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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-911

Medical Review(s)

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:NDA	20,911	APPLICATION TYPE:	Amendment
SPONSOR:	3M Pharm	PRODUCT/PROPRIETARY NAME:	QVAR
		USAN Established Name:	Beclomethasone dipropionate
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Inhalation aersol
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	12 September 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
29 August 2000	30 August 2000	Labeling amendment	see overview below

Overview of Application/Review: The sponsor has submitted revised labeling for QVAR in response to our FAX of 23 August 2000. Most of the changes made by the sponsor are consistent with our requests with a few exceptions. However, there are some aspects of the labeling that still need clarification and/or modification by the sponsor. These are (see below for further discussion): 1) the statement about onset of effect; 2) the heading in the Clinical Trials section relating to a study of patients responsive to oral corticosteroids; 3) the table on adverse events; and 4) the statement about reduction in 24 hour urinary free cortisol. After checking with Chemistry and Biopharm on the changes relevant to those disciplines: 1) Biopharm does not object to the addition proposed by the sponsor in the PK section but will recommend expansion of the sections on Absorption, Metabolism and Excretion (see Biopharm review); and 2) Chemistry recommends that the two sentences dealing with particle size on lines 37- 43 be deleted (see Chemistry review).

Outstanding Issues: the aspects of the labeling noted above

Recommended Regulatory Action: Approved with labeling changes

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: __x__ Approvable _____ Not Approvable

Signed: Medical Reviewer: /s/ Date: 9/12/2000

Medical Team Leader: _____ Date: 9/13/2000

- Background: On 23 August 2000, a fax was sent to the sponsor by the Division with comments on the labeling for this drug product. In this submission, the sponsor has revised the labeling in response. Comments by this reviewer are noted below, based on the order that the changes appear in tne labeling.

1. lines 6 and 10: Chemistry requested that the strength be added to the name of the drug product. The sponsor has made this change. This is acceptable.

2. Lines 37-43: The sponsor has added some descriptive comments about particle size and has left in the sentence ' ' that we had asked them to delete. After talking with Chemistry, it is recommended that these two sentences (lines 37-43) be deleted (see Chemistry review)

3. Line 67: The change requested by the Division from "bronchial" to "airway" has been made by the sponsor and is, therefore, acceptable.

4. Lines 78-87: The sponsor has deleted the comments about the PK of BDP previously in the labeling and substituted the statement, "Beclomethasone dipropionate undergoes rapid and extensive conversion to beclomethasone-17-monopropionate during absorption. The pharmaocokinetics of beclomethasone-17-monopropionate, the most active metabolite of beclomethasone dipropionate, has been studied in asthmatics given single doses." The second sentence of the new statement by the sponsor, considered from a clinical perspective, does not appear to serve any useful purpose, unless the sponsor provides results from the study. The first sentence is accurate, to the best of this reviewer's knowledge, and is acceptable to Biopharm. On the other hand, Biopharm feels that more information is needed in the sections on Absorption, Metabolism and Excretion (lines 89-102)(see Biopharm review).

5. Lines 104-108: The sponsor has deleted "advanced" before "age" on line 104. This is acceptable. The deletion of the " " information is acceptable since it relies on an insensitive assay.

6. Lines 111 and 353: At the request of the Division, the sponsor has submitted data to support the statement that "Improvement in asthma control following inhalation can occur within 24 hours of beginning treatment, although

maximum benefit may not be achieved for 1 to 2 weeks, or longer." This is acceptable, provided the sponsor adds "in some patients" after "can occur within 24 hours of beginning treatment" since not all patients had a > 12% increase in FEV-1 24 hours after the first dose of QVAR.

7. lines 115-116, 120: the change from daily to twice daily doses, as requested by the Division, is acceptable.

8. Lines 122-127: the additional sentence regarding reduction in 24 hour urinary free cortisol, requested by the Division, has been added by the sponsor, and therefore is acceptable.

9. Lines 146-150: the comment in parentheses regarding [redacted] has been deleted by the sponsor, as requested by the Division and is, therefore, acceptable.

10. Line 160: the change in dosage from daily to twice daily is acceptable.

11. Line 169: the legend in the figure has been changed to express doses in terms of twice daily and is, therefore, acceptable.

12. Lines 172-173, 176-177: the change from '[redacted]' to "comparable" improvement is acceptable as requested by the Division.

13. Line 180: the Division stated that the heading on page 5 that read [redacted] was inconsistent with the first sentence under the heading which stated that patients were treated "in some cases" with inhaled corticosteroids. The sponsor has not changed the first sentence but has changed the heading to read, [redacted] This is still unacceptable for two reasons: first, the heading to be accurate should be changed to "responsive to a short course of oral corticosteroids"; and second, the second paragraph and the second figure under this section deal with a different study where oral corticosteroid responsiveness was not a factor. A separate heading for the second paragraph could be added, entitled, "Patients previously on inhaled corticosteroids".

14. Line 190: [redacted] has been changed to "comparable" as requested by the Division and is, therefore, acceptable.

15. line 196: the legend in the figure has been changed to express doses in terms of twice daily and is, therefore, acceptable.

16. Lines 201-202: adjustment from daily doses to twice daily doses requested by the Division is acceptable.

17. Lines 205-210: the sentence dealing with [redacted] was deleted, as requested by the Division, and is, therefore, acceptable.

18. Line 216: the legend in the figure has been changed to express doses in terms of twice daily and is, therefore, acceptable.

19. Lines 220, 222: the sponsor has added "oral" before "corticosteroids" and substituted "oral" for "systemic" as requested by the Division and this change is, therefore, acceptable.

20. Line 291: the sponsor has changed "fast" to "short" as a qualifier of bronchodilator use as requested by the Division and this change is, therefore, acceptable.

21. Lines 304-308: the changes requested by the Division in regard to the effect of QVAR on adrenal cortisol production and the clinical relevance of this finding were made by the sponsor and therefore are acceptable.

22. Line 322: the changes requested by the Division in regard to effect on growth in children was made by the sponsor and therefore are acceptable.

23. Line 329: the change requested by the Division from "subjects" to "humans" was made and is, therefore, acceptable.

24. Lines 365-366: the change requested by the Division relating to different taste with QVAR and the inhaler containing the CFC propellant was made by the sponsor and is, therefore, acceptable.

25. Lines 411-418: as requested by the Division, a Geriatrics Use subsection was added by the sponsor, is consistent with the regulations and is, therefore, acceptable.

26. Line 430: the heading of the table has been revised with the addition of the word "Daily" as requested by the Division and is, therefore, acceptable.

27. Line 431-433: The sponsor has revised the table on adverse events to indicate that the doses given were daily doses and has indicated which of these adverse events occurred significantly more frequently in the QVAR group than in the placebo group. The sponsor should remove reference to statistically significant differences from placebo since the study was not designed to demonstrate such differences.

28. Lines 449-456: The sponsor has revised the first sentence under Dosage and Administration relating to priming, consistent with the Division's request and this is, therefore, acceptable.

29. Line 463: the sponsor has changed the time expected for maximum benefit from 1-2 weeks to 3-4 weeks. This change is consistent with the data and is, therefore, acceptable.

30. Line 477-480: The sponsor has deleted the sentence, [redacted] but has added the sentence, [redacted] This sentence added by the sponsor should be deleted, since it implies [redacted]

31. Line 492-495: The sponsor has deleted the statement about [redacted] from this place in the labeling as requested by the Division. This is, therefore, an acceptable modification of the labeling.

32. Line 508: "dependent on" has been removed as requested by the Division and this change is, therefore, acceptable.

33. Lines 539, 545: "oral" has been removed as requested by the Division, and this change is, therefore, acceptable.

34. Lines 541, 542, 647, 548: The sponsor has added actual NDC numbers. This is acceptable.

35. Lines 555-557, 644-646: The sponsor has added, at the request of Chemistry, information on the appropriate storage position of QVAR. This is an acceptable addition to the labeling.

36. Lines 562-563: "Actuator" has been substituted for "mouthpiece" as requested by the Division, and is, therefore, acceptable.

37. Line 606: The sponsor has changed the wording to "You should rinse your mouth with water after treatment" as requested by the Division. This modification is, therefore, acceptable.

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:NDA	20.911	APPLICATION TYPE:	Amendment
SPONSOR:	3M Pharmaceuticals	PRODUCT/PROPRIETARY NAME:	QVAR
		USAN Established Name:	Beclomethasone diproprionate HFA
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	MDI (solution)
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	11 February 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
17 August 1999	18 August 1999	Response to approvable letter	see overview below

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
None	None	None

Overview of Application/Review: The sponsor has submitted a response to comments in our approvable letter of 12 May 1999. Specifically, the sponsor has responded to our comments that: 1) comparability between QVAR and BDP-CFC had not been demonstrated to a degree that was sufficient to allow labeling for the dose of QVAR that should be prescribed for patients who had been receiving BDP-CFC; 2) comparability of the 40 and 80 mcg/actuation strengths had not been demonstrated and there was insufficient data to support labeling for use of the 80 mcg/actuation strength; and 3)

The labeling proposed by the sponsor to allow health care providers to switch patients from BDP-CFC to QVAR is acceptable with proposed revisions. Although the sponsor has not submitted any new clinical data to support approvability of the 80 mcg/actuation strength, review of all the PK data that is available comparing the 40 and 80 mcg/actuation strengths may be sufficient for this claim. The sponsor has not provided any new data that would support a labeling claim
QVAR, specifically, although class labeling for this effect is acceptable. The sponsor will need to delete the since QVAR was not evaluated in

Outstanding Issues: The sponsor needs to revise the proposed labeling as recommended.

Recommended Regulatory Action: Notify the sponsor of the proposed revision of their proposed labeling and that there is insufficient data to support approvability of the 80 mcg/actuation strength

N drive location:n:\QVAR4

NDAs:

Efficacy / Label Supp.: _____ Approvable ___x___ Not Approvable

Signed: Medical Reviewer: [signature] Date: 2/14/2000

Medical Team Leader: _____ Date: 2/15/2000

(See secondary review / TL Memo dated 2/15/2000)

2. QVAR is a solution with smaller mean particle size than BDP-CFC. Lung deposition of QVAR is ten times that of BDP-CFC. Therefore, QVAR can not be considered comparable to BDP-CFC on a 1:1 basis. It is important, therefore, to provide the health care provider with information about the comparative efficacy and safety of QVAR and BDP-CFC.

3. It is not reasonable to expect a specific consistent comparative ratio across measurements derived from biological systems that are known to vary independently to some degree. A specific computer program (RATIO) was developed to allow for correlation between deposition, distribution, and different spirometric measurements.

REVIEWER'S COMMENTS:

1. In regard to the sponsor's proposed labeling, the first sentence is correct and helpful for the health care provider. The second sentence is obvious and unnecessary and, therefore, should be deleted. The data suggests that QVAR should be initiated at approximately ½ the dose of BDP-CFC and therefore the third sentence is acceptable, but should be changed and an additional sentence added as follows; "QVAR should be initiated at approximately half the dose of BDP-CFC, recognizing that a consistent comparative ratio between QVAR and BDP-CFC was not achieved. As a result, any patient switched from BDP-CFC to QVAR must be monitored closely to determine if the dose selected for QVAR is efficacious and safe". The fourth sentence is acceptable and consistent with current recommendations.

2. It is agreed that QVAR is not [redacted], but unfortunately that can not be done because a consistent relationship between QVAR and BDP-CFC was not demonstrated.

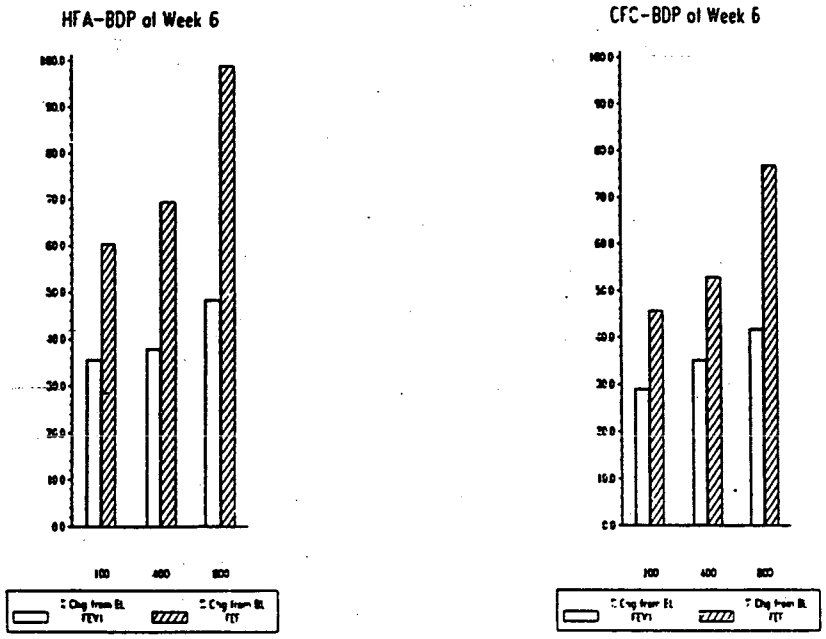
3. It is agreed that comparability between QVAR and BDP-CFC may vary depending on outcome measures (the computer program RATIO is not needed to convince the Division of this), but this does not help in the labeling to define a dose of QVAR that should be used as replacement for BDP-CFC. In addition, the lung deposition data once obtained can not be ignored, simply because it might not be expected to correlate with clinical outcome variables in terms of comparability.

4. If a single parameter had to be selected to establish a comparative dose between QVAR and BDP-CFC, the Division agrees that change from baseline in FEV-1 as percent predicted, based on the reproducibility of FEV-1 in general and the lower coefficient of variation in study 1192, would be appropriate. The selection of a single spirometric parameter may not be the best way, however, to reflect the comparative efficacy dose ratio of the two products, in part because of the difference in delivery of the two products.

5. For the reasons indicated above, FEV-1 is probably the best parameter to assess BDP-CFC. On the other hand, FEF 25-75 may be the best parameter to assess QVAR, because FEF 25-75 is generally considered to represent smaller airway function and QVAR has a smaller particle size, and, at least based on lung deposition studies, has greater penetration into smaller airways.

6. If the data from study 1192 (see figure and table below; fig 3.1.A, p49; tab 3.2.1.A, p52) is evaluated in terms of mean percent change from baseline in FEV-1 and FEF 25-75, the mean percent improvement from baseline in patients who received 800 mcg of QVAR, based on FEF 25-75 was 98% and in patients who received 800 mcg of BDP-CFC, based on FEV-1 was 40%, approximately a 2.5:1 ratio. Similarly, a 400 mcg dose of QVAR produced a 70% mean improvement, based on FEF 25-75, whereas 400 mcg of BDP-CFC, based on FEV-1 produced a 35% mean improvement, a ratio of approximately 2:1. A 100 mcg dose of QVAR, based on FEV 25-75 produced a 60% mean improvement, whereas 100 mcg of BDP-CFC produced a 30% mean improvement, again a 2:1 ratio. Using this approach, which intuitively seems most appropriate, the sponsor's proposal to label QVAR for use at ½ the dose of BDP-CFC is reasonable. However, as the sponsor notes "a consistent comparative ratio is unachievable" between QVAR and BDP-CFC. Therefore, while no precise recommendations can be given to the health care provider about the dose of QVAR that should be used in patients who have previously received BDP-CFC, the statement that QVAR should be initiated at approximately ½ the dose of BDP-CFC is not unreasonable.

Figure 3.1.A: **1192: Mean Percent Change from Baseline in FEV_1 and $FEF_{25-75\%}$ (Intent-to-Treat Population)**



[New Presentation not Included in NDA 20-911]

Table 3.2.1.A: **1192: Interpretation of Individual Dose Level (mcg) Comparisons Between HFA-BDP and CFC-BDP for FEV_1 and $FEF_{25-75\%}$ Based on the Proximity of the Means (Intent-to-Treat Population)**

Week 6 Result	100 HFA ≈ 100 CFC 1:1	100 HFA ≈ 400 CFC 1:4	100 HFA > 400 CFC (>1:4	400 HFA ≈ 400 CFC 1:1	400 HFA > 400 CFC >1:1	400 HFA ≈ 800 CFC 1:2	800 HFA ≈ 800 CFC 1:1	800 HFA > 800 CFC (>1:1
Change from baseline in FEV_1 percent predicted[a]		X			X			X
AUC for change in FEV_1 percent predicted[a]		X				X		X
Percent change from baseline in FEV_1[a]		X			X			X
AUC for Percent change in FEV_1[b]		X				X		X
Percent change from baseline in $FEF_{25-75\%}$[a]			X		X			X
AUC for Percent change in $FEF_{25-75\%}$[b]			X			X		X

[a] Per-protocol analysis
[b] Post-hoc analysis

6. The sponsor also proposes to use the data from study 1267, a foreign, open-label, parallel study comparing QVAR and fluticasone with randomized treatment over 8 weeks where patients received either 800 mcg/day of QVAR or 1000 mcg/day of fluticasone HFA, to support the comparability of QVAR and BDP-CFC, on the basis that the dose of fluticasone was selected to be approximately ½ the dose of BDP-CFC. The mean change from baseline in AM PEF at the end of treatment was used to assess equivalence of QVAR and fluticasone HFA. The mean change was 30 L/min for QVAR and 17 L/min for fluticasone. This study can not be used, as the sponsor proposes, as supportive evidence that QVAR should be administered at approximately ½ the dose of BDP-CFC for obvious reasons.

7. Study 1232 was a 12 week open label post-marketing surveillance study in approximately 6000 patients comparing the safety of QVAR and BDP-CFC in adults, with the primary outcome variable being number of hospital admissions due to the condition for which BDP was prescribed. The sponsor states that the interim results "provide reassuring evidence that in a "real-life" test in a large number of patients, HFA-BDP is safe and effective at approximately ½ the dose of CFC-BDP" since the number of patients requiring hospitalization was comparable. This type of data from an open study evaluating a parameter such as hospitalization is not adequate to support a claim for comparability of QVAR and BDP-CFC.

III. COMPARABILITY OF THE 50 AND 100 MCG CONCENTRATIONS

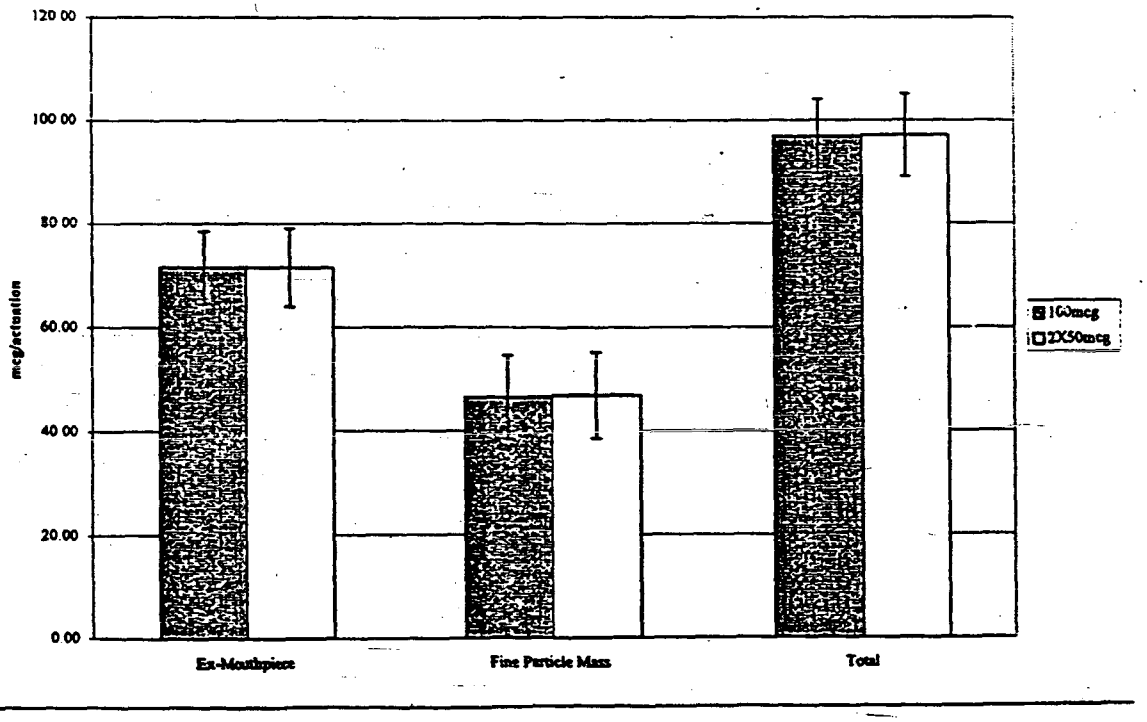
A. BACKGROUND: In the approvable letter of 12 May 1999, the Division indicated that the dose proportionality and clinical comparability in regard to safety and efficacy of the 40 mcg/actuator and 80 mcg/actuator concentrations had not been adequately established. The efficacy and safety of the 80 mcg/actuator concentration had only been evaluated in one adequate and well controlled study (study 1083) and only one dose level had been evaluated in that study. Therefore, the sponsor had not adequately linked the 80 mcg/actuator concentration with the 40 mcg/actuator concentration and there was inadequate data to establish the safety and efficacy of the 80 mcg/actuator concentration on a stand-alone basis across the range of doses proposed in the labeling. The Division met with the sponsor on 24 June 1999 to discuss this issue. The Division indicated it was possible that the submission of new data, especially PK data might support the approval of the 80 mcg/actuator concentration.

B. SPONSOR'S RESPONSE:

1. QVAR is a solution. The aerosol is therefore homogeneous. The concentration of drug in each droplet is proportional to the amount of drug in the formulation.

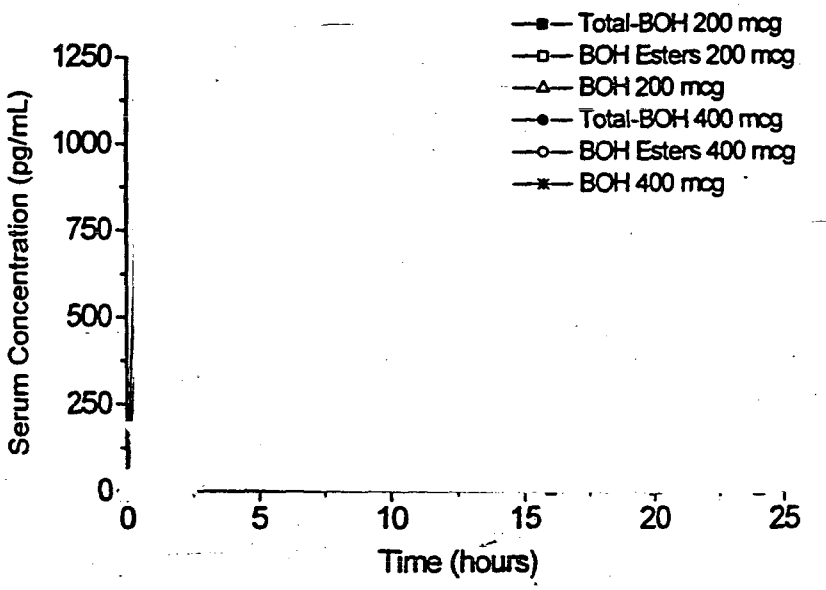
2. In-vitro cascade impactor data show that the fine particle mass is essentially the same when a dose of 100 mcg is delivered, regardless of whether it is 1 spray of the 100 mcg concentration or 2 sprays of the 50 mcg/spray concentration (see figure below; fig 2.A, p148). The sponsor has compared these results to those achieved using beclomethasone CFC at the same concentrations. The fine particle size achieved with the two concentrations of BDP-CFC is also very close, but not as close as was seen with QVAR.

Figure 2.A: QVAR Ex-mouthpiece, Fine Particle Mass and Total for 100 mcg and 2 x 50 mcg/Actuation Products



3. Validation for the analytical method of measuring BOH (beclomethasone free base) was shown. Serum concentration of BOH esters superimposed the serum concentration of total BOH at doses of 200 and 400 mcg. (see figure below; fig 3.1.A, p160). The sponsor demonstrated that in all probability the major analyte being measured in total BOH was 17-BMP (beclomethasone monopropionate) which is the major BOH ester of clinical significance.

Figure 3.1.A: 1075: Analytical Results for the HFA-BDP Doses



4. Study 1194 demonstrates the dose proportionality of a single dose of 400 mcg of QVAR using the 40 mcg/puff concentration and a single dose of 800 mcg of QVAR using the 80 mcg/puff concentration. Study 1194 was a single dose crossover study in 45 patients with asthma who received 400 and 800 mcg doses of QVAR from the MDI and Autohaler drug products. Mean total-BOH serum concentrations following the 800 mcg dose were aproximately twice those following the 400 mcg dose at all sampling times (see table and figure below; figure 3.2.A, p164. and table 3.2.B. , p164)

Figure 3.2.A: 1194: Mean Total-BOH Serum Concentrations

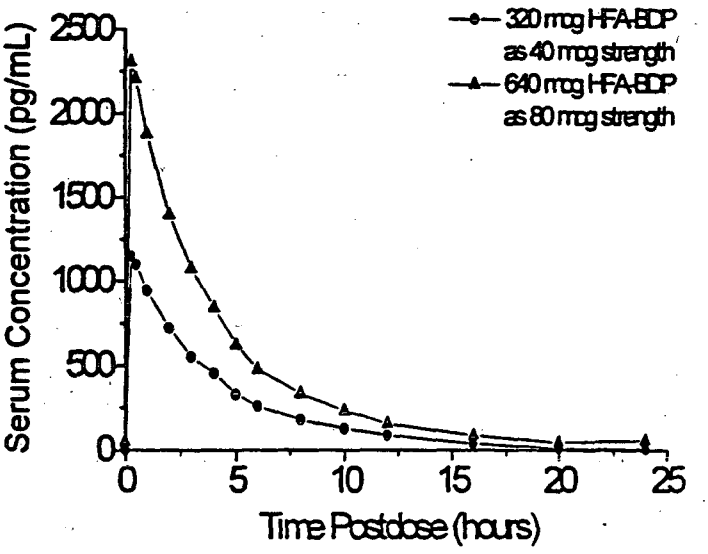


Table 3.2.B: 1194: Strength Proportionality of 40 mcg and 80 mcg HFA-BDP

	Total-BOH Cmax (pg/mL)	Total-BOH AUC (pg·hr/mL)
Geometric Mean:		
$HFA\text{-}BDP_{80}$ 800 mcg dose	2393	9478
$HFA\text{-}BDP_{40}$ 400 mcg dose	1181	4790
Ratio of Geometric Means (800-mcg/400-mcg)	2.03	1.98
Standard Error of Log_{10} Ratio	0.019	0.013
97.5% CI for Ratio	1.83 to 2.24[a]	1.85 to 2.12[a]

a: Met dose proportionality criterion; 2.00 contained within 97.5% CI
[New Data not Included in NDA 20-911]

5. Studies 1115 and 1267: These studies compared QVAR to fluticasone at similar dose levels. In study 1115, 400 mcg/day of QVAR was compared to 400 mcg/day of fluticasone both delivered at 50 mcg/puff concentrations. In study 1267, 800 mcg/day of QVAR delivered as the 100 mcg/puff concentration was compared to 1000 mcg/day of fluticasone delivered as the 250 mcg/puff concentration. Study 1115 was a blinded, parallel, foreign 6 week study and study 1267 was an open, parallel, foreign, 8 week study. The sponsor states that there was "an 18.6 L/min change from baseline for HFA-BDP 400 mcg and almost a doubling improvement (29.6 L/min) for twice the dose, 800 mcg/day)." (see table below; tab 4.2.1.2.C, p175)

Table 4.2.1.2.C 1115/1267: Mean Change in AM PEF at the End of Treatment (Intent-to-Treat Population)

		Study 1115 HFA-BDP$_{40}$ 400 mcg		Study 1267 HFA-BDP$_{80}$ 800 mcg	
			Within treatment p-value		Within treatment p-value
Baseline AM PEF (L/min)	Adjusted Mean[a] SD N	381.3 80.54 87	–	352.1 82.61 101	–
Change in AM PEF at Week 6 (1115) or Week 8 (1267) (Last 5 days)	Adjusted Mean SD N	18.6 43.63 86	< 0.001	29.59 49.77 92	< 0.01

[New presentation notIncluded in NDA 20-911]

REVIEWER'S COMMENTS

1. The fact that QVAR is a solution and the in-vitro data presented by the sponsor suggest that a similar clinical response would be seen when a given dose is administered using either the 40 mcg/actuator concentration or the 80 mcg/actuator concentration.

2. Study 1194 does not support the comparability of the 40 and 80 mcg/actuator concentrations since dose proportionality was based on using a 40 mcg/actuator concentration for the 400 mcg dose and an 80 mcg/actuator concentration for the 800 mcg dose. What was needed in this study was a comparison 400 and 800 mcg doses of QVAR delivered at both the 40 and the 80 mcg/actuator concentrations.

3. The sponsor has presented new clinical data from studies 1115 and 1267 in support of the dose proportionality of the two concentrations. Use of this data requires cross-study comparison of data, which is not acceptable. Therefore, the data from these studies can not be used to support the comparability of the two concentrations of QVAR.

4. The sponsor has presented no new clinical data that would support the approvability of the 80 mcg/actuator concentration. Therefore, there is no basis for changing our position as indicated in the approvable letter to the sponsor of 12 May 1999 in regard to non-approvability of the 80 mcg/actuator concentration.

IV. [redacted]

A. BACKGROUND: In the labeling for this drug product submitted in the NDA, the sponsor proposed to state in the CLINICAL PHARMACOLOGY section that: "[redacted] In addition, the sponsor stated in the INDICATIONS AND USAGE section that:

[redacted]

In the approvable letter to the sponsor of 12 May 1999, the Agency stated: "Since the clinical comparability of QVAR to an approved CFC-based beclomethasone diproprionate MDI has not bee established and since QVAR has not been studied in adequate and well-controlled trials to evaluate its ability to allow reduction of oral corticosteroids dosing in patients who require oral corticosteroids, specific dosing recommendations for QVAR for this indication are not appropriate. Delete all references to this indication from the DOSAGE AND ADMINISTRATION section of the draft labeling or submit new data that adequately support dosing recommendations for QVAR for this indication."

B. SPONSOR'S RESPONSE: The sponsor agrees that adequate [redacted] studies have not been performed with QVAR and agrees to remove any statements in the labeling that implies this. In an apparent contradiction to this statement, the sponsor states that [redacted] labeling that recommend [redacted] The sponsor is, therefore, proposing modification of the wording in the labeling for BDP-CFC for QVAR, to read as follows:

[redacted]

In addition, the sponsor proposes a table to base the recommended starting dose and highest recommended dose on the severity of the patient's asthma, as defined by the medication that they are receiving (see table below).

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators Alone	40 – 80 mcg twice daily	320 mcg twice daily
Inhaled Corticosteroids	40 – mcg twice daily	320 mcg twice daily

REVIEWER'S COMMENTS: The sponsor stated that had not been done with QVAR and therefore they would omit any wording implying this. Why then does the sponsor state that, "

Although the sponsor has submitted a reasonable argument for

Therefore, as stated in the approvable letter, the sponsor should delete all references to this indication and should not add the wording that has been proposed.

V. CONCLUSIONS:

1. Relating to the comparability of QVAR and BDP-CFC, the labeling should read:

Draft

2. The sponsor has not provided any new clinical data that would support the approvability of the 80 mcg/actuator concentration. The sponsor states that the Division indicated that consideration would be given to the approvability of the 80 mcg/actuation concentration if pharmaceutic, pharmacokinetic, AND supporting clinical data were convincing. Although the in-vitro and PK data are supportive, there is no supporting clinical data that is convincing enough to approve the 80 mcg/actuation concentration.
3. The sponsor's proposed claim for ——— is unacceptable.
4. The dosage proposed in the labeling that is based on previous therapy will need to be revised by deleting {

{

ADDENDUM of 11 February 2000

This review is a supplement to the MOR of 9 February 2000, based on discussion at the internal meeting for QVAR on 11 February 2000. The issues discussed at the meeting of 11 February 2000 were first raised in our approvable letter to the sponsor to which the sponsor responded with the submission of 17 August 1999. These issues are reviewed again below based on the discussion at the meeting of 11 February 2000.

1. **In regard to the sponsor's proposed labeling that would apply to patients who had previously been receiving BDP-CFC, the following modification of the sponsor's statement was agreed upon; "Lower doses of QVAR relative to BDP-CFC may achieve the same clinical effect. Recognizing that a consistent comparative ratio between QVAR and BDP-CFC has not been achieved, any patient who is switched from BDP-CFC to QVAR must be monitored closely to determine if the dose selected for QVAR is efficacious and safe. As with any inhaled corticosteroid, physicians are advised to titrate the dose to a lower level over time provided control of the patient's asthma is maintained."**

2. **Although the in-vitro data, and the summary of the PK data is compelling, a decision on the approvability of the 80 mcg/actuator strength can not be made until Biopharm has had an opportunity to review all the PK data.**

3. **In regard to the sponsor's claim for ——— , the sponsor can include in the labeling the class statement for inhaled corticosteroids dealing with this issue but can not include any specific reference to ——— demonstrated with QVAR.**

4. **The sponsor's proposed dosage for QVAR will need revision as discussed below. The sponsor has proposed that the starting dose and highest recommended dose be based on the severity of the patient's asthma as reflected by previous therapy.**

    a. **<u>bronchodilators alone</u>: recommended starting dose of 100-200 mcg/day; maximum dose 800 mcg/day; <u>comment</u>: Study 1081 demonstrated the efficacy and safety of 100 and 200 mcg/day doses over 6 weeks of treatment in patients on only bronchodilators. A dose of 800 mcg/day was not studied in patients who were just receiving bronchodilators. However, patients who were just on bronchodilators received 400 mcg/day of QVAR in study 1083, at which dose efficacy and safety were demonstrated. In conclusion,**

the studies done by the sponsor support a claim for a starting dose of 100-200 mcg/day and a maximum dose of 400 mcg/day. Since there is no reason to believe that the efficacy and safety of 800 mcg/day of QVAR would be different in patients taking only bronchodilators, and since the efficacy and safety of 800 mcg/day of QVAR has been demonstrated in other patient populations, it is reasonable to recommend a dose of 800 mcg/day as the highest dose for this patient population.

b. inhaled corticosteroids: recommended starting dose of 100-400 mcg/day; maximum dose of 800 mcg/day; comment: Patients in study 1192 were receiving inhaled corticosteroids prior to the study and received 100 and 400 mcg/day of QVAR for 5 weeks during the study. Both doses were safe and efficacious in this study. A dose of 800 mcg/day was evaluated over 12 weeks in patients on inhaled corticosteroids and found to be safe and efficacious. In conclusion, the safety and efficacy of a starting dose of 100-400 mcg/day and a maximum dose of 800 mcg/day has been demonstrated in patients on inhaled corticosteroids in the studies submitted by the sponsor.

c. [redacted]

5. Proposed Draft of Letter to Sponsor:

The paragraph that you propose to highlight the difference in dose recommendations for QVAR and CFC-BDP should be revised to read as follows:

In regard to an oral corticosteroid-sparing effect, the class statement for inhaled corticosteroids can be included in the labeling for QVAR but any specific reference to [redacted] of QVAR is unacceptable. Please revise the labeling consistent with the class labeling for inhaled corticosteroids.

The recommended starting and highest recommended dose for patients receiving [redacted] should be deleted from your proposed table. There is insufficient data evaluating QVAR in patients on [redacted] to support such a claim.

9 February 2000
QVAR
Beclomethasone diproprionate HFA

I. BACKGROUND: On 11 May 1998, the sponsor (3M pharmaceuticals) submitted the NDA for QVAR. On 12 May 1999, an approvable letter was sent to the sponsor. This letter informed the sponsor that from a clinical standpoint: 1) the safety and effectiveness of QVAR had not been demonstrated to be clinically comparable to the currently marketed CFC beclomethasone MDI; 2) the safety and effectiveness of the 80 mcg/puff concentration was not established across the range of doses proposed in the labeling and therefore the 80 mcg/puff concentration was not approvable; and 3) [redacted]; claim in the labeling. On 24 June 1999, the Division met with the sponsor to discuss these issues. On 17 August 1999, the sponsor submitted an amendment to the NDA, responding to the approvable letter.

II. COMPARABILITY BETWEEN QVAR AND BDP-CFC:

A. BACKGROUND: The Division cited the following to support our contention that comparability between QVAR and BDP-CFC had not been demonstrated: 1) a consistently comparable dose ratio between QVAR and BDP-CFC was not seen for lung deposition, PK, PD, and clinical parameters; 2) in study 1192, a consistent comparative dose ratio was not seen for all efficacy parameters, e.g. FEV-1 and FEF- 25-75; 3) the Finney Bioassay methodology had significant flaws; 4) the clinical relevance of the difference in efficacy between increasing dose levels was questionable; and 5) studies 1129 and 1163 had flaws that preventing their use in support of the comparability ratio proposed by the sponsor.

B. SPONSOR'S RESPONSE:

1. Comparability of BDP-HFA (QVAR) and BDP-CFC: The sponsor proposes that the labeling state that;

[redacted]

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

MAY 12 1999

APPLICATION #: NDA 20,911 | **APPLICATION TYPE: NDA**

SPONSOR: Sepracor | **PRODUCT/PROPRIETARY NAME: QVAR**

USAN / Established Name: Beclomethasone dipropionate-HFA

CATEGORY OF DRUG: corticosteroid | **ROUTE OF ADMINISTRATION: Inhaled solution**

MEDICAL REVIEWER: R. Nicklas MD | **REVIEW DATE: 12 May 1999**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
11 May 1998	12 May 1998	Original NDA submission	see below under overview

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
8 September 1998	4 month safety update/final report for study 1163	See below under overview

Overview of Application/Review: The sponsor submitted 7 key studies; studies 1081, 1083, 1192, 1129, 1130, 1163, and 1162, which were designed to demonstrate the comparability of BDP-HFA and BDP-CFC and to demonstrate the efficacy and safety of BDP-HFA. The sponsor did not demonstrate the comparability of BDP-HFA and BDP-CFC because the studies were not designed to demonstrate comparability. The sponsor has studied two concentrations of BDP-HFA, a 50 mcg/puff and a 100 mcg/puff concentration. Comparability of these two concentrations was not demonstrated. The 50 mcg/puff concentration was shown to be safe and efficacious at doses of 400 and 800 mcg/day. The 100 mcg/puff concentration was not shown to be safe or efficacious. There were no studies that were adequately designed to show

n summary, the 50 mcg/puff concentration of BDP-HFA has been shown to be safe and efficacious at doses of 400 mcg/day and 800 mcg/day, but extensive labeling changes will be needed before this drug product is approvable.

Outstanding Issues: extensive labeling changes are needed. In addition, the sponsor should provide the Division with an analysis of the data from study 1163, based on whether patients were receiving the 50 mcg/puff or the 100 mcg/puff concentration.

Recommended Regulatory Action: approvability of the 50 mcg/puff concentration with extensive labeling changes

N drive location: n:\mocov174

New Clinical Studies: N/A Clinical Hold N/A Study May Proceed

NDAs:

Efficacy / Label Supp.: X Approvable _____ Not Approvable

Signed: Medical Reviewer: [signature] Date: 5/12/99

Medical Team Leader: [signature] Date: 5/12/99

see Div Dir memo dated 5/12/99

QVAR
Beclomethasone diproprionate-HFA
NDA 20,911

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PROPOSED DRAFT OF CLINICAL PORTION OF LETTER TO SPONSOIR:

We have reviewed the data submitted for QVAR and have the following comments for you at this time:

1. **The comparability of QVAR and inhaled beclomethasone with CFC propellants has not been sufficiently demonstrated to allow for labeling**

2. **There is insufficient data to demonstrate the safety or efficacy of the 100 mcg/inhalation concentration of QVAR and this concentration has not been demonstrated to be comparable to the 50 mcg/inhalation concentration.**

3. **There is no data to support a claim that QVAR is**

PREFACE

BACKGROUND: A pre-IND meeting was held on 1 December 1992. IND [redacted] for BDP-HFA was submitted on 28 April 1993. An end-of-phase 2 meeting was held on 12 April 1995. A Pre-NDA meeting was held with the sponsor on 8 September 1997. At this time it was agreed that there were 6 key studies that should form the basis for any claims of efficacy for BDP-HFA. These were studies 1081, 1083, 1192, 1129, 1130, and 1163.

DRUG PRODUCT: Beclomethasone diproprionate (BDP) is a synthetic halogenated glucocorticosteroid that is believed to suppress chronic infiammation in the airways. BDP-HFA was developed as a formulation of beclomethasone diproprionate that contained the non-ozone depeleting propellant hydrofluoroalkane-134a (HFA). BDP-HFA is a solution, compared to the suspension formulation of BDP-CFC. This formulation has a smaller particle size than BDP-CFC (mass mean aerodynamic diameter of 1.0-1.2 microns compared to 3.5-4.0 microns with BDP-CFC). Studies using radiolabelled BDP-HFA and PK data suggest that there is greater pulmonary deposition of BDP-HFA than there is with BDP-CFC.

PLAN OF STUDY: The sponsor performed studies with BDP-HFA that were intended to demonstrate the efficacy and safety of BDP-HFA using concentrations of 50 and 100 mcg/puff at doses from 100-800 mcg/day, compared with placebo and BDP-CFC. In addition, the sponsor proposed to demonstrate the comparability of BDP-HFA and BDP-CFC in terms of efficacy and safety. The key to demonstrating the efficacy and safety of BDP-HFA were one study of 2 weeks duration evaluating adrenal function, three studies of 6 weeks duration, 2 studies of 12 weeks duration and one 12 month safety study. The results from these key studies are described and analyzed in this review.

QVAR

EXECUTIVE SUMMARY OF ISSUES

BDP-CFC (Beclovent, Vanceril) has been approved for the treatment of asthma. Approval of BDP-HFA (QVAR) could be obtained by either: 1) demonstrating a comparable response for BDP-HFA and BDP-CFC across the dose range proposed for clinical use; if this was accomplished it would be reasonable to conclude that the data that had been used to support the approval of BDP-CFC could be used to support the approval of BDP-HFA, as well; or 2) demonstrating the efficacy and safety of BDP-HFA across the dose range proposed for clinical use in studies of adequate length, design, numbers and an appropriate patient population, so that a conclusion on the approvability of BDP-HFA does not depend on data that has been generated with BDP-CFC.

Q. Has the sponsor demonstrated efficacy and safety of BDP-HFA on a stand-alone basis at the concentrations and across the dose range proposed for marketing? The response to this question must consider the two concentrations and the dose range proposed.

Q. Did the sponsor demonstrate the safety and efficacy of the 100 mcg/puff concentration of BDP-HFA?

BACKGROUND: There were 3 key studies in which the 100 mcg/puff concentration was evaluated: study 1083, study 1130 and study 1163. Study 1083 was a 6 week study designed to show the comparability of 400 mcg/day of BDP-HFA 50 mcg/puff and 400 mcg/day BDP-HFA 100 mcg/puff. Study 1130 was a 12 week study designed to show the comparability of 800 mcg/day of BDP-HFA and 1500 mcg/day of BDP-CFC. Study 1163 was a 12 month safety study with an 8 week switch evaluation. (NOTE: If the sponsor was able to demonstrate the comparability of BDP-HFA 50 mcg/puff and 100 mcg/puff in a well designed study, adequate data supporting the safety and/or efficacy of one concentration could be used to support the safety and/or efficacy of the other concentration, even if there was inadequate data with that concentration.)

Q. efficacy of the 100 mcg/puff concentration of BDP-HFA?:

- **study 1130: No, since there was no placebo control in the study and the active treatment control used a concentration not approved in the United States.**

- **study 1163: No, since this open study was not designed to demonstrate the efficacy of BDP-HFA.**

- **Study 1083: Yes, but only for 88 patients not on inhaled corticosteroids at a dose of 400 mcg/day. Since this study did not include more than one dose of BDP-HFA 50 mcg/puff and BDP-HFA 100 mcg/puff, the design is inadequate to make any conclusions about the comparability of the 50 and 100 mcg/puff concentrations. Failure to demonstrate comparability of the two concentrations prevents any link between the concentrations that would support doses other than 400 mcg/day. BDP-HFA 100 mcg/puff concentration could not be adequately labeled for clinical use based on a single study at one dose in a subset of patients for whom the drug will be prescribed.**

- **overall: No, for the reasons noted above.**

Q. safety of the 100 mcg/puff concentration of BDP-HFA?

- **Study 1130: Yes, for the parameters evaluated in 116 patients. However, plasma cortisol levels, which are not considered a reliable parameter for the assessment of adrenal function, was the only measure of adrenal function evaluated.**

- **Study 1163: No, since the data is not analyzed for the subset of patients receiving the 100 mcg/puff concentration. Therefore, despite the fact that ACTH stimulation testing was done and is considered an acceptable method for evaluation of adrenal function, this study can not be used to support the safety of the 100 mcg/puff concentration.**

- **Study 1083: Yes, for the parameters evaluated in 88 patients. However, no assessment of adrenal function was made in this study. Moreover, the study was not adequately designed to demonstrate the comparability of the 50 and 100 mcg/puff concentrations, so that data supporting the safety of the 50 mcg/puff concentration can not be used to support the safety of the 100 mcg/puff concentration.**

- **overall: No, because there is inadequate data on the effect of BDP-HFA at a 100 mcg/puff concentration on adrenal function and no comparability of the 50 mcg/puff and 100 mcg/puff concentrations was demonstrated to allow the adrenal function data with the 50 mcg/puff concentration to support the safety of the 100 mcg/puff concentration.**

CONCLUSION: The sponsor has not demonstrated a degree of efficacy and safety of BDP-HFA at the 100 mcg/puff concentration that would provide an acceptable database for labeling of this drug product.

Q. Did the sponsor demonstrate the safety and efficacy of the 50 mcg/puff concentration of BDP-HFA?

BACKGROUND: There were 6 key studies in which the efficacy and/or safety of the 50 mcg/puff concentration of BDP-HFA was evaluated: study 1081, study 1083, study 1129, study 1192, study 1163 and study 1162. Study 1081 was a 6 week study evaluating doses of 100 and 200 mcg/day of BDP-HFA. Study 1083 was a 6 week study designed to show the comparability of 400 mcg/day of BDP-HFA 50 mcg/puff and 400 mcg/day of BDP-HFA 100 mcg/puff. Study 1129 was a 12 week study designed to show the comparability of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC. Study 1192 was a 6 week study designed to compare 100, 400, and 800 mcg/day of BDP-HFA and BDP-CFC. Study 1163 was a 12 month safety study with an 8 week switch evaluation. Study 1162 was a 2 week safety study of 200, 400, and 800 mcg/day of BDP-HFA with measurement of 24 hour urinary free cortisol and ACTH stimulation.

Q. Efficacy of the 50 mcg/puff concentration of BDP-HFA?

- **study 1081: Yes, the efficacy of 100 mcg/day and 200 mcg/day of BDP-HFA 50 mcg/puff was demonstrated in 91 and 92 patients, respectively, who were not receiving inhaled corticosteroids.**

- **study 1083: Yes, the efficacy of 400 mcg/day of BDP-HFA 50 mcg/puff was demonstrated in 83 patients who were not receiving inhaled corticosteroids.**

- **study 1129: Yes, the efficacy of 400 mcg/day of BDP-HFA 50 mcg/puff was demonstrated in 113 patients, many of whom were taking inhaled corticosteroids.**

- study 1192: Yes, the efficacy of the 400 and 800 mcg/day of BDP-HFA 50 mcg/puff was demonstrated from a clinical standpoint in 51 and 56 patients, respectively, receiving inhaled corticosteroids, based on the dose-response seen with these two doses. Since there was no placebo control in this study and since there was no statistically significant difference in terms of efficacy parameters between the 100 mcg/day dose and higher doses of BDP-HFA, the efficacy of the 100 mcg/day dose has not been demonstrated

- study 1163: No, since the study was not designed to evaluate efficacy and there was no analysis of the subset of patients who received the 50 mcg/puff concentration.

- overall: Yes, the efficacy of BDP-HFA 50 mcg/puff concentration was demonstrated in an adequate number of patients in appropriately designed and analyzed studies over the dose range that is proposed for clinical use. The sponsor has not, howeveer, demonstrated that BDP-HFA is

Q. Safety of the 50 mcg/puff concentration of BDP-HFA?

- study 1081: Yes, for the parameters that were assessed. However, adrenal function was not evaluated in this study.

- study 1083: Yes, for the parameters that were assessed. However, adrenal function was not evaluated in this study.

- study 1192: Yes, for the parameters that were assessed. However, adrenal function was not evaluated in this study.

- study 1129: Yes, for the parameters that were assessed. However, adrenal function was not adequately evaluated in this study, since assessment of adrenal function was limited to serum cortisol levels.

- study 1163: No, since the data were not analyzed for the subset of patients who received the 50 mcg/puff concentration. Therefore, despite the fact that ACTH stimulation was performed and did not demonstrate any significant effect of BDP-HFA on the HPA axis, there is no analysis of this data in terms of the 50 mcg/puff concentration.

- study 1162: Yes, in terms of adrenal function, since 24 hour urinary free cortisol levels and response to ACTH injection were measured. No unexpected findings related to the HPA axis were found after administration of BDP-HFA 50 mcg/puff.

- overall: Yes, the safety of BDP-HFA 50 mcg/puff has been demonstrated, based on the data from studies 1081, 1083, 1129, and 1192 and the data from study 1162 in regard to adrenal effect.

CONCLUSION: The sponsor has demonstrated the efficacy and safety of BDP-HFA 50 mcg/puff over the dose range proposed for clinical use.

Q. Has the sponsor demonstrated a comparable response for BDP-HFA and BDP-CFC across the dose range proposed for clinical use?

BACKGROUND: There are 4 studies that can be used to address this question, studies 1192, 1129, 1130 and 1163. Study 1192 compared doses of 100, 400, and 800 mcg/day of BDP-HFA 50 mcg/puff and BDP-CFC over a period of 6 weeks. Study 1129 compared 400 mcg of BDP-HFA 50 mcg/puff with 800 mcg/day of BDP-CFC over 12 weeks. Study 1130 compared 800 mcg/day of BDP-HFA 100 mcg/puff with 150 mcg/day of BDP-CFC. Study 1163 compared doses of 400-1600 mcg BDP-HFA either 50 or 100 mcg/puff with 400-2250 mcg/day of BDP-CFC over 8 weeks in terms of efficacy and 12 months in terms of safety.

- study 1192: In terms of the primary efficacy parameter, mean change from baseline in percent predicted FEV1, there was a modest dose-response noted. Significant change from baseline in mean percent predicted FEV-1 occurred at all dose levels after the first week of treatment. The mean change in percent predicted FEV-1 through the first 4 weeks of treatment was most similar for doses of 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC. However, the difference in change from baseline in percent predicted FEV-1 after administration of 800 mcg/day of BDP-HFA was not clinically significantly different than the change seen after administration of 800 mcg/day of BDP-CFC. However, mean percentage change from baseline in FEF 25-75 and mean change from baseline in AM PEF, while also demonstrating comparability between 400 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC showed a substantially greater degree of improvement in the group that received 800 mcg/day of BDP-HFA than was seen in the group that received 800 mcg/day of BDP-CFC. In this study, 45% of the BDP-HFA 800 mcg/day patients as compared to 33% of the BDP-CFC 800 mcg/day patients had at least a 50% improvement in FEV-1 from baseline. On the other hand, an insignificant amount of difference was seen between 800 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC in terms of other efficacy parameters. In summary, there was no consistent indication of what dose of BDP-HFA was comparable to a given dose of BDP-CFC, i.e. based on some parameters 400 mcg/day of BDP-HFA was most comparable to 800 mcg/day of BDP-CFC, while for other parameters 800 mcg/day of BDP-HFA was comparable to 800 mcg/day of BDP-CFC. Therefore, this study can not be used to support a claim for comparability of given dose of BDP-HFA and a given dose of BDP-CFC.

- study 1129: A greater degree of improvement was seen for most parameters after administration of 400 mcg/day of BDP-HFA 50 mcg/puff than after administration of 800 mcg/day of BDP-CFC, although this difference was not clinically significant. However, the sponsor did not demonstrate comparability in this study because only one dose of BDP-HFA and BDP-CFC was studied.

- study 1130: This is the only study that could have been used to show comparability of a dose of BDP-HFA at the 100 mcg/puff concentration and a dose of BDP-CFC. This study can not be used to demonstrate comparability of BDP-HFA 100 mcg/puff and BDP-CFC, however, because: 1) there was no placebo control; 2) the active treatment control was administered at a concentration not approved in the United States; and 3) only one dose of BDP-HFA and BDP-CFC were evaluated.

- study 1163: This study can not be used to determine a dose of BDP-HFA that is comparable to a dose of BDP-CFC because during the first 8 weeks of the study, when doses remained constant, different doses of both products at different concentrations were being taken by patients in an uncontrolled manner.

- overall: The sponsor has not demonstrated the comparability of BDP-HFA and BDP-CFC at any dose for the 50 mcg/puff or the 100 mcg/puff concentration. Study 1192 generated data that suggested comparability of 400 mcg/day BDP-HFA and 800 mcg/day BDP-CFC for some parameters and 800 mcg/day of BDP-HFA and 800 mcg/day of BDP-CFC for others. Study 1129, on the other hand, showed a slightly greater improvement in most parameters with 400 mcg/day of BDP-HFA than 800 mcg/day of BDP-CFC. The design of studies 1129, 1130 and 1163 prevents use of data from those studies in defining comparability of BDP-HFA and BDP-CFC.

CONCLUSION: Comparability of BDP-HFA and BDP-CFC has not been demonstrated.

11 pages redacted from this section of the approval package consisted of draft labeling

ABSTRACT

METHODS: Study 1162 was a randomized, parallel, dose-ranging, dose-level patient and investigator-blind, placebo and active treatment-controlled , single center, repetitive dose study in 43 adult patients (8-9 per arm), who had mild asthma not receiving corticosteroids who had normal adrenal function. After screening, patients were sequestered and randomized to receive 200 mcg/day, 400 mcg/day or 800 mcg/day of BDP-HFA or 800 mcg/day of BDP-CFC or HFA placebo, given bid, at a 50 mcg/puff concentration, for 2 weeks. Only safety parameters were evaluated and included adverse events, laboratory tests, vital signs, serum osteocalcin and assessment of adrenal function. The primary safety parameter was change in mean 24 hour urinary free cortisol, but plasma cortisol levels and response to ACTH stimulation were also measured. Serum beclomethasone levels were also measured after the first dose and after 14 days of treatment.

RESULTS: There was a dose-dependent decrease in mean 24 hour urinary free cortisol levels after treatment with BDP-HFA, as compared to an increase in the HFA placebo group. The decrease in mean 24 hour urinary free cortisol was greater after 800 mcg/day of BDP-CFC than after 800 mcg/day of BDP-HFA. The change from baseline after administration of the 400 mcg/day and 800 mcg/day doses of BDP-HFA, as well as the 800 mcg/day dose of BDP-CFC were statistically significantly different from the change seen with placebo, using Dunnett's test. One patient in the 800 mcg/day BDP-HFA group had a decrease in urinary free cortisol from 73 nmol/24 hours at baseline to 23 nmol/24 hours after 14 days of treatment. This same patient was the only patient to have an abnormal ACTH stimulation test after 14 days of treatment. The dose-response seen in the patients that received BDP-HFA was driven by the change seen in the 9 AM to 8 PM aliquot of urine.

There was a significantly greater decrease in mean 7 AM plasma cortisol after 800 mcg/day of BDP-HFA than was seen in any other group. This difference was not seen with the mean 9 AM plasma

cortisol values. There were 3 patients whose plasma cortisol level after 14 days of treatment was below the lower limit of the NRR; 2 BDP-HFA 800 mcg/day patients and 1 BDP-CFC 800 mcg/day patient.

There was no statistically significant difference in the change from pre-injection plasma cortisol to cortisol measured 30 and 60 minutes after ACTH administration. There were 7 patients who had an abnormal incremental change after ACTH stimulation on day 15, but 3 of these patients were in the placebo group. There were 2 patients who had abnormal peak cortisol values after ACTH stimulation, one BDP-HFA 800 mcg/day patient and one BDP-CFC 800 mcg/day patient. One BDP-HFA 800 mcg/day patient had a low pre-injection cortisol level on study day 15 and an abnormally low peak value on the same day, that constituted an abnormal ACTH stimulation test.

There was a greater decrease in the mean serum osteocalcin level from baseline after administration of 800 mcg/day of BDP-HFA than was seen in any of the other treatment groups. Higher mean total belcomethasone concentrations, AUC, and Cmax were seen after administration of 400 mcg of BDP-HFA than after administration of 400 mcg of BDP-CFC, both as single doses and at steady state.

DISCUSSION: Based on individual patient 24 hour urinary free cortisol levels, individual plasma cortisol levels, and the response to ACTH stimulation, there was a suggestion that more adrenal suppression occurred after administration of 800 mcg/day of BDP-HFA for 14 days than occurred after administration of 800 mcg/day of BDP-CFC over this period of time. This impression was based on data from a small number of patients and very small differences in the parameters evaluated. On the other hand, there was less of a decrease in mean urinary free cortisol after 800 mcg/day of BDP-HFA than after the same dose of BDP-CFC. Nevertheless, it can be assumed that some patients will develop adrenal suppression after administration of high doses of inhaled corticosteroids, including BDP-HFA.

There was substantially greater mean total beclomethasone plasma levels, mean total belomethasone Cmax and mean total beclomethasone AUC both after a single dose of 400 mcg of BDP-HFA and at steady state after administration of 400 mcg/day bid of BDP-HFA for 14 days than was seen after a single dose of 400 mcg/day of BDP-CFC or at steady state after administration of 400 mcg bid of BDP-CFC. These data are based on a small number of patients, but suggest that, despite the findings from in-vitro and lung deposition studies, there is more systemic availability of BDP-HFA than BDP-CFC.

☛ Study 1162

☛ The primary objective of this study was to determine the effect of increasing doses of BDP-HFA on the HPA axis, in terms of change from baseline in 24 hour urinary-free cortisol. A secondary objective was to determine the relative potency of BDP-HFA to BDP-CFC in terms of 24 hour urinary-free cortisol levels.

☛ number of patients:

✦ 63 patients were screened

✦ 43 patients were randomized to treatment; 9 patients received 200 mcg/day BDP-HFA, 9 patients received 400 mcg/day BDP-HFA and 9 patients received HFA placebo; 8 patients received 800 mcg/day BDP-HFA and 8 patients received 800 mcg/day BDP-CFC

✦ 3 patients (1 HFA placebo, 1 BDP-HFA 200 mcg/day and 1 BDP-HFA 400 mcg/day) did not complete 14 days of treatment due to an adverse event (see discussion under Study Results: adverse events, below).

☛ age range: 18-60 years

☛ patient population: restricted to the clinical research unit

✦ mild asthma, not using inhaled corticosteroids for at least 3 months prior to the screening visit; FEV-1 60% or greater of predicted without inhaled beta agonists for 6 hours; reversibility of 15% or greater; using short acting inhaled beta agonists within 4 weeks of randomization.

✦ normal adrenal function defined as: 1) plasma cortisol level of 138 nmol/L or more (5 mcg/dL or more); and 2) a normal ACTH stimulation test at screening, defined as: 1) a pre-injection plasma cortisol level of 138 nmol/L or more (5 mcg/dL

or more); 2) an increment of 193.2 nmol/L or more (7 mcg/dL or more); and a peak value of 496.8 nmol/L or more (18 mcg/dL or more); at least 2/3 of these criteria had to be met.

☛ study design: dose-ranging, randomized, parallel, dose-level patient and investigator-blind, placebo and active treatment-controlled (HFA placebo), single center, repetitive dose study.

☛ drug administration:

- ✦ 200, 400, and 800 mcg/day (100, 200, and 400 mcg bid) of BDP-HFA compared to 800 mcg/day of BDP-CFC (400 mcg bid); the 800 mcg/day dose was selected as the minimum dose anticipated to give adrenal suppression.
- ✦ 50 mcg/puff concentration for both HFA and CFC products.
- ✦ patients did not prime inhalers during study.
- ✦ patients received 8 puffs bid (8 AM and 8 PM), e.g. 200 mcg daily of BDP-HFA was given as 2 puffs of BDP-HFA, and 6 puffs of placebo bid.
- ✦ a 50 mcL valve was used; lot numbers of PD3818 for BDP-HFA, PD3787 for HFA placebo, 4ZPA213 for BDP-CFC
- ✦ medication delivery testing can be seen in the table below (tab4, p51, v1.51) and were within specifications; the results of testing for respirable fraction and respirable mass for both BDP-HFA (lot PD3818) and BDP-CFC can be seen in the tables below; tab 5, p52, v1.51 and tab 6, p53, v1.51.

Table 4: Medication delivery results for HFA-134A BDP MDI

Vial #	Amount of BDP ex-adapter/actuation (mcg)
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
Mean	

Method Number : AMS-1754, effective date April 13, 1993. Data recorded on RFA 38177. Method Validation Reference: AMS-1754 method validation submitted to IND # [redacted] on 28 April, 1993, volume 1 page 250.

Table 5: Respirable Fraction and Respirable Mass for HFA-134a BDP (Lot # PD3818)

Vial #	Respirable Fraction (% of particles ≤ 4.7 microns)	Respirable Mass (mcg/actuation of BDP ≤ 4.7 microns)
1		
2		
3		
Mean	56.7	21.2

Method Number : AMS-1756, effective date October 4, 1994. Data recorded on RFA 38177. Method Validation Reference: AMS-1756 method validation submitted to IND # [redacted] on AIR-8892 December, 1992, volume 1 page 297.

Table 6: Respirable Fraction and Respirable Mass for CFC 11/12 BDP (Lot # 95-018)

Vial #	Respirable Fraction (% of particle ≤ 4.7 microns)	Respirable Mass (mcg/actuation of BDP ≤ 4.7 microns)
1		
2		
3		
Mean	35.0	16.1

Method Number : AMS-1756, effective date October 4, 1994. Data recorded on RFA 42210.

- ☛ periods of study: screening visit followed by sequestration for 3 days of baseline measurements followed by 14 days of randomized treatment; patients sequestered for baseline period and period of randomized treatment

- ☛ parameters evaluated: see flow chart below; there were no efficacy parameters

Table 1: **1162-BRON Procedures by Study Day**

PROCEDURE	Screen	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
24-hr Urine* Collection		x——x	x——x													x——x	x——x		
Plasma Cortisol (0700 & 0900 hrs)			xx	xx													xx	xx	
Serum Osteocalcin				x														x	
Serum total-BOH					x													x	
Cosyntropin test	x																		x
Blood Ethanol					x													x	
PFTs	x																		
Vitals	x																		x
AEs					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical Lab tests	x																		x
Physical exam	x																		x
ECG	x																		
Review inclusion/ exclusion criteria	x	x			x														
Medical History	x	x																	
Serum HCG**	x																		x
Urine Drug Screen	x																		
Randomization					x														
Dose					x	x	x	x	x	x	x	x	x	x	x	x	x	x	

*Two 24-hour urine samples were collected from Study Days -3 to -1 and 12 to 14 and analyzed for cortisol, creatinine and TFA. ** Females of childbearing potential

- ✱ adverse events

- ✱ blood ethanol levels: at baseline before treatment; 30 minutes and one hour after the first dose of study drug and on day 14; ethanol levels were measured because ethanol had been used in the reformulation of BDP-HFA.

* laboratory tests: baseline and study day 15.

* vital signs: baseline and study day 15.

* total serum and serum beclomethasone levels: baseline before starting treatment; at 1, 2, 4, 6, 9, and 12 hours after the first dose of study drug and on day 14; ten patients; total serum beclomethasone included 17 BMP (beclomethasone 17-monopropionate), 21 BMP (beclomethasone 21 monoproprionate), beclomethasone and BDP; Cmax and AUC were evaluated after the first dose and at steady state on day 14.

* serum osteocalcin: baseline; study day 14.

* trifluoroacetic acid (TFA) measurements: < 0.006% of HFA-134a is metabolized to TFA; 24 hour urine measurements were made on the first 12 patients randomized at baseline and on the two 24 hour urines obtained on days 12-14.

ASSESSMENT OF HPA FUNCTION

* ACTH stimulation test (rapid cosyntropin test): screening and on study day 15.

* 24 hour urinary free cortisol: baseline (day –3 to day –2 and day –2 to day –1); study days 12-13 and 13-14; aliquots of urine were taken for the periods 8PM-7AM, 7AM-9AM and 9AM-8PM; the change from baseline in 24 hour urinary free cortisol on "day 14" (the average across days 12-13 and 13-14) versus total daily dose was used to assess the regression line for BDP-HFA, where baseline was the average across days –3 to –2 and –2 to –1; an assessment of a "no effect" dose was made by comparing the active treatment groups with placebo using Dunnett's test.

* plasma cortisol: baseline (study day –2 and study day –1) and on study days 13 and 14 at 7 AM and 9 AM.

☛ statistical considerations:

* Two patient populations were analyzed: an intent-to-treat population (ITT) and an evaluable population. The ITT population comprised all patients who had received at least one dose of study medication while the evaluable population were all patients who were compliant for a specific parameter. In the ITT analysis, the last non-missing value while on study medication was carried forward in the analysis, regardless of the reason the patient withdrew.

* A post-hoc analysis of baseline 24 hour urinary free cortisol was performed using ANOVA to assess comparability of treatment groups prior to treatment.

STUDY RESULTS

☛ ineligible patients: of the 63 patients who were screened, 5 were screened twice and 3 of these patients were entered into the study because their baseline FEV-1 had improved sufficiently; see table 7, p84, v1.51 below).

Table 7: Number (%) of Patients Screened but Ineligible for Randomization by Reason

Reason	No. of patients (%)
Laboratory Abnormalities	7 (35.0%)
Violation of Inclusion/Exclusion Criteria	3 (15.0%)
FEV_1 < 60% of predicted	3 (15.0%)
FEV_1 Reversibility < 15%	1 (5.0%)
Abnormal ECG	1 (5.0%)
Screening Visit plasma cortisol not within reference range	1 (5.0%)
Other	4 (20.0%)
Total	20