a</sup>	31 (18M+13F)	30 (24M+6F)	37 (20M+17F)	26 (17M+9F)
C <sub>max</sub> Range (ng/ml)	BQL, 0.088	BQL, 0.053	BQL, 0.062	BQL, 0.075
Median C <sub>max</sub> (ng/ml)	BQL	BQL	BQL	0.034
Arithmetic Mean <sup>b</sup> C <sub>max</sub> (ng/ml)	0.005 (0.017)	0.008 <sup>c</sup> (0.016)	0.013 (0.022)	0.030 <sup>c</sup> (0.029)
% of Samples Being BQL <sup>d</sup>	87%	80%	70%	42%
Urinary Cortisol <sup>e,f</sup> (mg/24 hr)	8.7 (n=61)	8.4 (n=57)	8.4 (n=63)	7.7 (n=47)
% Change <sup>f,g</sup> from baseline	+9.6% (n=60)	+0.9% (n=55)	-11.9% (n=57)	-22.1% (n=45)

a. No. of subjects who had evaluable PK data.

b. Mean ± SD.

c. Statistically significant (p=0.001)

d. Below the quantitation limit (BQL: 0.025 ng/ml)

e. Geometric LS mean (placebo: 7.8 mg/24 hr; n=35)

f. Obtained from all available patients after treatment for 84 days.

In general, the following conclusions were made by the CPB reviewer of this NDA at that time:

- Study No. **FLTA2001** showed no significant differences in systemic exposure (FP PK) and plasma cortisol AUC<sub>0-12</sub> data (FP PD) as well for 500 mcg BID given via Flovent Diskhaler and Diskus to adults patients.
- For pediatric patients who participated in the PK study No. **FLTA 2006**, > 80% of plasma samples obtained from both 50 and 100 mcg BID dose groups were below the limit of quantitation (0.025 ng/ml). Therefore, the above pediatric PK study provided very limited information on the systemic exposure of FP using Flovent Diskus.
- Pediatric patients in the Diskus 100 µg BID group had a mean C<sub>max</sub> value significantly lower than that in the Diskhaler 100 µg BID group, but no significant difference was noted in the two lower-dose groups. Although the % changes in 24-hr urinary cortisol excretion were not significantly different from placebo group for both Diskus and Diskhaler groups, the lower changes found in Diskus groups as compared to Diskhaler groups were seemingly consistent with the PK findings, a trend towards less cortisol suppression in the Diskus group.

In September 1996 NDA 20,770 was submitted to support the approval of Rotadisk via Diskhaler in children 4 to 11 years of age. Normally this would be a supplemental NDA, but the original NDA for this product (NDA 20-549) had not been approved at that time. NDA 20-770 contained one PK study in pediatric children ages 4-11 years of age. This study was a randomized, double blind, placebo-controlled, parallel group study in patients 4 to 11 years of age with mild to moderate, stable asthma. Two

doses of FP (50 – and 100 mcg BID) and a placebo were studied. From this study a subset of patients had measurements for plasma FP performed at 20 and 40 min after dosing at one study visit. Most of the plasma concentrations for the 50 mcg dose group were below the level of quantitation (BLQ) of the assay. The PK results from this study are summarized in the Table below:

**Table 6.** Median (range) maximum plasma concentrations of FP in pediatric patients following administration of FP from the Rotadisk via Diskhaler

	Pediatric data		Adult data
	50 mcg BID	100 mcg BID	100 mcg BID*
N	16	13	8
Age (y)	8 (4-11)	8 (6-10)	31 (23-56)
Cmax (pg/mL)	BLQ (BLQ-117)	58.7 (28.1-154)	39.5 (BLQ-73.1)

\*Data from study FLD-230 (NDA 21-489)

The following comment was made by the CPB reviewer at that time:

- The sampling strategy of this study does not give an accurate estimate of Cmax. The Cmax in children appear slightly higher than those in adults. This difference is probably not clinically significant.

#### **This reviewer's comments**

The following tables summarizes the PK findings for FP and SAL in children and adults following administration of Advair Diskus, Rotadisk via Diskhaler and Flovent Diskus.

**Table 6.** Relative systemic exposure (Cmax) of FP from difference devices with respect to Rotadisk device in children and adult subjects.

	Advair Diskus	Rotadisk	Flovent Diskus
Adults	75	100	100
Children 4-11 years	unknown	100	↓ 100
Children/adults	unknown	~↑100	unknown

From the above table one can speculate that since the systemic exposure (Cmax) of FP following administration of Advair Diskus was lower than that after the administration of FP from the Rotadisk or the Flovent Diskus devices, and there was no significant difference between the exposure (Cmax) of FP in children and adults when dosed using the Rotadisk, then most likely the systemic exposure of FP in children from the Advair diskus device will be lower or similar to that from the Rotadisk and Flovent Diskus devices. Therefore, the safety data generated with the Flovent Diskus and Rotadisk may be used to make conclusion regarding the safety profile of FP delivered to children 4 to 11 years of age from the Advair Diskus. It is of importance to mention that these statement may be confirmed when the sponsor sends PK data of FP and SAL in asthmatic children receiving Advair Diskus 100/50 mcg. Meanwhile, this reviewer agrees with the sponsor's proposal for labeling the PK section of Advair Diskus pediatric section:

*Pediatric Patients:* In a clinical study conducted in patients with asthma aged 4 to 11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes after dosing with 50 and 100 mcg of fluticasone propionate inhalation powder twice daily using the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma concentrations at the 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

The above labeling recommendations made by the sponsor is in the approved labeling for Flovent Diskus. This paragraph may be modified appropriately when the Advair Diskus PK data in pediatric children 4 to 11 years of age is submitted by the sponsor and reviewed.

Although the SAL PK data obtained from a single-dose study **SFCB 1005** show that the combination product (**SFC**) had significantly higher mean  $C_{max}$  values for SAL as compared to the treatment where SAL was given concurrently with FP, these data should be viewed with caution since SAL plasma  $C_{max}$  values obtained were close to assay limits. In addition, no major differences were observed in PD between combination product and individual component of SAL. The labeling recommendations in the pediatric section with respect to SAL systemic exposure will be updated when PK data on this drug substance is submitted as promised by the sponsor.

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Sandra Suarez  
1/7/04 12:19:35 PM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
1/7/04 12:37:08 PM  
BIOPHARMACEUTICS  
I concur

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-077/S017**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION**

**Item 13 of sNDA 21-077  
Pursuant to 21 C.F.R. § 314.53  
for  
ADVAIR DISKUS® Inhalation Powder  
for  
Twice Daily Pediatric Administration**

---

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

**Trade Name:** ADVAIR DISKUS®  
**Active Ingredient:** fluticasone propionate/salmeterol xinafoate  
**Strengths:** fluticasone propionate 100mcg/salmeterol xinafoate 50mcg  
**Dosage Form:** inhalation powder  
**Route of Administration:** oral inhalation

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Please list the following patents in the U.S. Department of Health and Human Services "Orange Book" of Approved Drug Products.

	<b>US Patent Number</b>	<b>Expiration Date</b>	<b>Form of Patent Claims</b>
1	4,335,121	14 November, 2003	Drug Substance Drug Product
2	4,992,474	12 February, 2008	Drug Substance Drug Product Method of Use
3	5,126,375	12 February, 2008	Drug Substance Drug Product
4	5,225,445	12 February, 2008	Method of Use
5	5,270,305	7 September, 2010	Drug Product Method of Use
6	5,290,815	1 March, 2011	Method of Use

The undersigned declares the following:

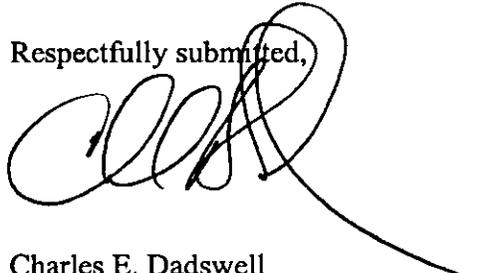
- 1) All of the above patents are owned by Glaxo Group Limited.
- 2) The United States Agent for Glaxo Group Limited is SmithKline Beecham Corporation doing business in the United States as GlaxoSmithKline.

- 3) The above Patents (4,335,121; 4,992,474; 5,126,375, 5,225,445, 5,270,305 and 5,290,815) are required to be the subject of a submission of information pursuant to 21 C.F.R. §314.53(b).
- 4) The above Patents (4,335,121; 4,992,474; 5,126,375, 5,225,445, 5,270,305 and 5,290,815) cover the Drug Substance, Drug Product and/or Method of Use of ADVAIR DISKUS®.

Please address all communications regarding the patent property of this sNDA to:

David J. Levy  
Vice President, Intellectual Property Counsel  
GlaxoSmithKline  
Corporate Intellectual Property Department  
Five Moore Drive  
Research Triangle Park, NC 27709  
919/483-2723

Respectfully submitted,



Date: 9 June, 2003

Charles E. Dadswell  
Vice President, US Intellectual Property  
GlaxoSmithKline  
Registered Patent Attorney  
Registration No. 35,851  
919/483-6983

Trade Name Advair Diskus

Generic Name fluticasone propionate and salmeterol xinafoate inhalation powder

Applicant Name GlaxoSmithKline (GSK)

HFD- 570

Approval Date April 21, 2004

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/\_\_\_/ NO /\_X\_/

b) Is it an effectiveness supplement? YES /\_X\_/ NO /\_\_\_/

If yes, what type(SE1, SE2, etc.)? SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /\_X\_/ NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X\_\_\_/ NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /\_X\_\_\_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_X\_\_\_/ NO /\_\_\_/

If yes, NDA # 21-077 Drug Name Advair Diskus

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_X\_\_\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_X\_/ NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_X\_/ NO  
/\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_X\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_X\_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_X\_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # SAS 30031

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_ \_/ NO /\_X\_/

Investigation #2 YES /\_\_\_/ NO /\_\_\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_X\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # SAS 30031

Investigation # 2 , Study #

Investigation # 3 , Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
IND # 57,151 \_\_\_\_\_ YES /\_X\_/ ! NO /\_\_\_/ Explain:  
!  
!  
!  
!

Investigation #2 !  
!  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain:  
!  
!  
!  
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
!  
\_\_\_\_\_  
!  
\_\_\_\_\_  
!  
\_\_\_\_\_

Investigation #2 !  
!  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
!  
\_\_\_\_\_  
!  
\_\_\_\_\_  
!  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/                      NO /\_X\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Ladan Jafari

Signature of Preparer

Date 4-23-04

Title: Regulatory Project Manager

Signature of Office or Division Director Badrul Chowdhury, M.D.,  
Ph.D.                      Date 4-23-04

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-610/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

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Badrul Chowdhury  
4/23/04 01:10:11 PM

**Marketing Exclusivity**

**NDA 21-077**

**Fluticasone Propionate/Salmeterol Inhalation Powder  
Request for Marketing Exclusivity**

Pursuant to Section 505(c)(3)(D)(iii) and 505(j)(5)(D)(iii) of the Federal Food, Drug, and Cosmetic Act and Section 314.108(b)(5) of Title 21 of the Code of Federal Regulations, GlaxoSmithKline requests three years of exclusivity from the date of approval of fluticasone propionate/salmeterol inhalation powder 100/50mcg for the long-term, twice daily maintenance of asthma in patients 4 to 11 years of age.

GlaxoSmithKline is entitled to such exclusivity as this application contain a report of a new clinical investigation (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by GlaxoSmithKline. The following investigation is "essential to the approval of the application" in that the application could not be approved by FDA without the following investigation:

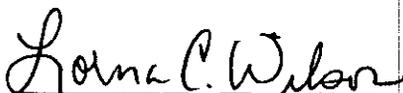
**Use of fluticasone propionate/salmeterol inhalation powder 100/50 mcg BID in children with asthma 4 – 11 years of age:**

**SAS30031: A Randomized, Double-Blind, 12-Week Trial Evaluating the Safety of the Fluticasone Propionate/Salmeterol DISKUS<sup>†</sup> Combination Product 100/50mcg BID Versus Fluticasone Propionate DISKUS 100mcg BID in Symptomatic Pediatric Subjects (4-11 Years) With Asthma**

To the best of GlaxoSmithKline's knowledge, and based on a thorough literature search, there are no other published studies or publicly available reports that are relevant to the proposed formulations or conditions of use.

To the best of GlaxoSmithKline's knowledge, the above-referenced clinical investigation is "new" in that it has not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and does not duplicate the results of such investigations.

The above-referenced clinical investigations were "conducted or sponsored by GlaxoSmithKline" in that GlaxoSmithKline was the sponsor of the U.S. investigational new drug application (IND 50,703) under which this study were conducted.



Lorna C. Wilson  
Director, Regulatory Affairs

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA # : 21-077 Supplement Type (e.g. SE5): SE-5 Supplement Number: 017

Stamp Date: June 26, 2003 Action Date: April 21, 2004

HFD-570 Trade and generic names/dosage form: Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder)

Applicant: GlaxoSmithKline (GSK) Therapeutic Class: Respiratory

Indication(s) previously approved: Asthma, and Chronic obstructive pulmonary disease associated with chronic bronchitis

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: Asthma

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

xNo: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 0 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. (b) (4) Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Inappropriate for asthma subjects <4.

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. >4 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 11 Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-077  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 12-22-03)

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2: obstructive pulmonary disease associated with chronic bronchitis**

Is there a full waiver for this indication (check one)?

**Yes: Please proceed to Section A.**

**No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed**

**NOTE: More than one may apply**

**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

**Products in this class for this indication have been studied/labeled for pediatric population**

**Disease/condition does not exist in children**

**Too few children with disease to study**

**There are safety concerns**

**Other:**

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

**Products in this class for this indication have been studied/labeled for pediatric population**

**Disease/condition does not exist in children**

**Too few children with disease to study**

**There are safety concerns**

**Adult studies ready for approval**

**Formulation needed**

**Other: \_\_\_\_\_**

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-077  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 10-14-03)

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/s/

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Ladan Jafari  
4/23/04 12:17:40 PM

Ladan Jafari  
4/23/04 12:17:40 PM

NDA 21-077 Advair Diskus  
(fluticasone propionate/salmeterol inhalation powder)

Supplemental New Drug Application:  
Labeling Revision for a Pediatric BID Indication

DEBARMENT CERTIFICATION

GlaxoSmithKline hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



\_\_\_\_\_  
Charles E. Mueller  
Director, North America Clinical Compliance  
Worldwide Regulatory Compliance

*22 APR 2007*

\_\_\_\_\_  
Date



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: March 24, 2004**

<b>To:</b> Lorna Wilson	<b>From:</b> Ladan Jafari
<b>Company:</b> GSK	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 919-483-5121	<b>Phone number:</b> 301-827-1084
<b>Subject:</b> NDA 21-077/S-017	

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**Total no. of pages including cover:** 47

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**Comments:** Labeling comments

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**Document to be mailed:** YES  NO

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NDA 21-077/S-017

Dear Ms. Wilson:

Please refer to your submission dated June 26, 2003, for Advair Diskus. We have completed the review of the labeling associated with this submission and have marked our comments on the attached document. Submit revised draft labeling reflecting these revisions. Please note that I have also scheduled a telecon for March 29, 2004, at 2:00 PM to discuss any questions or comments.

If you have any questions, I may be reached at 301-827-1084.

---

Ladan Jafari, Regulatory Project Manager

45 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

NDA 21-077/S-017

Initialed by: Barnes/3-24-04

Filename: N21077S17 label negotiations.doc

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CSO

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Badrul Chowdhury  
1/7/04 12:54:13 PM



NDA 21-077/S-017

GlaxoSmithKline  
P. O. Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Attention: Lorna C. Wilson  
Director, Regulatory Affairs

Dear Ms. Wilson:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Advair Diskus

NDA Number: 21-077

Supplement number: 017

Review Priority Classification: Standard (S)

Date of supplement: June 26, 2003

Date of receipt: June 27, 2003

This supplemental application provides for the use of Advair Diskus in children ages 4 through 11 years.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:  
Center for Drug Evaluation and Research  
Division of Pulmonary & Allergy Drug Products, HFD-570  
Attention: Document Room 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any question, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary & Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Ladan Jafari  
8/22/03 03:19:09 PM  
Signed for Sandy Barnes.



**NO FILING ISSUES IDENTIFIED**

NDA 21-077/S-017

GlaxoSmithKline  
P. O. Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Attention: Lorna C. Wilson  
Director, Regulatory Affairs

Dear Ms. Wilson:

Please refer to your June 26, 2003, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) 100/50 mcg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on August 26, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Badrul Chowdhury  
8/22/03 04:42:36 PM



Is the application affected by the Application Integrity Policy (AIP)? YES X NO  
 If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? X YES NO

• Was form 356h included with an authorized signature? X YES NO

**If foreign applicant, both the applicant and the U.S. agent must sign.**

• Submission complete as required under 21 CFR 314.50? X YES NO

If no, explain:

• If an electronic NDA, does it follow the Guidance? N/A X YES NO

**If an electronic NDA, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

• If in Common Technical Document format, does it follow the guidance? X N/A YES NO

• Is it an electronic CTD? N/A YES X NO

**If an electronic CTD, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information included with authorized signature? X YES NO

• Exclusivity requested? X YES, 3 years NO

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? X YES NO

**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification must have correct wording, e.g.: “I, the undersigned, hereby certify that \_\_\_\_\_ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix \_\_\_\_.” Applicant may not use wording such as “To the best of my knowledge . . . .”

• Financial Disclosure information included with authorized signature? X YES NO  
**(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)**

• Field Copy Certification (that it is a true copy of the CMC technical section)? X YES NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? X YES NO  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.  
 yes
- List referenced IND numbers: IND (b)(4) 50, 703, (b)(4) NDA 20, 121, (b)(4), 20-770, 21-433, 20-236, , 21-254, 20-833, 20-692, 21-077
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ X NO  
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) April 26, 2001 NO  
 If yes, distribute minutes before filing meeting.

**Project Management**

- Package insert consulted to DDMAC? YES X NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES X NO
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A YES X NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES X NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? N/A YES X NO
- Has DOTCDP been notified of the OTC switch application? YES X NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES N/A NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? X YES NO  
 If no, did applicant submit a complete environmental assessment? YES NO  
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES X NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? YES X NO

**If 505(b)(2) application, complete the following section: N/A**

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

\_\_\_ 21 CFR 314.50(i)(1)(ii): No relevant patents.

\_\_\_ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

\_\_\_\_ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

\_\_\_\_ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
 

	YES	NO
--	-----	----
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
 

	YES	NO
--	-----	----
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
 

	N/A	YES	NO
--	-----	-----	----
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
 

	N/A	YES	NO
--	-----	-----	----
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
 

	YES	NO
--	-----	----
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
 

	YES	NO
--	-----	----
  - EITHER  
 The number of the applicant's IND under which the studies essential to approval were conducted.
 

	YES, IND # _____	NO
--	------------------	----

 OR  
 A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?
 

	N/A	YES	NO
--	-----	-----	----
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?
 

	YES	NO
--	-----	----

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 8-6-03

**BACKGROUND:**

(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

Advair Diskus is approved for use in patients 12 years and above with asthma. GSK is now seeking approval in children ages 4 through 11.

**ATTENDEES:**

Marianne Mann, Lydia Gilbert-McClain, Carol Bosken, Lawrence Sancilio, Joe Sun, James Gebert, Sandra Suarez, Ladan Jafari

**ASSIGNED REVIEWERS:**

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Carol Bosken
Secondary Medical:	Lydia Gilbert-McClain
Statistical:	James Gebert
Pharmacology:	Lawrence Sancilio
Statistical Pharmacology:	
Chemist:	Craig Bertha
Environmental Assessment (if needed):	No
Biopharmaceutical:	Sandra Suarez
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	
DSI:	None needed
Regulatory Project Manager:	Ladan Jafari
Other Consults:	None

Per reviewers, are all parts in English or English translation? X    YES    NO  
 If no, explain:

CLINICAL FILE   X   REFUSE TO FILE \_\_\_\_\_

- Clinical site inspection needed: YES    X    NO
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ X    NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

	X	N/A	YES	NO
CLINICAL MICROBIOLOGY	FILE _____	REFUSE TO FILE _____	X	N/A
STATISTICS	FILE <u>  X  </u>	REFUSE TO FILE _____		
BIOPHARMACEUTICS	FILE <u>  X  </u>	REFUSE TO FILE _____		
• Biopharm. inspection needed:			YES	X
PHARMACOLOGY	FILE <u>  X  </u>	REFUSE TO FILE _____		
• GLP inspection needed:			YES	X
CHEMISTRY	FILE <u>  X  </u>	REFUSE TO FILE _____		
• Establishment(s) ready for inspection?	None needed		YES	NO
• Microbiology			YES	NO

ELECTRONIC SUBMISSION:  
Any comments:None

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

- \_\_\_\_\_ The application is unsuitable for filing. Explain why:
- X   The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- X   No filing issues have been identified.
- \_\_\_\_\_ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

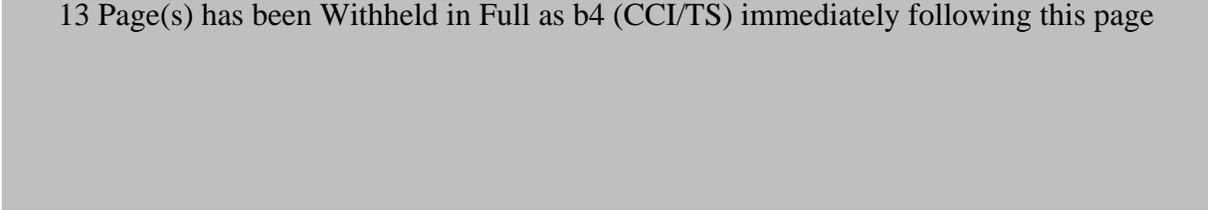
  Ladan Jafari    
Regulatory Project Manager, HFD-570

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this page is the manifestation of the electronic signature.**  
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/s/

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Ladan Jafari  
8/20/03 09:47:17 AM  
CSO

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 28, 2002

<b>To:</b> Lorna Wilson/Robert Bohinsky	<b>From:</b> Ladan Jafari
<b>Company:</b> GSK	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 919-483-5121	<b>Phone number:</b> 301-827-1084
<b>Subject:</b> NDA 21-077 & 21-254	

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:**       YES       NO

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NDA 21-254  
NDA 21-077

We completed the review of your submission dated April 25, 2002, containing comments regarding the meeting minutes of February 19, 2002, and we have the following comments.

1. This pertains to question 1 of your submission. The Division notes that clinical trials (b) (4) and SAS30021 were submitted to the Agency in October 2001. The Division also notes that neither of these two trials was reviewed or otherwise interpreted as (b) (4). Indeed, the meeting package submitted 19 November 2001 (p.87, item #1) states that (b) (4) referring to GSK's sNDA submitted October 26, 2001, in (b) (4).

It is the Division's position that to amend the approved meeting minutes in the manner proposed by GSK would be inconsistent with the Division's stated position at the time of meeting on the acceptability of the trials (b) (4). If you intend for these studies to be supportive of such a claim, you must submit an amendment(s) to the application clarifying the objectives and analytical plan of the two protocols.

2. This pertains to question 2 of your submission. Your position is noted. We will expect this submission.
3. This pertains to question 3 of your submission. Your position is noted. The Division is in agreement with GSK's description of the pediatric study endpoints and patient inclusion criterion stated in this response. We believe that the Agency's official minutes are reflective of both these points. This document will be used as an addendum to the meeting minutes to clarify this point.
4. This pertains to question 5 of your submission. Your position is noted. The Division reviewed (b) (4) as submitted in your November 19, 2001, meeting package. The Division had no specific comment on the necessity for or adequacy of washout periods for this protocol. As noted in the meeting minutes, the design of the protocol as reviewed is unlikely to provide an adequate link for the two Advair formulations in children. If you intend to amend the protocol, this should be submitted to the application and the Division will provide comments accordingly.
5. This pertains to the additional comment regarding studies SAS30021 and SAS30022. While we do not recall reaching any agreement that "PK would best be characterized in twice-daily studies, given the low plasma levels expected with once daily dosing," this approach is reasonable. If you intend to amend the protocol accordingly, the amendment should be submitted to the application and the Division may provide comments if so requested.

NDA 21-254  
NDA 21-077  
Page 2

If you have any questions, you may contact me at (301) 827-1084.

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Ladan Jafari, Regulatory Project Manager

NDA 21-254  
NDA 21-077  
Page 3

Initialed by: Purucker/5-24-02  
Fadiran/5-24-02  
Meyer/5-24-02

Filename: GSK mtgmin addendum

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this page is the manifestation of the electronic signature.**  
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/s/

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Ladan Jafari  
5/28/02 08:54:30 AM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 25, 2002

<b>To:</b> Ms. Lorna Wilson	<b>From:</b> Ladan Jafari
<b>Company:</b> GSK	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 919-483-5121	<b>Phone number:</b> 301-827-1084
<b>Subject:</b> Clinical comments for Advair Pediatric program	

**Total no. of pages including cover:** 2

**Comments:**

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**Document to be mailed:**      • YES                       NO

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NDA 21-254  
NDA 21-077

We completed the review of your submission dated March 14, 2002, which contained a list of questions and a request for a telecon to discuss these questions. These questions were generated based upon our meeting of February 19, 2002.

The following are the responses to the questions contained in your submission.

1. The Division agrees that the proposed 200-patient pediatric safety study SAS30031 includes an appropriate number of patients per treatment arm.
2. The proposed population PK analysis plan is acceptable.
3. We strongly recommend that the complete NDA package include the final study report from the newly proposed 200-patient study. While the NDA may still be filable without this study, any information submitted after the original filing may not be reviewed during the initial review given competing workloads.

If you have any questions, please contact me at 301-827-1084.

---

Ladan Jafari, Regulatory Project Manager

NDA 21-254  
NDA 21-077  
Page 2

Initialed by: Barnes/3-21-02  
Purucker/3-21-02  
Mann/3-21-02  
Suarez/3-25-02  
Fadiran/3-25-02

Filename: Advairpedscomments

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/s/

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Ladan Jafari  
3/25/02 11:02:53 AM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 19, 2002

<b>To:</b> Ms. Lorna Wilson	<b>From:</b> <b>Ladan Jafari</b>
<b>Company:</b> GSK	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 919-315-0033	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 919-483-5121	<b>Phone number:</b> 301-827-1084

**Subject:** Meeting minutes of February 19, 2002

**Total no. of pages including cover:** 10

**Comments:**

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**Document to be mailed:**      • YES                       NO

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NDA 21-254 Advair HFA  
NDA 21-077 Advair Diskus  
Sponsor: GlaxoSmithKline  
Meeting Date: February 19, 2002  
IMTS: 8077

Page 1

**GlaxoSmithKline (GSK) Representatives:**

Chai-Ni Chang, Ph.D., Senior Statistician  
Paul Dorinsky, M.D., Sr. Director, Clinical Development Medical Affairs  
Karen House, Director, Clinical Development Medical Affairs  
Elaine Jones, Ph.D., Director, Regulatory Affairs  
Robert L. Kunka, Ph.D., Section Head, Clinical Pharmacology & Discovery Medicine  
Yonghua Wang, Ph.D., Manager, Exploratory & Full Development Statistics  
Lorna Wilson, Director, Regulatory Affairs

**Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:**

Emmanuel Fadiran, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader  
James Gebert, Ph.D., Biometrics Team Leader  
Lydia Gilbert-McClain, M.D., Clinical Reviewer  
Ladan Jafari, Regulatory Project Manager  
Marianne Mann, M.D., Acting Division Director  
Mary Purucker, M.D., Ph.D., Clinical Team Leader  
Curtis Rosebraugh, M.D., Clinical Reviewer

**Background:** GSK submitted a meeting request dated November 19, 2001, to discuss the clinical program of Advair Diskus and Advair HFA in the pediatric population. This submission included a list of questions to be discussed at the meeting. GSK also submitted a second document dated February 11, 2002, which contained a presentation outlining the key safety data from three non-US well-controlled clinical studies to be submitted in a pediatric sNDA. The questions raised by GSK are printed in *Italics* below followed by the Division's responses and discussions. Please see Attachment 1 for Drs. Rosebraugh and Fadiran's slides.

**Clinical:**

1. *The fluticasone propionate treatment arms in both once daily studies SAS30021 and SAS30022 will be administered once daily, rather than twice daily as suggested by the Agency on April 26, 2001,* (b) (4)  
(b) (4)
- (b) (4)  
(b) (4)  
The Division warned GSK that to plan further drug development on the basis of a pending review represents a serious drug development risk. The Division agreed with GSK in terms of study design to include a fluticasone propionate only treatment arm. (b) (4)  
(b) (4)
2. *Both the pediatric study SAS30021 and the adolescent/adult study SAS30022 currently include 24-hour measurements of urinary cortisol and creatinine. In order to be consistent with other pediatric studies, increase compliance in obtaining the urinary cortisol measures, and reduce the number of urine collections that are inadequate for analysis, we are proposing to amend the protocols from a 24-hour urine collection to* (b) (4) *urine collection. Does the Agency agree with this change?*
- The Division agreed with the proposal for pediatric study SAS30021, as long as (b) (4)  
(b) (4) However, for the adolescent/adult study SAS30022, we would prefer a 24-hour urine collection.
3. *Given the acceptable extrapolation of efficacy data ADVAIR DISKUS down to age 4, we propose to obtain a pediatric indication for ADVAIR DISKUS 100/50mcg administered twice daily based upon safety data available from three completed non-US studies. Does the Agency agree with this proposal?*
- The Division indicated that we have serious concerns about the adequacy of the pediatric safety database. These concerns are summarized below:
  - a. Only 1 out of 3 trials provides the relevant comparison of Advair to the same nominal dose of fluticasone propionate, because children who are candidates for Advair will be those who are inadequately controlled on inhaled corticosteroids alone.

- b. There are only about 175 children/arm for the fluticasone 100 bid vs. Advair 100/50 bid comparison, and the trial from which this information was extracted had data integrity problems.
  - c. Non-concurrent control data available from the other two trials is not optimal for labeling.
- GSK asked for the Division's guidance in designing a trial that adequately addresses the pediatric program. The Division referred GSK to the growth study guidance document and stated that GSK should design the study in such a way to assess the risk/benefit of fluticasone vs. the combination product in children. GSK indicated that the AEs reported for Advair were no different from those reported for the fluticasone only product. The Division again stated that there were data integrity issues with the clinical trial from which those reports were taken, and therefore, they would not be a very reliable or quantitative source of information. Although GSK may have other data in support of the safety of Advair in the pediatric population, such as from a one-year open-label, uncontrolled clinical trial or information from post-marketing safety databases, these sources would not provide the type of information necessary for labeling purposes. The Division suggested that GSK consider performing a duplicate study, a 12-week pediatric asthma trial with two arms, fluticasone vs. Advair, designed primarily for comparative safety information, which would corroborate the results of the first study.

(b) (4)



The Division stated that GSK could submit their application, but all these questions would remain a review issue. GSK indicated that they were planning to submit their application by end of March or mid April of 2002, but they need to further discuss this internally to see if they should wait until they can further validate their first study or submit the application with the current available data.

4.  (b) (4)  
*(This is question 5 of the briefing package.)*

- The Division agreed with the proposal.

**Clinical Pharmacology & Biopharmaceutics:**

5.

(b) (4)

- The Division stated that GSK should assess the PK of fluticasone propionate and salmeterol xinafoate following administration from the ADVAIR devices in children 4-11 years of age. To do this study, GSK should use the sparse blood sampling technique for PK analysis of the drugs. The number/timing of blood sampling should be optimized using an appropriate model applied to historical adult PK data. The data should be analyzed using a population PK approach.
- The Division stated that GSK could better assess safety by including not only the endpoint value, but also the baseline assessment of the following parameters:
  - a. 24-hour urinary cortisol should be measured before the initiation of every treatment period.
  - b. Heart rate and QTc intervals should be measured before the initiation of every treatment period.
- GSK stated that they have some additional PK data from fluticasone Diskus (b) (4) and 24 hour urine cortisol, and plasma cortisol), but do not have any data for salmeterol that could be applied to Advair. GSK asked if they could do a PD assessment in a parallel study, because some investigators are concerned with the rate of drop-outs when PK measurements are involved. The PD study is easier to initiate.

6.

(b) (4)

•

(b) (4)

- The Division also had the following additional comments for protocols SAS30021 and SAS30022.

**SAS30021:**

Apply the sparse blood sampling technique for PK analysis of the drugs. The number/timing of blood sampling should be optimized using an appropriate model to apply to historical PK adult data. The data should be analyzed using a population PK approach. Use statistical analysis of comparative PK and PD exposure (i.e., 90% confidence level)

**SAS30022:**

Obtain PK measurement for both fluticasone and salmeterol. Use statistical analysis of comparative PK and PD exposure (i.e., 90% confidence limit)

NDA 21-254 Advair HFA  
NDA 21-077 Advair Diskus  
Sponsor: GlaxoSmithKline  
Meeting Date: February 19, 2002  
IMTS: 8077  
Page 6

Attachment 1:

<p><b>Advair Diskus and Advair HFA</b> <b>GlaxoSmithKline</b> NDA 21-077 NDA 21-254</p>
<p>Regulatory Meeting</p> <p>Rockville, Maryland February 19, 2002</p> <p> <b>Center for Drug Evaluation and Research</b></p>

<p> <b>Question #1</b> The fluticasone propionate treatment arms in both once daily studies SAS30021 and SAS30022 will be administered once daily, rather than twice daily as suggested by the Agency in April.</p> <p>(b) (4) (b) (4)</p>
<p><b>Answer:</b></p> <p>As stated in the meeting of April 26, 2001, (b) (4) (b) (4)</p> <p>(b) (4) As such, to plan further drug development on the basis of a pending review represents a serious drug development risk to the sponsor. In terms of study design, the Agency agrees with including a fluticasone propionate only treatment arm.</p> <p>(b) (4) (b) (4)</p> <p>(b) (4) (b) (4)</p>

 **Question #2**

Both the pediatric study SAS30021 and the adolescent/adult study SAS30022 currently include 24-hour measurements of urinary cortisol and creatinine. (b) (4)

**Answer:**

Yes for the pediatric study SAS30021. (b) (4)  
provides internal validation of the comparability of the two different collection periods. For the adolescent/adult study SAS30022, the Agency would prefer a 24-hour urine collection.

 **Question #3**

Given the acceptable extrapolation of efficacy data ADVAIR DISKUS down to age 4, we propose to obtain a pediatric indication for ADVAIR DISKUS 100/50mg administered twice daily based upon safety data available from three completed non-UIS studies. Does the Agency agree with this proposal?

**Answer:**

The Division has serious concerns about the adequacy of the pediatric safety database.

- Only 1 out of 3 trials provides relevant comparison of Advair to fluticasone
- Only ~175 children/arm for FP 100 bid vs. Advair 100/50 bid
- Non-concurrent control data not optimal for labeling

 **Question #5**

 (b) (4)

**Answer:**  
Yes.

 **COMMENTS TO THE DEVELOPMENT PLAN**

**Protocol SAS30021: A Stratified, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 12-Week Trial Evaluating the Safety and Efficacy of the Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg Once Daily Versus Fluticasone Propionate DISKUS 100 mcg Once Daily and Placebo in Symptomatic Pediatric Subjects (4 to 11 Years) With Asthma.**

**Recommendations:**

- *PK measurements for FP and salmeterol.* The sponsor should apply the sparse blood sampling technique for PK analysis of the drugs. The number/timing of blood sampling should be optimized using an appropriate model apply to historical PK adult data. The data should be analyzed using a population PK approach.
- Statistical analysis of comparative PK and PD exposure (i.e. 90% CI)



**Protocol SAS30022: A Randomized, Double-blind, Placebo-controlled Parallel-group, 12-week Trial Evaluating the Efficacy and Safety of the Fluticasone propionate/salmeterol DISKUS Combination Product 250/150mcg Once Daily versus Fluticasone propionate/salmeterol DISKUS Combination Product 100/50mcg Twice Daily versus Fluticasone propionate DISKUS 250 mcg Once Daily versus Placebo in Symptomatic Adolescent and Adult Subjects with Asthma.**

**RECOMMENDATIONS:**

- PK measurements for FP and salmeterol
  
- Statistical analysis of comparative PK and PD exposure (i.e. 90% CI)



The sponsor should consider the following recommendations with respect to the design/endpoints of the protocol:

- It is recommended that the sponsor assess the PK of FP and salmeterol following administration from the ADVAIR devices in children 4-11 years of age. For this purpose, the sponsor should use the sparse blood sampling technique for PK analysis of the drugs. The number/timing of blood sampling should be optimized using an appropriate model applied to historical PK adult data. The data should be analyzed using a population PK approach.
  
- The sponsor should conduct the baseline assessment of the following parameters:
  - 24-hrs urinary cortisol should be measured before the initiation of every period
  - Heart rate and QTc intervals should be measured before the initiation of every period

NDA 21-254 Advair HFA  
NDA 21-077 Advair Diskus  
Sponsor: GlaxoSmithKline  
Meeting Date: February 19, 2002  
IMTS: 8077  
Page 10

Initialed by:      Rosebraugh/3-12-02  
                         Purucker/3-19-02  
                         Fadiran/3-15-02  
                         Mann/3-19-02

Filename: GSKAdvairPeds.doc

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/s/

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Ladan Jafari  
3/19/02 03:17:35 PM

**Memorandum of Telephone Facsimile Correspondence**

Date: May 25, 2001  
To: Elaine Jones, Ph.D.  
Regulatory Affairs  
Fax: (919) 315-0677  
From: Parinda Jani  
Project Manager  
Subject: NDA 21-077 and (b) (4)  
Meeting dated April 26, 2001

Reference is made to the meeting held between representatives of your company and this Division on April 26, 2001. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1064.

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Thank you.

**Meeting Date:** April 26, 2001

**Time:** 11.00 – 12:30 PM

**Location:** Conference Room 10B45

**IMTS #** 6986

**Sponsor:** GlaxoSmithKline.

**NDAs:** 21-077 and 21-254

**Products:** Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder and Inhalation Aerosol

**Type of Meeting:** Pediatric Program

**FDA Attendees:**

Young-Moon Choi, Ph.D.	Clinical Pharmacology/Biopharmaceutics Reviewer
James Gebert, Ph.D.	Biometrics Reviewer
Lydia Gilbert-McClain, M.D.	Medical Officer
Parinda Jani	Project Manager
Robert Meyer, M.D.	Director, DPADP
Mary Purucker, M.D., Ph.D.	Medical Team Leader

**Glaxo Attendees:**

Paul Dorinsky, M.D.	Head, Respiratory Medical Affairs
Shu-Yen Ho, Ph.D.	Associate Director, Biostatistics
Karen House	Program Head, Respiratory Clinical Research
C. Elaine Jones, Ph.D.	Director, Advertising and Labeling Policy
Bob Kunka	Clinical Pharmacokineticist, Clinical Pharmacology
Tushar Shah, M.D.	Director, US Respiratory Clinical Development

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**Background:** See the submissions dated December 4, 2000 and April 5, 2001.

**The following general comments were provided by the Division for the proposed pediatric program for Advair Diskus in children for 4 to 11 years of age.**

The Division stated that to meet the regulatory requirements of the combination drug products, it would be acceptable to extrapolate efficacy data of Advair Diskus given twice daily down to the age of 4 years. However, the proposed pediatric program is for dosing these patients (b) (4)

and therefore efficacy of this dosing regimen cannot be extrapolated to the younger patients. (b) (4) regimen program for Advair Diskus would need a comparison to the same nominal total daily dose of fluticasone propionate (FP) dosed twice daily, either as FP twice daily or as Advair twice daily because (b) (4)

**The following general comments were provided by the Division for (b) (4)**

The Division stated that it is difficult to establish the diagnosis of asthma and to predict the course of the disease in this age group. The efficacy data can not be extrapolated to this age group. The Division has concerns about the non-titratable dose of corticosteroid in this age group and hence the suitability of Advair (b) (4)

(b) (4)  
GSK would need at least two adequate and well-controlled trials. A comparison to the same nominal dose of FP dosed twice daily either as a FP twice daily or Advair twice daily would be required.

The following issues from the submission dated April 5, 2001, were discussed. The industry issues are listed in bold, followed by the response from the Agency.

1. (b) (4)

The Division stated that at least two studies would be required (b) (4)  
Depending on the development path GSK decides to choose, one study in adult and adolescent population, followed by one study in pediatric population may be adequate. If GSK decides to study pediatric population only, two adequate and well-controlled trials in this population would be required.

- (b) (4)

2. **Does the Agency agree to a waiver for studies with Advair Diskus in subjects less than 4 years of age?**

The Division agrees that studies with Advair Diskus in pediatric patients less than 4 years of age would not be required. The Division explained the difference between the term "deferral" and "waiver." The studies for Advair Diskus in subjects less than 4 years would be deferred.

3. **Will the Agency agree that submission of clinical study reports for pediatric use in subjects 4 -11 years of age with Advair Diskus can be deferred until February 2003?**

The Division agrees with the proposed deferral date.

4. **Does the Agency agree that the evidence presented in this package, together with the evidence presented in the package submitted to NDA 21-077 on December 4, 2000,** (b) (4)

The Division stated that even though the submitted evidence presents sufficient rationale (b) (4) will be granted or not is a review issue.

5.

(b) (4)

The Division stated that it might be sufficient, but in case there are differences seen with the morning and evening dosing data, additional data may be required.

6.

(b) (4)

7.

(b) (4)

(b) (4)

GSK stated that it is difficult to conduct efficacy studies in this population and demonstrate superiority because of the variability involved. GSK requested additional guidance so that the requirements of the Pediatric Rule are met, and whether requesting deferral was an option.

The Division stated that deferral could be an option. Additional guidance would be provided after some additional internal discussion.

(b) (4)

(b) (4)

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/s/  
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Parinda Jani  
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