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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-911

Pharmacology Review(s)

Barnes

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Chemistry Consult #3

NDA No. 20-911 **Date of Consult:** 15 OCT 1999

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 27 JAN 2000

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: 3M Pharmaceutical Division

Drug Name: *Generic:* Beclomethasone dipropionate *Commercial:* QVAR™

Chemical name: 9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Formula: $C_{28}H_{37}ClO_7$

Molecular Weight:

Drug Class: Steroid

Proposed Clinical Dose:

Clinical formulation: Beclomethasone dipropionate (QVAR™) in propellant HFA-134a and ethanol

Review:
Dr. Alan Schroeder requested a safety assessment of the sponsor's responses to comments 6b(2), 13o and 22 in the Division's AE letter dated 5/12/99, which originated in pharmacology consult reviews dated 5/11/99 and 5/12/99. Each of the relevant responses by the sponsor will be individually evaluated for adequacy.

Division Comment 6b(2): Individually limit the levels of the —— —— and —— of beclomethasone dipropionate to less than or equal to 0.1% in the drug substance, or adequately qualify the compounds.

Sponsor's response: The drug substance supplier, —— has tightened their specification for the —— to not more than — %, and 3M Pharmaceuticals has adopted this limit. The sponsor will further adjust their specifications based upon the drug substance supplier's action.

Evaluation of Sponsor's response: The Sponsor's response to the Division comment is currently inadequate as they have not met the Division request to limit the levels of the — —— of beclomethasone dipropionate to less than or equal to 0.1% in the drug substance, or adequately qualify the compounds. In addition, in order to maintain consistency with other products in the Division, the sponsor should limit the substance levels to less than 0.1% in drug substance, rather than the previously requested less than or equal to 0.1%. This change is added since the previous request allows for levels in drug substance up to — % due to numerical rounding considerations.

Division Comment 13o: Limit the level of —— to less than or equal to 0.1% in the drug product, or provide adequate qualification for this degradation product. Additional comments on drug-related impurity specifications are withheld pending further information.

Sponsor's response: The drug substance supplier, —— has tightened their specification for the —— to not more than — %, and 3M Pharmaceuticals has adopted this limit. The level of — in the drug product has been tightened to not more than — %, considering the data generated in the stability program. The sponsor will further adjust their specifications based upon the drug substance supplier's action.

Evaluation of Sponsor's response: The Sponsor's response to the Division comment is currently inadequate as they have not met the Division request to limit the level of the —— —— of beclomethasone dipropionate to less than or equal to 0.1% in the drug product, or adequately qualify the compounds. As in the above case, in order to maintain consistency with other products in the Division, the sponsor should limit the substance levels to less than — % in drug product, rather than the previously requested less than or equal to 0.1%.

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secret and/or

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information

Overall Summary and Evaluation: The Sponsor submitted a response to some of the Division requests concerning degradation products in the drug product, impurities in the drug substance and extractable sin the drug product. The Sponsor's response to the Division's comments regarding drug substance and drug product degradants and extractables are currently inadequate since the Sponsor has not met the Division's request to limit the levels of the ——— ——— of beclomethasone dipropionate to less than 0.1% in the drug substance or product (——— only), or adequately qualify the compounds. Furthermore, the sponsor has not provided adequate information to mollify the Division's concerns over the presence of the extractables ——— in the drug product. These extractables are classified as ——— ——— and only limited toxicity information, especially via the inhalation route, was provided by the sponsor. Thus, the sponsor should either limit the levels of the the ——— ——— of beclomethasone dipropionate to less than % in the drug substance or product ——— only), or adequately qualify the compounds, and should provide adequate qualification for the extractables ———

HFD-570 : DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Labeling Review

NDA No. 20-911 **Submission Date:** 07 MAY 1999

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 12 SEP 2000

Information to be Conveyed to Sponsor: Yes (✔), No ( )

Sponsor: 3M Pharmaceutical Division

Drug Name: *Generic:* Beclomethasone dipropionate *Commercial:* QVAR™

Chemical name: 9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Formula: $C_{28}H_{37}ClO_7$

Molecular Weight:

Drug Class: Steroid

Route of Administration: Oral inhalation

Background: The sponsor was previously requested to update the Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy subsections of the PRECAUTIONS section of the label (see letter dated 5/12/1999). The sponsor submitted revised draft labeling to the NDA which is evaluated below.

The following sections of the proposed label should be revised as follows to achieve consistency with the most recent label for orally inhaled beclomethasone products (Vanceril 84 µg Double Strength; NDA 20-486) and 21 CFR part 201:

The section "**Animal Pharmacology and Toxicology**" should be deleted.

A "**Carcinogenesis, Mutagenesis, Impairment of Fertility:**" section should be added to the label prior to the "**Pregnancy**" section and should read as follows:

The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day.

Beclomethasone dipropionate did not induce gene mutation in bacterial cells or mammalian Chinese Hamster ovary (CHO) cells in vitro. No significant clastogenic effect was seen in cultured CHO cells in vitro or in the mouse micronucleus test in vivo.

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 200 times the maximum recommended human daily inhalation dose on a mg/m^2 basis). Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 20 times the maximum recommended — daily inhalation dose · —

— No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg (approximately 15 times the maximum recommended — daily inhalation dose · —

The "**Pregnancy**" section should read as follows:

Pregnancy: Teratogenic Effects: Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate was teratogenic and embryocidal in the mouse and rabbit when given at a dose of 0.1 mg/kg/day in mice and or at a dose of 0.025 mg/kg/day in rabbits. These doses in mice and rabbits were approximately one-half the maximum recommended — daily inhalation dose — No teratogenicity or embryocidal effects were seen in rats when exposed to an inhalation dose of —

—. There are no adequate and well controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The section entitled "**Non-teratogenic Effects:**" should read as follows: Findings of drug-related adrenal toxicity in fetuses following administration of beclomethasone dipropionate to rats suggest that infants born of mothers receiving substantial doses of QVAR during pregnancy should be observed for adrenal suppression.

The paragraph immediately following the "**Non-teratogenic Effects:**" section ("Well-controlled trials relating to fetal risk ...") should be deleted.

The section entitled "**Nursing Mothers:**" should be revised as follows:

Corticosteroids are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from QVAR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

An "**OVERDOSAGE**" section should be added to the label and should read as follows:

There were no deaths over 15 days following the oral administration of a single dose of 3000 mg/kg in mice, 2000 mg/kg in rats, and 1000 mg/kg in rabbits. The doses in mice, rats, and

rabbits were 19,000, 25,000, and 25,000 times, respectively,

APPEARS THIS WAY
ON ORIGINAL

Based upon the above comments, the following sections of the label should read as follows with additions and deletions marked accordingly:

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

RECOMMENDATIONS

1. The proposed labeling submitted by the sponsor is acceptable, with incorporation of the suggested revisions for the labeling sections entitled: Animal Pharmacology and Toxicology, Clinical Pharmacology, Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy, Nursing Mothers, and OVERDOSAGE as indicated above.

2. The sponsor should address a discrepancy related to the maximum dose tested in the Segment II reproductive toxicity study performed in rats using the QVAR formulation (Study number L08398). The available information suggests a maximum inhaled dose of 28.3 mg/kg/day was tested while the sponsor refers to a maximum dose of 15 mg/kg in the proposed label. Corrections to the label should be made accordingly.

/S/

Timothy J. McGovern, Ph.D., Pharmacologist

Original NDA 20-911
CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/S. Barnes
HFD-570/R. Nicklas
HFD-570/T.J. McGovern

Comment for Letter to the Sponsor:

The Division's records indicate that a maximum inhaled dose of 28.3 mg/kg/day was tested in the Segment II reproductive toxicity study performed in rats using the QVAR formulation (Study number L08398) while your proposed label refers to a maximum dose of 15 mg/kg. Please address this discrepancy and correct the label accordingly.

Drug: **QVAR**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric				0	3	0.00	25	0.00
Adult	>12	0.08	8	0.64	50	0.01	37	0.47

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	IH/oral	2.4	6	14.4	30.4	---	30	---
mouse			3	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
Reproduction and Fertility:								
rat	oral	16	6	96	202.7	N/A	200	N/A
rat			6	0	---	N/A	---	N/A
dog	oral	0.5	20	10	21.1	N/A	20	N/A
dog	IH	0.33	20	6.6	13.9	N/A	15	N/A
Teratogenicity:								
mouse	sc	0.1	3	0.3	0.6	N/A	1/2	N/A
rat	IH	28.3	6	169.8	358.5	N/A	360	N/A
rabbit	sc	0.025	12	0.3	0.6	N/A	1/2	N/A
rat			6	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
Overdosage:								
mouse	oral	3000	3	9000	19003.4	---	19000	---
rat	oral	2000	6	12000	25337.8	---	25000	---
dog			20	0	---	---	---	---
rabbit	oral	1000	12	12000	25337.8	---	25000	---
Other:	(Describe studies here)							
rat			6	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Chemistry Consult #4

NDA No. 20-911 **Date of Consult:** 29 OCT 1999
04 JAN 2000

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 17 FEB 2000

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: 3M Pharmaceutical Division

Drug Name: *Generic:* Beclomethasone dipropionate *Commercial:* QVAR™

Chemical name: 9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Formula: $C_{28}H_{37}ClO_7$

Molecular Weight:

Drug Class: Steroid

Proposed Clinical Dose:

Following discussion with the team Medical Officers, it was considered that 8 actuations/day is likely to be the maximum practical number of actuations.

Clinical formulation: Beclomethasone dipropionate (QVAR™) in propellant HFA-134a and ethanol.

Review:
Dr. Kevin Swiss and Dr. Alan Schroeder, in separate consults, requested safety assessments of information from DMF ( ) concerning canister residues and particles under — diameter, and safety assessments of updated placebo leachables data, qualification of drug product impurities and particles under — diameter in the drug product. The issues are assessed individually below.

Vol. of individual particle = 4/3 πr^3 = 1.33 (3.1416) $(5)^3$ = 522.29 μm^3 = 0.52229 x 10^{-9} cm^3

Weight of individual particles = (vol.)(density) = (0.52229 x 10^{-9})(1) = 5.2229 x 10^{-7} mg/particle

Total particulate mass = (particle #/day)(weight/particle) = (2136)(5.2229 x 10^{-7}) = 1.12 µg/day

Safety factor = EPA PM_{10} standard / total particulate mass = 700 / 1.12 = 627

The potential for inhaled particles using QVAR is approximately 627-fold below the EPA limit for particles under 10 µm. Even considering the more conservative number of daily actuations (16), a safety factor of 314 is expected. Thus, the expected particulate exposure from the use of the — canisters is considered to be reasonably safe.

3) The significant safety margin (approximately 625-fold) provided by the potential exposure to particulate matter less than 10 µm from QVAR suggests that the applicant does not need to institute quality controls. Secondly, the particle density calculations provided are acceptable, although the sponsor uses incorrect values for number of particles per actuation (— and number of actuations per day — in determining the total daily mass exposure. Also, the sponsor uses the ACGIH Threshold Limit Value of 10 mg/m^3 for Particles not Otherwise Classified (PNOC) and assumes 10 m^3 is the total inhaled volume for the average worker during an 8 hour day. The assessment provided in Point 2 above uses the more conservative EPA limit and calculations are based upon a total daily inhaled volume of 14 m^3 for a 50 kg individual. In addition, the sponsor assumes the particle diameter to be — µm and the particle density to be — g/cm^3. Although the sponsor's calculations result in a significantly greater safety margin compared to that calculated in Point 2 —, the overall conclusions derived from both approaches, namely the potential particle exposure less than 10 µm in diameter from use of — canisters is within safe limits, is consistent.

Foreign particles in the drug product formulation: The sponsor submitted additional information pertaining to potential exposure to particles less than 10 µm from the drug product formulation in an amendment dated 11/10/1999. A — technique was used to assess particles 2 µm or greater in diameter and laser light scattering was used to assess particles less than 2 µm in diameter. An — technique was used to test the drug product. Sample preparation required ten actuations into a clean glass vial fitted with a custom adapter. The particulate profile was evaluated by sequentially collecting groupings of ten actuations out to the labeled number of actuations of the product. Single units from six lots which were 18 to 24 months old were evaluated. Particulate counts were consistently higher in the first MDI actuations, with a plateau occurring at about 30 actuations. Therefore, the sponsor presented a worst case scenario based upon data from the initial MDI actuations. In terms of particle count, the maximum count per actuation was — with the average size distribution being —% less than 5 µm in diameter (—% less than 1 µm).

A particulate material analysis determined that the inorganic component was primarily [redacted] and that the organic component was primarily [redacted] %) by weight of material. The average particulate size in each count bin was used to determine particle volume, which in turn was used to determine particle mass in each size bin using the density and the ratio of the chemical components by the following equation:

$$Mass_{size} = (Count_{size} \times Volume_{size}\ cm^3 \times 4.0\ g/ml \times 0.57) + (Count_{size} \times Volume_{size}\ cm^3 \times 0.95\ g/ml \times 0.43)$$

Based on these calculations, it was determined that the maximum particulate mass per actuation was 5.44 µg (average mass = 2.15 µg), with only 16% of the total mass made up of particles less than 5 µm in diameter. Thus, the maximum mass/actuation for [redacted] is equal to 3.1 µg and 2.34 µg, respectively. Table 1, below, summarizes this information and contrasts the maximum expected particle exposures with relevant exposure limits.

Table 1

Compound	Max. mass (µg) per actuation	Max. daily exposure < 10 µm[1] (µg)	TLV[2] (µg)	Safety Factor[4]	EPA[3] (µg)	Safety Factor[4]	Max. daily exposure < 2.5 µm[1] (µg)	EPA[5] (µg)	Safety Factor[4]
[redacted]	3.1	24.8	70,000	2,800	NA	NA	NA	NA	NA
[redacted]	2.34	18.72	NA	NA	NA	NA	NA	NA	NA
Total	5.44	43.52	-	-	700	16	2.4	210	88

1 Based upon 8 actuations per day.
2 Threshold Limit Value = 10 mg/m³ = 70,000 µg based on assumed inhalation of 7 m³ for 8 hours for 50 kg individual
3 U.S. Environmental Protection Agency (EPA) daily PM_{10} exposure limit (annual basis) = 50 µg/m³ = 700 µg based on assumed 24 hour inhalation of 14 m³ for 50 kg individual.
4 Equal to relevant exposure limit divided by the Max. Daily Exposure
5 U.S. Environmental Protection Agency (EPA) daily $PM_{2.5}$ exposure limit (annual basis) = 15 µg/m³ = 210 µg based on assumed 24 hour inhalation of 14 m³ for 50 kg individual.
NA: Not applicable.

Based upon the information above, the maximum expected particulate exposure is considered to be reasonably safe since exposure to [redacted] is well below the TLV and both the individual and combined expected particulate exposure fall below the EPA limits set for particulate matter less than 10 µm or 2.5 µm in diameter. It should be noted that no exposure limits have been specifically set for [redacted] a component which may be a source of [redacted] However, the potential for pulmonary exposure to [redacted] via inhaled [redacted] particles is expected to be minimal compared to levels observed in placebo canisters (see the following section on placebo leachable data) due to particle clearance mechanisms in the lung and the greater potential for [redacted] leaching in the drug vehicle (HFA formulation) than in the pulmonary milieu.

By combining the canister particulate (1.12 µg) and drug formulation particulate (43.52 µg), the maximum expected exposure to particulate material less than 10 µm in diameter is equal to 44.64 µg/day. Thus, when compared to the EPA exposure limit of 50 µg/m³ per day for particulate

material less than 10 µm in diameter, a safety factor of 16 is achieved. Thus, the potential exposure to particulate material of less than 10 µm in diameter is considered to be reasonably safe.

Safety Assessment of Updated Placebo Leachable Data: A previous Chemistry Consult regarding placebo leachables (Chemistry Consult #1, dated 5/12/1999) did not include information pertaining to — — data was included in an amendment dated 8/17/1999 and the Chemistry reviewer, Dr. Alan Schroeder has requested a safety assessment of the observed — levels.

The determination of — in the HFA-134a MDI placebo formulation was performed at 35 month pull point at 25 degrees Celsius and 60% RH. The analytical method was based on the AOAC Official Method 987.05 and sample preparation consisted of pooling contents from 10 cans, addition of — as internal standard and evaporation of the solvent to a final volume of 1 ml. Table 2, below, summarizes the mean — levels found in actuator components versus the maximum values observed in QVAR Placebo Formulation from three test protocols.

A memo from Dr. Schroeder (dated 1/12/2000) indicates that the method used to evaluate levels of — in placebo provides low recoveries of —
%, respectively). Thus, reported placebo levels were adjusted for either their recovery percentages or for the maximum possible present to be considered BLQ.

Table 2

Compound	MDI Component					
	(ng/part)	(ng/part)	O-ring (ng/part)	Sum of Component Extractables (ng/can)	Maximum Placebo Leachables (ng/can)	Adjusted placebo findings* (ng/can)
	0.38	0.04	0.35	0.8	2.4	9.82
	0.18	0.02	0.26	0.5	1.3	2.89
	0.29	0.03	Blq	0.3	2.9	3.77
	Blq	Blq	Blq	Blq	Blq	1.07
	Blq	Blq	Blq	Blq	Blq	0.96
	0.12	0.01	0.79	0.9	Blq	1.59
Total				2.5	6.6	20.1

Blq = below limit of quantitation

Values in parentheses are the limits of quantitation of the individual

*Adjusted placebo findings are calculated based upon the lowest reported recoveries for each of the species — and
— and the maximum amount present for those species reported as Blq.

Based upon the maximum reported levels of total [redacted] in the placebo formulation, and the adjustments made for percentage recovery of the various species, the expected maximum exposure to total [redacted] is estimated to be 0.032 ng/kg/day. This estimate is based upon the following calculations:

20.1 ng total [redacted] /can ÷ 100 actuations/can = 0.201 ng/actuations

0.201 ng/actuations * 8 actuations/day = 1.61 ng/day or 0.032 ng/kg/day (for a 50 kg individual)

A previous safety assessment of inhalation exposure to total [redacted] (performed by Dr. Lawrence Sancilio for NDA 20-236, Chemistry Consult dated March 16, 1995) determined that the maximum acceptable inhalation dose of total [redacted] is 0.04 ng/kg/day in which the carcinogenicity risk was equivalent to 1 x 10^{-5} or 1:100,000 (determined from long term inhalation of [redacted] in rats). Thus, the expected maximum exposure to total [redacted] of 0.032 ng/kg/day in the current drug product is acceptable since it would pose a risk of less than 1:100,000 (1:125,000). In a previous Chemistry Consult by Dr. Mark Vogel for Proventil HFA (NDA 20-503, 10/28/2000), the total possible number of actuations based upon total formulation in the canister and total formulation/actuation was used rather than the recommended number of actuations/canister to determine the overall carcinogenic risk estimate. Using this approach, the total possible number of actuations for QVAR would be ~ 145 with a more realistic use of ~ 125. This latter estimate would result in a total possible [redacted] exposure of 0.025 ng/kg/day and a carcinogenic risk estimate of 1:155,000.

Qualification of Drug Substance and Drug Product Impurities/Degradation Products: The sponsor has been previously requested to lower their specifications for the drug product degradant and drug substance impurity [redacted] and the drug substance impurities [redacted] and [redacted] to less than [redacted] % or provide adequate qualification due to the presence of a structural alert for mutagenicity with the [redacted] molecule and inadequate toxicity assessment of [redacted] in preclinical toxicity studies (see Chemistry Consult #2 for NDA 20-911, dated May 11, 1999). The request for qualification was repeated in a response to the sponsor's comments concerning qualification of these molecules (see Chemistry Consult #3 for NDA 20-911, dated January 27, 2000). Specifically, the sponsor stated that the drug substance supplier, [redacted] had tightened their specifications for the [redacted] to not more than [redacted] % in the drug substance, and that the level of [redacted] in the drug product had been tightened to not more than [redacted] %. Specifications for [redacted] were not addressed. The sponsor's response was considered to be inadequate.

In an amendment dated November 10, 1999, the sponsor submitted further comments concerning qualification for these compounds. The sponsor states that all drug substance lots used during the QVAR development program were tested for purity at [redacted] and that the lots used in toxicology studies have equivalent purity levels to those used in clinical/stability studies (99.0-99.9%). Impurities methods were not available for characterization of the drug substance used in the early toxicology studies. However, the sponsor did include data from lot PD3511 used in the 52 week inhalation toxicity study (Report Number 0793CD0401) in dogs. Samples were tested

with the final finished product impurities method 46 months post manufacture and compared with the results of the finished product lots used in clinical studies. The levels of the compounds of concern in lot PD3511, as well as estimated safety factors, are summarized in Table 3. The calculations of safety factors are described below. Comparatively, levels determined in clinical drug lots were potentially greater than that used in preclinical studies; BLD (below limit of detection, < — %) to — % for —— BLD to —% for —— and BLD to — % for ——

The sponsor states that the purity level of BDP drug substance is very high and the impurity levels very low as the three compounds in question are only marginally above the 0.1% level. The sponsor concludes that there is no safety concern since the impurities have likely been present in both preclinical and clinical trials and since patient exposure to these impurities is extremely low.

The safety factors for —— range from < 0.26 to 2.34 and are below the safety margin of 6 needed for qualification using preclinical data from dogs. The sponsor should, thus, reduce their proposed specifications for the drug substance impurities to < 0.1% or adequately qualify the impurities according to ICH guidelines. In addition, proposed specifications exceeding ≥ 0.1% for —— in the drug product or drug substance should be supported by qualification for mutagenicity (one point mutation and one cytogenetic assay with the isolated compound) due to the presence of a structural alert.

Table 3:

Impurity	Abbr.	Proposed Limit %	max ng/kg	Preclinical Dose %*	ng/kg	Species	Duration	Route	Safety Margin
		≤ 0.3	38.4	BLD	<10	Dog	52 wk	IH	<0.26
		≤ 0.3	38.4	0.15	75	Dog	52 wk	IH	1.95
		≤ 0.2	25.6	0.12	60	Dog	52 wk	IH	2.34

* Percentage of individual impurities based upon drug product analysis of lot PD3511 performed 46 months after manufacturing. Only a total impurity level was determined after 12 months. Total impurities increased at 46 months (%), thus, levels at this time are assumed to be greater than when tested during the 52 week study (% at 18 months after manufacture). Levels of and are assumed to remain stable since they are drug substance process impurities only, while levels increase with time.

BLD: Below level of detection (below %, w/w, no peak detected).

Safety Factor Calculations

Maximum Clinical Dose - ——
(0.3% x 80 µg/actuation x 8 actuations/day) ÷ 50 kg person = 38.4 ng/kg/day

Preclinical Dose:
0.15% x 0.05 mg/kg (NOAEL dose, 52 wk juvenile dog) = 75 ng/kg/day

Safety margin = Preclinical dose ÷ Clinical dose
= 75 ng/kg/day ÷ 38.4 ng/kg/day = 1.95

Maximum Clinical Dose - ——
(0.3% x 80 µg/actuation x 8 actuations/day) ÷ 50 kg person = 38.4 ng/kg/day

Preclinical Dose:
0.02% x 0.05 mg/kg (NOAEL dose, 52 wk juvenile dog) = 10 ng/kg/day

Safety margin = Preclinical dose ÷ Clinical dose
= 10 ng/kg/day ÷ 38.4 ng/kg/day = 0.26

Maximum Clinical Dose - ——
(0.2% x 80 µg/actuation x 8 actuations/day) ÷ 50 kg person = 25.6 ng/kg/day

Preclinical Dose:
0.12% x 0.05 mg/kg (NOAEL dose, 52 wk juvenile dog) = 60 ng/kg/day

Safety margin = 60 ng/kg/day ÷ 25.6 ng/kg/day = 2.34

Overall Summary and Evaluation: A safety assessment of the acceptance criterion for residual —— in inhalation aerosol canisters, potential exposure to particulate matter under 10 µm in diameter from the inhalation canister and the drug product, updated —— leachable data and the sponsor's response to previous Division comments regarding drug substance impurities and drug product degradants was performed. The acceptance criterion set for residual —— in the inhalation canister was acceptable since the components were at relatively low levels (—— compared to the total drug product exposure. The potential for exposure to particulate matter from either the canister or from the drug formulation or both is considered to be reasonably safe as it is within set exposure limits by a factor of 16 to 625. As for the primary particulate components, the potential —— exposure provides a safety factor of > 2,800 in comparison to the TLV while no set standards have been set for —— —— levels in the placebo leachable data set are considered to be reasonably safe

from 3M

7/1/98 FAX
from 3M

NDA 20-911

Response to questions from Dr. Schroeder:

Have there been any changes in the formulation during the clinical program, NDA stability or from what is intended to be the marketed product.

The formulation has remained unchanged during the clinical program and NDA stability program, and is the same formulation as is intended to be marketed.

Have there been any changes in the valve and actuator during the clinical program, NDA stability or from what is intended to be the marketed product.

The actuator has remained unchanged throughout development, as discussed on page 10 of Volume 1.3 of the NDA (Section 2.6 of the Development Pharmaceutics Report). A ——— was used to produce actuators during development and this has been scaled up to ——— at two vendors. Information about qualification of the scale-up is presented on pages 43 – 51 of Volume 1.3 of the NDA (Section 3.7.4 of the Development Pharmaceutics Report).

Changes to the valve during development are described on pages 7 – 9 of Volume 1.3 of the NDA (Section 2.4 of the Development Pharmaceutics Report). The final revision to valve (improvement of stem manufacturing) was not used in the clinical program of this NDA. A comparison of this final version to the stability database begins on page 63 of Volume 1.3 of the NDA (Section 3.7.5.5 of the Development Pharmaceutics Report). A table of the sequence of modifications of the valve relative to the development cycle is presented below.

Development Time Scale:	**IND Stability**	**NDA Stability**	**Marketed Product**
Clinical Time Scale:	**Phase 1/Phase 2**	**Phase 3**	
Valve			
Canister	Unchanged throughout development		
O-ring	Unchanged throughout development		
Formulation Composition	Unchanged throughout development.		
Actuator	Unchanged throughout development.		

since they would pose a risk of less than 1:100,000 (1:125,000). The estimated safety factors for ——— range from < 0.26 to 2.34 and are below the safety margin of 6 needed for qualification. The sponsor should, thus, reduce their proposed specifications for the drug substance impurities to < 0.1% or adequately qualify the impurities according to ICH guidelines. In addition, proposed specifications exceeding ≥ 0.1% for ——— in the drug product or drug substance should be supported by qualification for mutagenicity (one point mutation and one cytogenetic assay with the isolated compound) due to the presence of a structural alert.

RECOMMENDATIONS

1. The acceptance criterion set by 3M Neotechnic Ltd. for residual ——— in inhalation aerosol canisters is acceptable due to the relatively low levels of potential exposure to the canister residue.

2. The potential exposure to particulate material of less than 10 μm in diameter from the ——— inhalation canister or the drug product formulation is acceptable.

3. The expected maximum ——— exposure based on placebo leachable data presents an acceptable carcinogenicity risk of below 1:100,000.

4. As recommended in Chemistry Consult #3, the sponsor should limit the specifications for ——— to less than 0.1% in the drug substance or qualify the compounds according to ICH guidelines.

5. The sponsor should limit the level of ——— to less than 0.1% in the drug product or provide adequate qualification for the degradant in terms of mutagenicity potential.

/S/ 2/17/2000
Timothy J. McGovern, Ph.D. Pharmacologist

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/A. Schroeder
HFD-570/K. Swiss
HFD-570/S. Barnes
HFD-570/T.J. McGovern

/S/ 2/17/2000
(See IL addendum) /S/ 02/17/00

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pages of trade

secret and/or

confidential

commercial

information

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original NDA Review

NDA No.: 20-911

Dates and content of submissions:
12 MAY 1998 Original submission
13 JAN 1999 Supplement, Response to Toxicology Concerns

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 06 MAY 1999

Information to be Conveyed to Sponsor: Yes (✓), No ( )

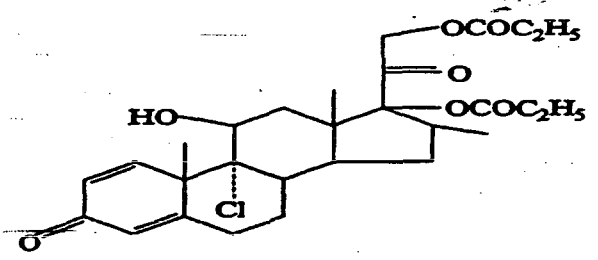
Sponsor: 3M Pharmaceutical Division
St. Paul, MN

Manufacturer: 3M Pharmaceuticals, Northridge, California
3M Health Care Limited, Loughborough, Leics, UK

Drug Name: *Trade:* QVAR™ —— Inhalation Aerosol; 50 (40) µg, 100 (80) µg
Generic: Beclomethasone dipropionate (BDP)

Chemical name: 9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Structure:



Formula: $C_{28}H_{37}ClO_7$

Molecular Weight: 521.05

Drug Class: Steroid

Indication: Asthma as prophylactic therapy —— and asthma for patients requiring systemic corticosteroid administration.

Proposed Clinical Dose:

Clinical formulation: A solution of BDP (QVAR™) in propellant HFA-134a and ethanol. Unit doses are packaged in two different sizes (100 or 200 actuations per cannister) and two strengths in each size (80 and 40 µg per actuation, ex-actuator).

Ingredient	**Amount (mg/actuation)**			
	100 actuation canister		**200 actuation canister**	
	50 µg (ex-valve)	100 µg (ex-valve)	50 µg (ex-valve)	100 µg (ex-valve)
BDP, USP				
Dehydrated Alc.				
HFA-134a				
Total:	**59.000**	**59.000**	**59.000**	**59.000**

Route of Administration: Oral inhalation

Related INDs/NDAs/DMFs:

NDA 17-573	Schering	Vanceril	metered dose inhaler
NDA 18-153	Glaxo Wellcome	Beclovent	metered dose inhaler
NDA 18-521	Schering	Vancenase	nasal inhaler
NDA 18-584	Glaxo Wellcome	Beconase	nasal inhaler
NDA 19-389	Glaxo Wellcome	Beconase AQ	42 µg nasal spray
NDA 19-589	Schering	Vancenase AQ	42 µg nasal spray
NDA 20-469	Schering	Vancenase AQ	84 µg nasal spray
NDA 20-486	Schering	Vancenase D.S.	84 µg MDI
NDA			
IND			
IND			
IND			
IND			
IND			
IND			
IND	3M Pharma.		
IND	3M Pharma.		
IND			

DMF — DMF — DMF — DMF — DMF — DMF —

Previous Review: None for this NDA.
IND

Original review by Dr. Mukherjee (submission date: 4/28/1993; review date 5/24/1993)
Review #2 by Dr. Choi (submission date: 1/16/1995; review date: 2/11/1995)
Review #3 Dr. Williams (submission date: 6/17/1997; review date: 2/23/1998)

Studies or responses reviewed within this submission:

Supplement, Response to Toxicology Concerns (dated January 13, 1999)

Studies reviewed under IND (see attached reviews for IND

Toxicology Studies

Study # 0791AD0137:	Acute toxicity of BDP/HFA-134a in dogs by inhalation.
Study # 0791RR0511:	7-day nose-only inhalation to BDP/HFA-134a formulation in rats.
Study # 0791AD0138:	7-day inhalation study to BDP/HFA-134a formulation in dogs.
Study # 0791SR0512:	28-day inhalation toxicity to BDP/HFA-134a formulation in rats.
Study # 0791SD0139:	28-day inhalation study in beagle dogs.
Study # 0792SR0390:	90-day inhalation toxicity study of HFA-BDP in rats.
Study # 0793CD0401:	52-week inhalation toxicity study in dogs.

Reproductive Toxicology

Study # 0792TR0435:	Pilot nose-only inhalation developmental toxicity study in rats.
Study # 0792TR0391:	Inhalation development segment II toxicity study of BDP study in rats.

Pharmacokinetics

Report #CTL/R/1090:	Kinetics and metabolism of HFA-134a after single dose exposure by inhalation in rats. (Submitted to IND only).

Note: Portions of this review were excerpted directly from the sponsor's submission.

Background: BDP is a diester of beclomethasone, a synthetic anti-inflammatory corticosteroid which is chemically related to prednisolone. BDP is approved for oral and nasal inhalation in asthma (Vanceril, NDA 17-573; Beclovent, NDA 18-153; Vancenase, NDA 18-521; Beconase, NDA 18-584, Beconase AQ, NDA 19-389; Vancenase AQ, NDA 19-589; Vancenase AQ, NDA 20-469; Vanceril Double Strength, NDA 20-486. This drug has been marketed in England since 1972. The present submission focuses on recent inhalation findings using HFA-134a propellant in the formulation.

This NDA submission has been filed under the provisions of 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. A significant portion of the preclinical development program for BDP was reviewed under the previously listed NDAs and related INDs. The new studies submitted in the present application include toxicology and reproductive toxicology studies to support an HFA-134a formulation using a metered dose inhaler for asthmatics aged 12 and over. The sponsor stated that the toxicology studies specific to the HFA formulation, and reviewed under IND ( ) utilized the same BDP, excipients, basic manufacturing process, and impurity levels as were utilized in the clinical program and are expected in the marketed product. Early toxicity studies (0791AD0137, 0791RR0511, 0791AD0138, 0791SR0512) employed a formulation containing — surfactant and ethanol (up to 15%). As development progressed, — was removed and the ethanol concentration was reduced to 8%. The remaining toxicity studies (0792SR0390, 0791SD0139, 0793CD0401) used no — and ethanol levels were 8% in the formulation to match the proposed marketed product.

REVIEW OF SPONSOR'S RESPONSE TO TOXICOLOGY CONCERNS (SUPPLEMENT #1)

Following submission of the Original NDA submission, the sponsor was asked to address three areas which were still outstanding from the previous IND reviews. These issues included an increased incidence of prostatitis in the high-dose BDP/HFA group in a 52 week juvenile dog study, a request for a more detailed examination of the trachea and alveoli, and an increased incidence of red/red foci in the adrenals at the two highest doses in a segment II reproductive toxicity study in rats. A review of the sponsor's response to these issues follows.

The 52-week juvenile dog study was originally requested to assess the potential for tracheal deformities. Although no positive findings were reported in this study, the standard gross and histological examinations of the pulmonary system employed were considered to be inadequate to detect possible morphometric, macroscopic, and/or microscopic changes in the trachea. The sponsor was asked at a pre-NDA meeting (September 8, 1997) to perform a more detailed examination of the trachea and lung tissues, if available, in order to address this particular concern. The sponsor addressed this concern in the original NDA submission, stating that comparative assessment of airway/alveolar caliber measurements was not possible since the exact airway generation present in a particular microscopic field could not be determined. The sponsor also stated that no evidence of incomplete maturation was present at any dose level following histological examination. The sponsor further responded in the following submission that gross observations and observations and interpretations by at least two pathologists using light microscopy indicated no treatment-related effects on tissue maturation in the trachea. Although no data was submitted, the sponsor stated that cell populations appeared to be proper for each area of the trachea examined, and there were no indications of increased basal cell numbers, a possible indicator of maturation arrest. Numbers and types of goblet cells and ciliated cells also appeared to be consistent with fully mature respiratory tracts. Thus, the sponsor's response to this issue is acceptable.

Generally, the toxicity profile in the 52-week juvenile dog study is consistent with chronic administration of corticosteroids. However, the sponsor was asked to address an increased incidence of prostatitis in high-dose BDP/HFA males (3 of 4) which was not observed with the CFC formulation. Increased systemic exposure in the BDP/HFA-administered animals compared to BDP/CFC dosing may have induced greater immunosuppressive effects leading to the increased incidence of prostatitis in the HFA group. However, the sponsor responded that the finding is possibly incidental due to the absence of a dose-response in terms of dogs affected (1 of 4 animals at the low-dose, none at the mid-dose) and severity grade (severe at the low-dose, moderate at the high-dose). The lack of inflammation in other organs, which would be associated with corticosteroid-related depression of lymphocyte populations also suggests that the findings are incidental. The sponsor also cited a reference (Jubb and Kennedy, Pathology of Domestic Animals, Academic Press, 1970) stating that prostatitis is common in the dog. The most recent edition of this text[1] also states that both acute and chronic prostatitis are common in dogs, although the text does not specify the expected incidence ratio in a population. In this regard, Maita et al[2] reported that prostatitis occurred in 13.7% of 420 beagles 1 to 4 years of age examined for spontaneous pathological changes. Although this percentage is significantly lower than that observed in the high-dose group of the 52-week juvenile study (75%), only 4 of 24 total males in the study (16.7%) demonstrated prostatitis. Thus, the sponsor's response to this issue is acceptable.

The sponsor's response to an increased incidence of red/red foci in the adrenals of F_1 fetuses at the two highest doses in a segment II reproductive toxicity study in rats was that these findings were due to congestion and/or hemorrhage in the adrenals and are expected following BDP exposure. These gross adrenal lesions confirm that dams received a large dose of BDP which was subsequently transferred to the pups in-utero. Thus, while the sponsor's response to this issue is acceptable, a statement should be included in the label indicating that BDP/HFA-134 can cross the placental membrane and induce adrenal toxicity similar to that in dams.

In all, the preclinical deficiencies cited in the Division's facsimile of December 4, 1998 have been adequately addressed.

OVERALL SUMMARY AND EVALUATION

Background: This NDA submission has been filed under the provisions of 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. A significant portion of the preclinical development program for BDP was reviewed under the previously listed NDAs and related INDs. The new studies submitted in the present application include toxicology and reproductive toxicology studies to support an HFA-134a formulation using a metered dose inhaler for asthmatics aged 12

[1] Pathology of Domestic Animals, Academic Press, Inc., 1993 (Eds.: Jubb, Kennedy and Palmer). Volume 3, Chapter 5: The Male Genital System.

[2] Maita K, Masuda H, Suzuki Y. 1977. Spontaneous lesions in the beagles used in toxicity studies. Jikken-Dobutssu: 26(2): 161-7.

and over. The sponsor stated that the toxicology studies specific to the HFA formulation, and reviewed under IND [redacted] utilized the same BDP, excipients, basic manufacturing process, and impurity levels as were utilized in the clinical program and are expected in the marketed product. Early toxicity studies (0791AD0137, 0791RR0511, 0791AD0138, 0791SR0512) employed a formulation containing [redacted] surfactant and ethanol (up to 15%). As development progressed, [redacted] was removed and the ethanol concentration was reduced to 8%. The remaining toxicity studies (0792SR0390, 0791SD0139, 0793CD0401) used no [redacted] and ethanol levels were 8% in the formulation to match the proposed marketed product.

SUMMARY OF ESTABLISHED PRECLINICAL PROFILE PRIOR TO IND [redacted]

Pharmacology: BDP produced typical glucocorticoid effects when assayed for thymolytic, pituitary-adrenal suppression and liver glycogen deposition activities in mice. BDP was as potent or more potent than dexamethasone or betamethasone, which in turn are more potent than hydrocortisone. No significant effect or slight, non-dose-related effects were observed in rats administered BDP, in contrast to findings with other glucocorticoids. BDP was also an effective anti-inflammatory agent in the rat with greater potency than hydrocortisone but similar to less potency compared to dexamethasone. No changes in the mucociliary function of the cat trachea was reported during a 30 minute observation period following administration of a 0.05% solution applied by aerosolization to exposed trachea in anesthetized cats as doses approximating 20, 50 and 130 µg/kg.

Pharmacokinetics: Oral absorption was generally low in dogs and the majority of the dose was excreted within 24 to 48 hours. However, absorption of BDP is rapid from the respiratory tract, gastrointestinal tract or when administered topically. Blood levels in rats following subcutaneous injection peaked at 5 hours after dosing. Metabolic studies in dogs showed that ~ 15% of the inhaled dose was present in the respiratory tract, two-thirds of which was in the lung and the remainder deposited in the larynx, trachea and main bronchi of dogs immediately after exposure. Corresponding values at 30 minutes post exposure were 4% and 1%, respectively. After 7 days, 0.3 to 0.5% was in the liver and smaller amounts in other tissues. About 70% of inhaled radioactivity had been released from the lung, trachea and bronchi after 30 minutes. There was no indication of storage in tissues obtained after 7 days. Drug-derived radioactivity was rapidly cleared from rat lungs following drug inhalation. BDP is metabolized to beclomethasone via beclomethasone 17-monopropionate. Other metabolites consisted of monopropionate ester, alcohol beclomethasone, and two unidentified compounds. In rats injected subcutaneously, a third unidentified metabolite was detected in the bile, urine and feces. The principle route of excretion is the feces for all routes of administration, although 12-15% of an oral dose was excreted in the urine as both conjugated and free metabolites. Rat and human lung tissue metabolized BDP to the monopropionate and beclomethasone in vitro. Plasma protein binding was reported as 87%.

Toxicology:

Acute Toxicity: Acute toxicity studies in three species revealed no deaths at 3 g/kg (mouse, sc, ip, po), 1 g/kg (rat, sc, ip, po), and 0.75 g/kg (rabbit, sc). Splenitis, fatty liver degeneration, slight kidney nephrosis and swelling of thymic reticular cells were demonstrated in animals dosed subcutaneously.

Repeated Dose Toxicity:

Local nasal irritation was not observed in a 14-day intranasal pilot study in cynomolgous monkeys (0.1 ml/nostril/qid of BDP (0.42% in suspension), Beconase (0.05% Aqueous Nasal spray), or Nasalide Nasal Solution (0.025%, 0.2 ml/nostril qid)), a one month nose-only inhalation study in the albino rat (12, 60 and 300 µg/k/day) or a one-month intranasal study in the beagle dog (6, 30 or 180 µg/kg/day). In rats, decreased WBCs and lymphocytes, increased neutrophils, and reduced liver weight (mid- and high-doses) were noted in the high-dose group. In dogs, primary findings included reduced absolute and relative adrenal weight at the mid- and high-doses, and adrenal atrophy of the zona fasciculata accompanied by coarse vacuolation of single or small groups of spongiocytes, and thymic cortex atrophy at the mid- and high doses. No toxicity was reported in dogs following 3-month inhalation of BDP (10% of dose reached the lung), while intramuscular injection of BDP in dogs for 4 months (0.5, 1.5, 4.5 mg/kg/day) induced changes indicative of excessive steroid dosage, although findings were less severe compared to doses of 0.45 mg/kg betamethasone. The differences in toxicity may be due to poor absorption of the dipropionate ester.

Chronic Toxicity: Chronic toxicity studies with BDP were performed in rats and dogs. Typical glucocorticoid effects were noted in animals administered BDP by the intramuscular (dogs) or subcutaneous (rats) routes: body weight depression, lymphopenia, liver glycogen depression, thymus involution, adrenal atrophy, and serum potassium elevation. Findings in the rat were less severe compared to those observed with dexamethasone, due possibly to poor absorption of the dipropionate ester. In rats treated by inhalation or inhalation/oral dosing for 6 months, reduced body weight, lymphopenia and low blood cortisol levels were noted in the absence of gross or microscopic lesions. Effects on the adrenal gland were specifically investigated in a 26-week rat study (inhaled aerosol doses of 400, 200 and 100 µg/kg/day) but demonstrated no organ weight or gross or microscopic changes.

A 26-week intranasal BDP exposure in dogs (up to 180 µg/kg) induced increased absolute and relative liver weights at the high-dose and a dose-related decrease in absolute and relative adrenal weight. Related microscopic changes included vacuolar changes in hepatocytes and adrenal cortical atrophy involving primarily the zona fasciculata. No microscopic alterations were detected in the nares, nasal turbinates and nasopharynx. Effects on the adrenal gland were also investigated in a 26-week dog study (inhaled doses of 20, 60 and 180 µg/kg/day). Findings included a dose-related decrease in absolute and relative organ weight; organs of high dose animals appeared small. Microscopic findings at the high-dose included severe cortical atrophy (primarily zona fasciculata and zona reticularis).

In dogs administered BDP for 12 months (up to 2000 µg/kg by inhalation plus 400 µg/kg orally), the principle toxic effects included increased liver weight, decreased adrenal weight and thymus weight, enlarged hepatocytes, atrophy of the adrenal zona fasciculata, and regression or absence of the thymus. These findings were associated with reduced lymphocytes, eosinophils, plasma cortisol levels, and adrenal axis function, and increased serum alkaline phosphatase, SGPT, and total protein. Other adverse reactions included a high incidence of convulsions and uncoordinated movement attributed to propellant and/or anoxia, narrowed or irregular tracheal caliber, and interference with sexual maturation or function in females. A second one-year inhalation/oral study (up to 2000 µg/kg IH, 1-2x daily, 500 µg/kg po, or both routes: 100 µg/day po plus 500 µg/kg IH, 1-2x daily) performed in dogs to assess effects on the reproductive tract and estrus of females and tracheal development demonstrated no abnormalities in tracheal dimensions. However, clinical suppression of estrus related to hypercortico-steroidism was noted in all treated dogs except the group dosed by inhalation only. Dogs dosed by inhalation also showed no effects on the ovary or uterus in terms of organ weight or gross and microscopic changes. Changes in organ weight and gross and microscopic changes following oral administration were related to the stage of the estrus cycle. The results were considered to negate concerns of effects on sexual maturation and tracheal development.

Reproductive Toxicology: Beclomethasone dipropionate was tested in the following reproductive toxicity studies:

ICI strain mice administered BDP (0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg/d, sc) from days 1-18 of pregnancy: increased incidence of cleft palate in fetuses and decreased thymus weight in dams at 0.1 mg/kg, increased resorptions and maternal mortality and decreased fetal weight at 3.0 mg/kg.

ICR strain mice administered BDP (0.01, 0.025, 0.05, 0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg/d, sc) from days 1-13 of pregnancy: decreased newborn and pup survival and an increased incidence of cleft palate at 0.3 mg/kg; complete mortality of offspring at 3 and 10 mg/kg.

Dutch Stride rabbits administered BDP (0.0025, 0.005, 0.01, and 0.1 mg/kg/d, sc) throughout pregnancy: decreased maternal weight gain, thymic involution, hepatic lipid and glycogen deposition, dilated renal tubules, 100% fetal resorptions, decreased live fetuses and fetal weight at 0.1 mg/kg, and malformed fetuses at 0.01 mg/kg.

Japanese White strain rabbits dosed with BDP (0.006, 0.025, 0.1, and 0.4 mg/kg/d, sc) from day 7-16 of pregnancy: decreased number of live fetuses, increased resorptions, external and skeletal abnormalities and delayed ossification at 0.025 mg/kg, reduced maternal weight gain at 0.1 mg/kg and 100% resorptions at 0.4 mg/kg.

AHA strain rats administered BDP (oral: 0.1, 1 and 10 mg/kg, inhalation: 0.1 mg/kg/d) from days 1-19 of pregnancy: subcutaneous hemorrhages in 4/62 fetuses at the low dose.

Thus, BDP produced teratogenicity and embryotoxicity in the mouse and rabbit. These adverse effects were not observed in rats dosed by inhalation or oral administration.

Carcinogenicity and Mutagenicity: The incidence and types of tumors observed in a 95-week rat study (100, 200 and 400 µg/kg by inhalation for 95 weeks; 0.2, 0.6 and 2 mg/kg, po, weeks 13-95) were comparable between control and drug-treated animals.

SUMMARY AND EVALUATION OF DATA SUBMITTED TO IND

Acute Toxicity: Food intake was reduced after the first day of exposure in a single male beagle dog, administered 250 inhalations of BDP (250 µg/actuation) in one day over a 5 hour period and 400 inhalations over a four hour period two days later (total nominal doses equaled 62.5 and 100 mg BDP (5.5 and 9.1 mg/kg), respectively). Clinical signs were unchanged.

Repeated Dose Toxicity: Typical glucocorticoid class effects were observed in rats administered BDP/HFA-134a for 7 or 28 days or 3 months (nose-only, one hour/day, chamber concentrations Day 7: 9, 58 and 463 µg/L, propellant concentration and dose in mg/kg not quantified; Day 28: 3, 25 and 47 µg/L BDP with HFA 134a, and 49 µg/L BDP with Propellant 11-12; dose in mg/kg not quantified 3 months: estimated inhaled daily doses excluding deposition factors were 0 (propellant control), 0.048, 0.24, and 1.25 mg BDP/kg, pulmonary doses 4.8, 24, and 125 µg/kg based upon 10% deposition). Significant findings after 7 days exposure included liver lesions, increased liver weight and reduced thymus weight at the mid- and high doses. After 28 days, body weight gain was reduced in high-dose males, and reduced thymus weight, associated with thymic atrophy, was noted in a dose-dependent manner. No hepatotoxicity was observed at 28 days, due possibly to the lower doses administered. The reviewer at the time noted that higher doses should have been administered in the 28-day study and that the sponsor did not calculate the dose deposited into the lung for both BDP and propellant. Following 3 months administration, the thymus was again the target organ as reduced organ weights and thymic lymphoid depletion were noted at the mid- and high-doses in females and the high-dose in males. Body weight gain was also mildly reduced in all treatment groups, and WBCs were reduced, due mainly to lymphocyte depletion, at the high-dose. All findings were reversible after 8 weeks. A NOAEL of 4.8 µg/kg (pulmonary dose) was identified in the 3 month study. The toxicity profile of BDP in the HFA formulation was comparable to that observed with the CFC formulation.

In dogs administered BDP/HFA-134a (with and ethanol via mouth-tube) for 7 or 28 days (7-day study: 0.54 or 5.43 mg BDP ex-valve/kg/day, propellant concentration not quantified; 28-day study: 0.22, 0.65 and 2.17 mg BDP ex-valve/kg/day), only findings related to the glucocorticoid effects of BDP were demonstrated. After 7 days, swollen hepatocytes and increased liver weight at the high-dose associated with increased transaminase levels, thymus and adrenal atrophy associated with reduced organ weights at both doses. After 28-days, hepatocytic inflammation (mid- and high-doses), adrenal (zona fasciculata) and thymic atrophy, and bone marrow hypocellularity were present. Alveolitis and bronchiolitis were present in all groups, although there were no tracheal effects. Histological alterations were associated with

increased liver weight and reduced thymus and adrenal weights, and increased alkaline phosphatase and protein levels. Clinical signs included reduced body weight gain at the mid and high-doses and increased salivation. The toxicity profile of BDP in the HFA formulation was comparable to that observed with the CFC formulation.

Chronic Toxicity: A one-year toxicity study in immature beagle dogs (2-3 months) was performed primarily to assess the local effects of inhaled steroid upon respiratory airways. Dogs were dosed with BDP by inhalation formulated in either HFA-134a (estimated inhaled doses of 0.05, 0.16, and 0.5 mg/kg/day) or in CFC (estimated inhaled dose of 0.5 mg/kg/day) for 52 weeks. Target organs of toxicity included the adrenals, liver, lymphoid tissue (lymph nodes, spleen, and Peyer's patches), skin, bone marrow (slight hypoplasticity), and exocrine pancreas (atrophy). There was also evidence of reproductive organ toxicity in both sexes. However, no effects on tracheal development were observed. Increased mortality was observed in the high-dose BDP/HFA group and the CFC group due primarily to treatment-related severe exacerbation of demodectic mange (skin lesions). Clinical signs included distended abdomen, skin thickening, excess body fat, hair loss, and skin reddening. Toxicokinetic data showed that total blood levels of BDP with the high-dose BDP/HFA formulation were significantly greater (almost 2X) compared to the CFC formulation. The NOAEL dose in this study was 0.05 mg/kg/day. All significant findings were considered to be typical corticosteroid effects and no differences in toxicity were noted between the HFA and CFC formulations.

Reproductive Toxicity: Inhalation administration of BDP/HFA-134a during the period of organogenesis in a segment II reproductive toxicity study in rats at estimated pulmonary doses (considering deposition factors) of 0.24, 1.15, and 2.83 mg/kg/day produced slight, yet reversible, suppression of maternal body weight gain at the mid- and high-doses. Beclomethasone dipropionate did not increase the incidence of external, visceral, or skeletal malformations in F1 offspring in rats. However, it was associated with delayed development at the mid- and high-doses, including reduced fetal weights and increased incidence of sternebrae variations (delayed ossification). These effects are consistent with the known effects of BDP and other corticosteroids on fetal development and are comparable to those observed with the BDP in CFC formulation.

LABELING

The proposed labeling needs to be updated since information is lacking. The doses (mg/kg) for preclinical studies referred to in the labeling should be stated and the preclinical and clinical exposures should be compared by mg/m^2 dose normalization or AUC, if available. The label should be structured as described in 21 CFR, 201.56 and 201.57. For example, teratogenicity findings should be included in the "Pregnancy" section of the label rather than in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section. In addition, the sponsor should add a statement in the "Pregnancy" section of the label under "Non-teratogenic Effects" indicating that findings of drug-related adrenal toxicity in fetuses following BDP/HFA-134 administration in rats suggest that infants born of mothers receiving substantial doses of BDP/HFA-134 during pregnancy should be observed for adrenal toxicity.

RECOMMENDATION

The application is approvable from a preclinical viewpoint pending incorporation of recommended changes to the label based upon the approved recommended dose.

/S/ May 7, 1999

Timothy J. McGovern, Ph.D., Pharmacologist

/S/ May 6, 1999

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/R. Nicklas
HFD-570/S. Barnes
HFD-570/T.J. McGovern

Attachments: IND reviews by Drs. Mukhergee, Choi and Williams.

Comments for Letter to the Sponsor:

1. The proposed labeling needs to be updated since information is lacking. The doses (mg/kg) for preclinical studies referred to in the labeling should be stated and the preclinical and clinical exposures should be compared by mg/m^2 dose normalization or AUC, if available. The label should be structured as described in 21 CFR, 201.56 and 201.57. For example, teratogenicity findings should be included in the "Pregnancy" section of the label rather than in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section.

2. A statement should be added to the "Pregnancy" section of the label under "Non-teratogenic Effects" indicating that findings of drug-related adrenal toxicity in fetuses following BDP/HFA-134 administration in rats suggest that infants born of mothers receiving substantial doses of BDP/HFA-134 during pregnancy should be observed for adrenal toxicity.

FEB 11 1995

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
SUBMISSION DATED 1/16/95, REVIEW NO. 2

IND [redacted] REVIEWER : Young S. Choi, Ph.D.

SERIAL NO : 2.

DATE OF SUBMISSION : Date Originated : 1/16/95
Date FDA Received : ?
Date Assignment Received : 1/25/95
Date Review Completed : 1/30/95

INFORMATION TO BE CONVEYED TO SPONSOR : Yes ( ), No (x).

SPONSOR : 3 M

NAME OF DRUG : Beclomethasone Dipropionate MDI HFA 134a.

CATEGORY : Steroid.

CLINICAL INDICATION : For the treatment of asthma.

ROUTE OF ADMINISTRATION : Inhalation.

DOSE : A. 200, 800 and 1,600 μg/day for 14 days.

B. 1,200, 2,000 or 2,800 μg/day for 10 days.

C. Comparison of 200 μg x 8 actuations (1,600 μg) of CFC MDI vs HFA-134a MDI.

DOSAGE FORM : MDI with HFA 134a and alcohol.

PREVIOUS REVIEWS AND DATES : #1 : The original review by Asoke Mukherjee, Ph.D., HFD-007 (completed 5/24/1993) : This review contained acute (metabolism), 7 day and 28 day toxicity studies in rats and dogs.

COMMENTS : This submission was made by the division's request for preparation of an In-House Premeeting for End of Phase 2 Meeting, requested by the sponsor.

Submitted materials are the same as submitted on 7/5/94, 12/2/94, and 1/4/95.

First two submissions are mostly clinical information, and the last one contained a summary table of preclinical studies.

OVERALL SUMMARY AND EVALUATION :

Sponsor requested a End of Phase 2 Meeting on 12/2/94 and submitted reports of completed clinical studies and a summary table of preclinical studies.

Pre-In-House meeting is scheduled for 1/31/95 to determine if any more information is needed from the sponsor for the End of Phase 2 Meeting.

The original submission of this IND contained acute (metabolism), 7 day and 28 day inhalation toxicity studies in rats and dogs, and these studies have been reviewed previously in HFD-007. Among 4 toxicity studies, a clear NOEL was established only in a 28 day dog study (2.5 mg/day $\approx$ 0.25 mg/kg/day).

A summary table in 1/4/95 submission shows that 90 day inhalation toxicity study and teratology, both in rats, have been completed and one year toxicity (no route was given) in dogs is in progress.

CONCLUSIONS/RECOMMENDATIONS :

Since high doses of BD (2,800 μg/day) have been used in their Phase 2 clinical studies already, and required preclinical studies for Phase 3 clinical studies are either completed or on going at present, no more information is needed from preclinical studies for the requested End of Phase 2 Meeting. Any addition will depend on results of ongoing studies.

/S/

Young S. Choi, Ph.D.
Pharmacologist

cc:
Original (IND /NDA)
HFD-150/Division File
HFD-150/DeGeorge
HFD-150/MO/Nicklas
HFD-150/Choi
HFD-151/CSO/Barnes
R/D by Y. S. Choi/1/30/95
R/D init. by Peer Reviewer/McGuinn/2/1/95
R/D init. by DeGeorge/2/1/95
F/T by Y. S. Choi/ / /95, WP #0754T

/S/

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Addendum to Original NDA Review

NDA No.: 20-911

Reviewer: Timothy J. McGovern, Ph.D. **Date of Addendum:** 10 MAY 1999

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: 3M Pharmaceutical Division
St. Paul, MN

Drug Name: *Trade:* QVAR™ — Inhalation Aerosol; 50 (40) µg, 100 (80) µg
Generic: Beclomethasone dipropionate (BDP)

Indication: Asthma as prophylactic therapy — and asthma for patients requiring systemic corticosteroid administration.

This Addendum is written for the purpose of correcting statements in the **Labeling** and **Comments for Letter to the Sponsor** sections of the Original NDA Review dated May 06, 1999. The statement '

in each section should read

/S/ May 10, 1999
Timothy J. McGovern, Ph.D., Pharmacologist

CC: HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/S. Barnes
HFD-570/T.J. McGovern

/S/
May 10, 1999

FEB 23 1998

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review #3

IND No.: [redacted]

Serial No.: N163 (IT)

Submission date: 17 JUN 97

Received at HFD 570: 25 JUN 97

Information to be Conveyed to Sponsor: Yes (X), No ()

Reviewer: Shannon Williams, Ph.D.

Date Review Completed: February 23, 1998

Sponsor: 3M Pharmaceuticals, St. Paul, MN

Drug Name: Beclomethasone Dipropionate in Propellant HFA 134a

Category : Corticosteroid

Clinical Indication: Treatment of Asthma

Route of administration: Oral Inhalation

Previous Reviews: 1) Pharmacology Review dated May 24, 1993 of original submission dated 5/28/93 by Dr. Asoke Mukherjee
2) Pharmacology Review dated February 11, 1995 of submission dated 1/16/97 by Dr. Young S. Choi.

Preclinical Studies Submitted and Reviewed Herein:

MULTIDOSE TOXICITY	[Ref. No.]	Vol./Tab
90-Day Inhalation Toxicity Study of HFA-BDP in Rats	0792SR0390	1/1
52-Week Inhalation Tox/TK Study of HFA-BDP in Dogs	0792CD0401	2/1
REPRODUCTIVE TOXICITY		
Inhalation Develop. Tox Study of HFA-BDP in Rats	0792TR0391	1/2
Pilot Nose-Only Inhalation Develop. Tox Study in Rats	0792TR0435	1/3

TOXICOLOGY

90-Day Inhalation Toxicity Study of HFA-BDP in Rats
Study Number: Report No. TF1-3
Testing Lab: [redacted]
Study Dates: February 16, 1993 through November 3, 1993
Test Article: Beclomethasone Dipropionate formulation; Lot # FN6036 and FN6037
Study Animals: Sprague Dawley [TAC:N(SD). ', 6-7 weeks old, Males: 152-212 g and Females 120-162 g.
GLP: A statement of compliance with the current FDA Good Laboratory Practice Regulations (21 CFR Part 58) was included..
QA Report: Yes (X) No ( )

Methods: Beclomethasone Dipropionate was suspended in HFA-134a (propellant) and administered via nose only inhalation to 3 groups of rats (24/sex/group) for 1 hr/per day at beclomethasone concentrations of 0.001, 0.005, and 0.026 mg/l for 90 consecutive days. Estimated daily inhaled doses (excluding deposition factors) were: 0 (propellant control), 0.048, 0.24, and 1.25 mg/kg and were calculated using the following formula:

$$\text{Dose to animal (mg/kg/day)} = \frac{RMV \times T \times C}{1000}$$

Where T = Time of exposure (min/day); C = Chamber concentration (µg/L);
RMV = Respired minute volume = 0.8 ml/min/g, based on a 250 g rat.

The Mass Median Aerodynamic Diameters (MMAD) of the beclomethasone dipropionate formulation aerosol was indicated to range from 1.23 to 1.66 µm of which approximately 10% is deposited in the lungs. Thus, the estimated pulmonary doses were 4.8, 24, and 125 µg/kg in the low, mid and high dose treated groups. Two additional groups of (24 rats/sex) were likewise administered filtered air (air control) or HFA 134a (propellant control). The basis of dose selection was not indicated. Blood was collected at the end of the dosing period prior to sacrifice for determination of hematological and clinical chemistry parameters. All rats, except recovery animals, were sacrificed after 91 days of treatment and underwent complete gross examinations. Organ weights were determined for heart, liver, right kidney, lungs, spleen, adrenals, thymus , brain, right testes and ovaries (paired weights). Four recovery rats/sex/group were retained for 8 weeks beyond the end of the dosing period. Complete histological examinations were conducted on all core study animals (10 rats/sex/group) in the filtered air control, the HFA-134a propellant control and high dose groups. Examinations also included the thymus of rats in the mid and low dose groups and any other lesions observed grossly in these groups. Plasma levels of beclomethasone were not determined.

Results:

Mortality (2 x daily): No drug-related mortality was observed.

Clinical Observations (2 x daily): No drug-related clinical signs were observed, red material around the nose and/or eyes or ocular discharge, with similar incidence in all treated and control groups. These signs were attributable to confinement in the nose only exposure tubes.

Ophthalmoscopy (prior to exposure and during final week of exposure): No treatment related ophthalmic effects were observed.

Body Weight (pretest and weekly thereafter): Beclomethasone treatment resulted in dose-dependent supression of body weight gains (14-23.6%, relative to the air treated control group) after 13-weeks of treatment. The HFA-134a Propellant alone treated group showed 10 % supression of body weight gains, relative to air controls. Thus, relative to the HFA control group, supression of body weight gains, directly attributable to beclomethasone treatment at the 0.048, 0.24, and 1.25 mg/kg doses were 3, 7, and 14% in males and 9, 15, and 18% relative to gains in the propellant control group. After 8 weeks of recovery, mean body weight gains were suppressed by 20.2 and 8.27% in males at the mid and high doses, relative to vehicle controls, whereas weight gains were suppressed by 14% relative to the air control and by 20% relative to vehicle controls (due to greater gains in the vehicle control group relative to the air controls).

Food and Water Consumption: Effects on food and water consumption were not determined.

Clinical Chemistry (prior to scheduled necropsy in 10 rats/sex/group in treated groups and in4 rats/group from recovery animals): There were no treatment-related effects on clinical chemistry observed at any dose level tested. In the absence of changes at the end of the treatment period clinical chemistry parameters were not determined at the end of the recovery period.

Hematology (prior to scheduled necropsy in 10 rats/sex/group in treated groups and in4 rats/group from recovery animals): : Treatment-related hematological effects observed at the end of the treatment period were limited to mild reductions in total white blood cells (32 and 39%) in males and females at the high dose, relative to vehicle control values. Reductions in total white counts stemmed mainly from reductions in lymphocyte counts (33% and 42% in males and females at the high dose. Reduced lymphocytes were also seen in females at the low (19%) and high doses (23%), with reduced neutrophils (40%)also seen in high dose females. By the end of the recovery period, there were no statistical differences in total WBC, lymphocyte or neutrophil counts

Urinalysis: Urinalysis was not performed.

Organ Weights: Table 1 below shows treatment related effects on absolute and relative weights for organs at the end of the treatment period.

Table 1. Treatment-related changes in absolute/relative (abs./relat.) organ weights (organ to body weight ratios) in rats following 90 days of dosing with beclomethasone. (Values represent percent change relative to the mean values in the vehicle control group.)

Organ	Low		Mid		High	
	♂ (abs./relat.)	♀ (abs./relat.)	♂ (abs./relat.)	♀ (abs./relat.)	♂ (abs./relat.)	♀ (abs./relat.)
Thymus	↓10/↓7	↓19/↓17	↓5/---	↓31/↓27	↓43/↓39	↓54/↓52
Right Kidney	---/---	---/---	---/---	---/---	↓10/↓4	---/---
Spleen	↓6/---	---/---	↓12/↓11	↓9/---	↓26/↓22	↓13/↓8
Adrenal	---/---	---/---	↓5/---	↑23/↑29	↑7/↑12	↑11/↑16

(abs./relat.) = Absolute and relative weights (organ to body weight ratios)
--- Changes less than 5%, relative to respective mean values in the vehicle control group.

The data in Table 1 show treatment-related reductions in organ weights for thymus (all doses) and spleen (mainly mid and high doses) and increased weights for adrenals (mid and high doses at the end of the 90 day dosing period. Males at the high dose also showed slight increases in weights for the right kidney. No other treatment-related effects on organ weights were evident. By the end of the recovery period, no significant differences in absolute or relative weights for any organ were observed.

Gross Pathology: No treatment-related gross pathological effects were noted.

Histopathology (limited to 10 rats/sex in control and high dose groups and to the thymus and other gross lesions in rats at the low and mid doses): Treatment related histopathological effects were limited to depletion of thymic lymphocytes in males at the high dose and in females at the mid and high doses. The incidence and severity of these findings is presented in Table 2 below.

Table 2. Incidence and Severity of Thymic Lymphoid Depletion (TLD)seen in rats following 90 days of inhalation exposure to Beclomethasone Dipropionate.

	Air Cont.		HFA-Cont.		Low		Mid		High	
TLD	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Incidence	0/20	1/20	1/20	0/20	0/20	1/20	0/20	4/20	8/20	11/20
Severity*	0.00	0.05	0.05	0.00	0.00	0.05	0.00	0.20	0.45	0.79

*Mean group severity score

Toxicokinetics: Drug concentrations were not measured in the study.

In conclusion, administration of beclomethasone dipropionate by nose only inhalation at pulmonary doses of 4.8, 24.0, and 125.0 µg/kg for 90 days was well tolerated in rats, with no mortality or drug-related clinical signs of toxicity observed. Mild reductions in body weight gains (3-14% in males and 9-18% in females) were observed in all drug-treated groups. Hematological effects of reduced white blood cells due mainly to lymphocyte depletion were seen in both sexes at the high dose. The thymus was identified as the target organ of toxicity with dose-dependent reductions in organ weights and histological findings of thymic lymphoid depletion observed at the mid and high doses in females and at the high dose in males. All effects were reversible after 8 weeks of recovery. The 4.8 µg/kg pulmonary dose was the NOAEL for the study.

52-Week inhalation Toxicity Study in Dogs. (Amendment No. 163, Dated 6/17/1/97)
Study Number: 3M Study No. 0793CD0401
Testing Lab: ———
Study Dates: October 28, 1993 through April 26, 1996
Test Article: Beclomethasone dipropionate formulated in HFA -134a propellant, batch number 93I01
Study Animals: Beagle Dogs, age 2½-3 months old, Weight 3.8-7.1 kg.
GLP: A statement of compliance with the current FDA Good Laboratory Practice Regulations (21 CFR Part 58) was included.
QA Report: Yes (X) No ( )

Methods: Three groups of Beagle dogs (4/sex/group) were administered beclomethasone dipropionate suspended in HFA 134a propellant via a dosing apparatus which incorporated an oral mouth piece, sealed face mask, clinical adapter (——— ———) and one way inlet and exhaust valves. Inhaled doses (excluding deposition factors) of 0.05 (Group 3), 0.16 (Group 4), and 0.50 mg/kg/day (Group 5) were administered for a period of 52 weeks. Estimated doses were accomplished by determining the amount of drug retained in the dosing apparatus versus the nominal amount actuated from the MDI during dosing (Note: this method of dose estimation could result in overestimation of doses). Three separate groups were likewise administered air, (Air control, Group 1), the HFA-134a propellant vehicle (Vehicle control, Group 2) or metered aerosol doses of an existing BDP chlorofluorocarbon (CFC) formulation (Becloforte®; 0.5 mg/kg/day, Group 6). Due to concern over possible immunosupression, doses in groups 5 and 6 were reduced by 50 % from day 6 of week 2 to day 2 of week 7 and up to 75% of the dose Days 3-7 of week 7 and returned to the full level by day 1 of week 8. Dose selection was based on the results of a 28-day inhalation toxicity study in dogs (— project No. 650974; Report No. 7700), where doses of 0.05, 0.16, and 0.50 mg/kg/day produced effects on thymus, lymphoid tissue, liver , adrenals, and bone marrow. Animals which died or were sacrificed at the end of the 52-week treatment period, underwent complete gross and histopathological analyses (except for

epididymis and seminal vesicles which were not listed as having been examined). Organ weights were determined for adrenals, brain, heart, kidney, liver, ovaries, pancreas, parathyroid, pituitary, prostate, spleen, testes, thymus, thyroid, uterus, and lungs. Other parameters determined in the study included: mortality, clinical signs, body weights, food consumption, ophthalmoscopy, respiratory function, electrocardiography, hematology, coagulation, bone marrow smears cortisol measurements, clinical chemistry, urinalysis, fecal occult blood, drug blood levels.

Results:

Mortality (daily): A total of 11 mortalities occurred during the course of the study. Two dogs (1/sex) in Group 6 (high dose BDP/CFC) died during the first 2 weeks of treatment due to opportunistic respiratory infections which probably occurred as a result of immunosuppression at a young age. Both of these dogs were replaced. Four other dogs in group 5 and 5 other dogs in group 6 were euthanized between weeks 36-46 due to treatment-related severe exacerbation of demodectic mange (skin lesions).

Clinical Observations (daily): Treatment-related clinical signs included: distended abdomen (all treated groups), excess body fat (obesity, Group 5 and 6 males), hair loss (all groups), skin reddening (group 5 and 6 males and females), and skin lesions, (demodectic mange; group 5 and 6 males and females).

Ophthalmoscopy (pretrial, and during treatment weeks 26 and 52): No treatment related ophthalmic effects were observed.

Respiratory function (pretrial, and during treatment weeks 26 and 52): By treatment-week 26, high dose group 5 and 6 males showed reduced tidal volumes (33 and 41%) relative to Group 1 (air control) values, whereas females in all treatment groups showed dose-dependent reductions in mean tidal volumes (17-41%, relative to air control values). Tidal volumes remained reduced by treatment week 52 (24and 39% in group 5 and 6 males and 20-37% in females in all treatment groups). There were no differences between effects on tidal volumes in the high dose CFC formulation versus those observed with the high dose HFA formulations, showing that the HFA formulation posed no additional risk. Tidal volumes in the HFA control (Group 2) were comparable to those seen in the air control group. Other parameters including respiratory rate, minute volumes or peak expiratory flow were not affected.

Electrocardiography (pretrial, and during treatment weeks 26 and 52): There were no effects on electrocardiographic parameters including: heart rate, P-R, QRS, or QT intervals at either the 26 or 52 week time periods.

Body Weight (weekly, beginning 2 weeks pretest): In males, weight gains were comparable between all groups through week 40 of treatment. At the end of the study, males in Groups 5 and 6 which survived beyond week 40 showed increased mean body weight gains (21 and 16%) relative to Group 1 (air control). In females, mean body

weights were reduced by 7-12% in all BDP/HFA treated groups, relative to weights in Group 1 (air control). Reduced mean body weights were evident from week 5 in the high dose group and from week 12 in the low and mid doses. By week 35 (the last week, prior to euthanasia of dogs at the high dose), body weights for females in groups 3, 4, and 5, (all BDP/HFA groups) were reduced by 9-12% , relative to air control weights, whereas 17% reductions were observed in group 6 females. Finally, surviving females both groups 5 and 6 showed gradual body weight losses over the remaining 12-weeks of the study. Body weights in males and females in the HFA control groups (Group 2) were comparable throughout the study.

Food Consumption (daily, beginning 2 weeks pretest): Over the last 23 weeks of the study, females in groups 5 and 6 groups showed 15 and 6% reductions in mean daily food consumption, relative to consumption in Group 1 (air controls). Group 6 males also showed an average of 6% less food intake over the last 23 weeks of the study. Slight inappetance was also observed in several animals prior to their early sacrifice, most notably in a Group 5 (high dose BDP/HFA group) male and female, which showed slight inappetance over several weeks prior to sacrifice.

Clinical Chemistry (Weeks 12, 26, and 52): Treatment-related changes in clinical chemistry parameters evident at weeks 26 and 52 are shown in Table 3 below.

Table 3. Effects of beclomethasone Dipropionate on clinical chemistry changes in dogs at 26 and 52 wks (Note: Values are expressed as percent changes relative to Air control values and pertain to males and females unless otherwise indicated)

	Group 4		Group 5		Group 6 (CFC)	
	Inter Dose		High dose		High dose	
Week #	26	52	26	52	26	52
alkaline phosphatase	---	↑64-117	↑112-120	↑31-250	↑129-159	↑107-157
total protein	---	---	↑11-12	↑17†	↑12†	↑15†
albumin	---	---	↑12†	↑17†	↑12†	↑10†
globulin	---	---	↑12‡	↑12†	↑12‡	↑16-35‡
cholesterol	---	↑50†	---	↑36†	---	↑57† & ↓14‡
triglycerides	↑73‡	↑53-54	↑122-134	↑79-174	↑87-300	↑336† & ↓25‡
phosphate	---	---	---	↓12‡	---	↓41‡
glucose	↓12-13	↓15‡	↓15-19	↓21‡	↓14-21	↓15‡
aspartate aminotransferase	↓16-23	↓21-28	↓16-18	↓34-46	↓27-31	↓15-59
alanine aminotransferase	↓28†	↓25†	↓23†	↑27†	↓18†	↓53†
creatinine	↓17-24	↓14-22	↓29-39	↓22-36	↓27-35	↓32†
chloride	---	---	↓4.5†	↓4.5†	↓3.5†	↓6.3†

Note at week 52, surviving animals were limited to 2 dogs/sex in group 5 and 2 males and 1 female in group 6. (--- No treatment related changes evident, † Males only, ‡ Females Only)

The Data in Table 3 show a wide variety of changes in clinical chemistry parameters. The most outstanding being increased alkaline phosphatase, and triglycerides. Other changes presented in Table 3 included: slight increases in total protein, albumin, and globulin and mild reductions in aspartate aminotransferase, alanine aminotransferase, creatinine and glucose. The majority of the aforementioned changes occurred at in animals at the high dose and were evident by week 26 of treatment. In general, the changes were dose-dependent and similar between weeks 26 and 52, with the exception of alkaline phosphatase which increased at the intermediate dose only at week 52. Changes in alkaline phosphatase, total proteins albumen globulin and triglycerides are expected following corticosteroid treatment and there was no evidence for increased toxicity with the HFA formulation versus the CFC.

Hematology (Weeks 12, 26, and 52): Relative to values in Group 1 (air controls), treatment-related changes in hematological parameters evident at week 26 included: slight increases in MCH (9% in Group 6 males, and 4.4-9.3% in females in Groups 4, 5, and 6), increased monocytes (107 and 117% in Group 5 and 6 males, respectively), dose-dependent reductions in lymphocytes in males (14-30 %) and females (30-49%) in groups 4, 5, and 6 and reduced eosinophils in males (56-95%) and females (51-90%) in groups 4, 5, and 6. By week 52, hematological effects were limited to reductions in lymphocyte counts (17-37%) in all BDP treated groups, except for the surviving group 6 female, where a 61% reduction was observed. Finally, group 5 and 6 males showed increased white blood cell counts (33 and 45%) and increased neutrophil counts (72 and 89%, respectively). In general, the observed changes were expected with chronic corticosteroid and there was no differences in the observed toxicity between the high dose HFA and CFC formulations.

Urinalysis (16 hr samples collected in 10 dogs/sex/group in drug weeks 11, 25, 40 and 51): A low urinary volume was recorded for group 5 animals (both sexes) during week 52 (Reduced by 87 and 93% in males and females, relative to air controls). By comparison, the surviving male and females dogs in the CFC group showed reductions of 66.8 and 21.9% relative to air controls. Although it appeared that the observed reductions in urinary volume were more pronounced in the HFA versus the CFC groups, effects in males were fairly comparable between the two groups and only one female survived in the CFC group, casting doubt on the significance of the apparent difference in females. In addition, plasma beclomethasone levels were much greater in the high dose HFA group versus those observed in the CFC group which could help to explain any apparent differences. There were no treatment-related effects on any other urinalysis parameter.

Cortisol: Treatment-related effects on blood cortisol levels could not be determined since levels in the majority of groups, including controls, were below the limit of detection.

Organ Weights: Organ weight changes are presented in Table 4 (below).

Table 4. Organ weight changes in dogs following inhalation with Beclomethasone Dipropionate (BDP). (Note: organ weight changes are expressed, relative to respective weights in the air control group)

Organ	Group 3 (BDP Low)		Group 4 (BDP Inter)		Group 5 (n) (BDP High)		Group 6 (Becloforte®)	
Sex (n)	♂(4)	♀(4)	♂(4)	♀(4)	♂(2)	♀(2)	♂(2)	♀(1)
Adrenal	↓29	↓16	↓50	↓31	↓61	↓68	↓66	↓64
Heart	---	↓13	---	↓15	↓6	↓22	↓24	↓40
Liver	---	---	↑22	---	↑71	---	↑59	↓29
Thymus	---	---	---	---	↓58	↓34	↓35	↓82
Lungs	---	---	---	↓10	↓17	↓22	↓34	↓14
Prostate	---	---	↓21	---	↓41	---	↓48	---
Testes	---	---	---	---	↓19	---	↓29	---

--- No treatment related changes evident.

Relative to mean air control values, treatment-related changes in organ weights included: dose-dependent reductions in mean absolute weights for adrenals (All BDP dose groups), heart (intermediate and high dose) thymus (high dose), lungs (intermediate and high doses), prostate (intermediate and high) and testes (intermediate and high dose) and dose-dependent increases in mean absolute weights for liver in males at the intermediate and both sexes at the high doses. The observed differences in organ weights were comparable in between beclomethasone treated groups exposed to the HFA versus the CFC formulations.

Gross Pathology: Gross changes are shown in Table 5 (succeeding page):

Table 5 Treatment related gross pathological findings in dogs following inhalation treatment with beclomethasone dipropionate (n = 4 animals/sex).

Group #	1	2	3	4	5	6
Organ †	♂/♀	♂/♀	♂/♀	♂/♀	♂/♀	♂/♀
Adrenal (small)	0/0	0/0	0/0	2/1	3/2	3/2
Liver (enlarged)	0/1	0/0	0/0	2/1	2/1	3/0
Lungs (small)	0/0	0/0	0/0	0/1	0/1	1/0
Lymph nodes						
Thymic (dark)	0/0	0/0	0/0	0/0	1/1	0/0
Mesenteric (dark)	0/0	0/1	1/0	0/2	1/1	2/1
Retropharyngeal (dark)	0/0	0/0	1/0	0/0	1/0	1/1
Submand. (dark/enlarg.)	0/0	0/0	0/0	0/0	1/0	1/2
Abdomen (distended, swollen, excess fat)	0/0	0/0	0/0	1/1	2/2	2/0
Skin						
Scabs	0/0	0/0	0/0	0/0	1/1	1/3
Hair loss	0/0	0/0	1/0	4/4	4/4	3/2
Thickened	0/0	0/0	0/0	0/0	2/0	2/0
Reddened	0/0	0/0	0/0	0/0	0/2	1/2
†Subcutaneous fat	0/0	0/0	0/0	0/1	1/0	1/0
Thymus (fatty)	0/0	0/0	0/0	0/0	0/1	0/1

Group 1 = Air control; Group 2 = HFA control; Group 3 = Low dose BDP + HFA ; Group 4 = Inter dose BDP + HFA; Group 5 = High dose BDP + HFA; Group 6 = High dose BDP + CFC (Becloforte®)

Gross findings attributable to beclomethasone treatment included: small adrenals and enlarged livers beginning at the mid dose, darkened lymph nodes (thymic, mesenteric, retropharyngeal, and submandibular, mainly at the high doses), distended or swollen abdomen with or with out excess fat (beginning at the mid dose) and various skin manifestations (scabs, hair loss, thickened/reddened skin, and or increased subcutaneous fat) observed in one or both sexes beginning at the mid dose. Small lungs were also noted in individual animals at the mid and high doses. As is shown in table 5, there were no differences between the incidence or severity of gross pathological effects in the animals treated with high dose beclomethasone formulated with the HFA (Group 5) versus the CFC (group 6) propellant.

Histopathology: Table 6 (succeeding pages) presents a listing of the treatment-related histological findings which included: atrophy of the zona faculata and diffuse hypertrophy of the glomerulosa of the adrenals, lymphoid depletion and or germinal center atrophy of the lymph nodes (bronchial, mesenteric, retropharyngeal, and submandibular), with granulomatous lymphadentitis also seen in the submandibular lymph node; atrophy of Pyers Patch in the ileum, focal basophilic tubules in the kidneys, Periportal and Midzonal clear vacuolation and perivascular inflammatory cell infiltration of the liver, atrophy of the exocrine pacreas, parasitic dermatitis, atrophy and/or follicular dilation of the skin/subcutis, lymphoid follicular atrophy of the spleen, hypoplasia of the bone marrow, mucusal mineral deposits in the stomach and increased severity of thymic involution. Males and females also showed apparent effects on reproductive organ

systems; in males: increased incidence of focal prostatitis, and bilateral or unilateral germinal epithelium degeneration or hypoplasia and in females; decreased No. of corpora lutea and or anoesterous morphology of the vagina at the high dose. The majority of the aforementioned findings are those which are expected following prolonged treatment with a corticoid steroid. However, findings of focal prostatitis in high dose HFA males were not observed in the high dose CFC formulation group. The etiology of the increased incidence of prostatitis in the high dose HFA males is unknown and the sponsor should address the toxicological significance of this finding in relation to the HFA formulation.

Table 6. **Incidence of histological findings in dogs following inhalation with Beclomethasone Dipropionate.** (N = 4/sex/group unless otherwise indicated)

	Males						Females					
Group #	1	2	3	4	5	6	1	2	3	4	5	6
Adrenals												
-Zona faculata, atrophy	0	0	0	4(4.0)	4(5.0)	4(5.0)	0	0	0	2(1.5)	4(4.3)	4(5.0)
-Diffuse zona glomerulosa hypertrophy	0	0	0	1(2.0)	3(2.3)	4(2.5)	0	0	0	0	1(2.0)	3(2.7)
Lymph Nodes												
-Bronchial												
Germinal center atrophy	0	0	0	2(1.5)	4(2.3)	3(2.0)	0	0	0	0	1(2.0)	2(2.5)
-Mesenteric												
Lymphoid depletion	0	0	0	0	4(1.5)	3(2.0)	0	0	0	0	1(2.0)	4(1.8)
Germinal center atrophy	0	0	0	3(1.0)	4(2.3)	3(2.7)	0	0	0	3(1.0)	3(1.3)	4(1.8)
Retropharyngeal												
Lymphoid depletion	0	0	0	3(2.3)	4(2.5)	4(3.0)	0	0	0	0	2(2.0)	3(1.7)
Germinal center atrophy	0	0	0	4(2.0)	4(2.5)	4(3.0)	0	0	0	0	3(2.0)	3(2.0)
-Submandibular												
Lymphoid depletion	0	0	0	2(1.5)	3(1.3)	2(1.5)	0	0	0	0	0	0
Germinal center atrophy	0	0	0	3(2.0)	4(1.3)	2(2.0)	0	0	0	1(2.0)	1(1.0)	0
Granulomatous lymphadentitis	0	0	0	0	1(2.0)	1(3.0)	0	0	0	0	0	3(1.3)
Ileum												
-Pyers Patch atrophy	0	0	0	4(2.0)	4(3.0)	4(3.0)	0	0	0	3(1.7)	2(1.0)	3(2.0)
Kidneys												
-Focal Basophilic Tubules	0	0	0	0	2(1.0)	3(1.0)	0	0	0	1(1.0)	2(1.0)	1(2.0)
Liver												
-Periportal clear vacuolation	0	0	0	0	0	0	0	0	0	1(2.0)	1(3.0)	2(2.5)
-Midzonal clear vacuolation	0	0	0	1(3.0)	2(3.5)	4(3.8)	0	0	0	1(3.0)	2(3.5)	0
-Inflam. cell infiltrate*	0	0	0	0	0	2(1.0)	0	0	0	0	1(2.0)	1(1.0)

Group 1 = Air control; Group 2 = HFA control; Group 3 = Low dose BDP + HFA ; Group 4 = Inter dose BDP + HFA; Group 5 = High dose BDP + HFA; Group 6 = High dose BDP + CFC (Becloforte®)
Numbers in (parentheses) represent the mean severity of the findings in the affected animals based on the following designations 1 = very mild; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe.
*Perivascular

Table 6. Histological Findings (continued)

	Males						Females					
Group #	1	2	3	4	5	6	1	2	3	4	5	6
Ovaries												
-immature							0	0	0	0	1	0
-1 No. Corpora Lutea							4	2	3	2	1	0
Pancreas												
-Exocrine atrophy	0	1(2.0)	2(2.0)	1(2.0)	4(2.0)	3(2.0)	1(2.0)	0	2(1.5)	1(2.0)	2(1.5)	3(1.7)
Prostate												
-Focal Prostatitis	0	0	1(4.0)	0	3(3.0)	0						
Skin/Subcutis												
-Parasitic Dermatitis	0	0	0	0	2(4.0)	2(3.5)	0	0	0	0	2(4.0)	4(4.3)
-Atrophy	0	0	0	0	2(2.0)	3(2.0)	0	0	0	0	2(1.5)	0
-Follicular Dilation	0	0	0	1(2.0)	2(2.0)	1(2.0)	0	0	0	0	1 (1.0)	0
Spleen (Lymphoid												
Follicular Atrophy)	0	0	0	1(2.0)	1(1.0)	2(2.5)	0	0	0	0	1(1.0)	3(1.0)
Sternum												
-hypoplasia	0	0	0	0	2	4	0	0	0	0	1	0
-Hyperplasia	0	0	0	0	0	0	0	0	0	0	1	0
Stomach												
-Mucosal Mineral Deoposits	0	1	1	0	2	2	0	0	0	1	2	4
Testes												
-Bilateral/unilateral Germinal epithelium degeneration	0	0	0	1(1.0)	2(1.0)	1(1.0)						
-Unilateral germinal epithelium hypoplasia	0	0	0	0	1(1.0)	1(3.0)						
Thymus												
-Involution	4(1.3)	2(1.0)	4(1.0)	3(1.7)	3(4.0)	4(4.0)	2(1.5)	3(1.3)	0	0	3(2.0)	4(4.0)
Vagina												
-Anoesterous morphology							1	2	1	2	2	4

Group 1 = Air control; Group 2 = HFA control; Group 3 = Low dose BDP + HFA ; Group 4 = Inter dose BDP + HFA; Group 5 = High dose BDP + HFA; Group 6 = High dose BDP + CFC (Becloforte®)

Note: Numbers in (parentheses) represent the mean severity of the findings in the affected animals based on the following designations 1 = very mild; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe.

Toxicokinetics: Blood levels of beclomethasone (BOH) and BOH total obtained from hydrolysis of the beclomethasone dipropionate and the monopropionates in the sample along with the BOH (Total BOH) were determined using [redacted] The minimum limit of detection was 10 pg/ml. Table 7 (succeeding page) presents a summary of the post dose serum BOH, and Total-BOH fraction.

Table 7. Mean blood levels of Beclomethasone (BOH) and Total BOH in Dogs following inhalation with BDP/HFA and BDP/CFC formulations.

		Mean ± SD Serum Level (pg/ml)			
		Day 1	Week 12	Week 26	Week 52
Group	Dose (mg/kg)	BOH	BOH	BOH	BOH
3	0.05 BDP/HFA	41 ± 53	104 ± 28	146 ± 53	92 ± 21
4	0.16 BDP/HFA	122 ± 59	563 ± 162	1034 ± 300	340 ± 116
5	0.50 BDP/HFA	392 ± 201	940 ± 283	1710 ± 431	413 ± 229
6	0.50 BDP/CFC	97 ± 59	583 ± 263	1076 ± 344	331 ± 167
Group	Dose (mg/kg)	Total BOH	Total BOH	Total BOH	Total BOH
3	0.05 BDP/HFA	1350 ± 768	3785 ± 1318	5685 ± 1997	4845 ± 1407
4	0.16 BDP/HFA	7101 ± 3789	15488 ± 2921	23738 ± 4663	17002 ± 5077
5	0.50 BDP/HFA	18313 ± 6914	21805 ± 4512	41705 ± 14084	19801 ± 16842
6	0.50 BDP/CFC	8432 ± 5916	12978 ± 4594	20212 ± 4923	10478 ± 6191

Total BOH = BOH + BOH obtained from hydrolysis of the dipropionate and the monopropionates

One female dog in the air control group showed BOH levels of 26 pg/ml during treatment week 26, without apparent explanation. The levels in this dog were below the mean values seen at the low dose and not seen at any other time point. Thus, the nominal levels and the isolated nature of this finding does not compromise the validity of the study. The data in Table 7 above show that the blood concentrations of BOH and or total BOH increased with increasing dose, although disproportionately (lower than expected) at the highest dose. Plasma concentrations at each dose level increased over the first 26 weeks of the study but appeared to have reached a steady state by Week 52. Plasma levels in the high dose BDP/CFC formulation group were comparable to those achieved at the mid dose in the HFA formulation, suggesting greater bioavaialbility for the HFA formulation.

In conclusion, dogs administered BDP by inhalation formulated in either HFA-134A at estimated inhaled doses of 0.05, 0.16, and 0.5 mg/kg/day or in CFC at estimated inhaled doses of 0.5 mg/kg/day for 52 weeks, showed severe exacerbation of demodectic mange at the 0.5 mg/kg/day high doses, which necessitated the premature sacrifice two to three dogs/sex in the high dose groups. Treatment-related effects included: clinical signs of distended abdomen, skin thickening, excess body fat, hair loss, skin reddening and increased incidence of demodectic mange (skin lesions). Target organs of toxicity included: adrenals, liver, lymphoid tissue (lymph nodes, spleen, and Peyer's patches), skin, bone marrow (slight hypoplasticity), and exocrine pancreas (atrophy). Evidence of reproductive organ toxicity was also observed in both sexes. In general, the toxicity profile is consistent with that expected following chronic administration of corticosteroids in dogs. However, there was an unexpected increased incidence of focal prostatitis in high dose HFA males which was not observed with the high dose CFC formulation. Although the exact etiology of the prostatitis in is unknown, bacterial infection is the most common cause in dogs. Since toxicokinetic data showed that systemic exposure (AUC values) with the high dose BDP/HFA formulation was

significantly greater (almost 2X) compared to the CFC formulation, it is possible that increased immunosuppressive effects due to increased systemic exposurecould account observed incidence of prostatitis in the high dose HFA group. The toxicological significance of the increased prostatitis in the high dose BDP/HFA group in relation to the clinical development of the HFA formulation should be addressed by the Sponsor. The 0.05 mg/kg inhaled dose of BDP/HFA was the NOAEL for the study.

Segment II
Inhalation Developmental Segment II Toxicity study of Beclomethasone Dipropionate Study in Rats.
Study Number: L08398
Testing Lab: [redacted]
Study Dates: January 7, 1993 through November 23, 1993
Test Article: Beclomethasone Dipropionate formulated with HFA-134a propellant (Batch No. FN6039 and FN6040)
Study Animals: Pregnant Sprague-Dawley Rats 7 weeks old; 138-179 g
GLP: A statement of compliance with GLP regulations was provided.
QA Report: Yes (X) No ( )

Methods: Pregnant Rats (26/group) were administered BDP by nose only inhalation at estimated inhaled doses (excluding deposition factors) of 0.0 (Filtered air control) 0 (propellant control), 2.4, 11.5, and 28.3 mg/kg/day during Gestation Days (GD) 6 through 15 (10 consecutive doses). These doses were calculated using the following formula:

$$\text{Dose to animal (mg/kg/day)} = \frac{RMV \times T \times C}{1000}$$

Where T = Time of exposure (min/day); C = Chamber concentration (µg/L); RMV = Respired minute volume = 0.8 ml/min/g, based on a 250 g rat.

and based on exposure periods = 60 min/day and chamber concentrations of 0, 0.02, 0.05, 0.24, and 0.59 mg/L. The Mass Median Aerodynamic Diameters (MMAD) of the beclomethasone dipropionate formulation aerosol was indicated to range from 1.27 to 1.50 µm of which approximately 10% is deposited in the lungs. Thus, the estimated pulmonary doses were 0.24, 1.15, and 2.83 mg/kg/day at the low, mid, and high doses.

Dose selection: Dose selection was based on a pilot Segment II developmental toxicity study in pregnant rats in which Beclomethasone formulated in the HFA 134a propellant was administered by inhalation at doses of 0.0 (filtered air control), 0.0 (vehicle control), 2.4, 13.8, and 28.3 mg/kg/day from GD 6 through LD 15 (Study No. 3). In that study, BDP at the high dose produced a an initial slight body weight loss (-0.14 g over days 6-8) and a reduction in the mean fetal weights (12.2 and 10.3%, relative to the air filtered control animals), but no teratogenic effects.

The following parameters were determined:
Clinical Signs of toxicity: 2x daily on week days and once daily on weekends.
Mortality: 2x daily on week days and once daily on weekends
Body weights: GD 0, 5, 6, 8, 10, 12, 14, 16, 18, and 20.
Food consumption: not monitored; this parameter was not changes in the pilot study
Plasma levels: Not determined.
Necropsy: All females were sacrificed on GD 20, with gross examinations of the thoracic and abdominal viscera conducted. Uterine examinations were conducted and maternal and fetal parameters were determined.
FI Examinations: All Fetuses were weighed and examined externally. One half of the fetuses underwent visceral examinations and the remaining were examined for skeletal abnormalities.

Results: BDP, given by inhalation to pregnant females at estimated pulmonary doses 0.24, 1.15, and 2.83 mg/kg/day produced transient suppression of body weight gains at the mid and high doses (32 and 47% days 6-8 and 24 and 18%, days 8-10, relative to gains in air controls over these same time periods). Suppressed weight gains returned to normal by gestation days 12-14. No treatment-related deaths, abortions, or gross lesions were observed at necropsy at any of the doses tested. Table 8 (below) provides a summary of maternal and fetal observations at the Cesarean Section on GD 20.

Table 8. Maternal and Fetal Observations in Rats at Cesarean Section

	Air Control	HFA Control	BDP (mg/kg) 0.24	1.15	2.83
Females mated	26	26	26	26	26
Pregnant (%pregnant)	26 (100%)	25 (96%)	24 (92%)	26(100%)	26(100%)
Aborted	0	0	0	0	0
Died	0	0	0	0	0
Corpora Lutea[1]	14.0 ± 2.5	12.3 ± 2.7	14.4 ± 1.8	13.4 ± 2.2	13.6 ± 2.2
No. Implantation sites[1]	12.3 ± 3.2	12.5 ± 2.9	13.8 ± 1.6	12.6 ± 2.3	13.0 ± 2.4
Preimplantation loss ± SD	11.9 ± 22.5	4.8 ± 17.3	4.5 ± 5.9	6.6 ± 8.8	5.7 ± 11.1
Resorptions[1]	0.67 ± 0.76	0.26 ± 0.45	0.39 ± 0.66	0.54 ± 0.72	0.58 ± 0.72
Postimplantation loss	5.4	2.1	2.8	4.3	4.5
Total No. of Fetuses	279	281	309	290	297
Viable	279	281	309	290	297
Dead	0	0	0	0	0
Sex Ratio (M/F)	1.1	1.0	0.9	1.1	0.9
Fetal Body Weight					
Males (g) ± SD	3.98 ± 0.26	4.05 ± 0.27	3.94 ± 0.25	3.82 ± 0.32	3.66 ± 0.25
Females (g) ± SD	3.84 ± 0.26	3.82 ± 0.28	3.73 ± 0.28	3.55 ± 0.36	3.44 ± 0.26
Combined fetal weights[1]	3.91 ± 0.25	3.96 ± 0.28	3.83 ± 0.25	3.70 ± 0.30	3.55 ± 0.24

Preimplantation loss (No. Corpora Lutea - No. Implants) / No. Corpora Lutea) x 100
Postimplantation loss (No Implants - No. Viable Fetuses) / No. Implants) x 100
[1] Values indicate the Mean ± SD value per litter

Analysis of the data in Table 8 (succeeding page) showed no treatment-related effects on maternal and fetal parameters at the Cesarean section on GD 20. However, mean pup weights for males, females, and the combined sexes were significantly reduced at the mid (4-8%) and high doses (8-10%), relative to air control values. Tables 9 and 10 below show a tabulated summary of the incidence of external, visceral and skeletal malformations and variations.

Table 9. Summary of the Incidence of Fetal External and Visceral Malformations and Variations in F1 Rats

			BDP/HFA (mg/kg)		
Dose groups (mg/kg)	Air Cont.	Placebo	0.24	1.15	2.83
		No. of Fetuses (No. of litters)			
No. Fetuses given					
External Exams (# Litters):	279(24)	281(24)	309(23)	290(24)	297(24)
External Malformations:	0(0)	0(0)	0(0)	0(0)	0(0)
External Variations:					
Red	0(0)	0(0)	1(1)	3(2)	0(0)
External surface[1]					
Red marks	13(10)	12(8)	23(15)	9(7)	18(12)
Pale	1(1)	2(1)	5(2)	5(5)	5(3)
No of pups given					
Visceral Exams (# Litters):	142(24)	140(22)	156(23)	146(24)	150(24)
Visceral Malformations:	0(0)	0(0)	0(0)	0(0)	0(0)
Visceral Variations					
-Kidney					
Hydroureter/					
Hydronephrosis	3(3)	3(3)	2(2)	9(4)	13(8)
% affected	2(13)	2(14)	1(9)	6(17)	9(33)
Umbilical Artery Reversed	0(0)	1(1)	0(0)	0(0)	1(1)
Red medulla	0(0)	0(0)	0(0)	0(0)	1(1)
-Stomach, Red Material	0(0)	1(1)	0(0)	0(0)	0(0)
-Spleen, Pale	0(0)	0(0)	0(0)	1(1)	1(1)
-Adrenals, Red/Red foci	0(0)	0(0)	0(0)	22(10)	72(20)

[1]head, body limbs, and tail.

Table 9 shows that treatment of F0 females with BDP produced no treatment-related external or visceral malformations in F1 offspring. Treatment-related visceral variations included an increased incidence of red/red foci in the adrenals and Hydroureter/hydronephrosis in F1 rats at the mid and high doses. No historical data relative to these findings were provided. The etiology or toxicological significance of the red/red foci in the adrenals is unknown. The incidence for hydroureter/ hydronephrosis is within the range of that reported to occur spontaneously in Sprague Dawley Rats (i.e. the reported mean fetal incidence for hydronephrosis is 7.65%; range