

These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

NDA

19-0009

NDA

19-0009

AP / Ltr

NDA 19-009

Pfizer, Inc.
Central Research
Eastern Point Road
Groton, CT 06340

DEC 30 1986

Attention: Norman Pitts, M.D.
Vice President, Department of Clinical Research

Gentlemen:

Reference is made to your new drug application dated April 21, 1983, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for EXIREL Inhaler (pirbuterol acetate inhalation aerosol).

We also refer to our letter dated October 17, 1985 which declared this application approvable and to your additional communications dated November 6, 18 and 24 and December 22, 1986.

We have completed the review of this application including the draft labeling submitted in your last amendment and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in that draft labeling. Accordingly, the application is approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling with these exceptions:

1. Delete the word "here" from the last sentence of the fifth paragraph of the CLINICAL PHARMACOLOGY section.
2. The word "be" is used twice in the second sentence of the Nursing Mothers subsection of the PRECAUTIONS section and one of them should be deleted.

Marketing the product with FPL that is not identical to the draft labeling, with the exceptions, may render the product misbranded and an unapproved new drug. Please submit twelve copies of the FPL to FDA as soon as available. For administrative purposes this submission should be designated "FPL Supplement" to the approved NDA 19-009. Approval of this supplement by FDA is not required before the labeling is used. Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

submit one market package of the drug product when it is available.

NDA 19-009

Pfizer, Inc.
Central Research
Eastern Point Road
Groton, CT 06340

DEC 30 1986

Attention: Norman Pitts, M.D.
Vice President, Department of Clinical Research

Gentlemen:

Reference is made to your new drug application dated April 21, 1983, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for EXIREL Inhaler (pirbuterol acetate inhalation aerosol).

We also refer to our letter dated October 17, 1985 which declared this application approvable and to your additional communications dated November 6, 18 and 24 and December 22, 1986.

We have completed the review of this application including the draft labeling submitted in your last amendment and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in that draft labeling. Accordingly, the application is approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling with these exceptions:

1. Delete the word "here" from the last sentence of the fifth paragraph of the CLINICAL PHARMACOLOGY section.
2. The word "be" is used twice in the second sentence of the Nursing Mothers subsection of the PRECAUTIONS section and one of them should be deleted.

Marketing the product with FPL that is not identical to the draft labeling, with the exceptions, may render the product misbranded and an unapproved new drug. Please submit twelve copies of the FPL to FDA as soon as available. For administrative purposes this submission should be designated "FPL Supplement" to the approved NDA 19-009. Approval of this supplement by FDA is not required before the labeling is used. Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package of the drug product when it is available.

MOR

NDA 19-009

23 December 1986

MOR

Product: Exirel (pirbuterol acetate) (P)

Route of Administration: Metered Dose Inhaler (MDI)

Category of Drug: BAA bronchodilator

Sponsor: Pfizer

Previous Medical Reviews: See Memo of Telephone Conversation of 9 December 1986 with sponsor.

Material Reviewed: Submission of 22 December 1986

I. This submission contains a final version of the draft package insert.

Paragraph 5 under Clinical Pharmacology is acceptable as long as the word "here" is removed from the last sentence. This reviewer as noted in the memo of the telephone conversation of 12/9/86 has no objection to the addition of the phrase "and twice the recommended dose (0.8 mg)."

II. This submission also contains an NDA Safety Update Report.

The reports of 2 patients, aged 68 and 69 years who suffered a myocardial infarction and died after receiving PMDI for 7 and 18 days respectively is of concern. Although it was felt by the sponsor that these 2 events were unrelated to PMDI administration and 1 patient was already taking nifedipine for angina, the temporal relationship between the use of PMDI and these events is hard to ignore. Therefore under General Precautions, the sponsor should be asked to include a new paragraph which states, "Two patients have been reported who developed a myocardial infarction and expired after 7 and 18 days treatment with Exirel inhaler. The degree to which the use of Exirel inhaler may have contributed to these events is unclear" unless the sponsor feels that there is substantial evidence that these events were not associated with the use of Exirel inhaler, in which case the sponsor should submit data/information to substantiate that position.

III. Proposed Draft of Clinical Portion of Letter to Sponsor:

We have reviewed your labeling submitted on 22 December 1986 and have the following comments:

1. The word "here" should be removed from the last sentence of the fifth paragraph under Clinical Pharmacology.

DEC 30 1986

2.

Based on your NDA safety update also submitted on 22 December 1986, we feel that the following paragraph should be added to the General Precautions section; "two patients have been reported who developed a myocardial infarction and expired after 7 and 18 days treatment with Exirel inhaler. The degree to which the use of Exirel inhaler may have contributed to these events is unclear." unless you have substantial evidence that there was no connection between the use of Exirel inhaler and the adverse events noted above. We will be glad to review any additional data which you have on these two patients.

P. E. Walters, M.D.

R. Nicklas, M.D. for -
12/23/86

NDA 19-009

HFN-160

HFN-340

HFN-160 Dr. Winkler

R/D RNicklas 12/23/86

R/D Init. by PGWalters 12/30/86

FT OLA 12/30/86 W2522N A0154N

Doc. Room 160

Product: Exirel (pirbuterol acetate) (P)

Route of Administration: oral inhalation (MDI)

Category of Drug: BAA bronchodilator

Sponsor: Pfizer

Previous Medical Reviews: See MOR of 5 September 1986.

Material Reviewed: Submission of 6 November 1986

I. This submission contains a response to our letter of 17 October 1986 to the sponsor, an approvable letter with labeling changes proposed. The sponsor objects to the following parts of the labeling.

A. Clinical Pharmacology:

1. COMT:

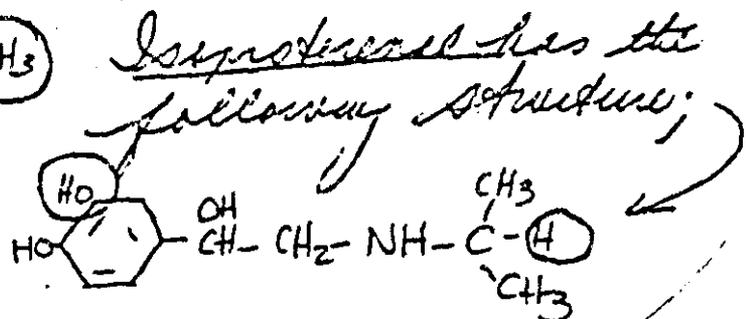
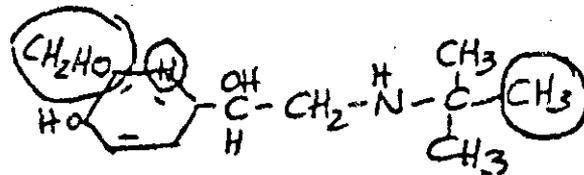
a. The sponsor states that:

The sentence has been deleted (page 1, between second and third paragraphs) that stated, "pirbuterol is longer acting than isoproterenol because it is not metabolized by catechol-o-methyltransferase."

The first component of the sentence on the increased duration of activity of pirbuterol is a statement of fact and should be retained. The second component of the sentence is based on pirbuterol metabolism data and is present in labeling for Ventolin, a structurally related product. The statement does not appear in Tornalate labeling, as that drug does not possess the same ring structural moiety involved in the biotransformation. We would accept a change to "... possibly because it is not metabolized ..."

2. Comment:

Pirbuterol has the following structure:



The differences in structure are circled. The key to metabolism by COMT is the 3,4 hydroxy structure of the benzene ring, i.e. that there are OH groups on the 3 and 4 carbons of the benzene ring. In order to be metabolized by COMT you must have a 3,4 OH structure, and Pirbuterol does not, because it is not a catecholamine, because it does not have this 3,4 OH structure. Therefore, the second part of this statement is true and should be allowed to remain. In regard to the first part of the statement, this reviewer can not find any studies in this NDA where aerosolized P was compared with isoproterenol. There are, in all likelihood studies either with other forms of P or studies reported in the literature which substantiate the first part of this statement, which is logical and expected based on the second part of this statement. The C50 will be asked to request that the sponsor indicate where the studies which compared isoproterenol and P are located.

2. Percent of patients demonstrating efficacy:

a. The sponsor states that:

In the sentence that describes the results of "controlled repetitive dose studies of 12 weeks duration involving 136 patients in comparison with metaproterenol . . .," 87% of the patients that showed a clinically significant improvement has been changed to 47% "based on a 15% or greater increase in FEV₁ on at least 4/7 evaluation days..." (page 2, paragraph 1, sentence 4). It is not possible to derive data to support the 47% calculation. Our analysis in support of the 87% value was explained in an August 13, 1986 submission, and we believe that to be most representative.

b. Comment:

In the submission of 8/13/86 the sponsor supports the 87% value for efficacy on the basis of improvement of 15% or more in FEV₁ on at least two clinic visits anytime during the 12-week period. This is unacceptable since the studies utilized by the sponsor, with the exception of the study, had at least 5 testing days and the multicenter studies had 6 and 7 testing days. Improvement on 2/5, 2/6 or 2/7 testing days (with corresponding lack of improvement on 3/5, 4/6 or 5/7 testing days) does not, in our opinion, demonstrate efficacy of the drug.

3. Pharmacology Data:

a. The sponsor states that:

A paragraph has been inserted at the end of this section (page 2) that appears to represent class labeling but does not appear in the inserts for other beta agonists, and in spite of the fact that in controlled clinical studies, we have shown some advantage over one of the other beta agonists (metaproterenol).

b. Comments:

This will be class labeling, will appear in inserts for other BAAs and should remain in the labeling.

4. Cardiac Effects:

1. The sponsor states that:

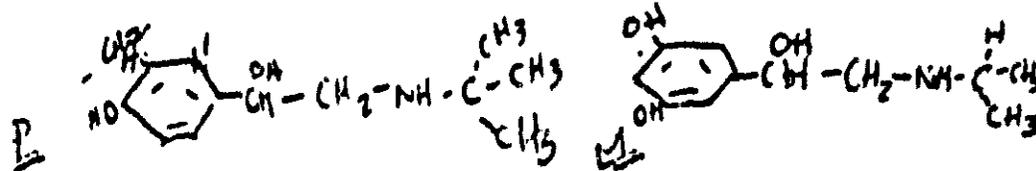
We also note that the last sentence of this section (page 2) has been deleted that read, "Cardiac effects with EXIREL were generally mild and/or clinically insignificant at the recommended dose." We recognize that to be an interpretation of the facts, but there should be no objection to stating the facts observed as they were, without interpretation. Therefore, we would suggest rewording the sentence to state that "Cardiac effects with EXIREL were generally mild and observed with an incidence of less than 2%."

2. Comments:

This reviewer continues to feel that this is an inappropriate place for the statement, even if it were acceptable. It is not acceptable, because it is misleading and unnecessary. It is unnecessary because the same statement regarding incidence is made under Adverse Reactions and it is misleading because it implies that there are less severe cardiac effects from P than other BAAs. Such a response would not be expected, i.e. it is not expected that P will behave differently than other BAAs, and a much larger study population would be needed to make a statement with such an implication.

B. Precautions (General)

1. The sponsor states that:



The statement has been deleted from the first sentence that explained while there was an association in some patients on chronic administration "with a slight increase in ectopic activity ... pirbuterol had significantly less ectopic beats than metaproterenol ($p < 0.005$)."

It was our understanding from earlier labeling discussions with Dr. Russell that facts as these from clinical trials may be quoted. We propose that the original findings be included.

2. Comments:

It is misleading to imply that P has less ectopic potential than M, when the structure of these drugs does not suggest that such will occur, and based on the limited number of patients studied in long-term (12 month) repetitive dose controlled studies in the NDA. The sponsor's proposal is not acceptable.

C. Overdose:

1. The sponsor states that:

The statement in the first paragraph has been changed to provide as examples of expected symptoms of overdose, those as listed in the Adverse Reactions section including angina, hypertension and arrhythmias. Those events are not listed and imply as now written that they were experienced in the clinical program. This section should be modified to clarify with examples of what was actually observed or what might only be expected to occur from "excessive beta-stimulation" and expressed more consistently with class labeling. We would, accordingly, offer that the sentence could be worded to replace "together with" with "and."

2. Comments:

The sponsor's point is well taken. We would not disagree with the sponsor's wording, although it might be better to separate this statement into 2 sentences, clearly distinguishing which statements could be expected to occur as a result of excessive beta stimulation and/or those symptoms listed under Adverse Reactions.

R. Nicklas MD
R. Nicklas, M.D.
11/7/86 11/18/86

TABLE 19

AVERAGE RESPONSE PATTERNS FOR COMPARABLE PATIENTS⁽¹⁾
ISOPROTERENOL VERSUS PIRBUTEROL

Dose of Pirbuterol	FEV ₁				MMF Peak	
	Peak		Duration		Pirb.	Isopro. 150 µg
	Pirb.	Isopro. 150 µg	Pirb.	Isopro. 150 µg		
0.1 mg	36.16%	40.72%	217.9 min	109.1 min	53.08	50.35
0.2 mg	41.29	40.35	200.7	78.5	52.87	50.35
0.3 mg	43.36	40.63	195.8	89.3	59.11	50.35
0.4 mg	48.38	38.51	206.8	75.0	62.68	50.35
0.6 mg	49.66	38.22	202.4	96.4	68.76	50.35
0.8 mg	49.12	40.07	229.1	112.3	64.79	50.35

(1) For FEV₁, includes only patients who responded to a given dose of pirbuterol (see text).

For MMF, includes all 24 patients.

Product: Exirel (Pirbuterol Acetate) (E)

Route of Administration: oral inhaler

Category of Drug: BAA bronchodilator

Sponsor: Pfizer

Previous Medical Reviews: See MOR of 7 November 1986.

Material Reviewed: Submission of 24 November 1986

- I. This submission contains proposed labeling changes by the sponsor.
- A. This reviewer met with the sponsor's representative to resolve the issue regarding the percentage of patients showing a clinically significant improvement. Based on the criteria agreed to by the sponsor and the agency, the sponsor's statement is accurate and acceptable. The labeling (Clinical Pharmacology, page 2, paragraph 1) would now read as the sponsor proposes:

"In controlled repetitive dose studies of 12 weeks duration, 74% of 156 patients on pirbuterol and 62% of 141 patients on metaproterenol showed a clinically significant improvement based on a 15% or greater increase in FEV₁ on at least half of the evaluation days."

- B. The sponsor proposes the addition of a new paragraph (Clinical Pharmacology, page 2, paragraph 2) which would compare the cardiac effects of Exirel with isoproterenol and metaproterenol, and which would have the following wording:

"A placebo-controlled double-blind study (26 patients per treatment group), utilizing continuous Holter monitoring showed no difference in ectopic activity between the placebo control group and EXIREL at the recommended dose (0.2 - 0.4 mg) and twice the recommended dose (0.8 mg). Ectopic activity following isoproterenol was significantly in excess of that seen with EXIREL. For some patients chronic EXIREL administration appeared to be associated with a slight increase in ectopic activity. However, in controlled comparative trials, EXIREL had significantly less ectopic activity than metaproterenol."

DEC 3 1986

Comments:

On re-evaluation of the data (page 68 - 70 in Vol. 1.3 dealing with the Tashkin Study 46-2 which is the study referred to by the sponsor above in sentence 1), this reviewer feels that the first sentence is acceptable as long as it is reworded in the following way: "A placebo-controlled, double-blind, single-dose study (24 patients per treatment group) utilizing Holter monitoring for 5 hours after drug administration showed no significant difference in ectopic activity between the placebo control group and Exirel at the recommended dose (0.2 - 0.4 mg)." The second sentence dealing with comparison with isoproterenol is not acceptable and should be removed. This reviewer does not feel that the limited data, without indication of a clinically significant difference between the two drugs is sufficient to make this statement. In regard to the sponsor's comparison of E with metaproterenol (M), in this reviewer's opinion, the data from the single dose studies (pages 2461 - 2463 of Vol. 1.9) do not show a significant difference between E and M, and M produced less ectopic activity than placebo (P). In regard to the multiple dose studies, it is inappropriate and misleading to base such a statement on ECGs done at a single time point which was 30 minutes after the dose in Studies A, B, Beumer and Bernstein and 15 - 20 minutes after the dose in the Schindl study, especially since E is longer acting than M with maximum effect occurring between 30-60 minutes. Therefore, sentences 3 and 4 should be removed as well. The revised first sentence should be placed under Warnings to precede the sentence that states that "Controlled clinical studies and other clinical experience have shown that inhaled pirbuterol like other BAAs, can produce a significant CV effect in some patients, as measured by pulse rate, BP, symptoms and/or ECG changes."

- C. The sponsor notes replacement paragraphs A and B which deal with our recommended wording for "beta - 2 specificity" and adenylyclase. Replacement paragraph A is acceptable. However, the second portion of our proposed statement i.e. "controlled clinical studies and other clinical experience ... and/or ECG changes" has not been totally included in the addition to the Warning section, so that this page should be resubmitted by the sponsor.

II. Proposed Draft of Medical Portion of Letter to Sponsor:

We have reviewed the labeling changes which you submitted on 24 November 1986 and have the following comments at this time:

1. The changes in the Clinical Pharmacology section referable to the percentage of patients showing a clinically significant improvement is acceptable.

2. The changes referable to the ectopic activity of Exirel and comparison of this activity with isoproterenol and metaproterenol are, on re-evaluation, not totally acceptable.

- a. We recommend that the first sentence be changed to read "A placebo-controlled, double-blind, single dose study (24 patients per treatment group) utilizing Holter monitoring for 5 hours after drug administration showed no significant difference in ectopic activity between the placebo control group and Exirel at the recommended dose (0.2 - 0.4 mg)" and that it be moved to follow the first sentence under Warnings and precede the statement that "Controlled clinical studies and other clinical experience ... and/or ECG changes." (Incidentally, the top part of this latter sentence was inadvertently omitted from the change under Warnings.)
- b. The second sentence should be removed since it is based on limited data and it is not clear that there is a clinically significant difference between the two drugs.
- c. Sentences 3 and 4 should be removed as well, since we do not feel that a single 12-lead ECG measurement at 15 - 30 minutes after drug administration, when the peak effect of the drug occurs 30 - 60 minutes after drug administration, is sufficient to make this claim, especially since it is questionable if there is a clinically significant difference between Exirel and metaproterenol and metaproterenol appears to have produced less ectopic activity than placebo.

R. Nicklas MD

R. Nicklas, M.D.

11/25/86

12/3/86

October 16, 1986

ADDENDUM MOR

PRODUCT: Pirbuterol acetate (Exirel)

ROUTE OF ADMINISTRATION: Oral Inhaler

CATEGORY OF DRUG: BAA bronchodilator

SPONSOR: Pfizer

PREVIOUS MEDICAL REVIEW: See MOR of 14 February 1985

- I. At Dr. Botstein's request, the General Precautions section was reviewed. As stated in the MOR of 14 February 1985 (page 6) (103) "comparison with metaproterenol is misleading even if accurate because all beta adrenergic agonists have the potential to produce this type of adverse effect." At the meeting with the sponsor, it was agreed that the rewording of the first 2 sentences in this section were acceptable as ~~they~~ now stand because they appeared to be accurate. This reviewer continues to feel that it would be better to remove the reference to metaproterenol, thereby agreeing with the recommendation made by Dr. Botstein.
- II. The first part of the General Precautions Section should now read, "In some patients, the chronic administration of pirbuterol appeared to be associated with a slight increase in VPBs or APBs. Since pirbuterol is a sympathomimetic amine" consistent with the recommendation made by Dr. Botstein

Richard A. Nicklas MD

Richard Nicklas, M.D.

10/16/86

10/16/86

RNW
10/17/86
CMT/PHR
10/17/86

NDA 19,009

MOR

13 August 1986

Product: Exirel (Pirbuterol acetate)

Route of Administration: oral inhaler

Category of Drug: BAA bronchodilator

Sponsor: Pfizer

Material Reviewed: Submission of 13 August 1986

I. This submission contains a response by the sponsor to questions raised in review of this NDA in response to the memo from Dr. Botstein and conveyed to the sponsor by telephone in order to obtain answers to these questions. Below are the questions raised (Q), the sponsor's response (SR) and our present comments (C).

A. Indications and Usage:

1. Q:

Would it be acceptable to revise the first sentence of the INDICATIONS AND USAGE Section (page 4) to read that "EXIREL Inhaler is indicated for use as a bronchodilator for bronchial asthma and/or reversible bronchospasm" rather than for ... "the relief of acute bronchospasm in patients with chronic reversible obstructive airway disease." The change would be more in line with class labeling language. If the original statement is to be retained, further justification from the NDA data base may be required.

2. SR: "The revised statement as proposed is acceptable."

3. C: This is an acceptable response.

B. Concomitant Drug Use:

1. Q:

Is there a data base to support the statement in the INDICATIONS AND USAGE Section (page 4) that EXIREL Inhaler "may be used with or without concurrent theophylline and/or steroid therapy?"

2. SR:

There is a data base in the NDA to support this statement. The data are confirmed as summarized in the enclosed table for

AUG 20 1986

both pirbuterol and metaproterenol (number of patients by study). See below.

Patients on Concomitant Theophylline Therapy

Study	Page in NDA (Vol.)	Number of Patients	
		Pirb.	Meta
Protocol A Multicenter	1269-1271 (1.6)	27	23
Protocol B Multicenter	1460-1463 (1.6)	58	56
63-3	1663 (1.7)	12	11
21-8	1695 (1.7)	6	0
14-4	1483 (1.7)	14	14
		117	104

Patients on Concomitant Steroids

Study	Page in NDA (Vol.)	Number of Patients	
		Pirb.	Meta
Protocol A Multicenter	1263-1264 (1.6)	14	17
Protocol B Multicenter	1453-1454 (1.6)	16	32
63-3	1738-1739 (1.7)	15	17
21-8	1645 (1.7)	3	2
14-4	1557 (1.7)	4	7
		52	75

3. C: This is an acceptable response by the sponsor.

C. Number of Patients:

1. Q:

In the CLINICAL PHARMACOLOGY Section (page 3, paragraph 3) reference is made to repetitive dose studies of 12 weeks duration involving 136 patients in comparison with metaproterenol, whereas N = 157 for pirbuterol in the table on page 10 of the ADVERSE REACTIONS Section. Why the difference?

2. SR:

Efficacy was evaluated in a total of 136 patients from multicenter multiple dose studies. There was one additional study following essentially the same protocol, but it was not a part of the multicenter efficacy data base

that was pooled for analysis. Thus only 136 patients were evaluated for efficacy, while 157 represents the total number of patients in all controlled studies assessed for safety. The enclosed table provides a breakdown of the number of patients evaluated, by study.

Table. Multiple Dose Double-Blind (3-Months) Parallel Comparison Studies of Pirbuterol and Metaproterenol Aerosols

Study	Number of Patients on Pirbuterol		No. Patients Assessed for Safety	
	Evaluated for Efficacy ¹	Percent of Patients Responding ²	Pirb.	Meta
Protocol A Multicenter	33	87.9	34	28
Protocol B Multicenter	66	90.9	66	67
63-3	18	77.8	18	18
21-8	19	84.2	19	19
14-4	--	--	20	21
Total	136	87.5	157	153

¹Based on all patients with two or more clinic visits. The data was excluded from analysis, as it did not share a common protocol with the remaining studies.

²Patients that showed an improvement of $\geq 15\%$ FEV₁ on at least two clinic visits anytime during the 12-week period of therapy.

3. C: This is an acceptable response by the sponsor.

D. Clinically significant improvement:

1. Q:

In the CLINICAL PHARMACOLOGY Section (page 3, paragraph 3) reference is further made that 87% of the above 136 patients in the multiple dose studies "showed a clinical significant improvement." Recalling our previous discussions on this point, can we reconstruct the analysis that yielded that value? Reference is made to the Division's letter of November 1, 1984 that had stated 47% of the evaluable patients demonstrated efficacy.

2. The analysis that yielded a value of 87% was that analysis to determine how many patients showed a clinically significant improvement in the multiple dose studies. Of the evaluable 136 patients, 87% responded in terms of improvement ($\geq 15\%$ FEV₁) on at least two clinic visits anytime during the 12-week period. This is summarized in the enclosed table.

This analysis of the number of patients responding is distinct from that which then determined continued effectiveness over the 12-week period of therapy in these responders. As we discussed and agreed with Dr. Nicklas in our communications of March 1 and 5, 1985, continued effectiveness and demonstrated in 94% of the above patients that responded. This was expressed in the final revised version as, "Continued effectiveness was demonstrated over the 12-week period in the majority (94%) of responding patients." Dr. Nicklas had initially determined using his own criteria in an informal tally the value of 47% by deriving the number of definite responders from the total number of evaluable patients in the two multicenter studies (Protocol A and B).

3. C:

We can not accept a general statement about "clinically significant improvement" based on $> 15\%$ improvement in FEV₁ on at least 2 of the evaluation days. Patients were evaluated at weeks 0, 2, 4, 6, 8, 10, and 12. There are therefore 7 evaluation points. As noted in the MOR of 14 December 1983, this reviewer used a 15% or greater improvement in FEV₁ on 4/7 evaluation days as a demonstration of efficacy. Using this criteria (which appears to be very fair) the studies referred to by the sponsor demonstrated efficacy in 47% of the patients evaluated. To make such a statement in the labeling about efficacy based on improvement on only 2/7 evaluation days is unacceptable. We would be glad to review carefully with the sponsor all individual patient data in order to resolve this issue. When reference is made to efficacy in 12 week studies, the number of patients responding is not distinct from some form of continued efficacy. If patients do not demonstrate efficacy on 5/7 test days, maybe the efficacy demonstrated on 2/7 days is not due to the drug.

E. Adverse Reactions:

1. Q:

Under the ADVERSE REACTIONS Section (pages 8-10):

- a) Frequency is stated to imply multiple dose therapy; however, the introductory paragraph appears to include single dose therapy in the total number of 761 patients?
- b) Does the frequency of 1 in 100 refer to 100 patients or adverse reactions?
- c) On page 8 (CNS) why is the incidence of tremor (6%) higher than as stated on page 10 in the comparative table (1.3%)?
- d) Do the percentages given in the comparative table on page 10 reflect the total number of patients?
- e) The Division has determined there were 145 metaproterenol patients, not 153?

2. SR:

- a) The total number of patients included both single and multiple dose therapy. The introductory sentence will be clarified to read, "The incidence of adverse reactions to pirbuterol is based on single and multiple dose clinical trials involving 761 patients; 406 of those received multiple doses over long-term periods (mean duration was 2.5 months; maximum of 19 months)."

Additionally, all three categories of frequency/causality expressed on page 8-9 will be headed to clarify that adverse reactions occurred ... "at the recommended dose of 0.4 mg q.i.d."

- b) Frequency is based on 1 in 100 patients.
- c) The incidence of 6% tremor on page 8 reflects the pooling of all NDA safety data, both open and comparative, while the table on page 10 represents only comparative data from the three-month controlled trials.
- d) The adverse reactions table on page 10 reflects the total number of patients.
- e) Our review of the NDA data base confirms that a total of 153 patients received metaproterenol; if the study is deleted, the total becomes 132 patients (reference enclosed table, Part A.).

3. C:

The response to a) is unacceptable since the sponsor has just restated what was already in the labeling. How can the incidence of adverse reactions be those occurring at a dose of 0.4 mg q.t.d. when they are supposed to represent both single and multiple dose studies? In regard to the differences noted in percent of CNS reactions, specifically tremor, since this is apparently based on the freedom with which the sponsor has jumped from one set of data to another (i.e. open plus controlled studies to controlled 12 month studies); the sponsor should be asked to relabel this section, more clearly indicating from what source the data is derived. Better yet, the sponsor should be asked to base this section on one set of data, probably best represented by data from both open and controlled studies. We are willing to accept the figure of 153 as the number of patients who received metaproterenol in the 3 month repetitive dose studies.

F. Overdosage:

1. Question: Are the symptoms of overdosage as stated in the OVERDOSAGE section (page 11) expected or observed?
2. Sponsor's Response: The symptoms are expected. The first sentence of this paragraph will be revised to clarify: "The symptoms of overdosage may be expected to be those of excessive beta-stimulation, together with any of the symptoms listed under adverse reactions, ..."
3. C: This is an acceptable response.

R. Nicklas, M.D.
R. Nicklas, M.D.
8/13/86

MOR

Product - Pirbuterol (Exirel)

Route of Administration - Oral Inhaler

Category of Drug - Bronchodilator

Sponsor - Pfizer

Previous Medical Reviews - See MOR of 14 Feb. 1985

Material Reviewed - Submission of 21 June 1986

1. This submission contains a response by the sponsor to our request for labeling changes in the letter of 21 May 1985 as agreed on at the meeting with the sponsor. These appear below in the same order as in the letter of 21 May 1985.

A. Indications and Usage Section:

1. Our comments 5/27/85: (C 5/21/85)

In the INDICATIONS AND USAGE section, the statement that pirbuterol can be used with or without concurrent theophylline and or steroid therapy should be removed or accompanied by a statement about the adverse cardiac effects seen after the concomitant administration of beta adrenergic agonists and methylxanthines in animals.

2. Sponsor's Response (SR):

The Item 1 reference to the statement in Indications and Usage on concurrent use with or without concurrent theophylline and/or steroid therapy will be retained in this section, as confirmed at the meeting.

3. Comments at this time (C):

This is acceptable and agreed on with the sponsor at the meeting.

B. General Precautions Section:

1. C 5/21/85:

In the WARNINGS section, the comments made about the use of pirbuterol in Clif under OVERDOSAGE should be included. We feel that the first sentence in the general PRECAUTIONS subsection is misleading and should be removed since some patients developed arrhythmias after pirbuterol who did not have arrhythmias at baseline. A comparison with metaproterenol as in the second sentence is also misleading and should be removed. We suggest that this section be reworded as suggested in the letter of November 1, 1984 to you.

2. SR:

Item 2: First two sentences in the general Precautions section relative to comparative cardiovascular safety (page 5).

3. C: The sponsor's response is unclear, although the first 2 sentences in this section have been changed as we requested and consistent with the agreement at the meeting. The Warnings and Overdosage comments will be addressed below. (See IE2 and IE3).

C. Drug Interaction Section:

1. C 5/21/85:

In the DRUG INTERACTION subsection, you have not included the additional paragraph as requested in the letter of November 1, 1984 to you, and therefore this section is unacceptable.

2. SR:

Item 3: Addition of the second sentence under the Drug Interactions subsection on precautions upon the coadministration of beta-agonists with monamine oxidase inhibitors or tricyclic antidepressants (page 7). It is understood that other product labeling will be so modified to conform.

3.C: This additional sentence is as we requested and is acceptable. CSO should clarify which labeling for beta agonists does not contain this statement and we should notify those sponsors that this change will be necessary.

D. Adverse Reactions Section:

1. C 5/21/85:

In the ADVERSE REACTION section, "wheezing" should be included in the section dealing with reactions where a causal relationship could not be determined.

2. SR:

Item 4: Inclusion of "wheezing" in the Adverse Reactions section where a causal relationship between pirbuterol could not be determined (page 9).

3.C. This is acceptable.

E. Overdosage Section:

1. C 5/21/85:

In regard to the OVERDOSAGE section, we recommend that you include the additional sentence requested in the letter of November 1, 1984. In addition, the two sentences relating to the effect of pirbuterol in CHF should be removed and placed in the WARNINGS section.

2. SR:

Item 5: Deletion of the last two sentences, first paragraph of the Overdosage section (intended for the Warnings sections but also to be deleted there), relating to the effect of pirbuterol in congestive heart failure (page 11). The proposed additional sentence on the concern for cardiac effects from overdose was confirmed unnecessary at the meeting.

3.C: This is consistent with our agreement with the sponsor in the meeting and therefore is acceptable.

F. Dosage and Administration Section:

1. C 5/21/85:

In the DOSAGE AND ADMINISTRATION section, you should include the frequency of administration with the usual dose i.e., "repeated every 4-6 hours."

2. SR:

Item 6: Clarification of the usual aerosol dosage frequency ("repeated every 4-6 hours") under Dosage and Administration and deletion of the word "oral" in the first line (page 11).

3.C: This is consistent with our request and therefore acceptable.

II. In summary, these changes are all consistent with our agreement with the sponsor and are therefore acceptable. We need to follow up on making the Drug Interaction section consistent for all beta agonists.

III. Proposed Draft of Medical Portion of Letter to Sponsor

The changes submitted by you on 21 June 1985 in regard to labeling for Exirel are acceptable.

R. Nicklas MD

R. Nicklas, M.D.
8/6/85 8/7/85

APR 30 1985

NDA 19,009

MEDICAL OFFICER'S REVIEW

April 19, 1985

PRODUCT: Exirel (pirbuterol acetate)
ROUTE OF ADMINISTRATION: Oral inhaler
CATEGORY OF DRUG: Bronchodilator
SPONSOR: Pfizer
MATERIAL REVIEWED: Submission of April 11, 1985.

I. This submission contains the following:

A. SAFETY UPDATE:

1. The sponsor states that the aerosol formulation has been approved by regulatory authorities in 12 countries but has been marketed only in the United Kingdom. The oral capsule form has been approved in 14 countries and is marketed in only 2 countries.
2. UNITED KINGDOM:
 - a. One study of over 2000 patients (2250) with chronic obstructive airway disease where pirbuterol aerosol was administered at doses of 0.2 or 0.4 mg (1 or 2 puffs) 3 or 4 times daily to a maximum of 2.4 mg/day for a period of four weeks. The sponsor states that "no clinically important changes in systolic and diastolic blood pressures or heart rate were observed. Side effects were similar to those previously reported. Withdrawals accounted for 8% of patients; most common side effects were tremors, palpitations, headache, and dizziness." (See attached Appendix 1)
 - b. The only serious adverse effect was in a 68 year old man who developed a MI after 7 days on pirbuterol aerosol and expired, although the attending physician did not feel that it was related to the use of Exirel.
3. NEW ZEALAND, ARGENTINA: Pediatric study ages 6-12 years)
 - a. 50 patients were treated for one month.
 - b. 2 of the patients were discontinued because of severe hyperactivity and severe palpitations.
4. SWITZERLAND: (Study published Schivej Med Wocheuschr 114:1660, 1984)
 - a. 12 asthmatic patients.
 - b. EIB
 - c. Pirbuterol compared with salbutomal
 - d. Dose of pirbuterol = 0.4 mg
 - e. The authors state that no significant changes in heart rate were noted and there were no side effects.

5. The sponsor concludes that this data shows no clinically significant changes in the nature and incidence of adverse reactions from those that are now characterized in the labeling.

B. REVISED PACKAGE INSERT:

1. The sponsor has made the changes in the Clinical Pharmacology section requested in a telephone conversation.
2. Apparently because the requests were never sent in a letter, the sponsor has not changed the other portion of the labeling as requested in the MOR of February 14, 1985. These recommendations should be conveyed to the sponsor.

II. Proposed Draft of Medical Portion of Letter to Sponsor: (Comments 2-7 in the PDMP to sponsor in the MOR of February 14, 1985, dealing with the Indications and Usage section, the General Precaution section, the Drug Interaction section, the Adverse Reactions section, the Overdose section, and the Dosage and Administration section should be conveyed to the sponsor as previously requested.)

R. Nicklas MD
R. Nicklas
4/29/85

All Side Effects

Side Effects	Total No. of Side-effects	Number of Patients Continued* Despite Side Effects	Number of Patients Discontinued* Tablets and/or aerosol
CNS			
Dizziness	26	12	14
Drowsiness/sedation	5	4	1
Headaches	46	29	17
Agitation/nervousness	4	2	2
Insomnia	6	3	3
Parosmia	4	2	2
Others	9	0	9
	100 SEs (3.5%)	52 SEs (2.1%)	48 SEs (1.7%)
Tremor			
	66 (2.9%)	23 (1.0%)	43 (1.9%)
Cardiovascular			
Painness	4	1	3
Palpitations	37	15	22
Tachycardia	7	3	4
	48 SEs (2.1%)	19 SEs (0.8%)	29 SEs (1.3%)
Respiratory			
Breathlessness	5	2	3
Chest pain/tightness	7	2	5
Cough	9	3	6
	21 SEs (0.9%)	7 SEs (0.3%)	14 SEs (0.6%)
Gastro-intestinal			
Indigestion	12	7	5
Nausea	19	12	7
Vomiting	8	2	6
Haematemesis	1	0	1
Unpleasant taste	2	0	2
Abdominal pain	3	2	1
Others	9	5	4
	54 SEs (2.4%)	28 SEs (1.2%)	26 SEs (1.2%)
Dermatological			
Rash	12	3	9
Itching	1	0	1
	13 SEs (0.5%)	3 SEs (0.1%)	10 SEs (0.4%)
Miscellaneous			
Dry/sore throat	28	18	10
Aches/pains	6	2	4
Fatigue/malaise	9	6	3
Oedema	6	5	1
Sweating	4	1	3
Flushing	3	1	2
Others	5	3	2
	61 SEs (2.7%)	36 SEs (1.6%)	25 SEs (1.1%)
T O T A L	344 Pts (15.3%)	160 Pts (7.1%)	184 Pts. (8.2%)

* Numbers in the table refer to the number of side effects and ages to patients

Occurred following aerosol administration in 80 year old male.

MOR

Product: Exirel (pirbuterol acetate)Route of Administration: oral inhalerCategory of Drug: bronchodilatorSponsor: PfizerPrevious Medical Reviews: See MOR ofMaterial Reviewed: Submission of 11 February 1985

I. This submission contains a response to our letter to the sponsor of 11/1/84. Noted below are our comments in the letter of 11/1/84 (C 11/1/84), the sponsor's response (SR) in the form of new labeling, and our present comments (C). The comments in the letter of 1 November 1984 dealt with our request for labeling changes.

A. Description Section:

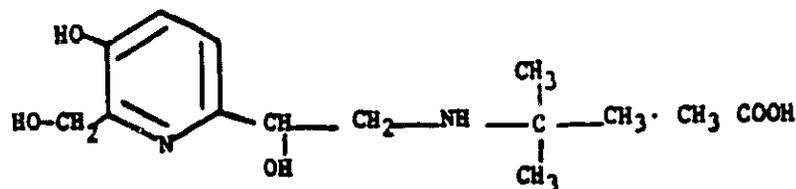
1. C 11/1/84:

Description Section: Paragraph 11. The statement that EXIREL is a "relatively selective beta-adrenergic bronchodilator" implies that it has less cardiac effect than other beta adrenergic agonists. The data generated by you does not support the statement that EXIREL has any less effect on the heart than other beta adrenergic agonists. This statement should be deleted.

2. SR:

DESCRIPTION

The active component of EXIREL Inhaler is a 6-[[[(1,1-dimethylethyl)amino]methyl]-3-hydroxy-2,6-pyridine-dimethanol monoacetate salt having the following chemical structure:



EXIREL (pirbuterol acetate) is a white, crystalline powder, freely soluble in water, with a molecular weight of 300.3 and empirical formula of $C_{12}H_{20}N_2O_3 \cdot C_2H_4O_2$.

EXIREL Inhaler is a metered-dose aerosol unit for oral inhalation. It provides a fine-particle suspension of pirbuterol acetate in the propellant mixture of trichloro-monofluoromethane and dichlorodifluoromethane, with sorbitan trioleate. It is formulated to deliver pirbuterol acetate equivalent to 200 mcg of pirbuterol per actuation from the mouthpiece. Each canister provides at least 300 inhalations.

3. C:

The reference to β_2 selectivity has been removed from the description section. It now appears to be clinically acceptable.

B. Clinical Pharmacology Section:

1. C 11/1/84:

Paragraph 1: The second sentence should begin with "In animals, it acts preferentially ..." so that it is clear to the practicing physician the studies in humans have not shown β_2 selectivity.

Paragraph 2: This paragraph is unnecessary, may be inaccurate, and should be removed.

Paragraph 3: The second part of the first sentence, "which is the probable mechanism ..." is unconfirmed, possibly irrelevant and unnecessary and should be removed. The second sentence is inappropriate, of no proven clinical significance, and should be removed. The third sentence needs to be more clearly stated or it should be removed. If reference is available for this, it should be provided for our consideration.

2. SR:

CLINICAL PHARMACOLOGY

Pirbuterol is a beta-adrenergic receptor agonist which has been shown by in vitro and in vivo animal studies to exert a preferential effect on β_2 adrenergic receptors, specifically those located in the bronchial smooth muscle, uterus and vascular supply to skeletal muscles. In animals

it acts preferentially on respiratory beta₂ receptors as opposed to cardiac beta₁ receptors. In animals the data indicate that pirbuterol is 9 times more selective than albuterol.

It is postulated that beta-adrenergic stimulants cause many of their pharmacological effects by activation of adenylcyclase, the enzyme which catalyzes the conversion of adenosine triphosphate to cyclic adenosine monophosphate, thus mediating cellular responses.

Pirbuterol is longer acting than isoproterenol because it is not metabolized by catechol-O-methyltransferase.

Bronchodilator activity was manifested clinically by an improvement in various pulmonary function parameters (FEV₁, MMF, PEFR, airway resistance [RAW] and conductance [CA/V_{Tg}])⁴.

In controlled double-blind single dose clinical trials, the onset of improvement in pulmonary function occurred within 5 minutes in most patients as determined by forced expiratory volume in one second (FEV₁). FEV₁ and MMF measurements also showed that maximum improvement in pulmonary function generally occurs 30-60 minutes following one (1) or two (2) inhalations of pirbuterol (200-400 mcg) and that clinically significant improvement is maintained for 5 hours (the time at which the last observations were made) in a substantial number of patients (67%). In repetitive dose studies of 12 weeks duration involving 136 patients in comparison with metaproterenol, 87% showed a clinically significant improvement. Onset and duration were equivalent to that seen in single dose studies. Continued effectiveness was demonstrated over the 12-week period in 94% of responding patients; however, chronic dosing was associated with the development of tachyphylaxis/tolerance to the bronchodilator effect in 5.9% of responding patients on pirbuterol and in 5.8% of responding patients on metaproterenol. Cardiac effects with EXIREL were generally mild and/or clinically insignificant at the recommended dose.

3. C:

The second paragraph was not removed as was requested. This reviewer no longer feels that it is mandatory that this paragraph be removed. It is unnecessary, and may be inaccurate, but it has been qualified by the sponsor (i.e. it is postulated") and therefore can remain. The sponsor has

not provided a reference for the single sentence in paragraph 3 although it has been more clearly stated. It is presumed that there is no reference. In regard to that portion of clinical pharmacology which was formerly under the Indications and Usage Section (see ICI below), the sponsor's statement that 67% of patients in double blind single dose studies demonstrated clinically significant improvement for 5 hours is, by our calculation, inaccurate. Therefore, this section is unacceptable unless the sponsor changes the wording to "maintained for 5 hours in some patients."

In regard to the question of tolerance, our evaluation of the data indicated that tolerance developed in 6% of the patients responding to pirbuterol. Since this is consistent with the sponsor's calculations, this is acceptable. However, since it is unclear if the 94% figure quoted by the sponsor refers to the percent of responding patients or the percent of responding patients who demonstrated continued effectiveness, the "(94%)" should be removed from the labeling. According to our evaluation, more than 50% of patients did not show continued effectiveness in the 12 week studies. In addition, by our calculation only 3% of the patients who responded to metaproterenol developed tolerance. Therefore the reference to metaproterenol should be changed to 3% (instead of 8.4%) or deleted. The sentence relating to cardiac effects is unnecessary since it is covered under Adverse Reactions and should be removed.

C. Indications and Usage Section

1. C 11/1/84:

Paragraph 1: The part of the first sentence that is in parentheses should be removed. It implies that chronic bronchitis and emphysema are reversible obstructive airways disease, and in addition, it is unnecessary.

Paragraph 2: This paragraph should be under Clinical Pharmacology. An addition to the first sentence should be, "In controlled ... within 5 minutes in most patients, as determined ...". The second sentence should be changed to read, "FEV₁ and MMF ... and that clinically significant improvement is maintained for 4-5 hours in a substantial number of patients (...). The fifth sentence should incorporate the following addition, "Continued effectiveness ... was demonstrated over a 12 week period in some patients in controlled clinical trials." The 3 controlled 12 week studies demonstrated that 54 out of 115 evaluable patients

(47%) who received EXIREL demonstrated efficacy based on 15% or greater improvement in FEV₁. Sentence 6 is incorrect. Tolerance did develop to EXIREL in some patients in the 12 week studies. This sentence could be restated that "Chronic dosing is not associated with the development of tolerance in most patients." The last part of sentence 7 is incorrect. The 12 week repetitive-dose studies do not demonstrate that EXIREL has "greater selectivity for beta-2 as opposed to beta-1 receptors." The sentence should be changed to read, "In these studies, EXIREL was shown to be an effective bronchodilator in many patients." Sentence 8 should be changed to read, "Cardiac effects from EXIREL were generally mild and/or clinically insignificant." We note that there were, for example, ECG changes which might be considered to be "limiting."

2. SR:

INDICATIONS AND USAGE. EXIREL Inhaler is indicated for the relief of acute bronchospasm in patients with chronic reversible obstructive airway disease. It may be used with or without concurrent theophylline and/or steroid therapy.

3. C:

The statement that it may be used with or without concurrent theophylline and/or steroid therapy is accurate. However, since this statement is not in the labeling for albuterol, and since we have clearly indicated our concern in the past in regard to concomitant administration of beta adrenergic agonists and methylxanthines, this statement (second sentence) should either be removed or an additional sentence should describe the findings in animal studies when these two drugs are given concomitantly. The majority of the changes requested by us are discussed under Clinical Pharmacology IB3 above, where they were placed at our request.

D. Precautions Section (General):

1. C 11/1/84:

Precautions Section: The first part of the only sentence in this section should be changed to read, "Although, it appears to have no significantly greater effect on the cardiovascular system than other beta adrenergic bronchodilators at recommended doses ...". Patients with convulsive disorders should be added to the list of patients with medical conditions where caution should be observed. EXIREL has been

used to treat congestive heart failure. You should comment on any significant adverse effects seen with the administration of EXIREL by other routes for other medical conditions.

2. SR:

In controlled double-blind trials comparing pirbuterol and metaproterenol, pirbuterol administration was not associated with an increase in arrhythmogenic activity. Metaproterenol was associated with a two-fold increase in premature ventricular activity. However, since pirbuterol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including coronary insufficiency and hypertension, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders.

3. C:

The sponsor has commented on reactions seen after pirbuterol administration in CHW under the OVERDOSAGE section (see IK below) which is inappropriate. It should be included in the WARNING Section. The first sentence in this section is misleading and, based on our evaluation, inaccurate. Patients developed palpitations and chest pain after pirbuterol administration. These symptoms can be due to arrhythmias. In addition, ectopic beats were noted in a number of studies after pirbuterol administration, and comparison with metaproterenol is misleading even if accurate because all beta adrenergic agonists have the potential to produce this type of adverse effect. Therefore, the first 2 sentences in this section should be removed and the section reworded as we had suggested in the letter of 11/1/84.

E. Drug Interactions Section:

1. C 11/1/84:

Drug Interactions Subsection: An additional paragraph should be added which states that, "EXIREL should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants since the action of EXIREL on the vascular system may be potentiated." (See page 197 and page 194 of Fourth Edition of AMA Drug Evaluations.)

2. SR:**Drug Interactions**

Other beta-adrenergic aerosol bronchodilators should not be used concomitantly with EXIREL because they may have additive effects.

3. C:

The sponsor has not included the additional paragraph as we requested, therefore this part of the labeling is unacceptable.

F. Nursing Mothers Subsection:1. C 11/1/84:

Nursing Mothers Subsection: This sentence should be changed to read, "It is not known whether EXIREL is excreted in human milk. Therefore, EXIREL should be used during nursing only if the potential benefit justifies any possible risk to the newborn."

2. SR:

It is not known whether EXIREL is excreted in human milk. Therefore, EXIREL should be used during nursing only if the potential benefit justifies any possible risk to the newborn.

3. C:

This is identical to our request and acceptable.

G. Usage in Pediatrics Subsection:1. C 11/1/84:

Usage in Pediatrics Subsection: "to establish safety and effectiveness." should be added at the end of the only sentence in this section.

2. SR:

EXIREL Inhaler is not presently recommended for patients under the age of 12 years due to insufficient clinical data in this pediatric age group to establish safety and effectiveness.

3. C:

This is identical to our request and acceptable.

H. Precautions Section (Carcinogenesis):1. C 11/1/84:

Precautions Section: Review to include these two subsections:

Carcinogenesis, Mutagenesis, and Impairment of Fertility.

Pirbuterol hydrochloride administered in the diet to rats for 24 months and to mice for 18 months was free of carcinogenic activity at doses corresponding to 200 times the maximum human inhalation dose. In addition, the intragastric intubation of the drug at doses corresponding to 250 times the maximum recommended human daily oral dose likewise resulted in no increase in tumors in a 12-month rat study. Studies with pirbuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

2. SR:

Pirbuterol hydrochloride administered in the diet to rats for 24 months and to mice for 18 months was free of carcinogenic activity at doses corresponding to 200 times the maximum human inhalation dose. In addition, the intragastric intubation of the drug at doses corresponding to 250 times the maximum recommended human daily oral dose likewise resulted in no increase in tumors in a 12-month rat study. Studies with pirbuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

3. C: Needs Pharmacology Review.I. Pregnancy Category C:1. C 11/1/84:

Pregnancy Category C: Reproduction studies have been performed in rats and rabbits by the inhalation route at doses up to 12 times (rats) and 16 times (rabbits) the maximum human inhalation dose and have revealed no significant findings. Animal reproduction studies in rats at oral doses up to 300 mg/kg (250 times the maximum recommended human daily oral dose) and in rabbits at oral doses up to 100

mg/kg (83 times the maximum recommended human daily oral dose) have shown no adverse effects on reproductive behavior, fertility, litter size, peri- and postnatal viability or fetal development. Only in rabbits at the highest dose level given (300 mg/kg, which corresponds to 250 times the maximum recommended human daily oral dose) were abortions and fetal mortality observed. There are no adequate and well controlled studies in pregnant women and EXIREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2. SR:

Reproduction studies have been performed in rats and rabbits by the inhalation route at doses up to 12 times (rats) and 16 times (rabbits) the maximum human inhalation dose and have revealed no significant findings. Animal reproduction studies in rats at oral doses up to 300 mg/kg (250 times the maximum recommended human daily oral dose) and in rabbits at oral doses up to 100 mg/kg (83 times the maximum recommended human daily oral dose) have shown no adverse effects on reproductive behavior, fertility, litter size, peri- and postnatal viability or fetal development. Only in rabbits at the highest dose level given (300 mg/kg, which corresponds to 250 times the maximum recommended human daily oral dose) were abortions and fetal mortality observed. There are no adequate and well controlled studies in pregnant women and EXIREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

3. C: Needs Pharmacology Review.

J. Adverse Reactions Section:

1. C 11/1/84:

Paragraph 2: This data is acceptable with the addition of tremor at incidence of 4%.

2. Paragraph 3: Under Cardiovascular, unless you can clearly show that there was no causal relationship, chest pain should be included. Under Gastrointestinal, nausea and vomiting should be included. Under Dermatological, pruritis should be added.

3. Paragraph 4: Under Central nervous system, headache, nervousness, and insomnia should be removed since they have been documented in paragraph 2 of this section.

4. Paragraph 5: The second part of the sentence is inappropriate, since, while accurate, it is misleading, and should be removed (i.e., "although the incidence of certain cardiovascular effects is less with EXIREL.").

2. SR:

ADVERSE REACTIONS. The incidence of adverse reactions to pirbuterol is based on clinical trials involving 761 patients, 400 of those received multiple doses over long-term periods (mean duration is 2.5 months; maximum of 19 months).

The following were the adverse reactions reported more frequently than 1 in 100 at the recommended dose of 0.4 mg q.i.d.

CNS: Nervousness (6.9%), tremor (6.0%), headache (2.0%), dizziness (1.2%).

Cardiovascular: Palpitations (1.7%), tachycardia (1.2%).

Respiratory: Cough (1.2%).

Gastrointestinal: Nausea (1.7%).

The following adverse reactions occurred less frequently than 1 in 100, and the probability exists that there is a causal relationship between pirbuterol and these reactions:

CNS: Depression, anxiety, confusion, insomnia, weakness, hyperkinesia, syncope.

Cardiovascular: Hypotension, skipped beats, chest pain.

Gastrointestinal: Dry mouth, glossitis abdominal pain/cramps, anorexia, diarrhea, stomatitis, nausea and vomiting.

Ear, Nose and Throat: Smell/taste changes, sore throat.

Dermatological: Rash, pruritis

Other: Numbness in extremities, alopecia, bruising, fatigue, edema, weight gain, flushing.

Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between pirbuterol and the reaction could not be determined: Migraine, productive cough and dermatitis.

In comparing the adverse reactions for pirbuterol acetate-treated patients to those of metaproterenol-treated patients during three-month clinical trials involving 310 patients, the following reactions as judged by the investigators were reported. The table does not include mild reactions.

PERCENT INCIDENCE OF MODERATE TO SEVERE ADVERSE REACTIONS

<u>Reaction</u>	<u>Pirbuterol</u> N = 157	<u>Metaproterenol</u> N = 153
<u>Central Nervous System</u>		
Tremors	1.3%	3.3%
Nervousness	4.5%	2.0%
Headache	1.3%	2.0%
Weakness	0.0%	1.3%
Drowsiness	0.0%	0.7%
Dizziness	0.6%	0.0%
<u>Cardiovascular</u>		
Palpitations	1.3%	1.3%
Tachycardia	1.3%	2.0%
<u>Respiratory</u>		
Chest pain/Tightness	1.3%	0.0%
Cough	0.0%	0.7%
<u>Gastrointestinal</u>		
Nausea	1.3%	2.0%
Diarrhea	1.3%	0.7%
Dry Mouth	1.3%	1.3%
Vomiting	0.0%	0.7%
<u>Dermatological</u>		
Skin Reaction	0.0%	0.7%
Rash	0.0%	1.3%
<u>Other</u>		
Bruising	0.6%	0.0%
Smell/Taste Change	0.6%	0.0%
Backache	0.0%	0.7%
Fatigue	0.0%	0.7%
Hoarseness	0.0%	0.7%
Nasal Congestion	0.0%	0.7%

3. C:

Under the section dealing with reactions where a causal relationship could not be determined, "wheezing" should be included. The sponsor has eliminated the sentence, "The adverse reactions of pirbuterol are similar in nature to those of other sympathomimetic agents." This reviewer feels that this is acceptable. In regard to the data on the 3 month clinical trials, we calculate that 145 patients, rather than 153 received metoprolol. This does not change the percent incidence of moderate to severe reactions significantly. Our computations agree with the sponsor's figures. Therefore, except for the need to include "wheezing" as an adverse reaction seen after pirbuterol administration, this section is acceptable.

K. Overdosage Section:1. C 11/1/84:

Overdosage Section Paragraph 1: An additional sentence should state, "Special concern should be directed at the possible cardiac effects from overdosage, especially the development of arrhythmias and/or decrease in coronary blood flow."

2. SR:

OVERDOSAGE. The symptoms of overdosage are essentially those of excessive beta-stimulation, together with any of the symptoms listed under adverse reactions, i.e., nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise and insomnia. At equivalent oral doses (10-20 mg) pirbuterol achieves at least two times higher blood levels in patients with congestive heart failure than in the asthmatic patient. With the above oral doses, pirbuterol has been associated with arrhythmias in congestive heart failure, but the relationship of these effects to pirbuterol is uncertain.

Treatment consists of discontinuation of pirbuterol together with appropriate symptomatic therapy.

The oral LD₅₀ in male and female rats and mice was greater than 2000 mg base/kg. The aerosol LD₅₀ was not determined.

3. C:

The sponsor has not included the additional sentence that we recommended. In addition, the two sentences relating to the effect of pirbuterol in CHF are helpful for the practicing physician but do not belong under OVERDOSAGE and should be placed in the appropriate section of the labeling, probably under WARNINGS.

L. Dosage and Administration Section:1. C 11/1/84:

1. Paragraph 1: This sentence should be changed to read, "The usual oral dose for adult and children 12 years and older is two inhalations (0.4 mg) repeated every 4-6 hours. One inhalation (0.2 mg) repeated every 4-6 hours may be sufficient for many patients."
2. Paragraph 2: The first sentence is inappropriate because it implies that aerosolized beta adrenergic agonist drugs alone may be acceptable for "severe" or "frequent" asthma. It should be removed.

2. SR:

DOSAGE AND ADMINISTRATION. The usual oral dose for adults and children 12 years and older is two inhalations (0.04 mg); repeated every 4-6 hours. One inhalation (0.2 mg) may be sufficient for many patients.

A total daily dose of 12 actuations should not be exceeded.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

3. C:

The sponsor has failed to include the frequency of administration with the usual dose i.e. "repeated every 4-6 hours." This should be added to the labeling.

II. Conclusions:

There are aspects of the sponsor's response which continue to be unacceptable. These are found in the Clinical Pharmacology Section, the Indications and Usage Section, the General Precautions Section, the Drug Interactions Section, the Adverse Reactions Section, the Overdose Section and the Dosage and Administration Section.

III. Proposed Draft of Medical Portion of Letter to Sponsor:

(Needs Chemistry and Pharmacology reviews.)

We have reviewed your submission of 11 February 1985, and still do not feel that the proposed labeling is completely acceptable. Below are our comments.

1. In the Clinical Pharmacology Section, we disagree with your calculation that 67% of the patients in single dose studies demonstrated clinically significant improvement for 5 hours. We recommend that the phrase "in some patients" be added to this statement. We recommend that "(94%)" be removed after "the majority of responding patients" in the last paragraph since it is unclear if it refers to "responding patients" or "responding patients who demonstrated continued effectiveness." In addition, by our calculation, only 3% of the patients who responded to metaproterenol developed tolerance. Therefore, the reference to metaproterenol should be changed from 8.4% to 3% or deleted. Finally, the sentence relating to cardiac effects is covered under Adverse Reactions and should be removed from this section.
2. In the Indications and Usage section, the statement that pirbuterol can be used with or without concurrent theophylline and/or steroid therapy should be removed or accompanied by a statement about the adverse cardiac effects seen after the concomitant administration of beta adrenergic agonists and methylxanthines in animals.
3. In the WARNING Section, the comments made about the use of pirbuterol in CHF under Overdosage should be included. We feel that the first sentence in the GENERAL PRECAUTIONS Section is misleading and should be removed since some patients developed arrhythmias after pirbuterol who did not have arrhythmias at baseline. A comparison with metaproterenol as in the second sentence is also misleading and should be removed. We suggest that this section be reworded as suggested in the letter of 1 November 1984 to you.
4. In the Drug Interaction Section, you have not included the additional paragraph as requested in the letter of 1 November 1984 to you, and therefore this section is unacceptable.
5. In the Adverse Reaction Section, "wheezing" should be included in the section dealing with reactions where a causal relationship could not be determined.

6. In regard to the Overdose section, we recommend that you include the additional sentence requested in the letter of 1 November 1984. In addition, the two sentences relating to the effect of pirbuterol in CHF should be removed and placed in the WARNING Section.
7. In the Dosage and Administration Section, you should include the frequency of administration with the usual dose i.e. "repeated every 4-6 hours."

A. Nicklas MD
A. Nicklas, M.D.
2/15/85
3/19/85

ADDENDUM HOR

Product: Pirbuterol Acetate (Exirel) (P)

Route of Administration: oral aerosol

Category of Drug: bronchodilator

Sponsor: Pfizer

I. Based on the serious questions which have been raised about the reliability of one investigator's data, it is necessary to reassess the approvability of this NDA.

A. This investigator evaluated 13 patients in Study A (long-term 3 month repetitive-dose multicentric study) and 15 patients in Study B (long-term 3 month repetitive-dose multicentric study) as noted below.

	<u>Total</u>	<u>Pirbuterol</u>	<u>Metaproterenol</u>
Study A	13	7	6
Study B	15	8	7

In these 2 studies there were still, without this investigator's patients, 71 patients seen by other investigators who received P. However, the effect that this investigator's patient data will have on the overall efficacy data is unknown until the sponsor submits an analysis of the data for efficacy with this investigator's patients excluded. Once all actions regarding this investigator have been concluded, the sponsor should be asked to submit this data as soon as possible and the NDA should be considered non-approvable at least until this data has been reviewed.

B. In addition, this reviewer now has doubts about the adequacy of the data submitted by the sponsor in the 2 multicentric trials in which this investigator participated. We should ask Biostatistics to carefully review the breakdown of patients in these studies to see if the data can be statistically analyzed. See below.

<u>Investigator</u>	<u>(Study)</u>	<u>PIRBUTEROL</u>	<u>Metaproterenol</u>	<u>Total</u>
Investigator I	(A)	7	6	13
	(B)	8	7	15
Investigator II	(A)	0	1	1
	(B)	7	5	12
Investigator III	(A)	3	6	14
	(B)	6	8	14
Investigator IV	(A)	2	1	3
	(B)	8	13	21
Investigator V	(A)	4	3	7
	(B)	8	7	15
Investigator VI	(A)	2	1	3
	(B)	12	10	22
Investigator VII	(A)	11	10	21
	(B)	3	4	7
Total		85	82	168

- C. Until the data without this investigator's patients has been analyzed by the sponsor and until Biostatistics has determined if the design of Multicentric Studies A and B are acceptable for the generation of statistically significant data, this reviewer now feels that this NDA is nonapprovable based on what may turn out to be an unacceptably small number of patients evaluated.

Richard Nicklas MD
 R. Nicklas, M.D.
 3/19/84
 6/2/84

MOR

Product: Pirbuterol Acetate (Exirel) (P)

Route of Administration: oral aerosol

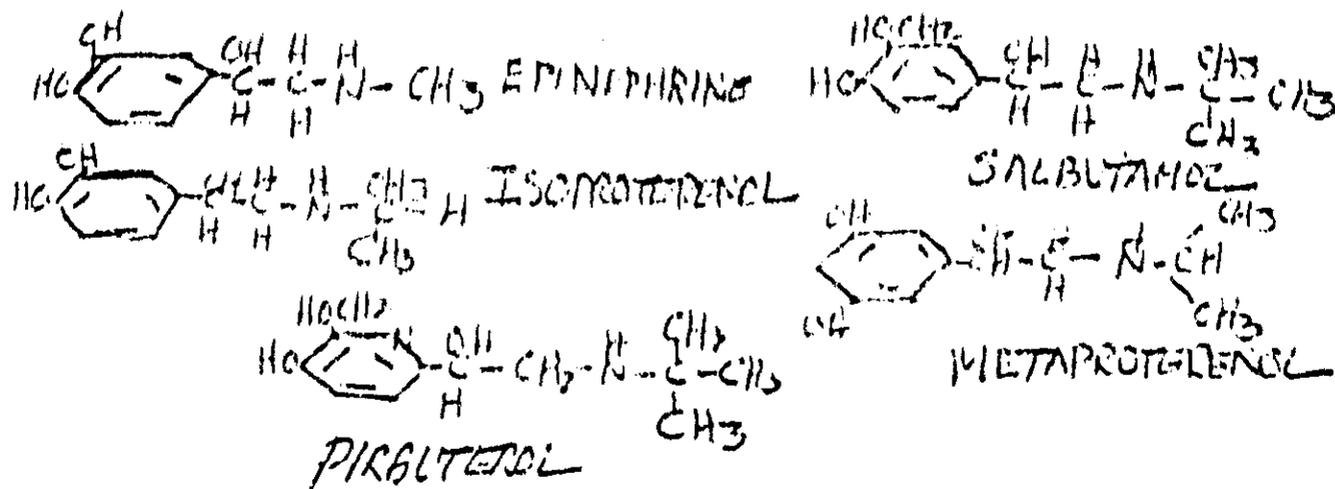
Category of Drug: bronchodilator

Sponsor: Pfizer

I. Introduction:

Pirbuterol acetate (P) is a beta adrenergic agonist (BAA) bronchodilator. It is not a catecholamine, and therefore is unlikely to undergo rapid inactivation from either catechol-O-methyl transferase (COMT) or monoamine-oxidase (MO). It is claimed that in animals, P is selective for B₂ (bronchial) receptors over B₁ (cardiac) receptors. It has not been demonstrated conclusively that B₂ selectivity is present in clinical studies. This is the aerosolized form of P and as such delivers a relatively small dose of the drug directly to the target tissue in the bronchial passageways. It is therefore, theoretically less likely to produce adverse effects or have a systemic effect. The sponsor has submitted adequately controlled and blinded single dose and repetitive-dose studies to make a claim for the effectiveness and safety of aerosolized P.

II. Chemistry:



JUN 05 1984

III. Pharmacology: See review by pharmacologist.

IV. Clinical Studies:

A. Repetitive Dose Studies with oral form of P:

The sponsor has submitted repetitive dose studies with the oral form of Pirbuterol (P) to substantiate the efficacy of the aerosolized form of P on a chronic repetitive-dose basis. This is Inappropriate. The efficacy of the aerosolized form of P should be based on studies with this form of the drug. Since these studies are unacceptable for any demonstration of efficacy with this form of the drug, they will not be reviewed here. The Medical Officer reviewing the NDA for the oral form of the drug will review them under that NDA.

B. Single-Dose Studies:

- a. number of patients - 26 (24 evaluable for efficacy)
- b. ages - 39-68 years
- c. disease studied - extrinsic asthma (8), intrinsic asthma (10), chronic bronchitis with or without emphysema (8)
- d. type of study - double-blind (DB), single-dose (SD), crossover (CX), placebo-controlled (PC), and active-treatment controlled (ATC), randomized (R) study.

- e. dosage used - 0.2 mg and 0.4 mg P; 1.3 mg metaproterenol (M)
- f. duration of study - single-dose
- g. parameters evaluated - patient self-ratings; investigator global evaluation; pulmonary function studies (PFTs) (FEV₁, MMF); Holter monitoring for up to 6 hours post-dose.
 - 1) % responders (50% responders at 0.2 and 0.4 mg)
 - 2) onset of response (sponsor: "within 5 minutes")
 - 3) degree of peak response (sponsor: significantly better than placebo)
 - 4) AMC (sponsor: significantly better than placebo)
 - 5) duration of response (sponsor: "median 4.9 hours")
- h. Comments:

1) Safety:

a) Side effects:

	P (3 patients)			Placebo (2 pts.)			M (4 pts.)		
	Mild	Mod-rate	Severe	Mild	Mod-rate	Severe	Mild	Mod-rate	Severe
dizziness	0	2	0	0	0	0	0	0	0
blurred vision	0	1	0	0	0	0	0	0	0
pruritis	0	1	0	0	0	0	0	0	0
rash	0	1	0	0	0	0	0	0	0
headache	0	0	0	0	2	0	1	2	2
chest pain	0	0	0	0	0	0	0	0	1
		<u>5</u>			<u>2</u>			<u>6</u>	

b) Lab Values:

<u>Lab test</u>	<u>P</u>	<u>Placebo</u>	<u>H</u>
<u>Hgb</u> ↓	9.3 → 8.9 (↓HCT) 13.6 → 13.0 (↓HCT)	8.9 → 10.7 12.4 → 11.4 (↓HCT) 15.7 → 11.2 14.1 → 13.1 (↓HCT)	8.9 → 8.9 (↓HCT) 15.3 → 13.7 14.1 → 13.3
<u>Lymphs</u> ↓	2400 → 1234 1694 → 600	∅	? → 1217 1773 → 1221 2400 → 1050
<u>Monos</u> ↑	746.7 → 2230.8	∅	149 → 1258
<u>SGOT</u> ↑ (N=10-50)	51 → 75 (↑SGOT)	43 → 62 (↑SGOT)	75 → 88 (↑SGOT)
<u>SGOT</u> ↑ (N=5-20)	61 → 69 23 → 36 46 → 85 (↑SGOT)	51 → 50 34 → 46 41 → 65 (↑SGOT) 20 → 35	85 → 82 (↑SGOT) 41 → 33 27 → 31 51 → 53
<u>BUN</u> ↑ (N=10-20)	30.2 → 27 (↑creatinine) 14 → 30 15 → 27	28 → 30.2 15 → 29	30 → 32 24 → 30 (↑creatinine) 21 → 29
↑ ↓ <u>K⁺</u>	∅	3.7 → 3 4.7 → 5.5	∅
↑ ↓ <u>CO₂</u> (N=24-32)	37 → 40	37.5 → 40	29 → 22
<u>Urinary units albumen</u>	0 → 6	0 → 3	0 → 4 0 → 2
<u>Urinary units glucose</u>	0 → 4	0 → 1	0 → 2
<u>RBCs/HPF</u>	1 → 4 (2)	∅	∅
<u>Casts/HPF</u>	1 → 2 (2)	0 → 2	0 → 3

Comment: The frequent admission of patients to this study with abnormal lab values makes evaluation of this data difficult. Overall, there does not appear to be any greater effect of P on lab values than that seen after placebo or H administration.

c) ECG's: There were no significant ECG findings after P administration that were not present prior to P administration. Ectopic beats per hour; 6 M patients, 3 0.2 mg P patients; 6, 0.4 mg P patients had increased numbers over placebo.

c) Vital Signs: Based on the average post-dose value, as compared with baseline, there did not appear to be clinically significant changes in BP or pulse.

2) Efficacy:

a) Overall Response Patterns (objective): (according to the sponsor)

(1) FEV₁

	<u># pts. evaluation</u>	<u># pts. effective</u>	<u>median peak effect</u>	<u>Median AUC</u>
placebo	25	3	5%	0
P 0.2 mg	24	15	24%	9%
P 0.4 mg	25	12	22%	0
M	24	10	19%	0

(2) MMF

	<u># pts. evaluation</u>	<u># pts. effective</u>	<u>median peak effect</u>	<u>Median AUC</u>
placebo	25	2	13%	0
P 0.2 mg	24	12	36%	3%
P 0.4 mg	25	12	32%	0
M	24	5	35%	0

(3) Duration of Action: FEV₁ (MMF)

<u># of pts. & duration of</u>	<u>2 hrs.</u>	<u>3 hrs.</u>	<u>4 hrs.</u>	<u>5 hrs.</u>	<u>No response</u>
P 0.2 mg (24)	4 (2)	1 (2)	1 (1)	9 (7)	9 (12)
P 0.4 mg (25)	3 (3)	0 (1)	1 (2)	8 (6)	13 (13)
M (25)	2 (0)	1 (0)	3 (1)	4 (5)	15 (19)
placebo (25)	0 (0)	1 (0)	1 (2)	1 (0)	21 (23)

Comment:

The 0.2 mg dose of P was more effective than the 0.4 mg dose. Neither M nor the 0.4 mg P were effective in the majority of patients. P was better than placebo and as effective as (or more effective than) M.

(4) Onset of Action: Generally 5 minutes, but up to 180 minutes in a few patients.

(5) Patient self-assessment*:

<u>Placebo</u>	<u>P 0.2 mg</u>	<u>P 0.4 mg</u>	<u>M</u>
8.111	8.439	8.491	8.465

*based on a rating of 0-14, where 7 = no improvement
 > 7 = improvement
 < 7 = worse

(6) Investigator's-assessment ⁽²⁾:

<u>Placebo</u>	<u>P 0.2 mg</u>	<u>P 0.4 mg</u>	<u>M</u>
3.3	2.0	2.1	2.4

⁽²⁾
 1 = marked improvement
 2 = moderate improvement
 3 = slight improvement
 4 = no change
 5 = worse.

2.

- a. number of patients - 26 (24 evaluable for efficacy)
- b. ages - 27-69 years
- c. disease studied - extrinsic asthma (8), intrinsic asthma (10), chronic bronchitis with or without emphysema (8)
- d. type of study - double-blind, single-dose, crossover, placebo-controlled, and active-treatment controlled, randomized study.
- e. dosage used - 0.2 mg and 0.4 mg P; 1.3 mg metaproterenol (M)
- f. duration of study - single-dose
- g. parameters evaluated - patient self-ratings; investigator global evaluation; PFTs (FEV₁, MMF)
 1) % responders (50% 0.2 mg and 70% 0.4 mg)

- 2) onset of response (sponsor: "within 5 minutes")
 3) degree of peak response (sponsor: significantly better than placebo)
 4) AUC (sponsor: significantly better than placebo)
 5) duration of response (sponsor: "median 4.8 hours")

n. Comments:

1. Safety:

a) Side effects:

	<u>P 0.2-0.4 (4 pts.)</u>			<u>Placobo (3 pts.)</u>			<u>M (4 pts.)</u>		
	<u>Mild</u>	<u>Mod- erate</u>	<u>Severe</u>	<u>Mild</u>	<u>Mod- erate</u>	<u>Severe</u>	<u>Mild</u>	<u>Mod- erate</u>	<u>Severe</u>
dizziness	1	0	0	2	0	0	0	0	0
nervousness	0	0	0	1	0	0	1	0	0
palpitation	3	0	0	0	0	0	0	0	0
dry mouth	0	0	0	0	0	0	1	0	0
cough	0	1	0	0	0	0	0	0	0
flatulence	0	0	0	0	0	0	1	0	0
diarrhea	1	0	0	1	0	0	0	0	0
headache	0	0	0	1	0	0	1	0	0
sedation	0	0	0	1	0	0	0	0	0
TOTAL	5	1	0	5	0	0	4	0	0

b) Lab Values:

	<u>P</u>	<u>Placebo</u>	<u>M</u>
<u>Hgb & Hct</u>	4	0	2
13 (36.7)			34.7
12.4 (36.6)			36
(36.3)			14.9-→10.8 (30.4)
(36.4)			
<u>Leukopenia</u>	6	2	6
6500-→3800			2800-→2300 (↓neutrophils)
6400-→3800			5500-→3600 (↓neutrophils)
6900-→2500 (↓neutrophils) (1650)			7100-→3200 (↓neutrophils)
7500-→2900 (↓neutrophils) (1566)			6300-→2500 (↓neutrophils)
5400-→1200 (↓neutrophils) (732)			7000-→2800
5300-→3500			5000-→3000
<u>Lymphopenia</u>	1	0	1
2052-→456			3150-→616
<u>SGOT Increase</u>	3	0	1
37-→81 (↑Alk phosph)			?-→458(↑SGPT & Alk phosph)
25-→54 (↑SGPT)			
35-→45			
<u>SGPT Increase</u>	2	0	1
12-→89 (↑SGPT)			?-→490(↑SGOT & Alk phosph)
39-→80			
<u>Alk Phosphatase</u>	1	0	1
122-→145 (↑SGPT)			?-→198(↑SGOT & SGPT)
<u>Serum Potassium</u>	0	0	1
			4200-→3200
<u>Casts</u>	0	0	1
			?-→6

c) ECG's:

No significant changes were noted after P administration that were not present before P administration, and in some instances after M and/or placebo.

d) Vital Signs:

No significant changes were noted in diastolic BP or pulse rate after P administration, except for one patient who went from a baseline value of 76 mm Hg to an average post-drug of 93 mm Hg. Systolic BP was apparently not measured.

2) Efficacy:a) Individual Patient Response:

Based on overall response patterns to FEV₁, 17/24 patients responded to P 0.2 mg while only 12/24 patients responded to P 0.4 mg. This data suggests that a top dose of 0.2 mg is adequate. In regard to MMF, 17/24 patients responded to P 0.2 mg and only 11/24 patients responded to P 0.4 mg, substantiating the above impression. Only 14/24 patients responded to M.

b) Duration of Action:

The average duration of action based on FEV₁ was 3.1 hours after 0.2 mg P and 2.1 hours after 0.4 mg P.

<u># of pts. with duration of</u>	<u>2 hrs.</u>	<u>3 hrs.</u>	<u>4 hrs.</u>	<u>5 hrs.</u>	<u>No response</u>
P 0.2 mg (24)	1	3	2	11	7
P 0.4 mg (24)	2	1	1	8	12
M (24)	0	4	4	6	10

Based on this data, which is not overly impressive at either dosage, there is no reason to use the 0.4 mg dose of P. None of the patients in this study who did not respond to a dose of 0.2 mg P had a significant response to the 0.4 mg dose of P (although 1 patient went from a 2 hour duration of action to a 3 hour response, and 1 other patient who didn't respond at 0.2 mg P responded for 2 hours with 0.4 mg P). Overall the efficacy appeared to be better than that obtained with M.

c) Onset of Action:

Most patients had a response within 5 minutes but the onset ranged between 5-30 minutes.

d) Area under the Curve:

	<u>Average of 24 patients</u>
0.2 mg P	15.12%
0.4 mg P	11.71%
H	9.46%

e) Duration of Action: Based on MMF values.

	<u>2 hrs.</u>	<u>3 hrs.</u>	<u>4 hrs.</u>	<u>5 hrs.</u>	<u>No response</u>
P 0.2 mg (24)	1	0	4	12	7
P 0.4 mg (24)	1	1	1	8	13
H (24)	1	1	3	10	9

f) Investigator's Global Assessment:

<u># of patients with</u>	<u>Improvement</u>				<u>pt. worse</u>
	<u>marked</u>	<u>moderate</u>	<u>slight</u>	<u>none</u>	
0.2 mg P	6	6	9	5	0
0.4 mg P	3	4	13	3	0
H	4	7	11	4	0
Placebo	2	0	12	10	0

3.

- number of patients - 26 patients (24 evaluable for efficacy)
- ages - 18-65 years
- disease studied - asthma and "asthma associated with chronic bronchitis"
- type of study - DB, SD, CX, placebo-controlled study.
- dosage used - 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7 mg, and 0.8 mg P
- duration of study - single-dose study

- g. parameters evaluated - PFTs (FEV₁, MMF); Holter monitoring (24 patients) for 6-7 hours post-dose.
 1) % responders (sponsor: greater than placebo at all doses)
 2) onset of action (sponsor: "within 5 minutes")
 3) peak effect (sponsor: 30 minutes)
 4) median duration (sponsor: median 3.9 hours)

h. Comments:

1. Safety:

a) Side effects: (6 patients)

Side Effects	0.1 mg		0.2 mg		0.3 mg		0.4 mg		0.6 mg		0.8 mg	
	Mild	Mod-erate										
nervousness	0	0	0	0	0	0	1	0	0	0	0	0
dizziness	1	0	0	0	0	0	0	0	0	1	0	0
tremors	0	0	0	0	0	0	0	0	0	1	0	0
breath-lessness	0	0	0	0	0	0	0	0	0	0	0	0
chest pain	0	0	1	0	0	0	0	0	0	0	0	0
headache	0	0	0	0	0	0	1	1	0	0	0	0

b) Lab Values: No significant abnormalities noted.

c) ECG's: No changes were noted after P administration that were not present before P administration.

d) Vital Signs: Only the average post-dose is supplied. Certain patients even had a significant change in diastolic BP based on the average post-dose, i.e. 85 baseline to 100 average post-dose after 0.1 mg P, 90 to 74 post 0.8 mg P, 80 to 95 post 0.6 mg P, or in pulse rate, i.e. 88 baseline to 128 average post-dose, or 68 to 54 average post 0.6 mg P. These might represent clinically significant changes in some patients.

e) Pharmacokinetics: P was not measurable in plasma, but both free P and conjugated P were measurable in 24 hour urine collections (mean of 51%).

2) Efficacy:a) Table: overall response

24 patients	mg P						
	0.1	0.2	0.3	0.4	0.6	0.8	Pl.
overall response \uparrow FEV ₁	13 (54%)	15 (63%)	18 (75%)	20 (83%)	18 (75%)	19 (7%)	4 (17%)
>15% \uparrow <30% \uparrow FEV ₁	7	4	6	4	5	4	
>30% \uparrow FEV ₁	6	11	12	16	13	15	
overall response MMF	12 (50%)	15 (63%)	18 (75%)	17 (71%)	19 (79%)	17 (71%)	4 (17%)
>20% \uparrow <40% \uparrow MMF	3	1	3	2	4	1	
>40% \uparrow MMF	9	14	15	15	15	16	

b) Onset of action: majority 5 minutes, but range of 5-120 minutes after 0.2 mg P and 5-90 minutes after 0.4 mg P.

c) duration of action: FEV₁ (MMF)

24 pts.	duration of				No response
	1 hr.	2 hrs.	3 hrs.	4 hrs.	
placebo	0 (0)	2 (2)	0 (0)	2 (2)	20 (20)
0.1 mg P	0 (0)	0 (1)	0 (1)	13 (10)	11 (12)
0.2 mg P	0 (0)	3 (3)	2 (2)	10 (10)	9 (9)
0.3 mg P	0 (0)	1 (6)	2 (0)	15 (12)	6 (6)
0.4 mg P	1 (0)	0 (2)	6 (4)	13 (11)	4 (7)
0.6 mg P	0 (0)	2 (4)	2 (3)	14 (12)	6 (5)
0.8 mg P	0 (0)	0 (1)	2 (0)	17 (15)	5 (8)

Average duration of action for responders at 0.2 and 0.4 mg P was respectively, 3.47 hours and 3.57 hours, using FEV₁ values.

d) patient self-evaluation: average of all patients*

Placebo	mg					
	0.1	0.2	0.3	0.4	0.6	0.8
7.6	0.4	0.0	9.3	8.9	8.8	9.2

*Rating of 0-14 with 7 = no improvement
>7 = improvement
<7 = worse.

e) Peak effect

<u>Placebo</u>	<u>mg</u>					
	<u>0.1</u>	<u>0.2</u>	<u>0.3</u>	<u>0.4</u>	<u>0.6</u>	<u>0.8</u>
8%	27%	27%	33%	35%	32%	37%

4.

- a. number of patients - 24
- b. ages - 31-62 years
- c. disease studied - intrinsic asthma (8), extrinsic asthma (8), chronic bronchitis with emphysema (8)
- d. type of study - double-blind, single-dose, crossover, placeb.-controlled, and active-treatment controlled, randomized study.
- e. dosage used - 0.2 mg and 0.4 mg P; metaproterenol (M) 1.3 mg (only the 0.4 mg P dose was evaluable for efficacy)
- f. duration of study - single-dose
- g. parameters evaluated - PFTs (FEV₁, MMF, Gaw/Vtg), peak, AUC, number of responders.
 1) onset of action (sponsor: "within 5 minutes")
 2) duration of action
 3) peak effect
 4) AUC
 5) number of responders
- h. Comments:
- 1) Safety:
- a) Side effects: None reported.

Lab values	14		
	b). Lab values:	Placebo	M
	P		
<u>Hgb</u> ↑	16.4→17.9 (1)	13 →16.8 (1)	0
<u>Hct</u> ↓	{ 37.8→35 37.5→34/5 (3) 44→36.5	{ 37.5→35.5 (1)	{ 38→36 (1)
<u>WBC</u> ↓	0	6.1→4.2 (2)	0
<u>Neutrophils</u> ↓	{ 2161→1804 2080→1575 (2)	{ 6.9→3.9 2080→1425 3171→1428 (2)	{ 2080→1815 (1)
<u>Total bilirubin</u> ↑	23→14(N=2-10) 14→11 11→17 (7) 10→12 9→13 7→22 12→17	11→12 27→23 12→12 (5) 9→11 10→12	23→22 7→11 (3) 8→11
<u>Lymphocytes</u> ↓	0	1311→701 (1)	1254→885 (1)
<u>SGO1</u> ↑	30→31(N=0-12) 23→25 19→18 (14) 15→17 18→15 19→15 14→17 10→13 12→13 11→13 12→15 12→16 12→15 35→74	30→34 25→14 (14) 13→15 15→18 15→13 17→13 16→18 61→70 7→13 11→19 12→19 11→14 15→24 12→17	30→31 25→23 (10) 17→14 15→13 16→13 16→17 74→48 11→15 13→19 11→14
<u>SGPT</u> ↑	25→29(N=0-12) 18→18 20→16 (13) 34→29 14→16 15→13 25→20 14→15 16→15 10→14 10→14 13→18 41→78	15→17 25→38 11→20 (10) 29→44 9→14 12→15 10→14 20→25 12→14 55→67	25→26 17→16 23→18 (9) 14→15 14→16 15→16 78→68 12→15 25→44
<u>Creatinine</u> ↑	135→135(N=9-12) 11→17 (2)	135→135 (1)	135→120 12→18 (2)
<u>K</u> ↓	3.1→3 (1)	3→2.8 (1)	3→3.2 (2)
<u>CO2</u> ↓	27→25 (1)	27→27 (1)	5.2→3.6 27→25 (1)
<u>RBC/HPF</u> ↑	0 (N=50-70)	0	3. (1)

Comment:

The sponsor and investigator have an obligation not to enter patients into a study of this type without establishing reasonable guidelines for lab studies. The data above suggest that at least for Hgb, Hct, bilirubin, SGOT, and SGPT this was not the case. If the range of normal for these lab values is acceptable, then an unacceptably large number of patients have been entered into the study with abnormal lab values. In either case, this data can not be used to substantiate the safety of P.

- c) ECGs: No significant changes after P were noted by the sponsor.
- d) Vital signs: Clinically significant increases in systolic BP according to the sponsor were noted in 2 patients after placebo, 4 patients after 0.4 mg P, and no patients after 0.2 mg P or M. Otherwise, there appeared to be no greater incidence of changes in pulse or diastolic BP after P than after placebo or M. Individual patients, however, had significant changes in systolic and diastolic BP and pulse rate after P, M, and placebo. Using a rise or fall in BP of 20 mmHg or greater and a change in pulse rate of 20 bpm or more as the cutoff point, the table below notes the largest number of patients in each group who had such a change.

	<u>Placebo</u>	<u>0.2mg P</u>	<u>0.4mg P</u>	<u>M</u>
<u>Systolic BP</u>	13/23	14/23	10/24	9/23
<u>Diastolic BP</u>	6/23	6/23	11/24	9/23
<u>Pulse rate</u>	5/23	6/23	4/24	3/23

This is an unacceptable number of patients with potentially clinically significant changes in blood pressure and pulse rate and will have to be explained by the sponsor if this study is to be used to demonstrate the safety of P.

2) Efficacy:a) Patient self-assessment**:

<u>disease</u>	<u>Placebo</u>	<u>P 0.2mg</u>	<u>P 0.4mg</u>	<u>M</u>
extrinsic asthma	7.5	8.1	8.4	8.1
intrinsic asthma	7.6	8.3	8.6	8.5
bronchitis/emphysema	7.4	8.6	7.6	8.1
All patients (mean)	7.5	8.3	8.3	8.2

**From 0-14 rating with 7 = no improvement
> 7 = improvement
< 7 = worse

b) Investigator assessment: (↑)

mean (# of patients with no change or worse)

<u>evaluable patients</u>	<u>Placebo</u>	<u>P 0.2mg</u>	<u>P 0.4mg</u>	<u>M</u>
extrinsic asthma (8)	3.25 (5)	2.12 (1)	2.00 (2)	2.37 (1)
intrinsic asthma (7)	4.14 (6)	1.71 (0)	1.86 (0)	2.28 (1)
bronchitis/emphysema (6)	4.00 (5)	2.82 (2)	2.33 (0)	3.00 (1)
All patients (mean)	3.81	2.22	2.06	2.55

(↑) 1 = marked improvement
2 = moderate improvement
3 = slight improvement
4 = no change
5 = worse.

c) Overall Response Patterns (Objective):

	<u># of pts.</u>	<u># of pts.</u>	<u>Mean</u>	<u>Median</u>
	<u>evaluation</u>	<u>effective</u>	<u>peak effect</u>	<u>AUC</u>
(1) <u>FEV₁</u>				
placebo	24	4	11.81%	- 0.46%
P 0.2mg	23	17	30.77%	20.52%
P 0.4mg	24	21	30.00%	20.90%
M	24	16	32.00%	19.16%
(2) <u>MMF</u>				
placebo	24	5	25.62%	1.29%
P 0.2mg	23	15	46.46%	23.93%
P 0.4mg	24	19	59.65%	35.56%
M	24	17	51.45%	34.90%

(3) GA/VTG (specific airway conductance):

	<u># of pts. evaluation</u>	<u># of pts. effective</u>	<u>Mean peak effect</u>	<u>Median AUC</u>
placebo	24	6	31.17%	1.62%
P 0.2mg	23	22	84.62%	43.14%
P 0.4mg	24	21	120.88%	70.79%
M	24	20	100.02%	62.47%

5.

- a. number of patients - 24
- b. ages - 17-61 years
- c. disease studied - intrinsic asthma (8), extrinsic asthma (8), chronic bronchitis with or without emphysema (8)
- d. type of study - double-blind, single-dose, crossover, placebo-controlled, and active-treatment controlled, randomized study.
- e. dosage used - 0.4 mg P; 1.3 mg metaproterenol (M)
- f. duration of study - single-dose
- g. parameters evaluated - PFTs (FEV₁, MMF)
 - 1) peak (sponsor: P significantly better than placebo)
 - 2) onset of action (sponsor: "within 5 minutes")
 - 3) duration of action (sponsor: 4.9 hours)
 - 4) number of responders: (sponsor: P significantly better than placebo)
- h. Comments:
 1. Safety:
 - a) Side effects: None reported.

Lab values	13 Lab values:		Placebo	M
	b).	P		
Creatinine ↑ (N=9-90)		80→102	85→115	80→91
		105→133		
		107→120		
		80→91		
		75→100		
BUN ↑ (N=2.5-7)		8→9	7.1→8	8.1→9.2
		7.1→8		
		8.1→10.4		
		6.9→7.7		
		6.7→8.1		
		6.9→8.2		
Hgb ↓ HBC ↓ SGPT ↑ (N=7.5-40)		7→6.4	9.3→7.8 U	6.8→6.2 4.6→3.8 0
		U		
		60→60		
		44→48		
K ↓ (N=3.5-5)		40→44	50→70(↑SGOT)	0
		72→90		
		3.8→3.4		
		3.7→3.4		
		3.7→3.3		

Comment: The sponsor's inclusion of patients with abnormal lab values at baseline has made assessment of these studies difficult, although there is some indication that more abnormal lab values were found after P as compared with M or placebo administration.

- c) ECG's: No changes were seen which could be directly related to drug administration. There was no increase in ectopic beats seen after P administration that was not seen after placebo administration.
- d) Vital signs: Arbitrarily using an increase or decrease in systolic BP, diastolic BP, or pulse rate of 20 mmHg or 20 bpm as the cutoff, the following number of patients were found to have such changes.

(24 pts.)	systolic BP	diastolic BP	pulse rate
placebo	9(3)*	5(1)*	4(1)**
P 0.2 mg	10(3)*	9(2)*	4(1)*
P 0.4 mg	11(0)*	11(2)*	5(1)*
M	4(1)*	6(1)*	0(0)*

*Number of patients with a 30 or 40 mmHg or bpm change after dosing, in parentheses.
**50 bpm change, in parentheses.

Comment: This data not only suggests that P may be more likely to produce significant changes in BP and pulse rate than other BAA drugs, but clearly indicates that there are some patients in whom the changes in BP and/or pulse rate noted after P administration may be clinically significant.

2) Efficacy:

a) patient self-assessment*:

<u>Placebo</u>	<u>P 0.2 mg</u>	<u>P 0.4 mg.</u>	<u>M</u>
7.7	8.4	8.3	8.3

*Based on a scale of 0-14 when 7 = no improvement
>7 = improvement
<7 = worse.

b) investigator's assessment :

<u>(24 patients)</u>	<u>Placebo</u>	<u>P 0.2 mg</u>	<u>P 0.4 mg</u>	<u>M</u>
marked improvement	0	1	3	3
moderate improvement	6	8	7	5
slight improvement	10	12	11	9
no change	8	3	3	7
worse	0	0	0	0

c) objective assessment:

(1) Overall response (FEV₁ and MMF)**

<u>(24 patients)</u>	<u>Placebo</u>	<u>P 0.2 mg</u>	<u>P 0.4 mg</u>	<u>M</u>
# responding	11 (4)	18 (8)	18 (7)	13 (7)
AUC	11.6% (3%)	23.7% (12.6%)	16% (12%)	13.5% (8.4%)
peak effect	23% (17%)	40% (19%)	30% (18%)	23% (13%)

**MMF data in parentheses.

(2) Onset of response: 5 minutes in the majority of patients who received P, but 60 minutes in one patient who received 0.20 mg P and 15-180 minutes in patients receiving 0.4 mg P based on FEV₁

(3) Duration of Action: (FEV₁)

	<u>P 0.2 mg</u>	<u>Placebo</u>	<u>P 0.4 mg</u>	<u>M</u>
all pts. (24)	3.1 hrs.	1.4 hr.	3 hrs.	2.3 hrs.
responders	4.2 hrs.	3 hrs.	4 hrs.	4.1 hrs.

6.

- a. number of patients - 24
- b. ages - 36-71 years
- c. disease studied - intrinsic asthma (8), extrinsic asthma (9), chronic bronchitis with emphysema (7)
- d. type of study - double-blind, single-dose, crossover, placebo-controlled, and active-treatment controlled, randomized study.
- e. dosage used - 0.4 mg P; 1.3 mg metaproterenol (M)
- f. duration of study - single-dose
- g. parameters evaluated - PFTs, FEV₁ duration (sponsor: 4 hours)
- h. Comments:
 - 1) Safety:
 - a) Adverse Reactions: The only adverse reaction was the development of a moderately severe skin rash after 0.4 mg P.

b) Lab values:

Lab values	P (48 pts.)	Placebo (24 pts.)	M (24 pts.)
Hgb ↓ (N=120-155) (130-180)	109 → 104 135 → 118 115 → 100 (↓ Hct)	111 → 108 (↓ Hct) 130 → 125 135 → 117	111 → 108 104 → 102 134 → 127
↑ SGOT (N=0-40)	42 → 48 (↑ SGPT) 10.4 → 14.2 12 → 15 10 → 15	48 → 43	48 → 50
↑ BUN (N=6.4-12)	{ 13.2 → 14.4* 22.4 → 25* 12.2 → 12.6 12.4 → 14.4 11.5 → 12.4 3.1 → 3.0 4.2 → 3.6 4.0 → 3.5	{ 11.2 → 13.2 10 → 12.8 ? → 14.2 11.4 → 14.6* ? → 15.4* 13.3 → 18.6 3.9 → 3.6 4 → 3.1	{ 12.4 → 14.8 13.8 → 14.6 11.6 → 13 14.6 → 17.6 10 → 15.2 0
↓ K ⁺ (N=3.7-5.3)			

* ↑ Creatinine also

Comment:

The number of patients who were entered into the study with abnormal lab values makes analysis difficult, but there does not appear to be any greater incidence after P as compared to control.

c) ECG's: No changes occurred following drug administration which were not present prior to drug administration, except for two P patients, one with no baseline ectopic beats and one with baseline activity, had an increase ^{in ectopic beats} after dosing.

d) Vital signs: Arbitrarily using an increase or decrease in standing or supine systolic BP, diastolic BP, or pulse rate of 20 mmHg or 20 bpm as the cutoff, the following number of patients were found to have such changes.

	systolic BP	diastolic BP	pulse rate
placebo (24 pts.)	3	1	1
P 0.4 mg (48 pts)	9	2	1
M (24 pts)	3	0	0

5/20/75
5/20/75
5/20/75

Comment: There are occasional patients in whom P produces an increase or decrease in vital signs of a magnitude which could produce a clinically significant effect in patients with underlying cardiovascular disease.

2) Efficacy:

a) patient self-evaluation: Avg. rating post-drug.

<u>Placebo</u>	<u>P 0.4 mg</u>	<u>M</u>
2.21	3.39	3.25

b) investigator's assessment:

	<u>Placebo</u> 24 pts.	<u>P 0.4 mg</u> 48 pts.	<u>M</u> 24 pts.
marked improvement	0	16	7
moderate improvement	0	14	9
slight improvement	5	15	7
no change	18	3	1
worse	1	0	0

c) Overall response patterns: FEV₁

	<u># of pts.</u> <u>responding</u>	<u>Peak</u>	<u>AUC</u>
P 0.4 mg (48 pts.)	27 (56%)	35.5%	21.5%
M (24 pts.)	15 (63%)	31%	21%
Placebo (24 pts.)	5 (21%)	10%	2%

	<u>MMF</u>		
P 0.4 mg (48 pts.)	9 (19%)	3.5%	1%
M (24 pts.)	3 (12%)	2%	1%
Placebo (24 pts.)	1 (4%)	0	-1%

d) Onset of action: Median of 10 minutes for P and M. Some P patients did not respond for 60 minutes, however.

e) Duration of action: 76% of P patients and 73% of M patients responded for 4 hours.

3) The sponsor reports on a second same basic design as the first. Study with the same basic design as the first. Comments on the safety data from that study are noted below.

- a) Adverse Reactions: None reported.
- b) ECG's: Apparently there were no abnormal ECGs noted after P administration.
- c) Lab Data:

<u>Lab value</u>	<u>P (48 patients)</u>	<u>Placebo (24 patients)</u>	<u>M (24 patients)</u>
Hgb ↓ (N=13-18)	12→11.7 (↓Hct)	12→11.7 (↓Hct)	12→11.8 (↓Hct)
WBC ↓ (N=4-11)	3.8→3.2 (↓neutrophils)	0	3.2→2.9 (↓neutrophils)
Neutrophils ↓	3.9→3.4 3430→1536 3665→1504 1443→791	0	1248→898 1504→572
↑ SGOT (N=0-40)	25→43 (↑SGPT) 35→43 (↑SGPT) 20→48	0	46→58
↑ SGPT (N=0-40)	35→61	0	30→41
K+ ↓ (N=3.7-5.3)	4.8→3.3	0	4.1→3.2
Total bilirubin ↑ (N=2-20)	0	14→27	0

- d) Vital signs: Arbitrarily using an increase or decrease in systolic BP, diastolic BP, or pulse rate of 20 mmHg or 20 bpm as the cutoff, the following number of patients were found to have such changes.

	<u>systolic BP</u>	<u>diastolic BP</u>	<u>pulse rate</u>
placebo (24 pts.)	0	1	0
P 0.4 mg (48 pts.)	5	3	4
M (24 pts.)	2	0	0

C. Repetitive-dose studies with the aerosolized form of P

1. Protocol A
 - a. number of patients - 34 received P; 28 received M
 - b. ages - 20-74 years
 - c. disease studied - extrinsic asthma (13), intrinsic asthma (10), chronic bronchitis with or without emphysema (11)
 - d. type of study - double-blind, repetitive-dose, multicenter, parallel (P), active-treatment controlled, randomized study.
 - e. dosage used - 0.4 mg q.i.d. P; 1.3 mg q.i.d. M
 - f. duration of study - 12 weeks
 - g. parameters evaluated - pulse; blood pressure; 12 lead ECGs; lab studies; PFTs (FEV₁, FEF₅₀); PEF by patient
 - h. Comments:
 - 1) The sponsor states that "P was clinically more effective than M in all parameters but only one parameter was statistically significant (average FEV₁ AUC across all visits)" 3/14 patients receiving P were able to decrease their steroid use and 6/17 M patients were able to decrease their steroid use.

- 2) median onset of response - "within 5 minutes" It should be noted that on many occasions, patients did not respond until after 5 minutes. Onset of response was noted to be up to 120 minutes in some patients on some evaluation days. Therefore the onset of efficacy can be said to be 5 minutes in most patients but not all patients.
- 3) 15 of 34 patients receiving P experienced 24 adverse reactions, while 12 of 28 patients receiving M experienced 20 adverse reactions (see table below).
- 4) There were several patients receiving P who developed new ECG changes over the study period. There was one patient with normal baseline ECG, who developed inverted T waves and another patient with other ECG changes when entering the study who developed non-specific ST-T wave changes. Other patients developed changes in conduction through the heart i.e. right ventricular conduction delay and incomplete bundle branch block. These probably were due to the patient's underlying disease but drug effect can not be ruled out. There was also one M patient who developed non-specific ST-T wave changes. There were also 3 patients who had an increase in ectopic beats after P as well as M. It has been clearly established, we feel, that BAA drugs can produce the changes noted above. Therefore, while these changes do not represent any additional safety concern, they can not be blindly attributed to the patient's underlying disease. Labeling will have to reflect, consistent with labeling for other BAA drugs, that a significant cardiac effect is possible after P administration.
- 5) Tolerance: In terms of patient self assessment and investigator assessment the sponsor states that there was no statistically significant change over the 12 week period or any difference between M and P. One patient, according to the sponsor, in each group i.e. M and P developed tolerance over 12 weeks based FEV₁ values*^{on} (see p 28)
- 6) Laboratory Data: Reviewer's interpretation of clinically significant abnormalities.

Significantly Abnormal Values

<u>Lab study</u>	<u>Pirbuterol</u>	<u>Metaproterenol</u>
<u>SGPT increase*</u>	10	4
32→75		30→111 (↑SGOT)
46→50 (SGOT↑)		70→78
42→47		41→52
34→55 (SGOT↑)		62→70
36→66 (LDH↑)		
26→56		
20→200 (SGOT↑)		
35→67 (UGT+LDH↑)		
48→66		
37→84 (SGOT↑)		
<u>WBC decrease</u>	6	2
7200→6100 (↓neutrophils)		6300→5200 (↓neutrophils)
9100→6600 (↓neutrophils)		? →5600
3800→3800 (↓neutrophils)		
4400→4500 (↓neutrophils)		
? →3900 (↓neutrophils)		
5300→4200 (↓neutrophils)		
<u>Neutropenia*</u>	9	1
3384→3213		2520→1456
23700→3237		
3886→3283		
5369→3498		
3920→2226		
1292→1216		
2112→1800		
? →1287		
2809→2268		
<u>Lymphopenia*</u>	3	0
1221→902		
1661→968		
1963→803		
<u>SGOT increase*</u>	6	3
31→75 (↑SGOT)		31→57 (↑SGOT)
35→46		43→54
43→52 (↑SGOT)		62→70 (↑LDH)
78→78		
53→74 (↑SGOT)		
27→98 (↑SGOT)		
<u>CO₂ decrease*</u>	3	0
30→18		
23→17		
24→19		

* Felt by reviewer to be significantly ↑ # of patients with abnormality (P > M)

<u>Lab study</u>	<u>Pirbuterol</u>	<u>Metaproterenol</u>
<u>Fasting Glucose increase</u>	4	4
330→252		? →141
87→144		97→155
107→143		169→164
63→163		64→66
<u>Urinary casts (HPF)</u>	2	1
4, 2/HPF		2/HPF
<u>RBC/HPF</u>	1	2
3/HPF		5, 3/HPF
<u>Serum potassium</u>	1	2
4.2→2.9		3.7→3.3
		?→3.1
<u>Total bilirubin</u>	1	0
1.9→2.3		
<u>Hemoglobin decrease</u>	3	2
14.3→13.5		12.2→11.1
13.1→12.4		(Hct 34)
12→11		13.7→13.1
<u>GGT increase</u>	2	2
49→36 (↑SGPT & LDH)		? →40
? →41 (↑LDH)		? →49
<u>LDH increase</u>	2	1
118→305 (↑GGT)		181→174 (↑SGOT)
113→210		
<u>Calcium</u>	1	0
5→10		
<u>Total Abnormalities</u>	<u>52</u>	<u>24</u>

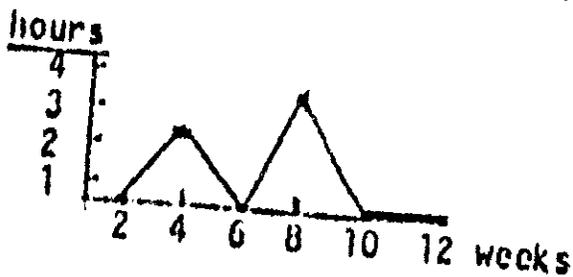
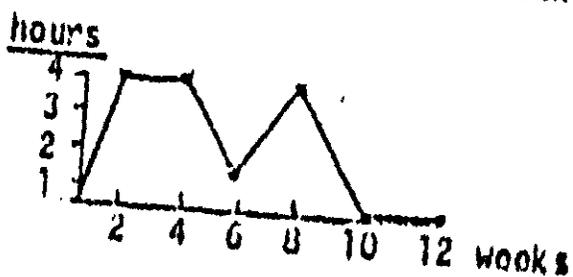
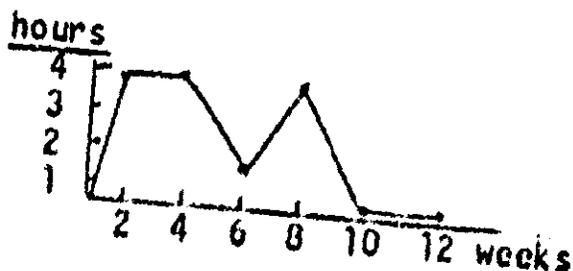
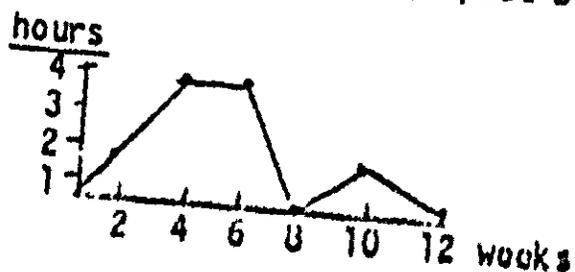
7) a) Number of patients responding:

<u>weeks</u>	<u>patients</u>	<u>hours</u>				<u>No response</u>
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	
P 0.4 mg						
2	30	0	4	1	16	9
4	30	2	4	0	14	10
6	30	2	3	3	16	6
8	29	0	0	2	17	10
10	29	0	3	1	14	11
12	31	0	1	3	16	11
M						
2	22	1	2	0	9	10
4	23	2	3	1	8	9
6	21	3	1	1	6	10
8	21	1	6	1	7	6
10	20	0	2	1	8	9
12	18	0	2	1	6	9

b) Number of Patients Demonstrating Efficacy: *

Category of response	P (34 pts.)	M (27 pts.)
Efficacy demonstrated	18	9
Questionable efficacy	2	2
Ineffective	8	9
Tolerance (initial efficacy)	0	0
Tolerance (questionable efficacy)	2	0
Non-evaluable	4	7

* Based on pulmonary function data (FEV₁) however, 4 patients appeared to develop tolerance. The duration of action of P in these 4 patients is graphed below.



0) Based on the same number or more testing days when there was no response to P as compared with testing days when there was some response to P, demonstrated by improvement in FEV₁ in terms of duration of action and AUC there were 8/34 patients where efficacy with P was not demonstrated, and another 2 patients where it was not clear based on placebo response at baseline or 2 study days without any response if efficacy had been demonstrated. There were 6 testing days. If the patient did not respond on 3 or more testing days, efficacy had not been demonstrated. If the patient failed to respond on 2/6 testing days, the efficacy was considered unclear.* Utilizing FEV₅₀ data, tolerance only appeared to develop in one patient, but P was ineffective based on the criteria used above in 8/34 patients and not clearly effective based on the criteria used above in another 9 patients.

M on the other hand, based on the same criteria as used above for P, and based on FEV₁ determination of duration of action and AUC, was ineffective in 9/27 patients and not clearly effective in another 2 patients. We question the value of the data based on 4 hours FEV₁ values as a percent of the peak.

- 9) Based on investigators global assessment, 4/33 patients overall for 12 weeks who received P experienced no effect, 2/33 patients had a minimal effect, 23/33 patients had a moderate effect, and 4 patients had a marked effect. In the 33 patients, who were evaluated at 2, 4, 6, 8, 10, and 12 weeks, there were 196 evaluations. Of these, 46 were judged to show no effect or deterioration, 35 experienced minimal effect, 89 had a moderate effect and 25 had a marked effect.

<u>Overall evaluation</u>	<u>Total</u>	<u>worse or no effect</u>	<u>minimal effect</u>	<u>moderate effect</u>	<u>marked effect</u>
Number of patients	33	4	2	23	4
Patient evaluation days	196	46	36	89	25

For M

Number of patients	27	6	5	13	3
Patient evaluation days	142	41	24	63	14

10) Summary:

a) Safety:

[1] Adverso effects:

<u>P (# of reactions) (15 patients)</u>				<u>M (# of reactions) (12 patients)</u>			
<u>Side effects</u>	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>	<u>Side effects</u>	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
nervousness	5	2	0		0	1	0
dizziness	1	0	0	sodation or drowsiness	0	0	1
tremors	2	0	0	nasal congestion	0	0	1
arrhythmia	1	0	0	flatulence	1	0	0
palpitations	0	1	0	vomiting	0	0	1
chest pain	0	1	0	skin reaction, rash	0	1	1
diarrhea	0	1	0		0	1	0
dry mouth	1	1	0		3	1	1
glossitis	0	1	0	back/pain	0	1	0
nausea	2	1	0		0	0	2
change taste/smell	0	1	0	flushing	1	0	0
hair loss	1	0	0		0	0	0
headache	2	0	0		1	2	0
total (24) =	15	9	0	(20) =	6	7	7

The sponsor states that M "was associated with more severe side effects." This is not incorrect, but the types of side effects seen with P i.e. arrhythmia, palpitations and chest pain were potentially more severe than any of the side effects seen with M.

[2] ECG data:

Labeling will have to reflect our concern that any BAA drug can, in individual patients, produce a significant cardiac effect. P is no exception. As noted above, patients can develop ST-T wave changes, conduction defects, and an increase in ectopic beats after receiving P. ECGs were done 30 minutes after drug administration which appears to be consistent with the overall peak effect of the drug.

[3] Lab data:

Overall, there appeared to be more abnormal lab values noted after P than M. If patients had not been entered into the study with abnormal lab values, the meaning of these findings would be clearer. The increases noted in SGPT, SGOT, and GGT as well as neutropenia, lymphopenia, and CO₂ decreases are of particular concern.

[4] Vital signs:

No significant changes were noted in blood pressure or heart rate.

[5] It is clear that P is not without safety concerns based on the data in this study.

b) Efficacy:

[1] Tolerance: Based on FEV₁ data, 3 P patients appeared to develop tolerance and another P patient may have. There was only 1 M patient who may have developed tolerance.

[2] Concomitant medication: 3/14 P patients and 6/17 M patients were able to decrease their steroid use.

[3] AUC: There were 13/34 P patients where efficacy was not demonstrated or where there was questionable efficacy based on FEV₁ data. There were 18/27 M patients who experienced the same results.

[4] Investigator's assessment: 4/33 P patients and 6/27 M patients experienced no improvement.

[5] It is clear that a substantial number of patients in this study did not demonstrate efficacy after P administration.

2. Protocol B

- a. number of patients - 66 received P; 59 received M
- b. ages - 18-73 years
- c. disease studied - COPD
- d. type of study - double-blind, repetitive-dose, multicenter, parallel, active-treatment controlled, randomized study.
- e. dosage used - 0.4 mg q.i.d. P; 1.3 mg q.i.d. M
- f. duration of study - 12 weeks
- g. parameters evaluated - pulse rate; blood pressure; 12 lead ECGs; PFTs (FEV₁, FEF₅₀); PEFR by patient
- h. Comments:
- (1) Safety:

a) Adverse effects:

<u>Side effects</u>	<u>PIRBUTEROL</u>			<u>Total</u>
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>	
nervousness	10	4	0	14
headache	3	0	0	3
personality change	1	0	0	1
dizziness	1	1	0	2
drowsiness/sedation	1	0	0	1
hyperkinesia	1	0	0	1
tremors	1	1	1	3
tachycardia	1	1	0	2
chest pain	0	1	0	1
abdominal pain	1	0	0	1
diarrhea	1	1	0	2
dry mouth	1	0	1	2
glossitis/stomatitis	2	0	0	2
nausea	3	1	0	4
bruising	0	1	0	1
total	27	11	2	40

<u>Side effects</u>	<u>METAPROTERENOL</u>			<u>Total</u>
	<u>Mild</u>	<u>Mod- erate</u>	<u>Severe</u>	
nervousness	5	1	1	7
headache	3	0	0	3
weakness	0	1	0	1
parasthesia	1	0	0	1
drowsiness/sedation	2	0	0	2
increased appetite	1	0	0	1
tremors	0	1	1	2
hoarseness	0	1	0	1
tachycardia	1	1	0	2
palpitations	1	0	0	1
flatulence	2	0	0	2
diarrhea	0	1	0	1
dry mouth	2	0	0	2
fatigue-malaise	0	0	1	1
nausea	0	0	1	1
rash	0	1	0	1
total	10	7	4	21

b) Lab values:Significantly Abnormal Values

<u>Lab study</u>	<u>P</u>	<u>Metaproterenol</u>
<u>SGOT</u>	9	10
TT→38		?→73 (↑SGPT)
264→235 (↑SGOT)		25→68
26→84 (↑SGPT)		?→73
36→74 (↑SGPT)		49→222
?→60 (↑LDH)		43→61 (↑SGPT)
52→85 (↑SGPT)		52→64 (↑SGPT)
31→107		?→59 (↑SGPT)
28→97		25→68
57→65 (↑SGPT)		113→162
		140→174
<u>Fasting BS↑</u>	10	8
93→124		?→132
108→192		105→167
110→142		?→157
159→135		102→132
100→251		?→150
109→149		88→176
106→140		83→134
129→146		?→142
168→270	↓ <u>Fasting BS</u>	2
105→136		90→59
		93→60

Significantly Abnormal Values

<u>Lab study</u>	<u>P</u>	<u>Metaproterenol</u>
<u>Hgb ↓</u>	3	3
12.5→12.7 (↓Hct)		12.5→11.3
10.2→9.1 (↓Hct)		13.8→13 (↓Hct)
13.4→11 (↓Hct)		12.9→12.3 (↓Hct)
<u>Hct ↓</u>	3	2
?→37.9		40.6→37.4
34.3→28.9		40→37
40→34		
<u>Leukopenia</u>	6	6
5200→2900 (neutrophils 1306)		5700→4000 (neutrophils 1960)
4700→4200 (neutrophils 2226)		3800→3000 (neutrophils 1890)
6400→4000 (neutrophils 2040)		3800→2900 (neutrophils 638)
5500→3900		5100→4700
5400→3400		4700→4600
5000→3800 (neutrophils 2052)		3900→3500 (neutrophils 2030)
<u>Lymphopenia</u>	0	3
		376
		702
		816
<u>SGPT ↑</u>	7	12
214→203 (↑SGOT)		38→49
28→78 (↑SGOT)		?→70
46→160 (↑SGOT)		61→73
41→88		?→64 (↑SGOT)
58→85 (↑SGOT)		36→61
61→82		46→68 (↑LDH)
70→93 (↑SGOT)		42→131 (↑SGOT)
		44→109 (↑SGOT)(↑LDH)
		92→119(↑SGOT)
		80→68
		55→64
<u>Alk Phosphatase ↑</u>	1	0
68→299		?→83
<u>Creatinine ↑</u>	5	1
0.9→2.5		1.2→4
1.0→1.6		
1.3→1.8 (↑BUN)		
1.1→3.0		
1.0→1.1		
<u>Uric acid</u>	0	1
		5.5→15.1
<u>H CO₂ ↓</u>	2	1
29→19		26→20
28→19		
<u>Serum Sodium</u>	0	1
		141→128

Significantly Abnormal Values

<u>Lab study</u>	<u>P</u>	<u>Metaproterenol</u>
<u>Urinary Casts</u> 4	1	0
<u>BUN</u> ↑ 19 → 30 (↑creatinine) 24 → 30	2	23 → 31 1
<u>RBC/HPF</u> 6, 4, 4, 5, 4, 4, 3	7	9 3, 3, 4, 3, 3 3, 5, 7, 3, Casts 3, 2, 2
<u>LDH</u> ↑ 156 → 186 ? → 174 (↑SGOT) ? → 160	3	188 → 305 (↑SGPT) & (↑SGOT) 137 → 168 (↑SGPT) & (↑SGOT)
<u>Total Bilirubin</u> ↑ 1.54 → 3.9	1	0
<u>Platelets</u> ↓ 206,000 → 101,000	1	1 219,000 — 142,000
<u>Serum K</u> ↓	0	4 3.1 → 2.9 4.2 → 3.4 3.6 → 3.2 ? → 3.3

c) ECG findings:

- [1] In terms of ectopic beats, there were 3 patients who developed single PACs or PVCs after P and 3 patients who developed them after M who did not have ectopic beats at baseline. There was a greater incidence of multiple ectopic beats after M than after P, none of the P patients developing 1 or more/minute after the drug was given and overall as many patients showing an increase as showed a decrease. Some of the M patients (8) on the other hand developed 1-21 ectopic beats/minute (PACs and PVCs) after receiving the drug, which were in some cases significantly higher than baseline.
- [2] The sponsor states that "there were no changes in the ECG attributable to either P or M." Only 1 patient had a change in the ECG after receiving P

which could have been drug-related i.e. non-specific ST abnormality and intra-ventricular conduction defect.

d) Vital signs:

There was a statistically significant decrease in mean standing diastolic BP and pulse rates in patients who received P, but we would agree that the mean decrease of 4.10 mmHg and 4.10 beats/min. is not clinically significant.

2) Efficacy

a) FEV₁:

There were 7 evaluation days. If the patient did not demonstrate efficacy on 4 or more of these days, P or M was determined by this reviewer to be non-effective. If the patient did not demonstrate efficacy on 3-testing days, there was in our opinion, questionable efficacy. If there was a clear-cut decrease in the duration of effect over at least the last 2 evaluation days (i.e. week 10 and week 12), we feel that tolerance had developed. Patients who did not complete the 12 weeks (data not available) were considered non-evaluable.

<u>Category of response</u>	<u>P (67 pts.)</u>	<u>M (59 pts.)</u>
Efficacy demonstrated	32	30
Questionable efficacy	8	3
Ineffective	16	16
Tolerance (initial efficacy)	6	1
Tolerance (questionable efficacy)	1	1
Non-evaluable	4	8
Total	<u>67</u>	<u>59</u>

b) FEF₅₀:

Based on the categories noted above the response to P was almost the same with 33 patients demonstrating efficacy.

c) Onset of action:

Based on FEV₁ values the onset of action for P was 5 minutes in most patients and up to 150 minutes in some patients.

d) Investigator's assessment:

<u>Overall (12 weeks)</u>	<u># of patients*</u>	
	<u>P</u>	<u>M</u>
marked improvement	5	4
moderate improvement	18	20
slight improvement	14	12
no improvement	16	8
worse	0	1
Total	53	45

<u>Individual testing days</u>	<u># of patient evaluations</u>	
	<u>P</u>	<u>M</u>
marked improvement	48	43
moderate improvement	91	111
slight improvement	59	54
no improvement	103	89
worse	57	46
Total	358	343

*Only considered if patients were evaluable on 6/7 or 7/7 testing days.

e) Duration of Action (FEV₁)

Week	Average in hours		# of pts. for 4 hours		# evaluable	
	<u>P</u>	<u>M</u>	<u>P</u>	<u>M</u>	<u>P</u>	<u>M</u>
0	2.74	2.90	38	32	67	59
2	2.90	2.23	41	28	67	59
4	2.34	2.41	30	31	66	58
6	2.63	2.60	31	28	62	53
8	2.53	2.25	29	21	62	53
10	2.39	2.54	28	27	60	51
12	2.62	2.35	33	25	59	50

3.

- number of patients - 20 received P; 21 received M
- ages - 32-73 years
- disease studied - extrinsic asthma (7), intrinsic asthma (7), chronic bronchitis with or without emphysema (6)

- d. type of study - double-blind, repetitive-dose, parallel, active-treatment controlled, randomized study.
- e. dosage used - 0.4 mg q.i.d. P; 1.3 mg q.i.d. M
- f. duration of study - 12 weeks
- g. parameters evaluated - pulse rate; blood pressure; 12 lead ECGs; PFTs (MEFR, FEV₁); PEFR by patient
- h. Comments:

(1) Safety:

- a) Adverse effects were seen in 9 instances in 5/20 patients receiving P and in 3 instances in 3/21 patients receiving M. There were no severe adverse effects. Two deaths during the study (1 on P, 1 on M) were not felt to be drug related.

<u>Side effects</u>	<u>P (5 patients)</u>				<u>M (3 patients)</u>			
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>	<u>Total</u>	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>	<u>Total</u>
nervousness	3	1	0	4	0	0	0	0
palpitations	1	0	0	1	0	0	0	0
headache	1	2	0	3	0	1	0	1
weight gain	1	0	0	1	0	0	0	0
weakness	0	0	0	0	0	1	0	1
sore throat	0	0	0	0	0	1	0	1
<u>Total</u>	<u>6</u>	<u>3</u>	<u>0</u>	<u>9</u>	<u>0</u>	<u>3</u>	<u>0</u>	<u>3</u>

- b) ECG's - 5 patients who received P and 2 patients who received M, all of whom had normal baseline ECGs, developed abnormal ECGs after drug administration. While the ECG changes in the group receiving P were not alarming changes (i.e. small q wave in one lead and clockwise rotation, heart rate of 100, slightly elevated ST segment, PACs and low voltage) it is not clear how the sponsor can claim that these are not drug related.
- c) The sponsor has included under abnormal lab values not related to drug deviations from normal that we do not agree are "normal" or "insignificant." We consider any lab value which is outside the normal range to be potentially significant and abnormal unless

repeated and found to be normal. There were abnormal lab values for both patients receiving P and those receiving M as noted below.

- [1] One patient receiving M and one patient receiving P had a slight but significant anemia after receiving the drug as reflected by a decrease in Hgb, Hct, and RBC.
- [2] Three patients receiving P and one patient receiving M had neutropenia.

	P	
(1)	WBC 0.3--4.7	neutrophils 6470--2064
(2)	WBC 5.9--4.5	neutrophils 3540--1927
(3)	WBC 5.2--3.5	neutrophils 3744--1920

	M
(1)	WBC 9.1--4.7
	neutrophils 5069--2214

Because there are more patients who developed neutropenia after P than after M, the sponsor should be asked to indicate why this data is not clinically relevant.

- [3] One patient receiving P and no patients receiving M had possible liver dysfunction. The P patient had an increased SGOT (97; normal 7-40) and SGPT (67; normal 0-35).
- [4] LDH blood sugar and uric acid levels were elevated in a number of patients who received P and M. Whether the lab used had too narrow a range, whether this is a result of beta adrenergic agonist stimulation, or whether there is some other basis for this finding is unclear. If the sponsor had not admitted these patients with, in most cases, abnormally high levels to begin with, the role played by the study drugs might be clearer. Because these increases are modest and because they were also seen with the marketed drug M, and were not associated with any clinical findings, they can not be clearly drug-related.
- [5] Serum K levels were decreased by both drugs in some patients. The comments made under (4) above apply to these findings as well.
- [6]) Vital signs: Based on average values there did not appear to be any clinically significant changes after P or significant differences from the average changes after M.

2) Efficacy

- a) Based on FEV₁ and MEF_R, peak and average (AUC) effects were not essentially different after P than those after M.
- b) In regard to tolerance, the sponsor states that there was no overall significant pattern of decreasing response for either drug. There is no indication of tolerance developing in any individual patient except for one patient receiving P and 2 patients receiving M.
- c) There was no evidence of any decrease in use of concomitant medications, specifically methylxanthines (CH₃X) or steroids by patients receiving P or M during the course of the study.
- d) Duration of Action: FEV₁

0.4 mg	# of patients with duration of		1 hour	2 hours	3 hours	4 hours	No response
	P	(M)					
week 2	18	20	0 (0)	1 (1)	2 (1)	4 (5)	11 (12)
week 4	18	20	0 (0)	1 (2)	1 (0)	8 (7)	8 (11)
week 6	18	19	0 (0)	2 (1)	3 (3)	5 (7)	8 (8)
week 8	17	18	2 (0)	1 (1)	2 (1)	4 (7)	8 (9)
week 10	17	18	0 (0)	0 (1)	2 (0)	3 (8)	12 (9)
week 12	17	18	0 (0)	2 (2)	1 (0)	5 (6)	9 (10)

There were 6 evaluation days. If the patient did not demonstrate efficacy on 3 or more of these days, P or M was determined by this reviewer to be non-effective. If the patient did not demonstrate efficacy on 2 testing days, there was in our opinion, questionable efficacy. If there was a clear-cut decrease in the duration of effect over at least the last 2 evaluation days (i.e. week 10 and week 12), we feel that tolerance had developed. Patients who did not complete the 12 weeks (data not available) were considered non-evaluable.

<u>Category of response (FEV₁)</u>	P (18 pts.)	M (20 pts.)
Efficacy demonstrated	4 > 6	4 > 7
Questionable efficacy	2	3
Ineffective	11	11
Tolerance (initial efficacy)	0	0
Tolerance (questionable efficacy)	0	0
Non-evaluable	1	2

e) Investigator Global Assessment*:

Drug	Week					
	2	4	6	8	10	12
P	3.4	3.2	2.4	2.6	2.9	2.1
M	3.7	3.3	2.5	2.4	2.8	2.6

*Based on 1 = marked effect
 2 = moderate effect
 3 = minimal effect
 4 = no effect
 5 = deterioration

f) Patient Self evaluation: Ratings were essentially the same overall for M and P.

4.

- a. number of patients - 38 patients (19 received P)
- b. ages - 41 to greater than 70 years (not accurately stated)
- c. disease studied - COPD (intrinsic asthma, extrinsic asthma, chronic asthmatic bronchitis)
- d. type of study - double-blind, repetitive-dose, parallel, active-treatment controlled, randomized study.
- e. dosage used - P 0.4 mg q.i.d.; M 1.3 mg q.i.d.
- f. duration of study - 12 weeks
- g. parameters evaluated - pulse rate; blood pressure; 12 lead ECGs; PFTs (FEV₁, MEF₅₀, PEF₅₀)
- h. Comments:
 - (1) Safety:
 - a) Adverse effects: No side effects after P administration were reported. Two adverse reactions were noted after M; mild tremor and severe cough.

b) Lab values:

<u>Lab study</u>	<u>P</u>	<u>M</u>
Hct ↓ (N=40-54)	0	40→37
K ⁺ ↑ (N=3.6-4.6)	5.1→5.8 4→4.7	4.4→5.2 4.5→4.9
Hgb ↓ (N=8.6-10.8)	9.8→8.3	8.5→7.7 9.3→8.2
Platelets ↓ (N=150-350)	124→114 219→103 (↑Clotting time) 1.3→5.1 3 →5.2 2 →4.15 2.15→5.3 1.15→6.45	0
Bleeding time ↑ (N=1-4)		1.3→13.0
↓ neutrophils	2494→1871 (↓WBC)	0
↑ monocytes	428→1121.9	945→2040 64→826
Clotting time ↑ (N=3-8)	4→11 4.3→9.2 4.4→9.2 6.5→14	5.45→10.3 4→9.2 5.3→13.0
↑ SGOT (N=3-36)	30→64 31→61 (↑SGPT) 169→271 (↑SGPT)	0
↑ CPK (N=0-60)	101→121 41→61 71→111 62→107	43→119 18→392
↑ SGPT (N=11-41)	26→45 (↑CPK & SGOT) 168→246 (↑SGOT)	0
BUN ↑ (N=3.3-6.7)	6.9→8.1 7.6→8.5 5.9→7 6→7.2 4.6→7.4 6.3→7.4	6.4→7.3 5.5→8.5
↑ FBS (N=4-6)	6.1→10.6 5.5→7.9	5.4→8.5 5.7→8.1 5.1→7.1
↑ Casts/HPF	2,2,	0

- c) ECG findings: The only possible ECG change due to either P or M was one patient with a "borderline" baseline ECG who developed ST segment depression after P. Significant increases in PACs were seen in 4 patients after P and 1 patient after M. In addition, 1 M patient had a significant increase in PVCs. No P patient had a significant increase in PVCs.
- d) Vital signs: Based on average values, there did not appear to be any clinically significant changes in BP or pulse rate from baseline and no significant difference from the effect seen after M.

2. Efficacy:

- a. Onset of Action (FEV₁): 5-60 minutes with the vast majority being 5 minutes.
- b. Duration of Action:

Week	Number of pts. responding		FEV ₁ hours				No response
	P	M	hours				
			1	2	3	4	
3	19	17	0 (0)	0 (0)	0 (1)	13 (12)	6 (4)
6	19	17	0 (0)	0 (0)	6 (0)	5 (12)	8 (5)
9	19	17	1 (0)	0 (1)	2 (4)	9 (8)	7 (4)
12	19	16	0 (0)	2 (0)	1 (1)	8 (8)	8 (7)

The response of patients to both P and M was significantly better as measured by MEFR as compared with FEV₁.

- c. Number of patients demonstrating efficacy:

Category of Response FEV ₁ (MEFR)	P (19)	M (17)
Efficacy demonstrated	8 (15)	8 (15)
Questionable efficacy	3 (2)	4 (1)
Ineffective	5 (1)	3 (1)
Tolerance (initial efficacy)	3 (1)	2 (0)
Tolerance (questionable efficacy)	0 (0)	0 (0)
Non-evaluable	0 (0)	0 (0)

If patients had a 15% or greater \uparrow in FEV₁ for any length of time on 3 or 4 of the 4 testing days they were classified as "Efficacy demonstrated"
Questionable efficacy = 0 response on 2/4 testing days
Ineffective = 0 response on 3/4 or 4/4 testing days
Tolerance = 0 response at the last visit or \downarrow effectiveness on last 2 visits.

d. Patient Self-assessment:

Drug	Week			
	3	6	9	12
M	8.4	8.2	8.2	8.2
P	8.5	8.3	8.2	8.5

e. Overall Response Patterns: FEV₁ (MEFR)

	Week 3	Week 6	Week 9	Week 12
P # pts. responding	13/19 (15/19)	11/19 (16/19)	12/19 (14/19)	10/19 (16/19)
M # pts. responding	13/17 (16/17)	12/17 (16/17)	13/17 (14/17)	9/16 (14/16)
P median peak resp.	32.5% (60.4%)	20.1% (55.9%)	22.8% (44%)	20.4% (35.1%)
M median peak resp.	36.1% (75.6%)	33.1% (80%)	25.3% (55.6%)	28.6% (80.4%)
P median AUC	10.2% (31.7%)	6.1% (22.7%)	8.4% (17.2%)	3.3% (18.6%)
M median AUC	11.9% (28.8%)	11.1% (42.7%)	10.1% (22.2%)	10.6% (39.4%)

6.

- number of patients - 18 patients received P; 18 received M
- ages - 32-75 years
- disease studied - asthma, chronic bronchitis
- type of study - double-blind, repetitive-dose, parallel, active-treatment controlled, randomized study.
- dosage used - P 0.4 mg q.i.d.; M 1.3 mg q.i.d.
- duration of study - 12 weeks
- parameters evaluated - PFTs (FEV₁, MMF, GA/Vtg); patient self-assessment; physician assessment; PEFR

h. Comments:1) Safety:

- a) Adverse effects: No patients were discontinued from the study due to side effects from either M or P, but 3 P and 5 M patients required a decrease in dosage.

<u>Side effects</u>	<u>P</u>				<u>M</u>			
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>	<u>Total</u>	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>	<u>Total</u>
nervousness	7	0	0	7	9	1	0	10
tremor	7	0	0	7	11	4	0	15
palpitations	0	1	0	1	6	2	0	8
tachycardia ^{†*}	2	1	0	3	4	2	0	6
weakness	0	0	0	0	1	0	0	1
Total	16	2	0	18	31	9	0	40

^{†*} of questionable significance.

b) Lab values:

<u>Lab study</u>	<u>P</u>	<u>M</u>
Platelets ↓ (N=150-350)	180→115 180→125 220→124 235→105 141→117 160→106	0
Hgb ↓ (N=14-18) (N=12-16)	0	17→13.4 16→11.8
*K ↓ (N=3.6-5.4)	3.7→2.4	0
BUN ↑ (N=8-23)	24→31	18→30 20→36
Creatinine ↑ (N=0.5-1.1)	0.9→1.9	0
↓ Fasting BS (N=60-110)	103→59 94→55 100→56 85→59	95→58 75→57 89→59 82→55
↑ Fasting BS RBC/HPF	82→143 6,4	97→161 4,4,3

Of primary concern are the P patients who had low platelet counts and the one P patient who had a substantial fall in serum K.

- c) ECG findings: Apparently there were no new ECG changes after P or M. None of the patients had significantly more ectopic beats after P. All ectopic beats were PACs.
- d) Vital signs: Changes in heart rate after P and M (bpm).

	<u>wk. 3</u>	<u>wk. 6</u>	<u>wk. 9</u>	<u>wk. 12</u>	<u>Overall</u>
P	3.167	1.722	2.722	1.611	2.306
M	1.299	1.588	0.824	0.765	1.118

Comment: The average increase in heart rate after P appears to be significantly greater than that after M.

Increases in heart rate > 10 bpm

P = 3 (10, 15, 17)
M = 1 (11)

Comment: These are probably not clinically significant increases in heart rate.

2) Efficacy:

a. Patient Self Assessment: There does not appear to be any significant difference between P and M but no patients apparently felt that their symptoms had deteriorated after either M or P.

b. Physician Global Assessment:

<u>Average for</u>	<u>Week</u>			
	<u>3</u>	<u>6</u>	<u>9</u>	<u>12</u>
M	3.3	3.3	2.9	2.7
P	3.1	3.7	3.4	4

Scale 1 = marked effect
2 = moderate effect
3 = minimal effect
4 = no effect
5 = deterioration

c. Overall Response Patterns: FEV₁ (IMF)

	<u># of patients responding</u>		<u>Median peak response</u>		<u>Median AUC</u>	
	<u>P</u>	<u>M</u>	<u>P</u>	<u>M</u>	<u>P</u>	<u>M</u>
Week 3	10/18 (8/18)	6/18 (7/18)	33% (59%)	21% (29%)	13% (37%)	10% (14%)
Week 6	12/18 (12/18)	9/18 (13/18)	33% (61%)	31% (56%)	25% (25%)	11% (33%)
Week 9	10/18 (8/18)	9/18 (10/18)	25% (32%)	30% (31%)	14% (15%)	16% (20%)
Week 12	8/18 (11/18)	8/18 (9/18)	22% (42%)	32% (40%)	10% (23%)	16% (16%)

Comment: Based on FEV₁ data in regard to number of patients responding, median peak response, and median AUC, tolerance appears to be developing after P use.

d. Onset of Action: (FEV₁) Most P patients experienced the onset of action in 5 minutes. In some, the onset of action was up to 120 minutes.

e. Duration of Action:

Week	Number of pts. responding	FEV ₁ hours				No response
		<u>P (18)</u>	<u>1</u>	<u>2</u>	<u>3</u>	
3	(18)	1 (0)	1 (2)	2 (0)	6 (4)	8 (12)
6	(18)	0 (0)	1 (0)	1 (1)	10 (8)	6 (9)
9	(18)	1 (0)	4 (0)	1 (3)	4 (6)	8 (9)
12	(18)	1 (0)	3 (0)	0 (1)	4 (7)	10 (10)

f. Number of patients demonstrating efficacy*: (over entire 12 weeks)

<u>Category of Response FEV₁ (MEFR)</u>	<u>P (18)</u>	<u>M (18)</u>
Efficacy demonstrated	5 (7)	4 (5)
Questionable efficacy	2 (4)	1 (6)
Ineffective	6 (5)	11 (6)
Tolerance (initial efficacy)	2 (2)	2 (1)
Tolerance (questionable efficacy)	3 (0)	0 (0)
Non-evaluable	0 (0)	0 (0)

*There were 5 evaluation days. If the patient had a 15% or greater improvement in pulmonary function on 4 or 5 days, efficacy was shown. If an adequate response (>15%) occurred 3 days, the patient was categorized as showing questionable efficacy. If an adequate response occurred on 0-2 days, the response was considered ineffective.

D. Single-blind and open studies (evaluated only for safety):

1.

- a. number of patients - 21
- b. ages - 18-65 years
- c. disease studied - asthma
- d. type of study - single-blind (SB), repetitive-dose, uncontrolled study.
- e. dosage used - up to 0.4 mg q.i.d.; (1.6 mg/day)
- f. duration of study - 4 weeks
- g. parameters evaluated for safety: side effects, EKGs, blood pressure and pulse rate
- h. Comments:

(1) Adverse Reactions:

<u>Symptoms</u>	<u>P (3 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
sore throat	1	0	0
headache	1	1	0
cough	0	0	1
Total	2	T	T

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↓ Hgb (N=8.6-10.8)	8.1→7.7	9.0→8.2
↓ WBC (N=4-10)	3.6→3.0*	2107→1634*
↓ Neutrophils (2000-7000)	2970→1750	900→626*
↓ Lymphocytes (N=1000-4500)	1980→784	132→637
↑ Monocytes (N=0-600)	536→1120	432→897
↑ Total bilirubin (N=0-17)	14.2→25.4	8.9→11.6
↑ BUN (N=3.3--6.7)	5.9→8.3	

*Same patient.

(3) ECGs: There were 3 patients with normal baseline ECGs who developed abnormal ECGs after P.

- a) p pulmonale
- b) elevated ST segment V₁-4, complete LBBB, and PVCs
- c) PVCs.

(4) Vital signs: The sponsor states that there were 2-5 patients who had at least a 10 mm fall in systolic BP and 1-4 patients who had the same fall in diastolic BP after P at different evaluation times. There was one patient who had a rise of at least 10 bpm in pulse rate after P.

2.

- a. number of patients - 8
- b. ages - 18-65 years
- c. disease studied - COPD
- d. type of study - open
- e. dosage used - up to 0.4 mg q.i.d. (1.6 mg/day)
- f. duration of study - 4 weeks
- g. parameters evaluated for safety: side effects, ECGs, vital signs, lab tests
- h. Comments:

(1) Adverse Reactions: Three of the 8 patients withdrew from the study because of side effects.

<u>Symptoms</u>	<u>P (8 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
depression	0	0	1
dizziness	0	1	0
tremors	1	0	0
anesthesia	0	1	0
tachycardia	0	0	1
nausea	0	0	1
Total	T	2	3

- (2) Lab Data: No clinically significant abnormalities.
- (3) ECGs: No abnormalities related to drug administration.
- (4) Vital signs: 2-4 patients had a 10 mmHg or greater fall in systolic BP and 1-2 patients had a similar fall in diastolic BP, while 0-2 patients had an increase of at least 10 bpm in pulse rate.

3.

- a. number of patients - 15
- b. ages - 18-65 years
- c. disease studied - COPD
- d. type of study - open
- e. dosage used - 0.4 mg q.i.d.
- f. duration of study - 16-125 days
- g. parameters evaluated for safety: side effects, lab data, ECGs, vital signs
- h. Comments:

(1) Side effects:

<u>Symptoms</u>	<u>P (2 patients)</u>			<u>Total</u>
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>	
tremors	2	0	0	2

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↓ Neutrophils (N=2000-7150)	4664	→1563
↑ Monocytes (N=0-880)	170	→904
↑ LDH (N=50-240)	185	→437
	186	→473
	208	→430
↑ Serum K (N=4-5)	4.6	→8.1
	4.3	→7.4
	4.1	→9.8
	4.1	→7.3
↓ FBS (N=70-110)	70	→57
	82	→59

- (3) ECGs: No abnormal findings on ECGs in patients who did not have abnormal ECGs at baseline.
- (4) Vital signs: The sponsor states that "There was so much missing and inconsistent blood pressure and pulse rate data that no clinically valid conclusion can be drawn."

4.

- a. number of patients - 31
- b. ages - 18-65 years
- c. disease studied - COPD
- d. type of study - open
- e. dosage used - 0.4 mg q.i.d.
- f. duration of study - 4 weeks
- g. safety parameters: side effects, lab data, ECGs, vital signs
- h. Comments:

(1) Adverse Effects:

<u>Side Effects</u>	<u>P (4 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
nervousness	1	0	0
tachycardia*	0	1	0
cough	1	0	0
anorexia*	0	1	0
flushing*	0	1	0
edema*	0	1	0
Total	2	4	0

*questionably drug related.

(2) <u>Lab Data:</u>	<u>Baseline</u>	<u>Post-drug</u>
↓ Hgb (N=13-16)	14.3	→12.3
↓ Neutrophils (N=2080-6800)	4988	→1679
↓ Lymphocytes (1000-4000)	2312	→985
↑ Total bilirubin (N=0-17)	8	→19.5
↑ SGPT (N=0-25)	24	→32
↑ GGT (N=0-28)	?	→86
		→78
↑ LDH (N=120-240)	275	→410
↑ BUN (N=3.5-6.8)	215	→270
↓	3.9	→8.5
	6	→8.6
	6.4	→8.3
	7	→10.2
	7.3	→10.4
↓ CO ₂ (N=24-32)	?	→18.5

(3) ECGs: Changes from baseline: (P)
 Incomplete bundle branch block → (R) atrial hypertrophy.
 Incomplete branch block → (R) atrial hypertrophy and PVC's

(4) Vital signs:

<u>Fall of at least 10 mmHg</u>	<u>rise of at least 10 bpm</u>	
<u>Systolic BP</u>	<u>Diastolic BP</u>	<u>pulse rate</u>

(run in period)

placebo	22/30	17/30	8/30
P	18/28	18/28	6/28

Comment: There are a significant number of patients with possibly significant changes in vital signs but fewer than seen after placebo in the baseline period.

5.

- number of patients - 13
- ages - 18-65 years
- disease studied - Asthma
- type of study - open
- dosage used - 0.4 mg q.i.d.

- f. duration of study - 4 weeks
- g. safety parameters: adverse effects, lab data, EKGs, vital signs
- h. Comments:

(1) Adverse Effects: None reported.

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↓ <u>WBC</u> (N=4.5-7)	5.6	2.7
↓ <u>Neutrophils</u> (2700-4900)	3359	840
	2499	1496
↑ <u>Total bilirubin</u> (N=0-10)	6	21
↑ <u>SGOT</u> (0-12=N)	48	135 (↑SGPT)
	12	41 (↑SGPT)
	9	25
↑ <u>CPK</u> (N=0-40)	30	72
	40	113
↑ <u>SGPT</u> (N=0-12)	26	80 (↑SGOT)
	12	34 (↑SGOT)
↓ <u>K+</u> (N=4-5.1)	4.1	3.8
	4.3	3.6
	4.4	3.5

(3) EKGs: Abnormalities post-drug not present at baseline: (P)

- a) supraventricular premature beats.
 b) Non-specific ST changes (also disappeared in another patient receiving P).

(4) Vital signs:

	<u>Fall of at least 10 mmHg</u>	<u>rise of at least 10 bpm pulse</u>
<u>Systolic BP</u>		
<u>Diastolic BP</u>		

(run in)			
placebo	4/10	3/10	1/10
P	5/10	7/10	3/10

6.

- a. number of patients - 20
- b. ages - 18-65 years

- c. disease studied - Asthma
- d. type of study - open
- e. dosage used - 0.4 mg q.i.d.
- f. duration of study - 4 weeks
- g. safety parameters: side effects, lab values, ECGs, vital signs
- h. Comments:

(1) Adverse Effects:

<u>Side Effects</u>	<u>P (7 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
anxiety	1	0	0
insomnia	1	1	0
nervousness	0	1	0
cough	0	0	1
dyspnea	0	0	1
indigestion	1	0	0
change smell/ taste	2	0	0
fatigue	1	0	0
Total	6	2	2

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
WBC (N=3.5-9)		?-→3.2
<u>Neutrophils</u> (N=1925-6850)		?-→1824
		?-→1584
<u>CPK</u> (N=0-3.5U)		?-→1548
		?-→52
		?-→414
BUN (N=120-340)		?-→434
1 pt with 4 casts/HPF		?-→463
		?-→437

- (3) ECG's: There were no drug related abnormalities.
- (4) Vital signs: 14/20 patients had a fall of at least 10 mmHg systolic BP and 9/14 patients had such a fall in diastolic BP after P initially. Over the 4 week period the frequency of such changes at least for systolic and diastolic BP in the supine position decreased substantially. The sponsor considered these changes to be clinically significant.

7.

- a. number of patients - 14
- b. ages - 18-65 years
- c. disease studied - COPD
- d. type of study - open
- e. dosage used - 0.4 mg q.1.d.
- f. duration of study - 4 weeks
- g. safety parameters: side effects, lab values, ECGs, vital signs
- h. Comments:

(1) Adverse Effects:

Side Effects	P (3 patients)		
	Mild	Mod-erate	Severe
insomnia	1	0	0
tremors	1	0	0
palpitations	1	0	0
cough	0	0	1
rash	0	1	0
Total	3	1	1

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↑ Alk phosphatase (N=12-30)		26→96
↓ Na (N=132-142)		141→124

(3) ECG's:

	<u>Baseline</u>	<u>Post-drug</u>
59y/oM	RAH & PVCs	->S. Tach, Improvement PBs, ST changes
51y/oM	ST changes + S. Tach	->ST changes + PVC's
59y/oM	IBBB	->ST changes + PAC's

- (4) Vital signs: 4-7/10 patients had a fall in systolic BP of at least 10 mmHg and 6-8/10 had a similar fall in diastolic BP after P. In addition 4-9/10 patients had a rise of at least 10 bpm in pulse after P. The sponsor considered these changes to be clinically significant.

8.

- a. number of patients - 20
- b. ages - 18-65 years
- c. disease studied - COPD
- d. type of study - open
- e. dosage used - 0.4 mg q.i.d.
- f. duration of study - 4 weeks
- g. safety parameters: side effects, lab data, ECGs, and vital signs
- h. Comments:

(1) Adverse Effects:

<u>Side Effects</u>	<u>P (3 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
cough	0	1	0
headache	1	1	0
Total	1	2	0

(2) Lab Data:Baseline Post-drug

↑ serum creatinine (N=0-1.4) 0.9 → 6.7
 ↓ FBS (N=65-110) 72 → 13

(3) ECG's: No changes occurring after P.(4) Vital signs: No significant changes noted.

9.

- a. number of patients - 19
- b. ages - 18-65 years
- c. disease studied - Asthma with or without emphysema.
- d. type of study - open

- e. dosage used - 0.4 mg q.i.d.
 f. duration of study - 4 weeks
 g. safety parameters: adverse effects, lab data, ECGs, vital signs.
 h. Comments:

(1) Adverse Effects:

<u>Side Effects</u>	<u>P (3 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
confusion*	0	0	1
syncope*	0	0	1
tremors	0	1	0
wgt. gain	1	0	0
Total	T	T	Z

*This patient was withdrawn from the study. He suffered a loss of consciousness lasting 10 minutes after receiving P for 5 days. He remained in a mentally confused state for the following 24 hours.

(2) Lab Data: Baseline Post-drug

↑monocytes (N=0-800) 648→1737
 ↑creatinine (N=5-12) 11→80

(3) Vital signs:

	<u>Blood Pressure</u>		<u>Pulse ↑ at least 10 bpm</u>
	<u>Fall of at least 10 mmHg systolic</u>	<u>diastolic</u>	
Placebo	2/14	1/14	2/14
P	0-3/14	2-3/14	1-5/14

(4) ECG's: No abnormalities noted after P administration that were not present at baseline.

10.

- a. number of patients - 10
 b. ages - 18-65 years

- c. disease studied - COPD
- d. type of study - open
- e. dosage used - 0.4 mg q.i.d.
- f. duration of study - 4 weeks
- g. safety parameters: adverse effects, lab data, ECGs, vital signs
- h. Comments:

(1) Adverse Effects:

<u>Side Effects</u>	<u>P (1 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
nervousness	0	1	0
tremor	0	1	0
Total	0	2	0

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↓ Hgb (N=14-18)	12.6	→ 11.4
	14.4	→ 13.4
↓ WBC (N=5-10)	6100	→ 4700 (↓ neutrophils)
↑ creatinine (N=0.7-1.5)	1.2	→ 1.92
↑ NPN (N=20-40)	40	→ 55

(3) ECG's: Sinus tachycardia after P in one patient. No other ECG changes noted.

(4) Vital signs:

	<u>Blood Pressure</u>		<u>Pulse ↑ at least 10 bpm</u>
	<u>↓ at least 10 mmHg systolic</u>	<u>diastolic</u>	
Placebo	6/10	5/10	4/10
P	7-8/10	5/10	4-5/10

11.

- a. number of patients - 20
- b. ages - greater than 65 years
- c. disease studied - COPD

- d. type of study - open
- e. dosage used - 0.4 mg q.i.d.
- f. duration of study - 25-27 days
- g. safety parameters: adverse effects, lab data, ECGs, vital signs
- h. Comments:

(1) Adverse effects:

<u>Side Effects</u>	<u>P (2 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
headache	1	1	0

(2) Lab Data: Baseline Post-drug
SGPT ↑ (N=0-22) 10 → 35

(3) ECG's: 1 patient developed PACs after P. Three other patients developed new abnormalities after P.

- a) 1st degree A-V block
b) 2 patients with PVCs.

(4) Vital signs:

	<u>Fall of at least 10 mmHg</u> <u>systolic BP</u>	<u>diastolic BP</u>	<u>Pulse rise of</u> <u>at least 10 bpm</u>
Placebo	8/20	5/20	1/20
P	4-5/20	9/20	2/20

12.

- a. number of patients - 20
- b. ages - 18-65 years
- c. disease studied - Asthma (17); bronchitis (3)
- d. type of study - open
- e. dosage used - 0.4 mg q.i.d.
- f. duration of study - 4 weeks

g. safety parameters: adverse effects, lab data, ECGs, vital signs

h. Comments:

(1) Adverse Effects:

<u>Side Effects</u>	<u>P (7 patients)</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
weakness	1	1	0
tremors	1	0	0
*hypotension	0	1	0
wheezing	0	1	0
cough	0	1	0
sore throat	1	0	0
edema	0	1	0
Total	3	5	0

*Not commented on further by sponsor.

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↑ BUN (N=0.15-0.44)	0.26→0.56	0.44→0.56
↓ serum K+ (N=3.5-5)	3.2→2.8	
↑ FBS (N=0.7-1.1)	1.02→1.60	
(N=12-16)	14.5→11.9	
↓ Hgb + Hct (N=36-47)	43.4→34.1	
↓ Lymphs (N=800-4950)	2730→581	
↑ CPK (N=0-100)	59→206	
	247→529	
	43→140	
	301→588	
(N=0-25)	19→33	
↑ SGOT & SGPT (N=0-25)	15→34	

(3) ECG's: A patient with a previous history of dysrhythmia D/C his anti-arrhythmic medication and went into atrial fib after P. Another patient developed PVCs on P.

(4) Vital signs:

	<u>Number of patients</u>		
	<u>Fall of at least 10 mmHg systolic BP</u>	<u>diastolic BP</u>	<u>Pulse rise of at least 10 bpm</u>
Placebo	10/14	10/14	3/14
P	9-11/14	6-7/14	5-7/14

13.

- a. number of patients - 17
- b. ages - over 18 years of age
- c. disease studied - asthma
- d. type of study - open
- e. dosage used - 0.4 mg t.i.d.
- f. duration of study - 4 weeks
- g. safety parameters: adverse effects, lab data, ECGs, vital signs
- h. Comments:

(1) Adverse Effects:

<u>Side Effects</u>	<u>P (9 patients)*</u>		
	<u>Mild</u>	<u>Mod-erate</u>	<u>Severe</u>
insomnia	1	1	0
nervousness	2	1	0
syncope	0	1	0
tremor	4	2	0
dry skin	1	0	0
fatigue	2	0	0
headache	0	1	0
Total	10	6	0

*One patient was withdrawn from the study because of side effects.

(2) Lab Data: Baseline Post-drug

SGPT (N=0-40)

14→48

- (J) ECG's: 43y/o male developed "competition of 2 types of P waves" and "two different foci, sinus and SA" with different rates and premature beats and was withdrawn from the study.

(4) Vital signs:

	Number of patients		
	<u>Fall of at least 10 mmHg systolic BP</u>	<u>diastolic BP</u>	<u>↑ Pulse rate of at least 10 bpm</u>
P	4-7/10	2-4/10	2-5/10

14.

- a. number of patients - 14
- b. ages - 18-65 years
- c. disease studied - COPD
- d. type of study - open
- e. dosage used - 0.4 mg t.i.d.
- f. duration of study - 4 weeks
- g. safety parameters: vital signs, ECGs, lab data, adverse effects
- h. Comments:

(1) Adverse Effects:

Side Effects	P (2 patients)		
	Mild	Mod-erate	Severe
nausea	0	0	1
headache	0	1	0
Total	0	1	1

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↓ WBC (N=4-10) ↓ same patient		6.4 → 3.2
↓ neutrophils (N=2200-7500) casts (urine)	4552	→ 1696 0 → 3

(3) ECG's: abnormalities noted after P.

- a. non-specific ST-T wave changes
- b. sinus arrhythmia and QRS changes (not clinically significant)

(4) Vital signs:

	Number of patients		
	↓ of at least 10 mmHg systolic BP	diastolic BP	↑ Pulse rate of at least 10 bpm
Placebo	5/13	2/13	1/13
P	3-5/14	0-5/14	0-1/14

15.

- a. number of patients - 10
- b. ages - 18-65 years
- c. disease studied - Asthma (8), chronic bronchitis (1), Farmer's Lung (1)
- d. type of study - open
- e. dosage used - 0.4 mg q.i.d.
- f. duration of study - 4 weeks
- g. safety parameters: adverse effects, ECGs, lab data, vital signs
- h. Comments:

(1) Adverse Effects:

Side Effects	P (4 patients)		
	Mild	Mod- erate	Severe
palpitations*	2	1	0
↑ bronchospasm	0	0	1
dyspnea*	0	0	1
sneezing*	0	1	0
eye irritation*	0	1	0
Total	2	3	2

*1 patient with all these adverse effects was withdrawn from the study. This could have represented an allergic reaction to the drug. He died suddenly during an acute asthmatic attack three days after D/C P. Another patient was withdrawn from the study when he developed acute bronchospasm after P.

(2) Lab Data: Baseline Post-drug

↑ creatinine (N=0.2-1.0) 1→1.2
 ↑ FBS (N=60-90) 86→107
 ↓ Hgb (N=14-18) 15.1→13.1

(3) ECG's: No changes due to P were noted.(4) Vital signs:

P	Number of patients		
	↓ > 10 mmHg systolic BP	↓ > 10 mmHg diastolic BP	↑ Pulse > 10 bpm
P	1-3/7	0-2/7	0/7

16.

- number of patients - 25
- ages - over age of 18 years
- disease studied - COPD
- type of study - open
- dosage used - 0.4 mg t.i.d.-q.i.d.
- duration of study - 6-14 months
- safety parameters: adverse effects, ECGs, lab data, vital signs
- Comments:

(1) Adverse Effects: None reported.(2) Lab Data: Baseline Post-drug

Hgb ↓ (N=8.6-10.8) 10.5→7.6 (Hct 53→36)
 8→7.2 (Hct 42→37)
 8.5→7.9
 FBS ↑ (N=4-6) 4.8→22.9
 5.7→7.1
 ↓ neutrophils (N=2000-7000) 3534→1782
 ↓ lymphs (N=1000-4500) 2301→560

	<u>Baseline</u>	<u>Post-drug</u>
↑ Honos (N=0-600)		?→576 312→924 248→702 618→1223 204→741 400→793 459→960
↑ SCOT (N=3-36)		111→209 (SCOT 118→168) ^p
↑ creatinine (N=60-115)		105→178 ?→140
↑ Na (N=133-143)		138→198

(3) ECG's: Six new abnormalities were noted after P administration.

- non-specific ST changes + sinus bradycardia
- PACs
- RAII + S tachycardia + PVC's + old MI
- S. bradycardia + non-specific ST-T changes
- S. bradycardia
- S. bradycardia

(4) Vital signs: "No obvious drug-related effects."

17.

- number of patients - 12
- ages - "over age of 18"
- disease studied - Asthma
- type of study - SB, CX, SD, R, PC & ATC study
- dosage used - P 0.2 and 0.4 mg; Salbutamol 0.2 mg
- duration of study - 4 study days
- safety parameters: side effects, EKGs, lab data, vital signs
- Comments:

(1) Adverse Effects: None reported.

- (2) Lab Data: No significant abnormalities noted.
- (3) ECGs: Two patients had an increase in ectopic $\frac{2}{12}$ beats after 0.4 mg P.
- (4) Vital signs: Arbitrarily using an increase or decrease in systolic BP, diastolic BP or pulse rate of 15 mmHg or 15 bpm or more as clinically significant, while recognizing that a smaller change in either of these parameters might in patients with CV disease be significant, the following were found:

	<u>systolic BP</u>	<u>diastolic BP</u>	<u>pulse</u>
Placebo	3/12	2/12	2/12
P	4/12	2/12	4/12
Salbutamol (S)	2/12	2/12	2/12

In addition, the sponsor has noted that a fall of at least 10 mmHg was found as follows:

	<u>systolic BP</u>	<u>diastolic BP</u>
Placebo	25%	25%
P 0.4 mg	42%	33%
S	42%	17%

The sponsor states that "an increase and not a decrease would be expected (after P). Therefore these changes are considered clinically insignificant." We do not agree either that P could not produce a significant decrease in pulse rate or that this \downarrow might not be clinically significant.

18.

- a. number of patients - 20
- b. ages - "over age 16"
- c. disease studied - COPD
- d. type of study - SB, CX, R, SD, ATC AND PC study
- e. dosage used - P 0.2 and 0.4 mg; S 0.2 mg

- f. duration of study - 4 study days
- g. safety parameters: side effects, EKGs, vital signs, lab data

h. Comments:

(1) Adverse Effects: None reported.

(2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↓ WBC (N-4-10)		6900→3800
↑ total bilirubin (N-4-20)		5→28
↑ SGOT (N-10-40)		30→60
		65→122

(3) EKG's: No abnormal changes noted after P.

(4) Vital signs:

	<u>Blood pressure</u>		<u>Pulse</u> ↑>10 bpm
	<u>Fall of >10 mmHg</u> <u>systolic</u>	<u>diastolic</u>	
Placbo	3/20	2/20	6/20
P	8/20	5/20	1-4/20
S	6/20	2/20	1/20

19.

- a. number of patients - 11
- b. ages - "over age 10"
- c. disease studied - COPD
- d. type of study - SB, SD, CX, PC and ATC, R study
- e. dosage used - 0.2 and 0.4 mg P; 0.2 mg S
- f. duration of study - four separate treatment days
- g. safety parameters: side effects, EKGs, lab data, vital signs
- h. Comments:
- (1) Adverse Effects: One patient developed mild sore throat and change in smell/taste.

- (2) Lab Data: No significant changes noted after P.
- (3) ECG's: No significant changes noted after P.
- (4) Vital signs: "A few patients showed clinically significant decreases in pulse rate following P and S." Arbitrarily using an increase or decrease in systolic BP, diastolic BP or pulse rate of 15 mmHg or 15 bpm or more as clinically significant, while recognizing that a smaller change in either of these parameters might, in patients with disease be significant, the following were found.

	<u>Systolic BP</u>	<u>Diastolic BP</u>	<u>Pulse</u>
Placebo	2/8	0/8	2/8
P	4/8	1/8	3/8
S	2/8	4/8	2/8

20.

- a. number of patients - 14
- b. ages - "over age of 18"
- c. disease studied - COPD
- d. type of study - SB, CX, SD, ATC + PC, R study
- e. dosage used - P 0.4 mg; S 0.2 mg
- f. duration of study - 3 separate study days
- g. safety parameters: side effects, ECGs, lab data, vital signs
- h. Comments:
- (1) Adverse Effects: No side effects were reported.
- (2) Lab Data:
- | | <u>Baseline</u> | <u>Post-drug</u> |
|---------------|-----------------|------------------|
| LUI (N=0-300) | | 233→5179* |
| BUN (N=15-50) | | 50→77 |
- (3) ECG's: No significant changes after P.

(4) Vital signs: Using the criteria explained above under IV D 19 h 4):

	<u>Systolic BP</u>	<u>Diastolic BP</u>	<u>Pulse</u>
Placebo	2/12	3/12	1/12
P	3/12	0/12	0/12
S	1/12	3/12	0/12

21.

- a. number of patients - 12
- b. ages - "over age of 18"
- c. disease studied - COPD
- d. type of study - SB, CX, SD, R, PC & AIC study
- e. dosage used - P 0.2, 0.4 mg; Salbutamol 0.2 mg
- f. duration of study - 4 separate study days
- g. safety parameters: side effects, ECGs, lab data, vital signs.
- h. Comments:
 - (1) Adverse Effects: None reported.
 - (2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
WBC (N=4000-10,000)	6700	→3400
neutrophils (N=1600-7500)	2814	→1563
 - (3) ECGs: No abnormalities recorded.
 - (4) Vital signs: There were no significant increases or decreases in BP or pulse rate.

22.

- a. number of patients - 20
- b. ages - "over age of 18"
- c. disease studied - asthma (18); chronic bronchitis (2)

- (2) Lab data: There did not appear to be any clinically significant abnormal lab values.
- (3) Vital signs: Using the criteria explained above under IV D 19 h 4):

	<u>Systolic BP</u>	<u>Diastolic BP</u>	<u>Pulse</u>
Placebo	0/14	0/14	1/14
P	1/14	1/14	3/14
S	1/14	0/14	1/14

24.

- a. number of patients - 12
- b. ages - "over age 18"
- c. disease studied - COPD
- d. type of study - SB, CX, SD, R, PC & ATC study
- e. dosage used - 0.4 mg P; 0.2 mg S
- f. duration of study - 3 separate study days
- g. safety parameters: side effects, EKGs, lab data, vital signs
- h. Comments:

(1) Adverse Effects: None reported.

(2) Lab Data: Baseline Post-drug

↑ DUN (N=20-40) 45→54 (same ↑ after salbutamol)

(2) EKG: No new abnormalities were noted after P. No significant ↑ in ectopic beats after either P or S.

(3) Vital signs: Using the criteria explained above under IV D 19 h 4):

	<u>Systolic BP</u>	<u>Diastolic BP</u>	<u>Pulse</u>
Placebo	0/12	1/12	1/12
P	0/12	0/12	1/12
S	0/12	0/12	0/12

25.

- a. number of patients - 24
- b. ages - 21-70
- c. disease studied - asthma + chronic bronchitis (5),
asthma + emphysema (1), asthma (17), chronic bronchitis
(1)
- d. type of study - SB, CX, SD, R, PC & ATC study
- e. dosage used - 0.2 and 0.4 mg P; 0.2 mg S; hydroxyzine
0.25 and 0.50 mg
- f. duration of study - 7 separate testing days at least 24
hours apart
- g. safety parameters: side effects, ECGs, lab data, vital
signs
- h. Comments:

(1) Adverse Effects: None clearly related to P.

(2) <u>Lab Data</u> :	<u>Baseline</u>	<u>Post-drug</u>
↓ Hgb & Hct	8.2→7.4	41→35
↓ WBC (N=4000-10000)	3800→3200	(neutrophils) 2052→1264
	?	→1000
↓ lymphocytes (N=1162-4752)	2160→141	?
↑ monos (N=0-864)	?	→1848
↑ SGPT (N=0-21)	9	→37
↑ BUN (N=3-7.8)	?	→14.6
↑ FBS (N=65-110)	?	→150
↑ Casts	?	→6

(3) ECGs: No significant changes after P.

(4) Vital signs: No significant changes noted.

26.

- a. number of patients - 25
- b. ages - 18-65 years

- c. disease studied - asthma (17), chronic bronchitis (8)
- d. type of study - DB, CX, SD, R, PC & ATC study
- e. dosage used - 0.2 and 0.4 mg P; 1.3 mg M
- f. duration of study - 4 separate test days
- g. efficacy and safety parameters: PFTs; side effects, EKGs, lab data, vital signs
- h. Comments:

- (1) Adverse Effects: None reported.
- (2) Lab Data: No significant abnormalities.
- (3) ECGs: No significant new findings after P.
- (4) Vital signs: No significant changes after P.
- (5) Efficacy: Patient self-rating (avg)

<u>Placebo</u>	<u>P 0.2 mg</u>	<u>P 0.4 mg</u>	<u>M</u>
7.7	8.3	8.2	8.3

Specific Conductance (Overall Response)

	<u># of pts. responding</u>	<u>Peak</u>	<u>AUC</u>
Placebo	14/25	46%	9.7%
P 0.2 mg	17/25	70%	29%
P 0.4 mg	16/25	77%	38%
M	18/25	132%	72%

The sponsor states that, "The clinical significance of these responses is somewhat decreased in view of the considerable response to placebo ..."

27.

- a. number of patients - 6 (only 5 completed study)
- b. ages - "over age of 18"

- c. disease studied - asthma and chronic bronchitis
- d. type of study - SB, CX, SD, R, PC & ATC study
- e. dosage used - P 0.2 and 0.4 mg; S 0.2 mg
- f. duration of study - 4 separate testing days
- g. safety parameters: adverse effects, ECGs, lab data, vital signs
- h. Comments:
 - (1) Adverse Effects: None reported after P.
 - (2) Lab Data: No significant changes after P.
 - (3) ECGs: No changes after P.
 - (4) Vital signs: No significant changes after P.

28.

- a. number of patients - 12
- b. ages - "over 16
- c. disease studied - chronic bronchitis and chronic bronchitis with emphysema
- d. type of study - SB, CX, SD, R, PC & ATC study
- e. dosage used - P 0.2 and 0.4 mg; fenoterol 0.2 mg
- f. duration of study - 4 separate testing days
- g. safety parameters: side effects, ECGs, lab data, vital signs
- h. Comments:
 - (1) Adverse Effects: None reported by investigator.
 - (2) Lab Data:

	<u>Baseline</u>	<u>Post-drug</u>
↓ Hgb (N=14-16.5)	12.6	→10.5
↓ Hct (N=39-52)	37.9	→31.1
	43.4	→35.2
	41.5	→36

(3) ECGs: No changes noted after P.

(4) Vital signs: No significant changes noted after P.

E. Double-Blind, Single-dose Studies using P dihydrochloride

1. These studies with investigators as follows:

were not reviewed because a different formulation was used. Therefore, these studies can not be used to demonstrate either the safety or efficacy of P acetate.

V. Number of patients evaluated:

A. Single-dose Studies (adequately blinded and controlled)

<u>Study</u>	<u>P</u>	<u>Placebo</u>	<u>M</u>	<u>S</u>	<u>F</u>
	26	26	26	-	-
	26	26	25	-	-
	26	-	-	-	-
	24	24	24	-	-
	24	24	24	-	-
	24	24	24	-	-
Total	150	124	124	-	-

A. Single-dose Studies (inadequately blinded)

<u>Study</u>	<u>P</u>	<u>Placebo</u>	<u>M</u>	<u>S</u>	<u>F</u>
	12	-	-	12	-
	20	-	-	20	-
	11	-	-	11	-
	14	-	-	14	-
	12	-	-	12	-
	20	-	-	20	-
	14	-	-	14	-
	12	-	-	12	-
	24	-	-	24	-
	25	-	25	-	-
	5	-	-	5	-
	12	-	-	-	12
Total	181	-	25	144	12

C. Repetitive-dose Studies (adequately blinded and controlled)

<u>Study</u>	<u>P</u>	<u>Placebo</u>	<u>M</u>	<u>S</u>	<u>F</u>
	34	-	28	-	-
	66	-	59	-	-
	20	-	21	-	-
	19	-	19	-	-
	18	-	18	-	-
Total	157	-	145	-	-

D. Repetitive-dose Studies (uncontrolled and/or unblinded) (only P)

21	19
8	10
15	20
31	20
13	17
20	14
14	10
20	25
	Total 277

VI. Summary

A. Safety:

1. Adverse Effects (single-dose studies)*:

<u>side effects (incidences)</u>	<u>P (331 pts.)</u>	<u>Placebo (124 pts.)</u>	<u>M (149 pts.)</u>
dizziness	4	2	0
blurred vision	1	0	0
pruritis	1	0	0
rash	2	0	0
headache	2	0	0
chest pain	1	3	6
nausea/vomiting	0	0	1
nervousness	1	0	0
palpitations	3	1	1
dry mouth	0	0	0
cough	1	0	1
diarrhea	1	0	0
sedation	0	0	0
sore throat	1	1	0
change in smell/taste	1	0	0
Total	19 = 6%	7 = 6%	9 = 6%

*Also 12 patients received fenoterol and 144 received S. There were no adverse reactions after either drug.

b. Adverse Effects (multiple-dose studies)

<u>side effects</u> <u>(incidences)</u>	<u>P</u> <u>(434 pts.)</u>	<u>H</u> <u>(145 pts.)</u>
nervousness	38	18
dizziness	4	0
tremor	26	18
insomnia	4	0
sedation/drowsiness	1	4
hypotension	1	0
nasal congestion	0	1
arrhythmia	1	0
syncope	2	0
palpitations	7	9
nausea/vomiting	0	6
indigestion	1	0
chest pain	2	0
edema (wgt. gain)	3	0
rash	2	3
anorexia	1	0
diarrhea	3	2
wheezing	2	0
dry mouth	4	7
glossitis	3	0
sore throat	2	1
back pain	0	1
change taste/smell	3	0
dyspnea	2	0
flushing	1	1
hair loss	1	0
headache	14	7
(depression, anxiety)		
personality change	4	0
eye irritation	1	0
weakness	5	3
paresthesia/anesthesia	1	1
tachycardia	7	8
cough	6	1
hoarseness	0	1
bruising	1	0
sneezing	1	0
Total	<u>162</u> 37%	<u>91</u> 63%

c. Adverse Effects by organ system (# of instances):

	<u>P</u> (765 pts.)	<u>M</u> (294 pts.)
Cardiovascular	22 (3%)	18 (6%)
CNS	58 (8%)	23 (8%)
tremor	26 (4%)	18 (6%)
respiratory (lower)	12 (2%)	2 (1%)
headache	16 (2%)	13 (4%)
GI	14 (2%)	7 (2%)
upper respiratory	8 (1%)	3 (1%)

d. Comments on Adverse Effects:

There were 2 deaths in the study where patients were taking P. One was a 37 y/o man. P was D/C 3 days before his death because his asthma was not improved. While it does not appear that P was directly responsible, it is not clear if it exacerbated his asthma and contributed to his acute asthmatic attack. The other was a 45 y/o man who received P for 6 1/2 weeks. In addition to P as a cause for the exacerbation of his asthma, there is the possibility that he was overusing his BAA aerosol and he was also receiving theophylline. It appears that P was associated in a small number of patients with potentially severe adverse effects, such as hypotension, arrhythmia, syncope, angina, wheezing, dyspnea, and severe personality changes, which are not incompatible with the administration of a BAA drug, but were not seen or were seen less often after M. There does not appear to be any profound tendency for recurrent severe side effects which would prevent approval on that basis alone but at the very least the labeling should clearly indicate that severe side effects can occur in individual patients. As the sponsor states, "The overall incidence for all side effects in the patients included in the double-blind controlled multiple dose studies at optimum doses of 0.4 mg q.i.d. was 37.6%." This is an unacceptably high level. On the other hand 35.3% of the M patients in the same studies had side effects. In the DB, RD studies:

<u>Drug</u>	<u># of patients</u>	<u>tremor</u>	<u>CNS</u>	<u>CVS</u>	<u>Patients with any side effects</u>
P	157	12 (7.6%)	34 (21.7%)	8 (5.1%)	59 (37.6%)
M	153	18 (11.8%)	24 (15.7%)	15 (9.8%)	54 (35.3%)

Nine out of 411 patients (2%) who received P in all multiple-dose studies were withdrawn due to side effects and 27.3% of these patients had some side effect.

2. Summary Lab Data:

a. S.D. Studies**:

- 1) The sponsor states that "all lab abnormalities in the SD studies were below 1% in incidence."
- 2) This reviewer's calculations of significantly abnormal lab data in SD studies, where possible, compared to active treatment or placebo controls (it could be noted that the sponsor attributes much of this abnormal data to other factors and does not consider most of these abnormal results to be drug related).

**It is difficult to assess the importance of abnormal findings on lab studies. The sponsor has chosen to attach little if any significance to abnormal lab studies noted after P (or for that matter H) administration, as related to the possibility that the abnormal lab study was drug-related. We, on the other hand, have chosen to consider the possible clinical significance of all the lab data presented irregardless of the sponsor's or the investigator's conclusion that it was not drug-related. It should be pointed out that these values are not all the abnormal lab data found in these studies, but reflects the subjective assessment of this reviewer. While the findings may be biased in this regard, the same thought processes went into the selection of the lab data that we considered possibly clinically significant after H administration. Therefore, there may be some value in comparing individual and total numbers of lab abnormalities. If so, there appears to be significantly more abnormal lab values which may be clinically significant after P than after H, especially in the single-dose studies. Nevertheless, these abnormal lab values occur relatively infrequently, the highest frequency being 12% of patients who had what we considered to be a significant increase in SGPT after P in the RD studies.

Total number of patients = 355

<u>Lab values</u>	<u>P</u>	<u>Placebo</u>	<u>M</u>
↑↓ Hgb or Hct	21*	11	11
↓ lymphocytes	4	1	5
↓ neutrophils	8*	2	3
↓ WBC	12	4	8
↑ monos	2	0	1
↑ SGOT	21*	16	14
↑ SGPT	26*	15	15
↑ FBS	1	0	0
↑ BUN	22*	9	9
↑ creatinine	9	4	3
↑ or ↓ K+	8	6	4
↑ LDH	1	0	0
↑ or ↓ CO ₂	2	2	2
↑ total bilirubin	8	6	3
Total	145/355	76/355	78/355

b. Repetitive-dose Studies:

The sponsor comments on 7 lab parameters:

- 1) Platelet counts: Decrease in 4/169 patients, all from one study. We would not agree with the sponsor's assessment that this data "is not supported by data from 20 other multiple dose studies," since platelet counts were noted to be low in 3 other patients in 2 other studies and actually in 6 patients (instead of 4) in the study mentioned by the sponsor above.
- 2) SGPT: "These scattered abnormalities observed in only 4/371 patients do not show a consistent drug-related pattern." While it is not clear how many patients showed a "drug-related pattern" it appears to us that there was no significant difference in the frequency with which elevations of SGPT occurred after P relative to M.
- 3) Total serum bilirubin: We would agree with the sponsor that these elevations are probably not clinically relevant.

*Significantly different from M.

- 4) CPK: We would agree that an increase in this Laboratory parameter was probably not clinically significant, and when present may have been related to muscle tremor in some cases.
- 5) BUN: While the incidence of ↑BUN and ↑creatinine was not great, such increases did appear to occur more frequently with P than with M.
- 6) FBS: We agree that there was no consistent increase or decrease in FBS seen after P administration or that was not ~~seen~~ after M administration as well. see
- 7) Serum K⁺: There were no consistent changes after P that were not seen as frequently after M.

Repetitive-Dose Studies**

Lab Value	(Patients)			
	P		M	
↑SGPT	(157)	20	(153)	15
WBC ↓	(157)	*15	(153)	9
↓ neutrophils	(157)	*17	(152)	6
↓ lymphs	(157)	3	(152)	3
↑ S/GI	(157)	19	(153)	13
↓ ↑ CO ₂	(100)	5	(96)	1
↑ ↓ FBS	(157)	21	(152)	22
casts	(157)	5	(147)	3
RBC/HPE	(156)	10	(149)	19
↑ ↓ Serum K ⁺	(157)	4	(153)	8
↑ total bilirubin	(157)	2	(152)	0
Hgb or Hct ↓	(157)	11	(152)	13
↑ G/G	(?)	2	(?)	2
↑ LDH	(157)	5	(153)	3
↑ Ca II	(?)	1	(?)	0
↑ alk phosph	(157)	1	(117)	0
↑ creatinine	(157)	*0	(152)	1
uric acid	(155)	0	(151)	1
↓ Na ⁺	(?)	0	(?)	1
↑ BUN	(121)	*9	(115)	5
↓ plat.	(157)	*9	(?)	1
bleeding time	(?)	5	(?)	1
↑ monocytes	(?)	1	(152)	2
clotting time	(?)	4	(?)	3
Total		175		133

*See footnote on page 79.

**See footnote on page 78.

3. ECGs: The following changes were noted in patients who received P in repetitive dose studies:

- a. inverted T waves - 1 patient
- b. non-specific ST-T wave changes - 9 patients
- c. significant increase ectopic beats - 7 patients
- d. conduction delays:
 - R. Vent. conduction delay - 1 patient
 - IBBB - 1 patient
 - complete LBBB - 1 patient
 - 1st degree AV block - 1 patient
- e. ST segment depression - 1 patient
- f. P pulmonale - 1 patient
- g. elevated ST segment - 1 patient
- h. R atrial hypertrophy - 2 patients
- i. two different atrial foci - 1 patient
- j. sinus bradycardia - 4 patients

In the 5 double-blind RD studies, 29/143 P patients and 27/146 M patients had PACs or PVCs during the study (about 20%).

Single-dose studies: No significant changes were noted after P. On Holter monitoring, there were some patients who had what could have been a clinically significant increase in ectopic beats after P.

4. Vital Signs: In single-dose studies, "there was no difference between placebo and P in terms of percent of patients who developed clinically significant increases in standing pulse rate and standing diastolic blood pressure after single-dose administration." There were individual patients who had what could have been clinically significant changes in either BP or pulse rate after P. Such patients were not rare. In the _____, as many as 14/23 P patients had such changes. In the _____, in terms of diastolic BP, such changes were significantly greater than placebo or M. Overall, it appears, based on the criteria for

clinical significance explained above, that slightly more patients had such changes after P than after S, M or Placebo (see table below) although such changes in diastolic BP are less than after H, and changes in pulse rate are the same as placebo.

	<u>systemic BP</u>	<u>diastolic BP</u>	<u>pulse rate</u>
Placebo	40/169 (24%)	24/169 (14%)	29/169 (17%)
P	60/193 (31%)	36/194 (18%)	32/193 (17%)
S	16/98 (16%)	16/98 (16%)	9/98 (9%)
H	16/71 (22%)	15/71 (21%)	3/71 (4%)

Nevertheless, the labeling must reflect the potential danger of the administration of P to certain individual patients i.e. those with cardiovascular disease, in terms of changes in blood pressure or pulse rate. In regard to the long term repetitive dose studies, only the study shows a significantly greater increase in heart rate than H. In summary, the changes in vital signs after P may in individual cases be clinically significant (and the labeling should reflect this) but overall is not significantly different from the active treatment control or placebo control.

5. Overall, the incidence of side effects after P appears to be comparable to the ATC and increased lab abnormalities, occasional ECG changes and clinically significant individual changes in vital signs, would not in our opinion make this drug non-approvable as long as the sponsor can demonstrate a degree of efficacy for P compared with active treatment controls and the labeling reflects these safety aspects.

B. Efficacy: Overall the double-blind well-controlled studies demonstrate that P is as efficacious as H and more efficacious than placebo (see table below):

1. Single-dose studies:

- a.

- 1) PFTs: P >> Placebo (PL)
P > H
- 2) patient evaluation: P > P1
- 3) investigator evaluation: P > P1

b.

- 1) PFTs: $P > M$
- 2) patient evaluation: not done
- 3) investigator evaluation: $P = P1$
 $P >> M$

c.

- 1) PFTs: $P >> P1$
- 2) patient evaluation: $P > P1$
- 3) investigator evaluation: $P > P1$

d.

- 1) PFTs: $P > M > P1$
- 2) patient evaluation: $P = M$
 $P > P1$
- 3) investigator evaluation: $P > M > P1$

e.

- 1) PFTs: $P > M > P1$
- 2) patient evaluation: $P = M$
 $P > P1$
- 3) investigator evaluation: $P > M > P1$

f.

- 1) PFTs: $P > M$
 $P >> P1$
- 2) patient evaluation: $P = M$
 $P > P1$
- 3) investigator evaluation: $P > M$
 $P >> P1$

2. Repetitive-dose studies:

a.

- 1) Tolerance: yes, some patients
- 2) PFTs: $P > M$
- 3) patient evaluation: $P = M$
- 4) investigator evaluation: $P > M$
- 5) concomitant Rx (ConRx) - $\downarrow M > P$

b.

- 1) Tolerance: yes, some patients
- 2) PFTs: $P = M$
- 3) patient evaluation: $P = M$
- 4) investigator evaluation: $P = M$
- 5) ConRx - $P = M$ and not \downarrow

c.

- 1) Tolerance: no
- 2) PFTs: $M = P$
- 3) patient evaluation: $P = M$
- 4) investigator evaluation: $M = P$
- 5) ConRx - $P = M$ and no \downarrow

d.

- 1) Tolerance: yes, some patients
- 2) PFTs: $M = P$
- 3) patient evaluation: $M = P$
- 4) investigator evaluation: not done
- 5) ConRx - $P = M$ and no \downarrow

e.

- 1) Tolerance: yes, some patients
- 2) PFTs: P = M
- 3) patient evaluation: M = P
- 4) investigator evaluation: M > P
- 5) ConRx - M = P and no ↓

VII Labeling: (See attachment.)

A. Description:

1. Paragraph 1: The statement that P is a "relatively selective beta-adrenergic bronchodilator" implies that it has less cardiac effect than other BAAs. The data generated by the sponsor does not support the contention that P has any less effect on the heart than other BAAs. In fact, in 331 patients in the single dose studies there was no report of tremor, which is associated with increased D₂ effect.
2. Paragraph 2: Needs Chemistry review and comment.
3. Paragraph 3: Needs Chemistry review and comment.

B. Clinical Pharmacology:

1. Paragraph 1: Needs Pharmacology review and comment. The second sentence should begin with "In animals, it acts preferentially ...," so that it is clear to the practicing physician the studies in humans have not shown D₂ selectivity.
2. Paragraph 2: This paragraph is unnecessary, may be inaccurate, and should be removed.
3. Paragraph 3: The second part of the first sentence, "which is the probable mechanism ..." is unconfirmed, possibly irrelevant and unnecessary and should be removed. The second sentence is inappropriate, of no proven clinical significance, and should be removed. The third sentence needs to be more clearly stated or it should be removed. It should also be referenced and if it can't be, it should be removed.

C. Pharmacokinetics: The entire paragraph needs to be reviewed and commented upon carefully by Biopharmaceutics Division to determine if it is accurate and acceptable. It is consistent with what the sponsor has stated in the NDA submission. The last sentence should be removed. If the sponsor can not make a definitive statement, the statement should not be made.

D. Indications and Usage:

1. Paragraph 1: The part of the first sentence that is in parentheses should be removed. It implies that chronic bronchitis and emphysema are reversible obstructive airways disease, and in addition, it is unnecessary.
2. Paragraph 2: This paragraph should be under Clinical Pharmacology. In addition to the first sentence should be, "In controlled ... within 5 minutes in most patients, as determined ..." The second sentence should be changed to read, "FEV₁ and MMF ... and that clinically significant improvement is maintained for 4-5 hours in a substantial number of patients (...). The third sentence is accurate and acceptable. The fourth sentence appears to be accurate based on the 2/4 studies for which the sponsor has indicated the duration of action for individual patients

The fifth sentence should be accurate with the following addition, "Continued effectiveness ... was demonstrated over a 12 week period in some patients in controlled clinical trials." The 3 controlled 12 week studies demonstrated that 54 out of 115 evaluable patients (47%) who received P demonstrated efficacy based on FEV₁ data, compared with 43 out of 99 evaluable patients (47%) who received M. Sentence 6 is incorrect. Tolerance did develop to P in some patients in the 12 week studies. This sentence could be restated that "Chronic dosing is not associated with the development of tolerance in most patients." The last part of sentence 7 is incorrect. The 12 week repetitive-dose studies do not demonstrate that P has "greater selectivity for beta-2 as opposed to beta-1 receptors." The sentence should be changed to read, "In these studies, P was shown to be an effective bronchodilator in many patients." Sentence 8 should be changed to read, "Cardiac effects from P were generally mild and/or clinically insignificant." There were, for example, ECG changes which might be considered to be "limiting."

E. Contraindications: This appears to be acceptable.

F. Warnings:

1. Paragraph 1: This appear to be acceptable.

2. Paragraph 2: This appear to be acceptable.
 3. Paragraph 3: This appear to be acceptable.
- G. Precautions: The first part of the only sentence in this section should be changed to read, "Although, it appears to have no significantly greater effect on the cardiovascular system than metoprolol at recommended doses ..."
Patients with convulsive disorders should be added to the list of patients with medical conditions where caution should be observed. P has been used to treat congestive heart failure. The sponsor should comment on any significant adverse effects seen with the administration of P by other routes for other medical conditions.
- H. Information for patients: Sentence 1 is acceptable.
Sentence 2 is acceptable. Sentence 3 is acceptable.
Sentence 4 is acceptable.
- I. Drug Interactions:
1. Paragraph 1: This is acceptable.
 2. Paragraph 2: This is acceptable.
 3. An additional paragraph should be added, which states that, "P should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants since the action of P on the vascular system may be potentiated."
(See page 197 and page 194 of Fourth Edition of AMA Drug Evaluations.)
- J. Usage in Prognancy: Needs Pharmacology review and comments.
This sentence should be changed to read, "There are no adequate and well-controlled studies in pregnant women. Therefore, P should be used during pregnancy only if the potential benefit justifies any possible risk to the fetus."
- K. Nursing Mothers: Needs Pharmacology review and comment.
This sentence should be changed to read, "It is not known whether P is excreted in human milk. Therefore, P should be used during nursing only if the potential benefit justifies any possible risk to the newborn."
- L. Usage in Pediatrics: "to establish safety and effectiveness." should be added at the end of the only sentence in this section.

M. Inhalation Toxicology: Needs Pharmacology review and comment.

N. Carcinogenesis and Mutagenesis:

1. Paragraph 1: Needs Pharmacology review and comment.
2. Paragraph 2: Needs Microbiology review and comment.

O. Reproduction and Teratology:

1. Paragraph 1: Needs Pharmacology review and comment.
2. Paragraph 2: Needs Pharmacology review and comment.

P. Adverse Reactions:

1. Paragraph 1: The only sentence is acceptable.
2. Paragraph 2: This data is acceptable with the addition of tremor at incidence of 4%.
3. Paragraph 3: Under CV, unless the sponsor can clearly show that there was no causal relationship, chest pain should be included. Under GI, nausea and vomiting should be included. Under Derm., pruritis should be added. Otherwise this paragraph is acceptable.
4. Paragraph 4: Under CNS, headache, nervousness, and insomnia should be removed since they have been documented in paragraph 2 of this section. The remainder of this paragraph is acceptable.
5. Paragraph 5: The second part of the sentence is inappropriate, since while accurate, it is misleading, and should be removed (i.e. "although the incidence of certain CV effects is less with P.")

Q. Overdosage:

1. Paragraph 1: An additional sentence should state, "Special concern should be directed at the possible cardiac effects from overdosage, especially the development of arrhythmias and/or decrease in coronary blood flow."
2. Paragraph 2: This is an acceptable sentence.
3. Paragraph 3: This needs Pharmacology review.

R. Dosage and Administration

1. Paragraph 1: This sentence should be changed to read, "The usual oral dose for adults and children 12 years and older is two inhalations (0.4 mg) repeated every 4-6 hours. One inhalation (0.2 mg) repeated every 4-6 hours may be sufficient for many patients."
2. Paragraph 2: The first sentence is inappropriate because it implies that aerosolized BAA drugs alone may be acceptable for "severe" or "frequent" asthma. It should be removed. The second sentence is acceptable.
3. Paragraph 3: This sentence is acceptable.

VIII Conclusion: We feel that P aerosol is approvable based on the demonstration of efficacy in well designed studies of 3 month's duration, and no increased or unexpected adverse effects. We feel that this drug in this dosage form is safe and effective. Approvability is dependent however upon the sponsor's willingness to change the labeling as indicated under Section VII above. Without these changes, the labeling is misleading and in some instances incorrect and makes it impossible for the physician to prescribe the drug in a safe way.

IX Proposed Draft of Medical Letter to Sponsor:

Will follow after review of WDA by all concerned is completed.

R. Nicklas MD
R. Nicklas, M.D.
2/9/84
6/3/84

NDA

19-0009

Chemist Revs

Division of Surgical-Dental Drug Products

Chemist's Review #5

Dated: March 20, 1985⁶A. 1. NDA: 19-009

Applicant: Pfizer Central Research
 Medical Research Laboratories
 Attn: Harold L. Howes Jr. Ph.D.
 Director, Drug Regulatory Affairs
 Groton, CONN 06340

2. Product Names:

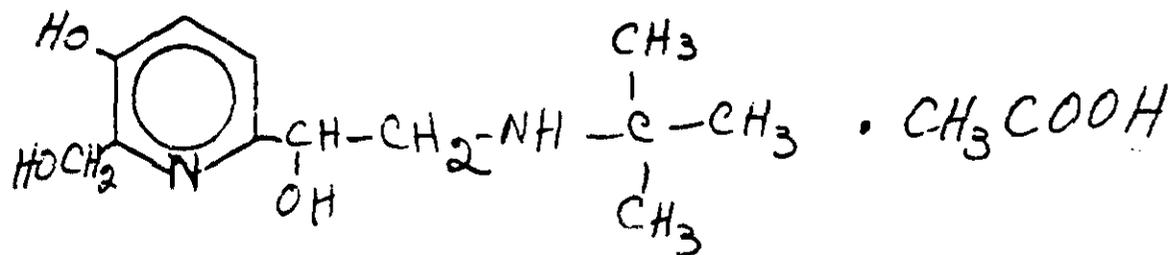
Proprietary: Exirel Inhaler
 Non-Proprietary: Pirbuterol Acetate
 USAN: Pirbuterol Acetate
 Code Names: CP-24,314 refers to the base
 ($C_{12}H_{20}N_2O_3$);
 CP-24,314-14 refers to the acetate salt
 ($C_{12}H_{20}N_2O_3 \cdot CH_3COOH$);
 CP-24,314-1 refers to the dihydrochloride salt
 ($C_{12}H_{20}N_2O_3 \cdot 2HCl$).

3. Dosage Form and Route of Administration

Rx; oral inhalation pressurized metered dose aerosol product delivering 200 ug of pirbuterol base from the mouthpiece per actuation. Each unit consists of a suspension of micronized Pirbuterol acetate (117 mg. equ'v. to 93.6 mg base) a dispersant, sorbitan trioleate (78 mg), and a mixture of propellants trichloromonofluoromethane (7.634g) and dichlorodifluoromethane (17.787g). Total wt. 25.616 gm equivalent to 18.7 ml.

4. Pharmacological Category and/or Principal Indication:

Bronchodilator.

5. Structural Formula and Chemical Names:Mol. Formula: $C_{12}H_{20}N_2O_3 \cdot CH_3COOH$ (Mol Wt. 300.3)

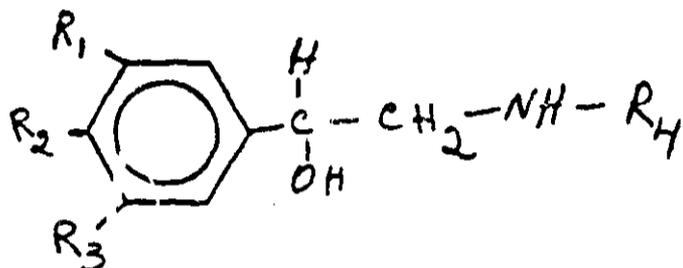
MAR 25 1985

NDA 19-009
Page 2

Chemical Names:

- a) 2-Hydroxymethyl-3-hydroxy-6-(1-hydroxy-2-tert-butylaminoethyl)pyridine acetate.
- b) 2, 6-Pyridinedimethanol, α^6 -[[1,1-dimethylethyl)amino]methyl]-3-hydroxy-, monoacetate (salt)
- c) α^6 -[(tert-Butylamino)methyl]-3-hydroxy-2,6-pyridinedimethanol monoacetate (salt)

Structural relationship of pirbuterol of pirbuterol to other related bronchodilators is as follows:



	R ₁	R ₂	R ₃	R ₄
Isoproterenol	H	OH	OH	CH(CH ₃) ₂
Metaproterenol	OH	H	OH	CH(CH ₃) ₂
Fenoterol	OH	H	OH	CH(CH ₃)CH ₂ C ₆ H ₄ OH
Terbutaline	OH	H	OH	C(CH ₃) ₃
Salbutamol	H	OH	CH ₂ OH	C(CH ₃) ₃
Isoprenaline	H	OH	OH	CH(CH ₃) ₂
Ibuterol	-OCOCH(CH ₃) ₂	H	-OCOCH(CH ₃) ₂	C(CH ₃) ₃
Salmefalol	H	OH	CH ₂ OH	
Carbuterol	H	OH	NHCONH ₂	CH(CH ₃)CH ₂ C ₆ H ₄ OCH ₃ (P)
soterenol	H	OH	NHSO ₂ CH ₃	C(CH ₃) ₃
				CH(CH ₃) ₂

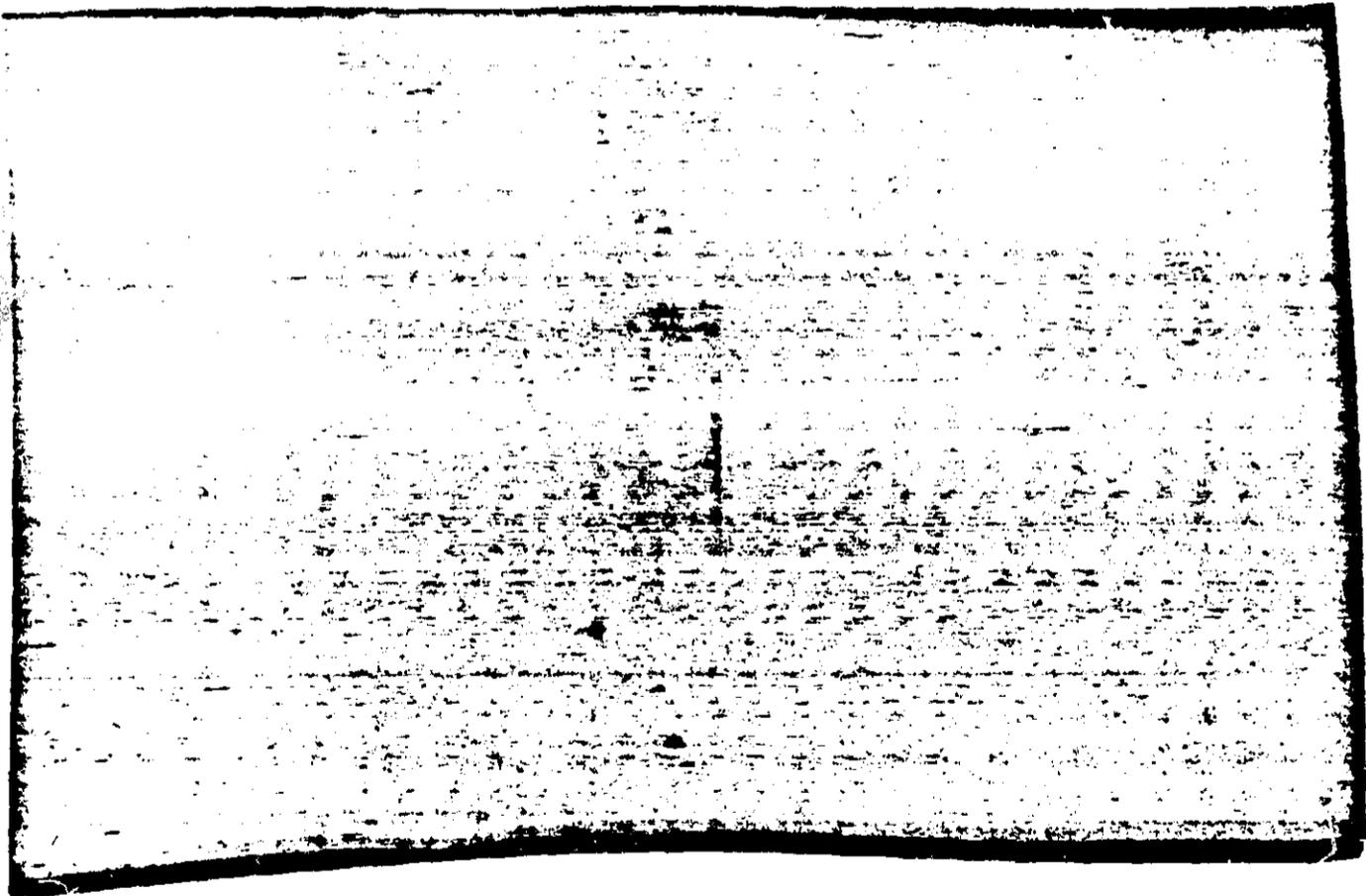
B. 1. Initial Submission: Dated April 2, 1983, Received at NCDB April 21, 1983; HFN-160 May 21, 1983; by Chemist October 31, 1983.

- 2. Amendments:
 - (a) Resubmission dated April 13, 1984 was received at CDB on April 13, 1984 and by Chemist on 4/13/84. FDA letter dated 5/9/84 considered the application as withdrawn and resubmitted on April 13, 1984.
 - (b) Resubmission dated November 13, 1984 was received at HFN-160 on November 13, 1984 and by chemist on November 20, 1984.
 - (c) Amendment dated February 11, 1985 was received by Chemist on 2/12/85.

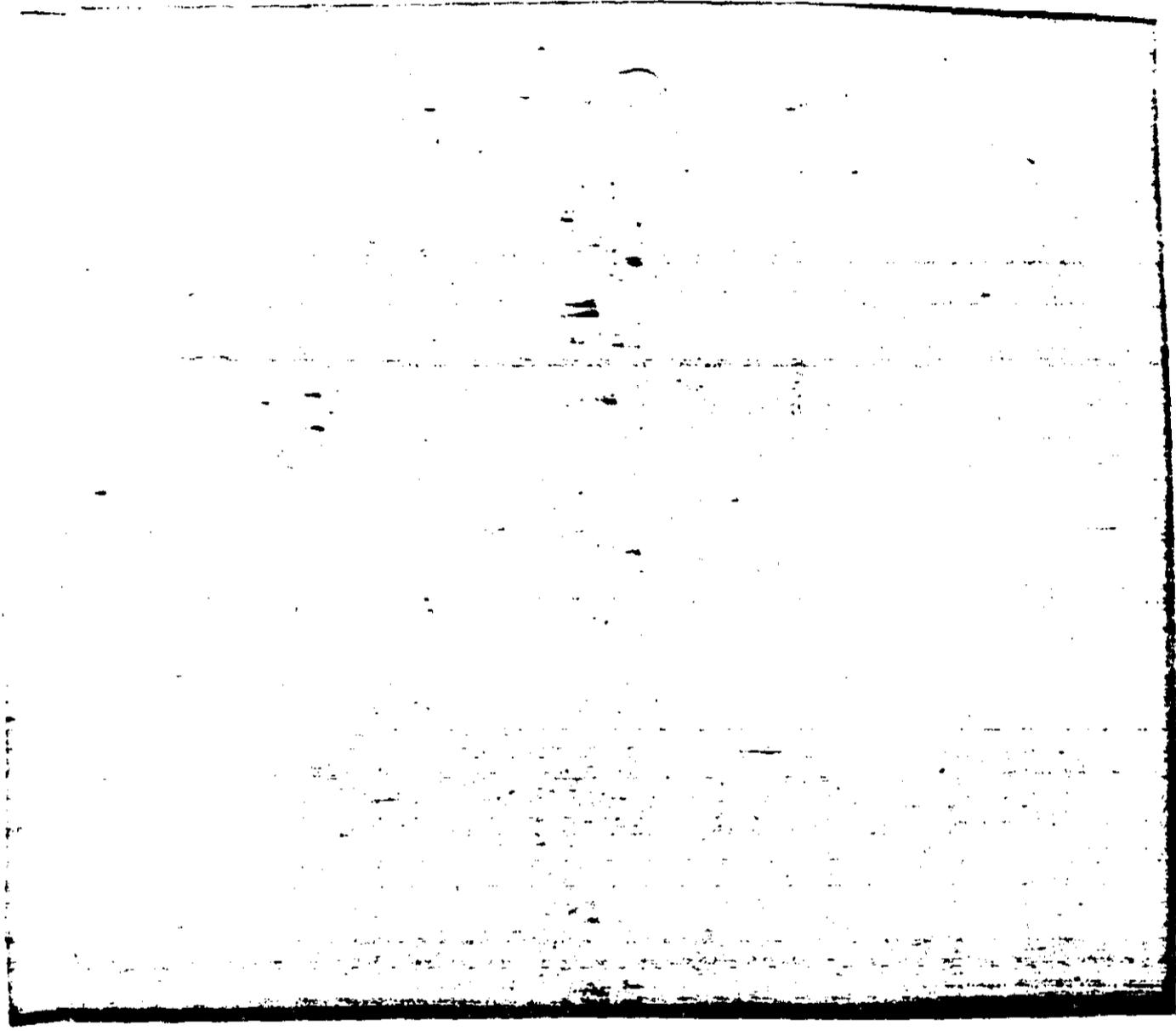
- (d) Amendment dated April 11, 1985 provides no information on chemistry.
- (e) Resubmission dated June 21, 1985 was received by Chemist on July 25, 1985. This resubmission was in response to a telecon on 2/27/85 and FDA letter issued on 5/21/85.
- (f) Amendments dated February 25 and March 13, 1986. The first amendments provides labeling commitments, while the latter responds to method validation comments transmitted to them on February 28, 1986. These amendments are subject of this review.

- 3. Supporting See Chem. Rev. #4.
- 4. Related Documents: See Chem. Rev. #4.

C. Comments



NDA 19-009
Page 4



D. Recommendations/Conclusions

From manufacturing and control viewpoint an approvable letter is recommended. However, the applicant should be reminded of their commitment #2 outlined in Chemistry Review #4.

The FPL should be in accordance to their commitments outlined in amendments dated Sept. 9, 1985 and February 25, 1986.

NDA 19-009
Page 5

Please consult the microbiologist (Ms. Greenman) concerning item E(2)(b) in amendment dated June 21, 1985 and micro amendment dated February 19, 1986.

G. Poochikian
G. Poochikian, Ph.D.

cc: NDA 19-009
/HFN 160, Doc Room 160
R/D GPoochikian, 3/20/86
R/D init.CPHoiberg, 3/20/86
FT/jb, W4797P, D3630P, 3/20/86

PHARM

REV

Date: 2/19/85

NDA 19-009

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Resubmission of 11/13/84
Amendment of 2/11/85

APPLICANT: Pfizer Inc.

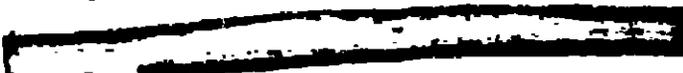
DRUG: EXIREL (pirbuterol acetate, CP-24,314-14) Inhaler, Bronchodilator

CATEGORY: Bronchodilator

COMPOSITION:

<u>Component</u>	<u>Gm/Aerosol Unit</u>
Pirbuterol Acetate	0.117*
Sorbitan Trioleate	0.078
Trichloromonofluoromethane	7.634
Dichlorodifluoromethane	17.787
Total	<u>25.616**</u>

*Equivalent to 93.6 mc pirbuterol
** Equivalent to 18.7 ml

RELATED NDA: 

RELATED NDA: 

COMMENT:

The pharmacologist approved the resubmission of NDA 19-009 in his review of April 13, 1984, but outlined suggested revisions for two subsections of the "Precautions" section of the package insert. The subsections in question were:

- (1) Carcinogenesis, Mutagenesis, and Impairment of Fertility
- (2) Pregnancy Category C

The applicant has incorporated verbatim the wording from our letter of November 1, 1984, in his draft labeling for the two subsections mentioned above.

Included in the package insert is also a subsection on "Nursing Mothers".

CONCLUSION:

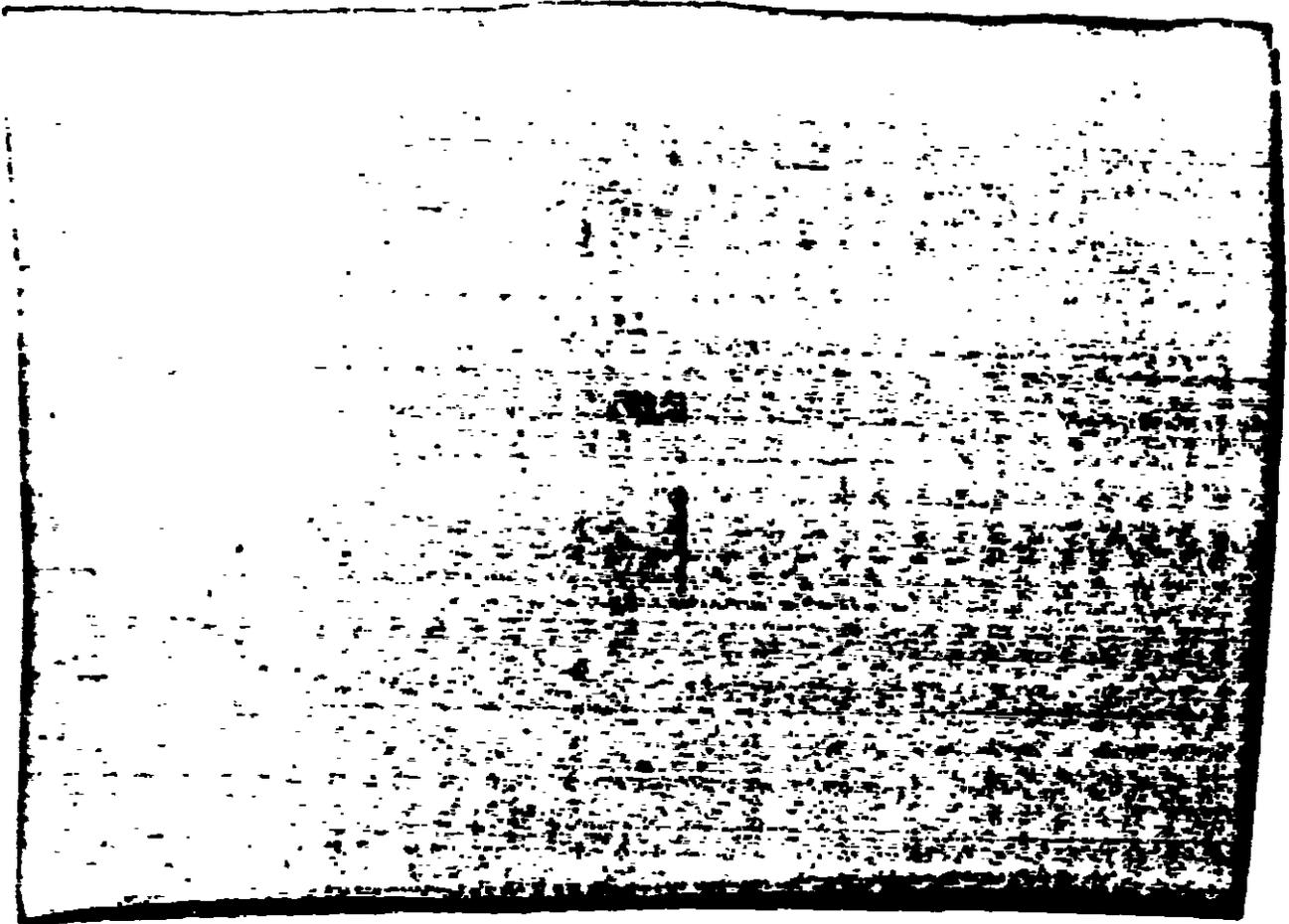
The resubmitted application is approvable from the standpoint of pharmacology.

Submitted labeling was examined for conformity to the Labeling Format Revision Program and found adequate from the standpoint of pharmacology.

J. Wilson

J. Wilson, Ph.D.

2/19/85



NDA 19-009

Page 3

cc: NDA 19-009
/ HFN 160, HFN 340
Doc Room 160
HFN 102 Clocklin
HFN-160, Dr. Holberg
R/D JEWilson, 2/19/85
R/D Inlt. JKinsce, 2/19/85
FT-jb, W3488P, D0083P, 2/20/85

BIO/DIS

REV

DATE : JUL 11 1985

TO : Patricia H. Russell, M.D.
Acting Director, Division of Dental & Surgical
Drug Products (HFN-160)

FROM : Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics (HFN-220)

SUBJECT: Waiver of In Vivo Bioavailability Study

Pirbuterol	NDA 19-009
Exirel ^R Aerosol	
Pfizer Corporation	April 21, 1984

Background

Pirbuterol is a beta₂ adrenergic agonist.

In this submission, the sponsor not only requested for a waiver under 21 CFR 320.22 but also submitted information available on the absorption, metabolism and disposition of pirbuterol in sections

Discussion

It is not uncommon for beta₂-agonist to show local therapeutic effect. For example, it was demonstrated for albuterol in J. Clin. Pharmacol. Ther. (1972; 13:861-867).

18-559, the Division of Biopharmaceutics was able to compare the difference in onset time of FEV₁ responses between oral and inhalation formulations. The medians of onset time were 60 minutes and 5 minutes for

200 mcg to 800 mcg inhalation dose respectively. The fact that there was fast onset in the low inhalation dose

, suggests that pirbuterol is locally active.

Despite the sensitivity limitation in the plasma level assay, the sponsor managed to analyze the urinary recoveries of the drug and the metabolite. Although the data was erratic which might be due to low dose given, the mean % urinary recovery as parent drug was comparable with the that obtained in the previous . The mean apparent half-life of the parent drug was about 2.4 to 2.7 hours.

Taking into consideration that local therapeutic effect suggested, basic information of the drug disposition given, and clinical trials performed, the Division of Biopharmaceutics has decided that the waiver for in vivo bioavailability study should be granted under CFR 21 320.22b(2).

Overall Conclusion

The Division of Biopharmaceutics has reviewed the submission and recommends that the waiver for in vivo bioavailability study be granted under CFR 21 320.22b(2).

Henry J. Malinowski for

Jerome V. Skelly, Ph.D.
Acting Director of
Division of Biopharmaceutics

Prepared by Mei-Ying Huang, Ph.D.
FT Initialed by CT Viswanathan, Ph.D. CV 7/11/85

cc: NDA 19-009 orig., HFN-220(Skelly, Shulman), HFN-226(Huang), Chron, and
Drug Files

JPS:dea:smj: [redacted] (7/11/85)

07 36 1 1

Pirbuterol
Exirel[®] Aerosol
200 mcg/actuation
300 actuation/container
NDA 19-009
Reviewer: Mei-Ying Huang, Ph.D.
Wang [REDACTED]
ISID

Pfizer Corporation
Greton, C.T.
Submission Date:
April 21, 1984

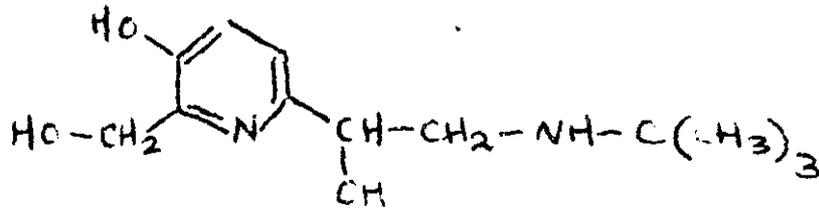
JUL 11 1985

Review of a Submission and Request
For a Waiver

Background

Pirbuterol is a beta₂ adrenergic agonist.

This NDA 19-009 deals with aerosol dosage form. In this submission, the firm not only requested for a waiver under 21 CFR 320.22 but also submitted information available on the absorption, metabolism and disposition of pirbuterol in sections



Study #46-2

Title

Pirbuterol Acetate Bioavailability Study.

Investigator

Donald Tashkin, M.D.

Clinical Laboratory

Pulmonary Research Laboratory

Objective

A double-blind, cross-over study of single doses of pirbuterol acetate aerosol.

- 1) To evaluate dose response efficacy parameters.
- 2) To measure plasma levels and urinary excretion of the drug.

Patients

Twenty-six patients (3 females and 23 males) with bronchial asthma and bronchial asthma associated with bronchitis.

Drug Administration

Single doses of pirbuterol acetate aerosol; _____, 200 mcg, and placebo, were randomly administered to 26 patients.

Analytical Method
GC-Mass Spectrometry

Blood Samples

Sufficient venous heparinized blood samples (10cc) to supply 5 ml of plasma were withdrawn from each patients on the designated test day at the following times:

0 (predose), and immediately after the 5, 30, 60, and 180 minutes pulmonary function testing.

Results:

Analytical Validation

The firm has validated the assay methodology.

Individual Dose Response of FEV₁

The individual dose response of FEV₁ (onset, duration, peak, AUC) is shown in Table 1. Average data is shown in Table 2. The drug has a very fast onset with median of 5 minutes.

Plasma Levels

The firm indicated that at the highest dose level of 800 mcg, plasma concentrations of pirbuterol were below the limit of detection (from 2 to 5 ng/ml) at all time points in all patients. Plasma samples from six patients (No. 1-6) receiving mcg of pirbuterol were also assayed for total pirbuterol (free pirbuterol and pirbuterol conjugate) and found to have undetectable levels.

Urinary Data

Although plasma levels of pirbuterol were below the limit of detection, the detection of drug-related material in the urine of all patients indicated that all patients were exposed to pirbuterol. Mean urinary recoveries of drug as free pirbuterol, pirbuterol conjugate and total pirbuterol (free plus conjugate) revealed similar patterns of drug excretion for corresponding time intervals across the three dose levels. Mean total urinary recoveries of drug-related material for the 0-24 hr interval were 53.4, 47.3 and 51.9% of the administered dose, for the 400, 600, 800 mcg doses of pirbuterol respectively. No significant differences were noted between the different dose levels for total drug recovery. See Table 3 for individual urinary data.

Comments:

1. The fast onset of FEV₁ peak (with median of 5 minutes) after the administration of 0.1 mg to 0.8 mg metered dose inhalation

similar

magnitude in peak % improvement in FEV₁ for both routes of administration strongly suggest that this metered dose inhaler is locally active. This is not uncommon with beta₂-agonists. For example, this phenomenon has been demonstrated in albuterol metered dose inhaler (J. Clin. Pharmacol. Ther. 1972; 13: 861-867).

2. The flat dose-response curve suggested that for some individuals, a dose as low as 0.2 mg is already effective (See Fig.1). The drastic difference in doses given between inhalation and ~~but~~ similar magnitude in FEV₁ response further suggests that it might be beneficial for patients to take the relatively low dose of the drug through inhalation in order to reduce beta₁-related side effects.
3. Despite the sensitivity limitation in assaying the plasma levels, the firm managed to analyze the urinary recoveries of the drug. The % dose recovered as parent drug, conjugate, and total (parent plus conjugate) are as follows:

P	PC	Total
---	----	-------

The mean urinary recovery as parent drug was comparable with that obtained in the previous ~~study~~, although the variability was large. The mean apparent half-life of the parent drug was about 2.4 to 2.7 hours (information obtained from capsule formulation in NDA 18-559).

Conclusion:

The Division of Biopharmaceutics has reviewed the submission and taking into consideration of the above three comments and the fact that clinical trial was performed for this dosage form, we have decided that the waiver for in vivo bioavailability study should be granted under CFR 21 320.22 b(2).

M. Y. Huang 7/11/85
 Mei-Ying Huang, Ph.D.
 Pharmacokinetic Evaluation Branch

RD Initialed by C.T.Viswanathan, Ph.D.

FT Initialed by C.T. Viswanathan, Ph.D. CTV ~~7/11/85~~

cc: NDA 19-009 orig., HFN-160, HFN-226(Huang), Chron, Drug, and FOI Files.

MYH:kek:dea:smj:(~~redacted~~): 7-11-85

Table 2

RESPONSE PATTERNS FOR ACTIVE DRUGS:
 COMPARISON OF MEDIAN PEAK AND AUC
 AS % IMPROVEMENT OVER BASELINE-FEV 1
 TASHKIN AEROSOL STUDY (46-2)

TREATMENTS	R E S P O N D E R S		O N L Y		A L L P A T I E N T S	
	MINIMAL RESPONSE*	EXTREME RESPONSE**	MINIMAL RESPONSE*	EXTREME RESPONSE**	EVALUATED	ALL PATIENTS
	PEAK	AUC	PEAK	AUC	PEAK	AUC
PIRBU TEROL						
PIRBU TEROL 0.2 MG.	26.15%	9.98%	38.46%	15.69%	26.62%	10.77%
PIRBU TEROL						
PIRBU TEROL						
PIRBU TEROL						

*FOR FEV1: 15-29% PEAK IMPROVEMENT **FOR FEV1: 30% OR MORE PEAK IMPROVEMENT

TABLE 13

Microbiology Reviews

NDA 19-009

Date: 7/27/84

Review and Evaluation of Pharmacology and Toxicology Data
Resubmission of 4/13/84
Amendment of 5/25/84

4

APPLICANT: Pfizer Inc.

DRUG: EXIREL (pirbuterol acetate, CP-24,314-14) Inhaler, Bronchodilator

CATEGORY: Bronchodilator

COMPOSITION:

<u>Component</u>	<u>Gm/Aerosol Unit</u>
Pirbuterol Acetate	0.117*
Sorbitan Trioleate	0.078
Trichloromonofluormethane	7.634
Dichlorodifluoromethane	17.787
Total	<u>25.616**</u>

*Equivalent to 93.6 mg pirbuterol

** Equivalent to 18.7 ml

RELATED INDS:

RELATED NDA:

COMMENT:

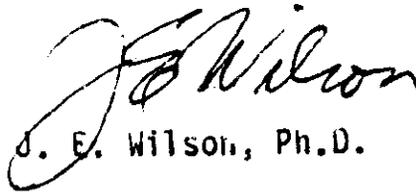
The pharmacologist in his review dated September 9, 1983, approved the original submission of NDA 19-009 from the standpoint of preclinical animal testing. The resubmission of April 13, 1984, and subsequent amendment contain primarily clinical and manufacturing controls information and add nothing, in this reviewer's opinion, that would alter the approvability of the NDA from the standpoint of preclinical animal testing.

The reviewing pharmacologist in his review of the original submission made a number of suggested changes in the package insert. Two changes were incorporated in the DRAFT OF PHARMACOLOGY PORTION of LETTER TO APPLICANT. Since no letter was issued to the applicant these suggestions are repeated below along with a note to the reviewing medical officer.

JUL 20 1984

CONCLUSION:

The resubmitted application is approvable from the standpoint of preclinical animal testing.


J. E. Wilson, Ph.D.

NDA 19-009
HFN-160, HFN-340
R/D JEWilson 7/27/84
R/D init by JKinscoe7/27/84
Doc Rm 160
Ft/MPatterson (w0925k) 7/30/84

STAT

REVIEW

Statistical Review and Evaluation

Date: MAR 22 1984

NDA#: 19-009/Drug Class: 1C

Name of Drug: Exirel (pirbuterol Aerosol)

Applicant: Pfizer Inc.

Documents Reviewed: Volumes 1.3 - 1.9 dated 4/21/83

This review pertains to clinical studies evaluating the safety and efficacy of Exirel aerosol for treatment of bronchial disorders. In particular it was requested that statistical methods and efficacy analyses be evaluated for 15 single-dose placebo-controlled studies, as well as 5 multiple-dose comparative studies and 16 other open studies.

1. Single-dose, placebo-controlled, double-blind studies.

A. These studies were all crossovers involving pirbuterol aerosol and various other active agents, as well as placebo. All studies required that patients demonstrate reversibility of bronchospasm on the 1st evaluation day; they were then randomly allocated to receive single doses of study medications on separate test days. Some studies instructed patients not to take any sustained release preparations at least 12 hours prior to each drug evaluation (Studies #65-1 and #63-2). Protocols for studies #61-3 and #60-2 excluded all patients taking corticosteroids. Studies #31-4 and #66-2 required that corticosteroids and cromoglycate be discontinued at least 12 hours before testing. Studies #02-2 and #47-1 required that corticosteroids and cromolyn sodium and theophylline be discontinued at least 12 hours before testing.

Pulmonary function tests (PFTs) were performed on each test day at baseline (predose) and at specified intervals from 5 to 240 mins. postdose. Spirometric measurements usually included forced expiratory volume at 1 sec. (FEV₁) and maximum mid-expiratory flow rate (MMF). Subjective ratings of response were also made by patient and physician on each test day. The analysis of PFTs was based on the following definitions:

Response = at least 3 consecutive observations for which FEV₁ was 15% or more above baseline for a given day.

Onset - point at which response sequence first began.

Duration = time from onset until at least 2 consecutive observations were less than 15% above baseline (0 if no onset).

Peak = maximum % increase over baseline.

AUC = weighted sum of % values above baseline from onset thru duration (0 if no onset).

For MMF, the definitions were similar except that the benchmark for response was 20%.

1) Study #02-2 (Dr. Chodosh)

This study involved 26 patients with intrinsic and extrinsic asthma and asthma with bronchitis or emphysema who were randomly assigned to single doses of the following drugs in a crossover manner: placebo aerosol, pirbuterol acetate aerosol 0.2 and 0.4 mg and metaproterenol aerosol at 1.3 mg. Pirbuterol acetate suspensions 0.2 mg/actuation, metaproterenol 0.65 mg/actuation and placebo were given in two actuations to make the placebo/pirbuterol 0.4 mg comparison completely double blind. Also, a placebo canister was supplied along with the pirbuterol 0.2 mg canister to insure blinding. Drugs were randomly assigned within the 3 asthma subgroups using the method of random permuted blocks.

One patient did not receive a 0.2 mg pirbuterol test day and another only received metaproterenol. These two patients were excluded from the efficacy analyses which included 24 patients.

Intervals of at least 1 day separated drug test days. For each patient, drug response was characterized according to extent of response (0 = No response; 1 = Minimal, 15% Response over baseline for FEV₁; 2 = Extreme, 30% Response over baseline for FEV₁) [the sponsor has labeled the analysis of this variable "number of responders" in the submission], onset, duration, peak and AUC for FEV₁ and MMF measured on each treatment day. These responses were tested using Friedman rank ANOVA. Once the Friedman ANOVA's showed significance at p less than 0.10, the ranks were subjected to standard two-way analysis of variance and contrasts were made between treatments using studentized ranges (Tukey contrasts).

In terms of FEV₁, both doses of pirbuterol produced statistically significant improvement over placebo in duration, peak and AUC. None of the 3 active therapies were significantly different at the 0.05 level, though near significance in favor of pirbuterol 0.2 mg over metaproterenol was seen in AUC ($.05 < p < .10$).

In terms of MMF, both doses of pirbuterol showed a significantly greater effect than placebo in peak effect and AUC. Peak effect in MMF was also significantly greater on metaproterenol than on placebo. Pirbuterol 0.4 mg had a significantly greater effect on AUC than metaproterenol, while results for this measure favored pirbuterol 0.2 mg over metaproterenol to a nearly significant extent ($.05 < p < .10$).

The most common side effects were CNS symptoms (headache, dizziness, etc.) which were reported more frequently on metaproterenol than pirbuterol.

2) Study #47-1 (Dr. Grieco)

This study involved 26 patients with intrinsic and extrinsic asthma and chronic bronchitis with or without emphysema. Two patients who took only one treatment (metaproterenol in both cases) were excluded from efficacy analyses. The study design, drug sequences, efficacy endpoints and analysis

were similar to those of Study #02-2 with the exception that there was no mention of using a placebo canister along with the pirbuterol 0.2 mg aerosol. The sponsor indicates that a third party administered the aerosol to the patients on test days. Intervals of 1 to 7 days separated drug test days.

In terms of FEV₁, both doses of pirbuterol showed a significantly greater effect than placebo on number of responders, duration, peak effect and AUC. Metaproterenol also had a significantly greater effect than placebo on number of responders, duration and peak effect. The only significant difference between active drugs was seen in peak effect, with pirbuterol 0.2 mg producing significantly more improvement than metaproterenol.

In terms of MMF, all three active drugs produced significant improvement over placebo in number of responders and peak effect. For AUC, both 0.2 mg pirbuterol and metaproterenol were significantly better than placebo, while the result for pirbuterol 0.4 mg was of borderline significance ($0.05 < p < 0.10$). The only significant difference between active drugs was seen in AUC in favor of 0.2 mg over 0.4 mg pirbuterol.

Side effects were reported by 4 patients on each active drug (palpitations, nervousness, headache) and by 3 patients on placebo.

3) Study #31-4 (Dr. Pariente)

This study involved 24 patients with intrinsic and extrinsic asthma and chronic bronchitis with emphysema. One patient did not receive pirbuterol 0.2 mg and was excluded from the efficacy analyses. Otherwise the study was similar to Study #02-2 with two exceptions. The first difference was that an additional pulmonary function test was done. Specific airways conductance (GA/Vtg) was measured using a plethysmography. The second difference was that pirbuterol 0.2 mg was given as only one actuation. Therefore this treatment was not blinded from either the patient or the investigator. The sponsor has excluded data for this treatment period from the efficacy analysis. Both pirbuterol 0.4 mg and metaproterenol produced significant improvement over placebo in peak, AUC and number of responders in the three measures of pulmonary function FEV₁, MMF and GA/Vtg. For changes in GA/Vtg, 20% improvement above baseline was taken as the benchmark to define response. Otherwise, all definitions were the same as for FEV₁. The only significant difference between active drugs was seen in peak effect for GA/Vtg in favor of pirbuterol 0.4 mg over metaproterenol.

No side effects were reported for any of the treatments.

4) Study #96-1 (Charpin)

This study involved 24 patients with intrinsic and extrinsic asthma and chronic bronchitis. The study was similar to Study #02-2 except that pirbuterol 0.2 mg was given as only one actuation and hence not blinded from the patient or investigator. The sponsor has excluded the pirbuterol 0.2 mg data from the efficacy analysis.

In terms of FEV₁, 0.4 mg pirbuterol had a significantly greater effect than placebo on peak, AUC and number of responders. The effect of metaproterenol on AUC was nearly statistically significant over placebo ($0.05 < p < 0.10$).

Active drug comparisons showed the average peak effect of pirbuterol 0.4 mg to be greater than that of metaproterenol ($0.05 < p < 0.10$).

In terms of MMF, both pirbuterol 0.4 mg and metaproterenol produced significant improvement over placebo in AUC. No significant differences were detected between active drugs for any measure.

No side effects were reported for any treatment.

5) Study #66-21 (Salorinne)

This study involved 24 patients with chronic obstructive pulmonary disease (COPD). This study enrolled nearly equal numbers of patients with extrinsic asthma (9 patients), intrinsic asthma (8 patients) and chronic bronchitis (7 patients). The design was similar to Study #02-2 with the exception that the pirbuterol 0.2 mg dose was replaced by another 0.4 mg dose. The sponsor has included the second administration of pirbuterol 0.4 mg in some of the efficacy summary tables and labeled its results "pirbuterol 0.2 mg". This treatment was excluded however from the statistical analyses of the efficacy measures.

In terms of FEV₁, pirbuterol 0.4 mg and metaproterenol effected statistically significant improvement over placebo in onset, peak response and AUC. For number of responders, metaproterenol was significantly better than placebo, while the effect of pirbuterol 0.4 mg over placebo was only marginally significant ($0.05 < p < 0.10$). There were no statistically significant differences between active drugs.

In terms of MMF, no statistically significant improvement over placebo was seen for any active drug, and no significant differences were found between active drugs.

A single patient reported a moderately severe skin rash of one day duration on one of the pirbuterol 0.4 mg administration days. This was the only reported side effect in this study.

6) Study #66-1 (Salorinne)

This study involved 24 patients with chronic obstructive pulmonary disease (COPD); of these, 19 had bronchial asthma (type unspecified) and 5 had asthma associated with chronic bronchitis. This study was similar to Study #66-2 with the same double administration of pirbuterol 0.4 mg. Again the sponsor has labeled the second administration "pirbuterol 0.2 mg" in some efficacy summary tables and has excluded it from the efficacy analyses.

In terms of FEV₁, both pirbuterol 0.4 mg and metaproterenol effected statistically significant improvement over placebo in numbers of responders, peak response, onset and AUC. No significant differences were detected among active drugs.

In terms of MMF, the pirbuterol 0.4 mg dose produced significant improvement over placebo in numbers of responders and AUC. Significant differences favoring metaproterenol over placebo were found in peak response and AUC. No significant differences were detected among active drugs.

No side effects were recorded for any treatment.

7) Study #28-21 (Holten)

This crossover study involved 20 patients with chronic obstructive pulmonary disease (COPD) who were randomly assigned to single doses of placebo aerosol, pirbuterol 0.2 mg, pirbuterol 0.4 mg and salbutamol 0.2 mg. Pirbuterol 0.2 mg was given as 1 actuation whereas all the other doses were given as 2 actuations.

In terms of FEV₁, all three active drugs effected statistically significant improvement over placebo in onset, peak, AUC and number of responders. No significant differences were detected among active drugs.

In terms of MMF, the 0.4 mg dose of pirbuterol produced significantly more improvement than placebo in onset, peak, AUC and number of responders. Salbutamol showed a significant effect over placebo in onset, AUC and number of responders, while pirbuterol 0.2 mg produced significant improvement over placebo in onset and number of responders. The only significant difference between active drugs was seen in peak response, favoring pirbuterol 0.4 mg over the pirbuterol 0.2 mg dose.

No side effects were recorded for any drug.

8) Study #21-6 (Beumer)

This study involved 12 patients with bronchial asthma. It was similar to study #28-2 except that a fifth treatment (0.6 mg pirbuterol) was administered at the end of each sequence and maximum expiratory flow rate (MEFR) was measured rather than MMF. For MEFR as with MMF, a clinically significant response was 20% or more above baseline. The 0.6 mg pirbuterol data was excluded from the efficacy analyses.

In terms of FEV₁, all three active drugs were significantly more effective than placebo in onset, peak and AUC. Salbutamol also showed a significantly greater effect than placebo in number of responders. The only significant difference between active drugs was seen in AUC in favor of salbutamol over pirbuterol 0.2 mg.

In terms of MEFR, significant differences favoring active drugs over placebo were found for salbutamol in onset, peak and AUC, pirbuterol 0.4 mg in peak and AUC, and pirbuterol 0.2 mg in AUC only. The only significant differences between active drugs were detected in peak response and AUC in favor of salbutamol over pirbuterol 0.2 mg.

No side effects were reported by the patients after any of the treatment.

9) Study #60-2 (Kok-Jensen)

This study involved 11 patients with chronic obstructive pulmonary disease (COPD). Otherwise the study was similar to study #28-2 with the exception that peak expiratory flow rate (PEFR) was measured rather than MMF. For PEFR as with MMF, the benchmark for improvement was 20%. Two patients discontinued

the study after pirbuterol doses because of unrelated illness and inability to withhold concomitant PRN bronchodilator therapy for the required 8 hours before testing. These patients were removed from the efficacy analyses.

In terms of FEV₁, all active drugs effected statistically significant improvement over placebo in peak response and AUC. Pirbuterol 0.4 mg and salbutamol also effected significant improvement over placebo in onset of response. No significant differences were detected among active drugs.

In terms of PEFr, both pirbuterol 0.4 mg and salbutamol effected statistically significant improvement over placebo in onset, peak and AUC. Significant differences were also found to favor pirbuterol 0.4 mg over placebo in number of responders, and pirbuterol 0.2 mg over placebo in AUC. The only difference among active drugs that approached significance was that for onset of response, which favored salbutamol over pirbuterol 0.2 mg ($.05 < p < .10$).

A single side effect was reported in this study. The patient was on pirbuterol 0.4 mg.

10) Study #68-1 (Lulling)

Fourteen patients with chronic obstructive pulmonary disease (COPD) received single doses of 0.4 mg pirbuterol, 0.2 mg salbutamol and placebo. The pulmonary function tests measured were FEV₁ and PEFr. One patient received only pirbuterol while another received only salbutamol. These two patients were excluded from the efficacy analyses.

In terms of FEV₁, both active drugs effected statistically significant improvement over placebo in onset of response, peak response, AUC and number of responders. Pirbuterol 0.4 mg provided significantly more improvement than salbutamol in peak response and AUC.

In terms of PEFr, both active drugs effected significantly more improvement than placebo in peak response and AUC. Pirbuterol 0.4 mg also effected significant improvement over placebo in onset of response and number of responders. No significant differences between active drugs were detected.

No side effects were recorded.

11) Study #65-1 (Schanning)

This study was conducted on 12 patients with chronic obstructive pulmonary disease (COPD). This study was similar to Study #28-2.

In terms of FEV₁, all active drugs effected statistically significant improvement over placebo in AUC. Salbutamol and pirbuterol 0.4 mg also effected significantly more improvement than placebo in peak response and onset of response respectively. No significant differences among active drugs were detected.

In MMF, both pirbuterol 0.4 mg and salbutamol effected statistically significant improvement over placebo in peak response and AUC. Pirbuterol 0.4 mg also provided a significantly shorter onset of response than placebo whereas for the same measure the difference was only nearly significant for

salbutamol vs. placebo ($0.05 < p < .10$). No significant differences among active drugs were detected, although salbutamol was favored over pirbuterol 0.2 mg for peak response to a nearly significant extent ($0.05 < p < .10$).

No side effects were recorded.

12) Study #63-2 (Schindl)

This study involved 20 patients with asthma (unspecified) and chronic bronchitis. The design was similar to Study #28-2. In terms of FEV₁, all active drugs effected statistically significant improvement over placebo in peak response and AUC. Significant differences also favored pirbuterol 0.4 mg and salbutamol over placebo in peak response and number of responders. No significant differences between active drugs were detected.

In terms of MMF, pirbuterol 0.4 mg effected statistically significant improvement over placebo in onset of response and AUC. Salbutamol showed a significant effect over placebo in onset of response. No significant differences between active drugs were detected.

For GA/Vtg, all three active drugs effected statistically significant improvement over placebo in number of responders, onset of response, peak response, and AUC. No significant differences between active drugs were detected.

No side effects were reported in this study.

13) Study #61-3 (Van der Straeten)

This crossover study involved 14 patients with chronic obstructive pulmonary disease (COPD). These patients received single doses of 0.4 mg pirbuterol, 0.2 mg salbutamol and placebo on each of 3 days. Pulmonary function tests performed were FEV₁ and GA/Vtg.

Both active drugs effected statistically significant improvement over placebo for number of responders, onset, peak and AUC for both FEV₁ and GA/Vtg. The only significant difference between active drugs was detected in peak response for FEV₁ in favor of pirbuterol 0.4 mg over salbutamol.

No side effects were reported in this study.

14) Study #74-1 (Verstraeten)

Twelve patients with chronic obstructive pulmonary disease (COPD) were randomly assigned single doses of 0.4 mg pirbuterol, 0.2 mg salbutamol and placebo on consecutive days. Pulmonary function tests measured were FEV₁ and forced vital capacity (FVC). One patient did not satisfy the protocol criterion of showing 15% improvement in the reversibility test and was excluded from the efficacy analysis.

In terms of FEV₁, pirbuterol 0.4 mg effected statistically significant improvement over placebo in number of responders, onset of response, peak and AUC. Salbutamol had a significantly better effect than placebo in onset and

AUC only, although the difference in peak response was nearly significant ($0.05 < p < .10$). No significant differences between active drugs were detected.

In terms of FVC, both pirbuterol 0.4 mg and salbutamol effected statistically significant improvement over placebo in onset and AUC. No significant differences between active drugs were detected.

No drug related side effects were recorded.

15) Study #70-1 (Ulmer)

This study involved 12 patients with chronic bronchitis and chronic bronchitis associated with emphysema who were randomly assigned to receive single doses of 0.2 mg pirbuterol, 0.4 mg pirbuterol, 0.2 mg fenoterol and placebo. Pirbuterol 0.2 mg and fenoterol were administered in 1 actuation, the other treatments in 2 actuations. Airways Resistance (RAW) was measured by Plethysmography. For RAW, the benchmark response was 20% over baseline.

In terms of RAW, both 0.4 mg pirbuterol and fenoterol effected statistically significant improvement over placebo in peak response and AUC. The 0.2 mg pirbuterol dose showed a significantly greater effect than placebo in peak response. Significant differences favored fenoterol over both doses of pirbuterol in AUC and over the 0.2 mg pirbuterol dose in peak response. The fenoterol vs. pirbuterol 0.4 mg difference in peak was only marginally significant, with $0.05 < p < .10$.

No side effects were reported on any treatment.

B. Reviewer's Comments on Single-dose, Placebo-controlled Studies.

Derived efficacy variables (response, onset, duration, peak and AUC) appear to have been extracted properly from data. Dr. Nicklas considers that the definitions applied by the sponsor were clinically appropriate for reducing the large amount of data from pulmonary function tests to a smaller set of meaningful efficacy criteria. However, he does not feel that studies of a single dose administration of this bronchodilator are as clinically relevant to its actual prescribed use as are long term 12 week trials.

It should be noted that the designs of these studies (crossovers with multiple active controls) were not balanced for residual effects; for each study the validity of results depends on the assumption that the baseline bronchial condition of each patient remains stable throughout the trial (i.e., pulmonary function should return to the initial baseline level prior to each test). To this end, protocols required that other bronchodilators be discontinued at least 6 hours prior to drug evaluation. However, there was no check on patient adherence to this requirement and it is not clear that the length of washout periods was sufficient to discount the influence of previously taken drugs. An analysis of baseline values before administration of drug would help rule out studies where there were problems. In this reviewer's opinion, the general consistency among the results of the studies would not necessitate such a check for this submission.

In some studies, the sponsor has done a poor job of double-blinding the pirbuterol 0.2 mg treatment. It was only double-blinded in 1 out of the 12 clinical trials in which this dosage was tested. The pirbuterol 0.2 mg data should not have been entirely excluded from the efficacy analyses even when it was only partially blinded because of the additional information that it might provide.

2. Long-term multi-dose comparative studies

A. These 12-week parallel comparison studies were designed to address the questions of comparative efficacy, tolerance and safety of multiple doses of pirbuterol acetate aerosol. Metaproterenol aerosol was used as the standard comparative agent. The studies enrolled patients with intrinsic asthma, extrinsic asthma and chronic bronchitis. All studies required that patients demonstrate reversibility of bronchospasm on the 1st evaluation day. The daily dosages of pirbuterol and metaproterenol were 0.4 mg q.i.d and 1.3 mg q.i.d. respectively. Prior to being assigned to active drugs, patients had a one-week placebo washout period.

During the treatment period, patients returned to the clinic every two weeks for 12 weeks. At each visit, measurements were taken just before and for four hours after the morning dose (at 5, 15, 30, 60, 90, 120, 180 and 240 minutes post-dosing). Patients were instructed to abstain from all conventional bronchodilators for at least six hours and all sustained action bronchodilators for 12 hours prior to each test day visit.

Spirometric measurements were: forced vital capacity (FVC) (data were collected but not assessed); forced expiratory volume at 1 sec. (FEV₁); and either forced expiratory flow rate, 50% of lung volume (FEF₅₀) or maximum expiratory flow rate (MEFR).

In these studies the question of possible tolerance development was assessed from two points of view:

The first method used by the sponsor involved fitting linear least squares slopes to each patient's pulmonary function test responses measured throughout the 12 weeks study. The sponsor tested whether each drug showed tolerance by testing whether the mean slope for each drug group was significantly different from zero using a one sided t-test. The sponsor tested whether the drugs showed comparable tolerance by testing whether the mean slopes of the drug groups were equal using a two sided t-test.

The second method used by the sponsor to address whether the two drug groups were showing comparable tolerance was by tabulating the number of patients showing "tolerance" on each drug. The sponsor has defined a patient to show drug "tolerance" if he fails to respond during his last three visits after having responded at an earlier visit. Since so few patients showed tolerance according to the sponsor's definition, the sponsor did not use any statistical test to compare the percentages of patients showing tolerance in the two drug groups.

In these long term studies, the question of whether the drugs were of comparable efficacy was also assessed from two points of view.

- Peak and AUC effects at the end of 12 weeks of therapy.
- Average peak and average AUC across all clinic visits.

The sponsor has indicated that prior analysis of the efficacy data at week 12 had indicated that they were badly skewed so Normal theory tests would be inappropriate. Non-parametric tests were considered by the sponsor to be unnecessarily inefficient because of the large number of patients involved. As a compromise the sponsor chose to transform the individual patient-specific values by taking the inverse hyperbolic sine. The sponsor claims that this transform will stabilize the variance for distributions whose variance is a quadratic function of the mean, a condition he claims to hold true for a large class of skewed distributions. The sponsor further claims that it can be applied to data which has a large positive skew but for which some negative values can occur (which cannot be done for the log or square root transforms). For each of the transformed efficacy measures, the sponsor compared mean values of the 2 drug groups using a t-test.

- 1) Multi-center multi-dose double-blind study (Protocol A) (Studies #13-5, 47-2, 32-1, 35-1, 09-5, 46-3, 15-1, 20-6).

The original protocol (protocol A) called for the first active drug measurements to be taken after two weeks. After patients were started on protocol A, it was suggested by the FDA that the protocol be modified in order to investigate the possibility of tolerance developing in the first two weeks of chronic therapy. The new patients (under protocol B) were given a week of placebo as before, but the dose given in the morning of the final day of the placebo week and for which pulmonary function tests were measured was to be the first dose of active medication for that patient.

This analysis included patients from only seven of the eight clinics. Study #09-05 (Spector) did not enroll any patients under protocol A. There were 34 patients in the pirbuterol group and 28 patients in the metaproterenol group. One patient from the metaproterenol group was excluded from the efficacy analyses because he only had one clinic visit.

An inspection of the table of concomitant bronchodilator therapy while on active drug revealed that 31 out of 34 patients on pirbuterol took aminophylline oral, comb. as compared to only 1 out of 28 patients on metaproterenol.

The sponsor concludes that patients in the pirbuterol group responded significantly better than those in the metaproterenol group with respect to the average AUC for FEV₁ across all clinic visits. Results almost reached significance (p=.06) with respect to FEF₅₀ average AUC across all clinic visits. No significant differences between drugs were detected for either FEV₁ or FEF₅₀ in peak at week 12, AUC at week 12 and average peak across all visits.

There was no statistically significant trend to indicate a decrease across time in FEV₁ in either the pirbuterol or metaproterenol groups, on the basis of the number of patients responding, peak response, AUC or duration of response. The sponsor reports that a single patient from both the pirbuterol

and metaproterenol groups showed "tolerance" in FEV₁. The results for FEF₅₀ were identical with the exceptions that duration of response was not assessed and 2 patients in each group showed "tolerance".

There were 24 side effects during pirbuterol therapy and 20 side effects during metaproterenol therapy. The majority of side effects reported during pirbuterol therapy were of the CNS type: nervousness, followed in frequency by nausea, dry mouth and tremors. All side effects reported due to pirbuterol were of the mild and moderate type. Metaproterenol patients had 7 severe side effects.

2) Multi-center multi-dose double-blind study (Protocol B) (Studies #13-5, 47-2, 32-1, 35-1, 09-5, 46-3, 15-1, 20-6).

Under protocol B, new patients were given active drug in the morning of the last day of the placebo week to check whether tolerance was developing during the first two weeks on drug.

There were 66 patients in the pirbuterol groups and 67 patients in the metaproterenol group. Eight patients in the metaproterenol group had only one clinic visit and thus were excluded from the efficacy analyses.

An inspection of the table of concomitant bronchodilator therapy while on active drug revealed that 10 out of 66 patients on pirbuterol took aminophylline oral, comb., as compared to only 2 out of 67 patients on metaproterenol.

There were no significant differences between drugs in the efficacy measures for either FEV₁ or FEF₅₀ although the average AUC across all visits for FEV₁ was nearly significant in favor of pirbuterol over metaproterenol (p=.06).

The sponsor found no statistically significant linear trend to indicate a decrease in FEV₁ or FEF₅₀ across time in either treatment group, based on numbers of patients responding, peak response and average (AUC) response. The observed FEV₁ at 240 minutes as a percentage of the peak FEV₁, which was used as a surrogate for duration of response, showed a significant decrease over time for the pirbuterol groups and a nearly significant decrease for the metaproterenol group (p=0.08).

In terms of individual patient failures to respond in FEV₁, only 4 out of 59 patients on pirbuterol and 3 out of 47 on metaproterenol showed "tolerance". For FEF₅₀, the corresponding numbers of patients showing "tolerance" were 5 out of 59 and 2 out of 50 for the pirbuterol and metaproterenol groups respectively.

Forty side effects were reported in the pirbuterol group and 30 side effects were reported in the metaproterenol group. One patient in each group discontinued treatment because of side effects. Two side effects on pirbuterol were reported as severe (tremors and dry mouth). There were 3 side effects reported as severe on metaproterenol.

3) Study #14-4 (Bernstein)

The pirbuterol and metaproterenol groups had 20 to 21 patients respectively. All patients were taken off cromolyn sodium before entering the study.

No significant differences between treatments were seen in any of the efficacy measures although the average peak across weeks 2 to 12 for MEFR was nearly significant in favor of pirbuterol ($p=0.08$).

There were no statistically significant linear trends over time in number of patients responding, peak response, AUC or duration of response for either treatment in both FEV₁ and MEFR. For FEV₁ duration of response, a comparison of the two slopes (average rates of change) achieved near significance in favor of metaproterenol ($p=.058$). The average slopes for this measure were -0.791 and 1.631 for pirbuterol and metaproterenol respectively.

One out of 13 patients on pirbuterol and 2 out of 15 patients on metaproterenol showed "tolerance" for FEV₁. For MEFR (the sponsor's table labeled it MMF), 3 out of 15 patients on pirbuterol and 2 out of 13 patients on metaproterenol showed "tolerance".

There were 9 side effects in the pirbuterol group and only 3 in the metaproterenol group. All side effects were of mild or moderate severity. One patient on pirbuterol died of an acute fulminant asthmatic attack superimposed on atherosclerotic heart disease. He was on pirbuterol therapy for 6.5 weeks. Another patient in the metaproterenol group died of an acute myocardial infarction. Neither death was considered by the sponsor to be drug-related.

4) Study #21-8 (Beumer)

The pirbuterol and metaproterenol groups each had 19 patients. The protocol excluded all patients on cromolyn sodium.

No significant differences between drugs were detected in the efficacy parameters measured.

There were no statistically significant linear trends over time in number of patients responding, peak response, AUC or duration response for either treatment group in both FEV₁ and MEFR. For FEV₁ duration of response the comparison of the two average rates of change achieved near significance in favor of metaproterenol ($p=0.09$). The average slopes for this measure were -0.97 and 0.56 for pirbuterol and metaproterenol respectively.

One out of 16 patients on pirbuterol and 2 out of 15 patients on metaproterenol showed "tolerance" in FEV₁. For MEFR, no patient showed "tolerance" for either treatment.

The only 2 side effects reported were in the metaproterenol group. One patient in the metaproterenol group died. Death was thought to be related to pulmonary embolism or myocardial infarction.

5) Study #63-3 (Schindl)

The pirbuterol and metaproterenol groups each had 18 patients. This study analyzed MMF and GA/Vtg in addition to FEV₁.

No significant differences between drugs were detected in the efficacy parameters measured for the 3 pulmonary function tests analyzed.

There were no statistically significant linear trends over time in number of patients responding, peak response, AUC or duration of response for either treatment in FEV₁, MMF or GA/Vtg.

No patient on either treatment showed "tolerance" in any of the three pulmonary function tests analyzed.

There were 11 and 17 side effects reported in the pirbuterol and metaproterenol groups respectively. All were mild to moderate in severity.

B. Reviewer's Comments On the Long-Term Multi-Dose Comparative Studies

The use by the sponsor of the inverse hyperbolic sine transformation for the efficacy analyses has not been justified. This transformation will only stabilize the variance for distributions whose variance is exactly $[1+(\text{mean})^2]$ and not any quadratic function of the mean as indicated by the sponsor. The sponsor did not provide any evidence that the variance was a quadratic function of the mean. The sponsor used the transformation to gain additional power to detect treatment differences via normal theory tests, but has not demonstrated that the transformed data are normally distributed.

The sponsor has found only one significant difference between treatments in the long-term efficacy analyses. This difference was detected in the study (Protocol A) with the large disparity in the use of aminophylline oral, comb. between the two treatment groups.

The sponsor has addressed the question of drug tolerance by estimating a linear least squares slope for each patient across all visits for number of responders, peak response, AUC and duration of response. The sponsor has then tested whether the mean slope was significantly different from zero. Although these analyses can be informative, a linear slope may not demonstrate the tolerance that develops either because of the intrinsic variability of the pulmonary function test measurements or because the response pattern is extremely different from a linear relationship. It would seem appropriate to include a comparison of data from each clinic visit with the results of the first period on active drug. At each visit, a Wilcoxon signed-rank test could be used to test for a significant change in pulmonary function measures from the first on-drug visit. Likewise, a Wilcoxon rank sum could be used to determine whether the two drugs are showing comparable tolerance at each clinic visit.

3. Open Multi-dose Studies (Study #21-7, 25-2, 77-1, 39-3, 93-1, 78-1, 38-1, 54-3, 53-2, 57-1, 31-3, 71-1, 73-1, 74-2, 21-9)

Of the other 15 open studies submitted by the sponsor, only (Study #21-9) was of more than a month duration and hence most were insufficient to measure drug tolerance.

In study #21-9 (Beumer), 25 patients received pirbuterol aerosol for periods up to 14 months. All patients had shown at least 15% improvement in FEV₁ after isoprenaline aerosol 0.16 mg at the start of the previous study #21-8. Patients were permitted to adjust their own doses of pirbuterol, but the most frequently used dose was 0.4 mg either t.i.d. or q.i.d. Eight patients used oral salbutamol on a regular basis. On test days at intervals of approximately 4 to 6 weeks during the study, FEV₁ was measured immediately before and at 30, 60 and 120 minutes after the morning dose of aerosol.

In study #21-9, the sponsor fit linear least squares slopes over time to the percent improvement in FEV₁ averaged over the two-hours post dose period. Using a Wilcoxon Signed Rank statistic, 90% confidence intervals were computed for the median slope estimate. For the 15 patients who did not receive salbutamol on a regular basis, this interval was (-1.242, 0.439). The observed median for these patients was -0.217. Thus although response to pirbuterol tended to show a decrease over time, it was not significantly different from zero.

In these 15 open studies (262 patients) there were 72 side effects (17 in study #71-1) of which 10 were considered severe (cough, non-productive (2); dyspnea (2); nausea (2); tachycardia; depression; confusion; syncope). Seven patients discontinued treatment because of their side effects. One patient in Study #74-2 (Verstraeten) died of an asthmatic attack 3 days after pirbuterol therapy. The investigator is of the opinion it was not drug related.

4. Overall Conclusions

Single doses of pirbuterol at either 0.2 mg or 0.4 mg were found to be superior to placebo in improving pulmonary function of patients with asthma and chronic bronchitis. The acute effect of a single dose of pirbuterol 0.4 mg is comparable to that of a single dose of metaproterenol 1.3 mg or salbutamol 0.2 mg while it appears to be somewhat inferior to 0.2 mg fenoterol. The sponsor has not provided sufficient data to evaluate the comparative efficacy of pirbuterol 0.2 mg with the other active drugs. The 0.2 mg dosage of pirbuterol was only double-blinded in 1 out of the 12 clinical trials in which this dosage was tested.

Pirbuterol 0.4 mg tid/qid and metaproterenol 1.3 mg tid/qid provided comparable efficacy in the chronic treatment (12 weeks) of patients with asthma and chronic bronchitis.

The sponsor has attempted to address the question about whether drug tolerance develops by fitting a linear least squares slope to efficacy data for each patient over time, and then testing whether the mean slope was significantly different from zero. Although this test is a reasonable general approach to the problem, it is insufficient to evaluate all aspects of drug tolerance.

5. Comments to be Communicated to the Sponsor

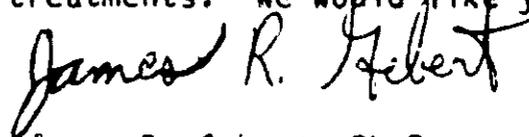
A. Though administration of a single dose of 0.4 mg pirbuterol aerosol has been shown to produce acute improvement in pulmonary function relative to placebo, none of the placebo-controlled, single dose comparative studies directly address the efficacy and safety of pirbuterol under prescribed conditions of chronic tid/qid dosing.

B. In single-dose studies, the sponsor should have employed appropriate techniques to double-blind the 0.2 mg dose of pirbuterol. Even if its administration was only partially blinded, all data collected for this dosage should still have been included in efficacy analyses and summary tables. It would be justifiable to qualify any comments about its performance in discussions of the efficacy findings.

C. In the analysis of chronic dosing studies, the sponsor has given insufficient justification for the use of the inverse hyperbolic sine transformation. This transformation will only stabilize the variance if it is exactly $[1+(\text{mean})^2]$ which has not been demonstrated. We would not consider it appropriate for the sponsor to perform such a transformation unless they can show that the transformation produces more appropriate analyses.

D. The test using linear slopes may fail to detect drug tolerance in many situations either because of the extreme variability of pulmonary function tests or because of the non-linear nature of treatment response. In the 12 week comparative trials, the sponsor should perform additional tests to check whether tolerance developed. This could be done by comparing the pulmonary function tests measured on each visit period with those measured after the first period of active drug. At each visit, a Wilcoxon signed-rank test could be used to test for a significant change in pulmonary function measures from the first on-drug visit. Likewise, a Wilcoxon rank sum test could be used to determine whether the two drugs are showing comparable tolerance at each clinic visit. Efficacy variables analyzed might include peak, AUC and number of responders for FEV₁. It is realized that this involves a lot of multiple comparison tests, but they should help in the determination about whether tolerance develops.

E. It appears from the studies conducted under protocols A & B that pirbuterol and metaproterenol are comparable in terms of efficacy. However, we are concerned that the disparate use of aminophylline (31 out of 34 pirbuterol patients vs. 1 out of 28 metaproterenol patients in the study under protocol A and 10 out of 66 pirbuterol patients vs 2 out of 67 metaproterenol patients in the study under protocol B) could have been the cause of the apparent comparable efficacy of the two treatments. We would like you to comment upon this possibility.



James R. Gebert, Ph.D.
Mathematical Statistician

cc: Orig. NDA 19-009
HFN-160
HFN-160/Dr. Nicklas
HFN-224/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Gebert

~~Chron~~

File: DRU 1.3.2 NDA

JGebert/kh/plt/njs/03/15/84/34594/#0211H

Concur: Dr. Johnson ^{1 H for}

Dr. Dubey ^{3/16/84}

02 3/21/84

Statistical Review and Evaluation

Date: AUG 23 1985

NDA #: 19-009/Drug Class:1C

Applicant: Pfizer, Inc.

Name of Drug: Exirel (pirbuterol acetate) Inhaler

Documents Reviewed: Vol. 2.1 dated 11/13/84 and NDA amendment dated 4/11/85

Background

A statistical review (3/22/84) cited several deficiencies of the 4/21/83 NDA submission which were communicated to the sponsor by HFN-160 (FDA letter dated 9/24/84).

In a telephone conversation on 10/2/84, this reviewer and Pfizer's statistician, Dr. David Salsburg, agreed on the additional analyses which would be required to address our concerns whether tolerance to pirbuterol was developing over 12 weeks of treatment.

Volume 2.1 (11/13/84) of this submission contains the results of these analyses. The NDA amendment includes the sponsor's response to this reviewer's request in another telephone conversation (3/19/85).

FDA's Comments and Sponsor's Response

A. Though administration of a single dose of 0.4 mg pirbuterol aerosol has been shown to produce acute improvement in pulmonary function relative to placebo, none of the placebo-controlled, single dose comparative studies directly address the efficacy and safety of pirbuterol under prescribed conditions of chronic tid/qid dosing.

The sponsor stated that the single-dose studies provide the most appropriate setting in which to evaluate the "absolute" (relative to placebo) and "comparative" efficacy, degree of effect, time to onset and duration of effect of a new bronchodilator. At a meeting with the sponsor on 1/11/85, Dr. Nicklas indicated that these parameters should be measured in multi-dose studies since this was very important in labeling; values of these parameters from single-dose studies could also be included in the label, if the sponsor wished to provide them.

B. In single-dose studies, appropriate techniques should have been employed to double-blind the 0.2 mg dose of pirbuterol. Even if its administration was only partially blinded, all data collected for this dosage should still have been included in efficacy analyses and summary tables. It would be justifiable to qualify any comments about its performance in discussions of the efficacy findings.

The sponsor was requested by the Division of Biometrics to include an analysis of peak FEV₁ response for the four studies that were inadequately blinded. In the two studies involving the 0.2 mg dose, both doses (0.2 and 0.4 mg) of pirbuterol were significantly better than placebo but showed no significant differences from each other or from metaproterenol. The sponsor stated that in the overall analysis of all studies combined, an increase in duration of action was associated with increased dose.

C. In the analysis of chronic dosing studies, insufficient justification was provided for the use of the inverse hyperbolic sine transformation. This transformation will only stabilize the variance if it is exactly $[1 + (\text{mean})^2]$ which has not been demonstrated. We would not consider it appropriate to perform such a transformation unless the transformation can be shown to produce more appropriate analyses.

The sponsor stated that the transformation was used to make the data more symmetric. This was illustrated with two plots of the Parzen-kernel type density estimators for the average peak FEV₁ of the metaproterenol patients.

Although the density appeared more like a normal distribution after the transformation, the sponsor did not test the transformed data for normality. If the data are not normally distributed, significance levels based on standard normal theory are inaccurate. For this reason, a non-parametric test was requested.

The sponsor performed a Wilcoxon rank sum test for peak FEV₁ (averaged over visits) to compare treatment groups. No significant differences between pirbuterol and metaproterenol were detected in the analyses of protocol A and protocol B.

D. The test using linear slopes may fail to detect drug tolerance in many situations either because of the extreme variability of pulmonary function tests or because of the non-linear nature of treatment response. In the 12 week comparative trials, the sponsor was asked to perform additional tests to check whether tolerance developed.

The sponsor stated that the slope analyses were not intended to characterize the nature of any trend over time and that, if there was a monotone trend over time, then a patient-specific estimate of linear slope should be sensitive to that trend. This reviewer does not entirely agree with the sponsor's explanation because there are important cases where the trend would not be monotone with the development of treatment tolerance.

This reviewer requested and the sponsor agreed to perform a non-parametric analysis that does not require a monotone trend assumption. As agreed upon in a telephone conversation, the sponsor performed the Friedman's two-way non-parametric ANOVA on four measures of FEV₁ response (peak, area under the curve, the categorization of FEV₁ response and duration of response) for the pirbuterol patients in separate analyses of protocols A and B.

Reviewer's Comments

Table (7) supplied by the sponsor lists the sum of within patient ranks at various visits for the response variables in protocols A and B and the results of the Friedman ANOVA test. Only patients on pirbuterol who showed a response on all seven visits were included in the analyses. However, this included almost all patients (33/34 under protocol A and 59/66 under protocol B). The results for protocol B were not statistically significant. Multiple comparisons among the on-treatment visits (Weeks 2 thru 12) showed no significant differences for protocol A. The significant differences noted in table 7 for protocol A seem therefore to be attributable to the results at week 0 being lower than the results at the later weeks. The results at week 0 for protocol A were from a run-in placebo period whereas the results from week 0 for protocol B were measured after the use of pirbuterol.

The results at Week 2 and Week 12 for FEV₁ duration, peak and AUC (worst case analyses) were also compared. No significant differences between the results at Week 2 and those at Week 12 were detected for either pirbuterol or metaproterenol.

E. It appeared from the studies conducted under protocols A and B that pirbuterol and metaproterenol are comparable in terms of efficacy. However, we were concerned that the disparate use of aminophylline (31 out of 34 pirbuterol patients vs. 1 out of 28 metaproterenol patients in the study under protocol A and 10 out of 66 pirbuterol patients vs. 2 out of 67 metaproterenol patients in the study under protocol B) could have been the cause of the apparent comparable efficacy of the two treatments. We asked the sponsor to comment on this possibility.

The sponsor pointed out a transcription error in Protocol A. There were only 3 patients (not 31) using aminophylline under protocol A. Furthermore, the sponsor considered it more appropriate to focus on xanthine therapy in toto (including both aminophylline and theophylline) to evaluate the comparability of treatment groups. When patients on either form of xanthine therapy are counted, the figures were:

Protocol A: Pirbuterol 24/34, Metaproterenol 21/27
Protocol B: Pirbuterol 54/66, Metaproterenol 57/59

Thus, there did not appear to be a great imbalance between groups in the use of concomitant xanthine therapy; the slightly greater use in the metaproterenol group would not tend to favor the study drug.

Conclusions

The sponsor has adequately addressed all of the statistical deficiencies cited in FDA's letter of 9/24/84. The results of the clinical trials for this NDA discussed in this review and the previous statistical review, can be summarized as follows:

1. A single dose of pirbuterol 0.4 mg was found to be superior to placebo in improving pulmonary functions in patients with asthma and chronic bronchitis.
2. The acute effect of a single dose of pirbuterol 0.4 mg was comparable to that of a single dose of metaproterenol 1.3 mg or salbutamol 0.2 mg.
3. Pirbuterol 0.4 mg tid/qid and metaproterenol 1.3 mg tid/qid provided comparable efficacy in the chronic treatment (12 weeks) of patients with asthma and chronic bronchitis. For improvement over pre-dose baseline (measured at each visit), the results of the largest 12-week trial (protocol B) indicated that, with 95% confidence, pirbuterol might be 7.94% worse than metaproterenol for average weeks 0-12 peak FEV₁ or as much as 20.32% better and might be only 0.12% worse for average weeks 0-12 AUC FEV₁ but as much as 19.92% better than metaproterenol. The average weeks 0-12 peak FEV₁ improvement over pre-dose baseline were 29.79% and 26.85% for pirbuterol and metaproterenol respectively. The average weeks 0-12 AUC FEV₁ improvement over pre-dose baseline were 12.16% and 7.52% for pirbuterol and metaproterenol respectively.
4. Although the data is suggestive that some tolerance to chronic pirbuterol develops [see rank sums in table 7], the sponsor's analyses (some at the suggestion of the reviewer) did not detect any significant ($p < 0.05$) tachyphylaxis.


James R. Gebert, Ph.D.
Mathematical Statistician

cc: Orig. NDA 19-009
HFN-160 HFN-160/Dr. Nicklas
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Gebert
Chron. File: DRU 1.3.2 NDA
JRGebert/rp/njs/8/22/85 #1499r

Concur: Dr. Leung *H. L. 8/22/85*

Dr. Dubey MJ for SDD 8/22/85

TABLE (7)

FRIEDMAN'S ANOVA'S COMPARING ACUTE RESPONSES TO PIRBUTEROL ACROSS VISITS

Sum of Ranks Within Patient:

	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
Protocol A (N=33)							
Peak FEV-1	55.5	138	146.5	146	157	135	146
AUC FEV-1	71.5	138.5	146	154.5	148.5	129	136
3-Way Response							
FEV-1	74.5	145	140	152	146	128.5	138
Duration FEV-1	70.5	142.5	143.5	144.5	151	132.5	139.5
Protocol B (N=59)							
Peak FEV-1	210	265.5	246	230.5	255.5	216.5	228
AUC FEV-1	217.5	263	242	246.5	238	227.5	217.5
3-Way Response							
FEV-1	233	266	218.5	242	245.5	222	225
duration FEV-1	253	263	227	234.5	224.5	222	228

FRIEDMAN ANOVA CHI SQUARES:

	Protocol A		Protocol B	
	X ² (6)	Sig	X ² (6)	Sig
Peak FEV-1	46.26	<.001	9.08	0.17
AUC FEV-1	30.53	<.001	5.94	0.43
3-Way Response				
FEV-1	27.17	<.001	6.02	0.42
Duration FEV-1	29.86	<.001	5.42	0.49

SBA

Summary Basis of Approval

NDA-19,009

Drug Generic Name:
Pirbuterol Acetate

Applicant:
Pfizer, Inc.
Groton, Connecticut

Drug Trade Name:
EXIREL Inhaler

I. Indications for Use:

EXIREL Inhaler is indicated for the relief of acute bronchospasm in patients with chronic reversible obstructive airway disease (extrinsic asthma, intrinsic asthma and chronic bronchitis/emphysema).

II. Dosage form, route of administration and recommended dosage:

Metered dose aerosol, oral inhalation, for adults and children 12 years and older one inhalation (0.2 mg) or two inhalations (0.4 mg) repeated at 4-6 hour intervals depending upon response.

III. Manufacturing and Control:

Remains under review.

IV. Pharmacology:

A. Pirbuterol is a potent long-acting sympathomimetic bronchodilator with selectivity for pulmonary beta₂-adrenergic receptors. This selectivity has been demonstrated pharmacologically on isolated guinea pig tissue which showed a tracheal B₂/cardiac B₁ muscle selectivity index 9 times that of albuterol and 1500 times that of isoproterenol suggesting a greater safety margin for pirbuterol vis-a-vis cardiotoxicity. In conscious guinea pigs, pirbuterol antagonized both histamine and acetylcholine-induced bronchoconstriction and "microshock" anaphylaxis. Pirbuterol and other beta-adrenergic agonists antagonize the increase in cutaneous vascular permeability mediated by histamine released from mast cells via IgE (immunoglobulin E) but not that due to exogenous histamines. It is believed that this action is exerted by stabilizing mast cell membranes through cyclic AMP elevation.

B. Pirbuterol appears to be well absorbed following oral administration to man and to rats and dogs (the toxicology species). Peak human plasma concentrations are about 6 and 10 ng/ml after single oral administration of the recommended doses of 10 and 15 mg. At the highest doses of oral toxicology studies, peak plasma concentrations were 1600 and 240 ng/ml in dogs and rats, respectively. Drug is slowly absorbed in man, with peak concentrations at 2 to 3 hours; levels decline thereafter with a mean half-life of 2.2 hours. Thus, levels at 6 hours are generally still one-third to one-half of peak

concentrations. The profile of plasma concentrations in man does not change upon repeated administration of pirbuterol. These data are consistent with the duration of bronchodilator effect demonstrated in the oral clinical studies.

When administered to man by aerosol, plasma concentrations are below the limit of detection, as predicted by extrapolation from higher oral doses. This is consistent with the excellent toleration of pirbuterol aerosol in man in terms of systemic side effects. Drug appears to be well absorbed, however, with about 50 percent of the dose appearing in urine as drug plus metabolite. The presence of about half of the excreted material in the 6-24 hour urine suggests relatively slow absorption from the sites of deposition in the respiratory tree. This data parallels very closely the clinical results. Approximately 75% of patients were still displaying 70% of their peak effect at 4-5 hours. The duration of action of pirbuterol aerosol is significantly longer than that of metaproterenol. When administered by aerosol to rats, pirbuterol was deposited at high concentrations (100 x plasma) in the larynx, trachea, and lung. A similar pattern was seen in dogs.

Pirbuterol is metabolized in the rat by glucuronide conjugation and in the dog and man by sulfate conjugation. A considerable fraction of the dose is also excreted by all three species as unchanged pirbuterol. Drug and metabolite are cleared primarily via the feces of rats and the urine of dogs and man.

- C. Inhalation studies, designed to deliver daily doses of 200, 400 and 800 ug pirbuterol base/kg/day, representing approximately 10, 20 and 40 times the maximum anticipated daily human dose level (200 ug x 6), to dogs and monkeys for six months and to rats and rabbits in Segment II teratology studies, were free of adverse effects. These experiments were carried out by multiple actuations of the pirbuterol acetate (200 ug/puff) aerosol canisters developed for clinical use. The plasma levels attained were much less than those that were measured in the corresponding oral studies.

The oral acute toxicity of pirbuterol base administered as the dihydrochloride salt is greater than 2000 mg/kg in mice and rats providing greater than 2000 fold safety margins when compared to the human dose. Most deaths were acute, within 1, 20 or 40 minutes after intravenous, subcutaneous, or oral administration, respectively. There was no evidence of delayed toxicity. The ratios of intravenous to subcutaneous to oral LD₅₀ values are 1:7:60 in mice and 1:12:50 in rats. These data reflect the differences in the times of development of peak blood levels following these routes of administration.

The pharmacological effects of beta-adrenoreceptor stimulation such as hypotension, tachycardia, ptosis, muscular weakness were readily apparent in dose-related magnitude in oral and parenteral studies. These effects were not seen in inhalation studies because of the virtual absence of measurable blood levels.

The beta-sympathomimetic cardioactivity of pirbuterol dihydrochloride was demonstrated by tachycardia at all dose levels, 0.125 mg/kg and above, in 3-month and 1-year oral and in 30-day intravenous studies in dogs. Isolated instances of premature ventricular beats were noted electrocardiographically in 2/8 animals receiving 2 mg/kg/day orally and was probably related to the high plasma levels (>100 ng/ml) at this dose in the dog. Electrocardiograms were otherwise unremarkable.

In a one month rat study, extremely high oral dose levels of 500, 1500 and 4000 mg/kg/day caused slight increases in heart weight accompanied, in a few animals, by focal fibrosis of the myocardium. The lesions occurred in the subendocardium near the apex. In a one year rat study, similar changes were seen in 11/13 males at 300 mg/kg compared to 7/12 control males. The occurrence of focal myocardial fibrosis in the other groups (10, 30, 100 mg/kg) could not be distinguished from the age related incidence of this lesion in the control group. The "no effect level" of cardiotoxicity in that study was determined to be 30 mg/kg. The drug-related cardiac effects are considered to have resulted from primary and reflex cardiac beta-adrenoreceptor stimulation leading to increased cardiac rate and contractility. In rats, enlargement of the myocardial fibers and increased mass of the heart in response to the increased workload imposed by the hypotensive and other hemodynamic effects of the compound occurred following doses of 500 mg/kg and above for 1 month and 100 mg/kg in males for 1 year.

A moderate drug-related hyperkalemia occurred at all dose levels (1, 3 and 10 mg/kg/day) from three months onward in the one year dog study and in male rats in the one year study (10-300 mg/kg). It did not occur in the 2-year rat study in which the highest dose was 10 mg/kg. No electrocardiographic, postmortem histopathological or other chemical modifications were recorded which could explain whether the hyperkalemia was due to modifications in myocardial, renal or skeletal muscle metabolism.

Long-term safety and oncogenicity studies were carried out for 24 months in rats and 18 months in mice at 1, 3 and 10 mg/kg administered in the diet. In none of these studies was there evidence of tumorigenicity. Reports that other beta-adrenergic stimulants such as soterenol, mesuprine and salbutamol induce mesovarial leiomyomas prompted the microscopic re-evaluation of tissue sections of the mesovarial tissue of all females in the 24-month rat study. There was no evidence of mesovarial tumors in that study nor in a high dose 12 month oral (10, 30, 100, 300 mg/kg) rat study, whereas, such tumors have been reported at 12 months for salbutamol (20 mg/kg), mesuprine (40 mg/kg) and soterenol (10 mg/kg).

Pirbuterol dihydrochloride showed no evidence of mutagenic potential in a battery of in vitro and host-mediated microbial (*Ames*) assays for point mutation, and in in vivo tests for somatic cytogenetic or germ cell effects following acute and subacute treatment.

Segment I, II and III studies in rats at oral doses of 1, 3 and 10 mg/kg caused no adverse effects on fertility, litter size, upon fetal or maternal health or upon neonatal or postnatal viability of offspring. The only drug-related effect noted was a slight decrease in body weight gain of ten pregnant dams receiving 10 mg/kg pirbuterol in the Segment II study.

Additional reproductive and teratology studies were performed in rats at oral dose levels of 30, 100 and 300 mg/kg/day. These experiments further confirm the safety of pirbuterol when administered prior to mating, during pregnancy, parturition and lactation. Neurological and behavioral tests performed on F₁ offspring of pregnant dams treated during the period of organogenesis were normal. The growth, fertility and reproductive capacity of the F₁ generation was normal as was the in utero development of the F₂ fetuses.

In rabbit teratology studies, no drug-related malformation occurred in two oral studies conducted at 1, 3 and 10 mg/kg or in another employing doses of 30, 100 and 300 mg/kg. In the latter study, abortions and fetal mortality occurred at 300 mg/kg.

Hence, pirbuterol dihydrochloride, administered to laboratory animals in daily doses for periods up to two years in duration produced only effects attributable to exaggerated pharmacological stimulation of beta-adrenoreceptors in the cardiovascular system. There was no evidence of carcinogenicity, teratogenicity or of mutagenicity in any of the studies.

V. Medical:

A. General Information

EXIREL Inhaler (pirbuterol acetate, metered dose aerosol) sponsored by Pfizer, Inc. and studied under IND- is a beta-adrenergic agonist bronchodilator proposed for "the relief of acute broncho-spasm in patients with chronic reversible obstructive airway disease (extrinsic asthma, intrinsic asthma and chronic bronchitis/emphysema)". Pirbuterol belongs to the newer group of bronchodilators with a higher selectivity for pulmonary beta₂-adrenergic receptors compared to cardiac beta₁ receptors.

Pirbuterol has been marketed in England since 1983 in both the oral and aerosol form and in Japan since 1982 as the oral form. The drug has also been approved in both aerosol and oral forms for marketing in Switzerland, Ireland, Denmark and Italy, and in principle in Belgium and the Netherlands. Registration submissions have been filed or are imminent in eight additional European countries. There have been numerous publications in the medical literature on the use of pirbuterol by oral and aerosol delivery for the treatment of reversible obstructive respiratory disease.

B. Adequate and well-controlled studies providing evidence of efficacy and safety:

Approach to Data Analysis

Graphic representation of group means across time for individual parameters was not employed for efficacy display. This tends to distort drug effect since the kinetics of response are not identical for all patients in a group.

Definitions which are key to the analysis of efficacy are:

- i. FEV₁ was the primary efficacy parameter used and a clinically significant drug effect was defined as an improvement over baseline of $\geq 15\%$ (FEV₁). In addition many studies also used MMF and/or plethysmography. A clinically significant improvement in these latter parameters was considered to be $\geq 20\%$ (MMF) and $\geq 20\%$ GA/V_{tg}.
- ii. Responder:
To be considered a responder, a patient was required to have achieved a clinically significant response ($\geq 15\%$ FEV₁) on at least three consecutive occasions following drug. Mean peak response is shown a) for responders and b) for all patients both responders and non-responders.
- iii. Onset of effect:
Defined as the first point in time at which a clinically significant effect ($\geq 15\%$ FEV₁) is seen - providing that the subsequent two spirometric readings also show a clinically significant effect.
- iv. Duration of effect:
Determined by that point in time at which two consecutive spirometric readings fall below clinically significant levels of improvement ($\geq 15\%$ FEV₁).

SINGLE DOSE STUDIES

Seven adequate and well-controlled studies followed a similar protocol and compared two doses (0.2 mg, 0.4 mg) of pirbuterol aerosol with metaproterenol 1.3 mg and placebo. The patterns of statistical significance seen in these individual studies were consistent in establishing efficacy for pirbuterol relative to placebo. In comparative terms pirbuterol was comparable or superior to metaproterenol:

1. DOUBLE-BLIND, SINGLE DOSE, CROSSOVER COMPARATIVE STUDY OF PIRBUTEROL ACETATE AEROSOL, PLACEBO AND METAPROTERENOL AEROSOLS. Dr. S. Chodosh, Boston City Hospital, Boston, Massachusetts 02-2

- a. TYPE OF STUDY** A single dose randomized double-blind comparative crossover study of pirbuterol, metaproterenol and placebo.
- b. NUMBER OF PATIENTS** Twenty-six of whom 24 were used in the efficacy analysis.
- c. AGE AND SEX** Thirteen females (43 to 66 years)
Thirteen males (35 to 68 years)
- d. DISEASE STUDIED** COPD (mild, moderate and severe):
extrinsic asthma (8)
intrinsic asthma (10)
chronic bronchitis with or without emphysema (8)
- e. PURPOSE OF THE STUDY**
- To determine the bronchodilator efficacy of pirbuterol acetate aerosol.
 - To compare this effect to that of placebo and metaproterenol aerosols.
 - To determine effects relative to the laboratory and CVS parameters and side effects compared to placebo and metaproterenol.

f. EFFICACY

In FEV₁, pirbuterol was significantly superior to placebo in peak effect for both 0.2 and 0.4 mg ($p < 0.01$); AUC ($p < 0.001$ for 0.2 mg and $p < 0.01$ for 0.4 mg). For 0.2 mg the number of responders was 15 (63%) with peak of 24%. For 0.4 mg the number of responders was 12 (48%) with a peak of 22%.

In MMF 0.2 mg and 0.4 mg was superior to placebo in peak effect ($p < 0.01$ and $p < 0.05$ respectively); for AUC ($p < 0.05$ for 0.2 mg and $p < 0.001$ for 0.4 mg). For 0.2 mg, the number of responders was 12 (50%) with a peak of 36%. For 0.4 mg the number of responders was 12 (48%) with a peak of 32%.

Pirbuterol 0.2 mg was nearly significantly superior to 1.3 mg metaproterenol in FEV₁ and MMF, AUC effect ($p < 0.10$). Pirbuterol 0.4 mg showed significance over metaproterenol in MMF, AUC effect ($p < 0.01$).

Onset of action for both active drugs was within 5 minutes. Duration of action of pirbuterol (median 295 minutes) was one hour longer than metaproterenol (median 230 minutes).

The spirometry results were supported by the subjective ratings. The overall average post-dose patient self-ratings on each test day were higher for pirbuterol than placebo. The investigator global evaluation was also significant as compared to placebo ($p < 0.001$) for both doses of pirbuterol.

This study shows pirbuterol to possess a selective effect in relieving acute bronchoospasm, this effect was superior to that of metaproterenol in terms of degree and duration of response (5 hours for pirbuterol and 3.5 hours for metaproterenol).

Pirbuterol was well tolerated and was free from adverse CVS or laboratory parameter effects.

g. RESULTS

CVS: Relative to placebo and metaproterenol, pirbuterol evidenced no clinically significant effect on blood pressure and pulse rate.

No effects on EKG.

Continuous Holter Monitoring: Sixteen patients had continuous Holter monitoring on all test days from 0 to 5-6 hours post dose. There was no increase in the total count of ectopics from pre-dose to post-dose after any treatment.

Laboratory Parameters. No significant effect on laboratory parameters.

Side Effects. Rash, itching, dizziness and blurred vision. Similar incidence was reported for metaproterenol with headache, as the main complaint.

2. DOUBLE-BLIND, SINGLE DOSE, CROSSOVER COMPARATIVE STUDY OF PIRBUTEROL ACETATE AEROSOL, PLACEBO AND METAPROTERENOL AEROSOLS. Dr. M.H. Grieco, Roosevelt Hospital, New York 47-1

a. TYPE OF STUDY

A single dose randomized double-blind comparative crossover study of pirbuterol, metaproterenol and placebo.

b. NUMBER OF PATIENTS

Twenty-six of whom 24 were used in the efficacy analysis.

c. AGE AND SEX

Twelve females (27 to 80 years)
Fourteen males (30 to 89 years)

d. DISEASE STUDIED

COPD (mild, moderate and severe):
extrinsic asthma (8)
intrinsic asthma (10)
chronic bronchitis with or without emphysema (8)

e. PURPOSE OF THE STUDY

- To determine the bronchodilator efficacy of pirbuterol aerosol.
- To compare this effect to that of placebo and metaproterenol aerosols.
- To determine effects relative to the laboratory and CVS parameters and side effects compared to placebo and metaproterenol.

f. EFFICACY

In FEV₁, the 0.2 mg and 0.4 mg pirbuterol was significantly superior to placebo ($p < 0.001$). Peak FEV₁ was 29% for both doses of pirbuterol. The number of responders to 0.4 and 0.2 mg was 70% and 50% respectively. For AUC 0.2 and 0.4 mg achieved significances of $p < 0.01$ and $p < 0.01$ respectively over placebo.

In MMF 0.2 mg pirbuterol was superior to placebo ($p < 0.001$) for peak effect (32%), number of responders (71%) and AUC. 0.4 mg was significant ($p < 0.001$) for peak effect (43%).

Pirbuterol 0.2 and 0.4 mg were significantly superior to 1.3 mg metaproterenol ($p < 0.05$) for peak FEV₁ and MMF, AUC respectively.

Onset of effect for both active medications was within 5 minutes. The median duration of action of pirbuterol was 200 minutes, approximately one hour longer than metaproterenol (median 235 minutes).

The spirometry results were supported by the subjective ratings. Patient self-rating showed pirbuterol 0.2 mg and 0.4 mg superior to placebo ($p < 0.05$).

Investigator global evaluation showed similar results for 0.2 mg ($p < 0.01$) and 0.4 mg ($p < 0.05$).

This study shows pirbuterol to possess a selective effect in relieving bronchospasm.

Effects are superior to those of metaproterenol. Onset of effect is prompt with a sustained duration of action.

Pirbuterol is well tolerated and free from adverse CVS or laboratory parameter effects.

g. RESULTS

CVS: Relative to placebo, no evidence of a clinically significant effect on blood pressure or pulse rate for pirbuterol or metaproterenol.

No effects on EKG.

Laboratory Parameters. No significant effect on laboratory parameters.

Side Effects. Cough noted with active medication but also present with placebo.

3. DOUBLE-BLIND, SINGLE DOSE, CROSSOVER CONTROLLED STUDY OF PIRBUTEROL ACETATE AEROSOL AND PLACEBO AEROSOL Dr. D. Tashkin, UCLA 46-2

a. TYPE OF STUDY

A single dose randomized double-blind comparative crossover study of pirbuterol acetate and placebo aerosols.

b. NUMBER OF PATIENTS

Twenty-six of whom 24 were used in the efficacy analysis.

c. AGE AND SEX

Three females (50 to 65 years)
Twenty three males (18 to 85 years);

d. DISEASE STUDIED

Bronchial asthma and bronchial asthma associated with chronic bronchitis.

e. PURPOSE OF THE STUDY

- To determine the bronchodilator efficacy and dose response relationships of pirbuterol acetate aerosol.
- To compare this effect to that of placebo.
- To measure the plasma levels and urinary excretion of the drug.
- To determine effects relative to the laboratory and CVS parameters and side effects compared to placebo.

f. RESULTS

CVS: Relative to placebo, there was no evidence of a clinically significant effect on blood pressure and pulse rate.

No effects on / EKG.

Continuous Holter Monitoring. Twenty four patients had continuous Holter monitoring for one hour before and 6-7 hours post-dose on each test day. Relative to placebo there was no evidence of drug induced arrhythmic activity for any of the doses of pirbuterol. Isoproterenol showed a significant ($p < 0.05$) arrhythmic (increase in ectopic activity) effect.

Laboratory Parameters. No significant effect on laboratory parameters.

Side Effects. Only few scattered incidences of mostly mild to moderate side effects were reported; all were tolerated.

At the 0.2 mg dose there was only one incidence of mild chest tightness and pressure.

At the 0.4 mg dose there were two incidences of headache and one incidence of nervousness; all were mild in severity.

No side effects were reported at the 0.8 mg dose.

Pharmacokinetics/Metabolism: Plasma and urine samples analyzed from six subjects after administration of 800 mcg of pirbuterol aerosol showed plasma levels below the limit of detection for all six subjects (2.5 ng/ml). However, the mean overall urinary recovery for free pirbuterol and pirbuterol conjugate in the 0-24 hour collections was 50.9% of the dose. This level was not different from that of oral pirbuterol.

Efficacy. All doses of 0.1, 0.2, 0.3, 0.4, 0.6 and 0.8 mg pirbuterol were statistically significantly superior to placebo ($p < 0.001$) for most measures as determined by FEV₁ and MMF data.

Clinically, all doses of pirbuterol were superior to placebo both in terms of number of responders and degree of response. A clear dose response pattern was seen as the dose was increased from 0.1 mg to 0.4 mg with a plateauing of effect beyond 400 mg. Response to the lower doses of pirbuterol was equal to isoproterenol while response to higher doses was greater.

The onset of action was 5 minutes after administration, peaked at approximately 30 minutes and lasted for a median duration of 235 minutes.

In this study pirbuterol at optimum doses of 200-400 mg demonstrated a selective effect in relieving acute bronchoospasm associated with bronchial asthma as supported by the lack of an increase in and severity of ectopic beats, and an absence of tachycardia after single dose administration. These results are supported by the absence of detectable serum levels of pirbuterol.

4. DOUBLE-BLIND, SINGLE DOSE, CROSSOVER COMPARATIVE STUDY OF PIRBUTEROL ACETATE AEROSOL, PLACEBO AND METAPROTERENOL AEROSOLS. Dr. R. Pariente, Clichy, France 31-4

- a. TYPE OF STUDY** A single dose randomized double-blind comparative crossover study of pirbuterol acetate aerosol, placebo and metaproterenol aerosols.
- b. NUMBER OF PATIENTS** Twenty-four patients
- c. AGE AND SEX** Four females (50 to 61 years)
Twenty males (31 to 62 years)
- d. DISEASE STUDIED** Intrinsic asthma (8)
Extrinsic asthma (8)
Chronic bronchitis with emphysema (8)
- e. PURPOSE OF THE STUDY**
- To determine the bronchodilator efficacy of pirbuterol acetate aerosol.
 - To compare this effect to that of placebo and metaproterenol aerosols.
 - To determine effects relative to the laboratory and CVS parameters and side effects compared to placebo and metaproterenol.
- f. RESULTS**
- CVS:** No clinically significant changes were seen in the diastolic and systolic blood pressures after pirbuterol.
- Few cases of clinically significant increases (>10 beats/minute) in pulse rate were seen after pirbuterol, placebo and metaproterenol. No effects on electrocardiograms.
- Laboratory Parameters.** No significant effect on laboratory parameters.
- Side Effects.** No side effects were reported in this study.
- Efficacy.** Pirbuterol 0.4 mg was significantly superior to placebo ($p < 0.001$) in all measures of efficacy: FEV₁, MMF and G_AN_{1g} peak, AUC and number of responders.
- In FEV₁, for both 0.2 and 0.4 mg the number of responders (74 and 88%) and peak responses (31 and 30%) were superior to placebo. MMF, for both doses of pirbuterol the number of responders (65 and 79%) and peaks (46 and 80%) were also superior to placebo. In G_AN_{1g}, for both doses of pirbuterol the number of responders (65 and 85%) and peaks (85 and 121%) were superior to placebo.
- Pirbuterol 0.4 mg was superior to metaproterenol ($p < 0.05$) in peak G_AN_{1g} and nearly reached significance ($p < 0.10$) in average G_AN_{1g} effect and in FEV₁ duration of effect.

The spirometry results were supported by subjective ratings: the overall post-dose patient self-rating and the investigator global assessment were significantly superior to placebo ($p < .001$).

The onset of action of pirbuterol and metaproterenol was within 5 minutes of administration, however, the duration of effect for pirbuterol was half an hour longer than for metaproterenol.

Selectivity was demonstrated for pirbuterol based on a lack of adverse CVS effects coupled with concomitant relief of acute bronchospasm.

Pirbuterol was very well tolerated.

5. DOUBLE-BLIND, SINGLE DOSE, CROSSOVER COMPARATIVE STUDY OF PIRBUTEROL ACETATE AEROSOL, PLACEBO AND METAPROTERENOL AEROSOLS. Dr. J. Charpin, Marseille France 96-1

- a. TYPE OF STUDY** A single dose double-blind randomized crossover comparative study of pirbuterol, metaproterenol and placebo aerosols.
- b. NUMBER OF PATIENTS** Twenty-four patients
- c. AGE AND SEX** Eight females (17 to 58 years)
Sixteen males (30 to 61 years)
- d. DISEASE STUDIED** Intrinsic asthma (8)
Extrinsic asthma (8)
Chronic bronchitis with and without emphysema (8)
- e. PURPOSE OF THE STUDY**
- To determine the bronchodilator efficacy of pirbuterol acetate aerosol.
 - To compare this effect to that of placebo and metaproterenol aerosols.
 - To determine effects relative to the laboratory and CVS parameters and side effects compared to placebo and metaproterenol.
- f. RESULTS**
- CVS:** There were scattered increases and decreases (≥ 10 mmHg) in supine systolic and diastolic blood pressures seen after both drugs and placebo, no specific pattern.
- A few incidences of increases in post-dose average pulse rates were seen after pirbuterol.
- No effects on the electrocardiograms.
- Laboratory Parameters.** No significant effect on laboratory parameters.

Side Effects. No side effects were reported after any of the active treatments or placebo.

Efficacy. Pirbuterol 0.4 mg was significantly superior to placebo ($p < 0.05$) in FEV₁, peak, average effect and number of responders. The same level of significance was also reached in average MMF.

In FEV₁, for both 0.2 and 0.4 mg, the number of responders (75 and 75%) and peak responses (40 and 30%) were superior to placebo. In MMF for both doses of pirbuterol the peak response was only slightly higher than placebo (19 and 18%). The number of responders for both doses, however, was higher than placebo (33 and 29%).

Pirbuterol 0.4 mg was superior to metaproterenol 1.3 mg in FEV₁, peak response (nearly significant; $p < 0.10$), and clinically in the number of responders in terms of FEV₁.

The onset of action for both pirbuterol and metaproterenol was within 5 minutes of administration. The duration of action in this study for both active medications was 295 minutes.

The response in spirometry was supported by subjective ratings: the overall post-dose patient self-rating reached significance against placebo ($p < 0.01$). The investigator global evaluation after pirbuterol also reached significance against placebo ($p < 0.05$); metaproterenol did not.

Pirbuterol proved to be a selective active bronchodilator, well tolerated and free from adverse CVS or laboratory parameter effects.

6. DOUBLE-BLIND, SINGLE DOSE, CROSSOVER COMPARATIVE STUDY OF PIRBUTEROL ACETATE AEROSOL, PLACEBO AND METAPROTERENOL AEROSOLS. Dr. Y. Salorinne, Helsinki, Finland 66-2

- | | |
|------------------------------|--|
| a. TYPE OF STUDY | A single dose double-blind randomized crossover comparative study of pirbuterol, metaproterenol and placebo. |
| b. NUMBER OF PATIENTS | Twenty-four patients |
| c. AGE AND SEX | Fifteen females (36 to 67 years)
Nine males (44 to 71 years) |
| d. DISEASE STUDIED | Intrinsic asthma (8)
Extrinsic asthma (9)
Chronic bronchitis with emphysema (7) |

e. PURPOSE OF THE STUDY

- To determine the bronchodilator efficacy of pirbuterol acetate aerosol.
- To compare this effect to that of placebo and metaproterenol aerosols.
- To determine effects relative to the laboratory and CVS parameters and side effects compared to placebo and metaproterenol.

f. RESULTS

CVS: Compared to metaproterenol, no evidence of a clinically significant effect on blood pressure and pulse rate after pirbuterol.

No effects on EKG.

Laboratory Parameters. No significant effect on laboratory parameters.

Side Effects. Only one side effect (rash) was reported after one of the two administrations of 0.4 mg and reported also on the test day prior to metaproterenol.

Efficacy. In FEV₁, pirbuterol 0.4 mg was significantly superior to placebo in peak and average responses ($p < 0.001$).

For 0.4 mg pirbuterol, the number of FEV₁ responders was 58% with a peak of 31%. In MMF, the number of responders was 25% with a peak of 3%.

Metaproterenol achieved the same significance against placebo in all but one measure — the patient self-assessment. For this parameter the statistical significance was more powerful for pirbuterol than for metaproterenol.

In this study the subjective measurements of patient self-rating and investigator global evaluation reached a high level of significance for pirbuterol 0.4 mg against placebo ($p < 0.001$).

Pirbuterol was equal to metaproterenol in terms of FEV₁ clinical response. The onset of action for both active medications was within 10 minutes of administration. No 5 minute measurement was taken in this study. The duration of action for both medications was up to 4 hours with 70% of patients still responding at 4 hours to both active medications.

Pirbuterol was well tolerated and was free from adverse CVS or laboratory parameter effects.

7. DOUBLE-BLIND, SINGLE DOSE, CROSSOVER COMPARATIVE STUDY OF PIRBUTEROL ACETATE AEROSOL, PLACEBO AND METAPROTERENOL AEROSOLS. Dr. Y. Salorinne, Helsinki, Finland 66-1

- a. TYPE OF STUDY** A single dose double-blind randomized crossover comparative study of pirbuterol, metaproterenol and placebo.
- b. NUMBER OF PATIENTS** Twenty-four patients
- c. AGE AND SEX** Twelve females (28 to 68 years)
Twelve males (38 to 71 years)
- d. DISEASE STUDIED** Bronchial asthma (type unspecified) (19),
Asthma associated with chronic bronchitis (5)
- e. PURPOSE OF THE STUDY**
- To determine the bronchodilator efficacy of pirbuterol acetate aerosol.
 - To compare this effect to that of placebo and metaproterenol aerosols.
 - To determine effects relative to the laboratory and CVS parameters and side effects compared to placebo and metaproterenol.

f. RESULTS

CVS: Compared to metaproterenol and placebo, no evidence of a clinically significant effect on blood pressure and pulse rate after pirbuterol.

No effects on EKG.

Laboratory Parameters. No significant effect on laboratory parameters.

Side Effects. No side effects were reported in this study.

Efficacy. Pirbuterol 0.4 mg was significantly superior to placebo in FEV₁, number of responders, peak and average responses ($p < 0.001$). In MMF pirbuterol was superior to placebo in number of responders ($p < 0.05$) and in average response ($p < 0.01$).

For pirbuterol 0.4 mg, the number of responders in FEV₁ was 63% with a peak of 42%. In MMF, the number of responders was 58% with a peak of 48%.

This objective response was supported by subjective patient self-rating which reached significance ($p < 0.001$).

Pirbuterol was superior to metaproterenol in only peak MMF response (nearly significant $p < 0.10$).

The onset of action was seen at 10 minutes within administration, however, in this study there was no 5 minute measurement taken. The duration of action for both drugs was up to 4 hours. 80% of the pirbuterol patients and 84% of metaproterenol patients were still responding at 4 hours.

Pirbuterol was well tolerated, no side effects were reported and no adverse CVS or laboratory parameter effects were seen.

MULTIPLE DOSE STUDIES

Data on the efficacy and safety of the continuous administration of pirbuterol aerosol were provided by five adequate and well controlled studies of three months duration. The five adequate and well-controlled studies followed a similar protocol and compared pirbuterol aerosol with metaproterenol over a three month period. Synopses of the study summaries of these five studies follow:

1. MULTICENTER, MULTIPLE DOSE, DOUBLE-BLIND, (3 MONTHS) PARALLEL COMPARISON OF PIRBUTEROL ACETATE AND METAPROTERENOL AEROSOLS. Drs. M. Brandon, M. Grieco, D. Pierson, R. Rosenthal, D. Tashkin, D. Tinkleman, and B. Votteri. 13-5, 47-2, 32-1, 35-1, 46-3, 15-1, 20-6. (Protocol A)

- a. TYPE OF STUDY** A multiple-dose randomized double-blind comparative parallel study of pirbuterol acetate and metaproterenol aerosols. The duration of study was 12 weeks of double-blind therapy following a washout period of at least one week of placebo.
- b. NUMBER OF PATIENTS** A total of 82 — (34 pirbuterol and 28 metaproterenol).
- c. AGE AND SEX** females (23 to 72 years)
males (20 to 74 years)
- d. DISEASE STUDIED** COPD (mild, moderate, and severe)
Extrinsic asthma: 22 (13 pirbuterol and 9 metaproterenol)
Intrinsic asthma: 18 (10 pirbuterol and 8 metaproterenol)
Chronic bronchitis with or without emphysema: 22 (11 pirbuterol and 11 metaproterenol)
- e. PURPOSE OF THE STUDY** To address the questions of chronic efficacy, tolerance development and safety of multiple doses of pirbuterol acetate aerosol.
- f. DOSAGE** Pirbuterol 0.4 mg q.i.d.
Metaproterenol 1.3 mg q.i.d.
- g. RESULTS**
Safety
CVS: 12 lead EKGs did not show any drug-related abnormalities throughout the 12 weeks of therapy.
The ectopic beat counts, PVCs and PACs, in the 12 lead EKGs and the one minute lead II rhythm strips did not show increase in frequency after pirbuterol administration.

There were no clinically or statistically significant changes in standing diastolic blood pressure and pulse rate following the morning doses of pirbuterol throughout the 12 weeks of double-blind therapy as taken from the measurements at each office visit.

Side Effects: The number and severity of side effects reported during pirbuterol therapy were minimal and mild in comparison to metaproterenol.

Laboratory Parameters: No significant drug-related effects were seen in blood chemistry, hematology, hepatic, and renal functions.

Efficacy

Chronic Comparative Efficacy: In this study pirbuterol was clinically more effective than metaproterenol in all parameters. One parameter reached statistical significance in favor of pirbuterol; average FEV₁ (AUC) across all visits ($p > 0.05$).

Tolerance Development:

Subjective — Patient self-assessment did not show statistically significant change across time for either pirbuterol (34 patients) or metaproterenol (28 patients), and there was no statistically significant difference between the two drugs.

Investigator global evaluation did not show statistically significant change across time ($p > 0.20$).

Objective — Investigator's Spirometry Measurements:

FEV₁: There was no evidence of deterioration in response across 12 weeks of therapy in terms of number of responders, median peak improvement, AUC and duration of response. 31/32 patients continued to respond and did not show tolerance over time.

FEF₂₅₋₇₅: There was no evidence of deterioration in response across time in number of responders or median peak response for either drug.

Patients' Measurements:

PEFR: The weekly average 30 minutes postmorning dose improvements over baseline values on the same days were increased across the 12 weeks of therapy. The same values for metaproterenol, although maintained over the 12 week therapy period, showed no trend increase.

2. MULTICENTER, MULTIPLE DOSE, DOUBLE-BLIND, (3 MONTHS) PARALLEL COMPARISON OF PIRBUTEROL ACETATE AND METAPROTERENOL AEROSOLS. Drs. M. Brandon, M. Grleco, R. Rosenthal, S. Spector, D. Pierson, D. Tashkin, D. Tinkleman, and B. Votteri. 13-5, 47-2, 35-1, 09-5, 32-1, 46-3, 15-1, 20-6. (Protocol B)

- a. TYPE OF STUDY** A multiple-dose double-blind comparative parallel study of pirbuterol acetate and metaproterenol aerosols. The duration was 12 weeks of double-blind therapy following a washout period of at least one week of placebo.
- b. NUMBER OF PATIENTS** A total of 133 patients (66 pirbuterol and 67 metaproterenol).
- c. AGE AND SEX** Females (23-73)
Males (18-73)
- d. DISEASE STUDIED** COPD (mild, moderate, and severe).
- e. PURPOSE OF THE STUDY** To address the questions of chronic efficacy, tolerance development and safety of multiple doses of pirbuterol acetate aerosol.
- f. DOSAGE** Pirbuterol 0.4 mg q.i.d.
Metaproterenol 1.3 mg q.i.d.
- g. RESULTS**
- CVS:** 12 lead EKGs did not show any drug-related abnormalities throughout the 12 weeks of therapy.
- The ectopic beat counts (PVCs and PACs) in the 12 lead EKGs and the one minute lead II rhythm strips showed no increase postdose except in a few patients after both pirbuterol and metaproterenol.
- In these patients the increase was not clinically significant.
- There was neither a statistically nor clinically significant decrease in the overall average standing diastolic blood pressure or increase in pulse rates from 0 to 40 minutes postdose.
- Side Effects:** The 12 week therapy with pirbuterol was associated with only mild to moderate side effects, mainly of the CNS type (headache, nervousness). Only one patient from the pirbuterol group and one patient from the metaproterenol group were discontinued because of side effects.
- Efficacy**
- Chronic Comparative Efficacy.** Pirbuterol was clinically comparable to metaproterenol in all efficacy parameters except the peak FEV₂₀ at week 12. In this parameter pirbuterol showed superiority.
- Statistically there was no difference between the 2 drugs. However in one parameter (average 0-12 weeks FEV₁) pirbuterol nearly reached significance ($p = 0.06$) over metaproterenol.

Tolerance Development:

Subjective:

Patients' Self-Assessment: There was no statistically significant change in the average post-treatment values across time for either drug.

Investigator's Global Evaluation: As judged by the investigator, the pirbuterol group averaged better than metaproterenol in the average individual values from week 0 to week 12. The linear trend for this period reached a statistically significant increase for pirbuterol only, ($p > 0.05$).

Objective

Investigator's Spirometry Measurements:

FEV₁: There was no statistically significant trend toward a decrease in response to pirbuterol across the 12 weeks of therapy. This was seen in terms of number of responders, median peak, and AUC. 55/59 patients continued to respond and did not show tolerance over time.

FEF₂₅₋₇₅: There was no evidence of decrease in response across time in number of responders, peak, and AUC.

Patients' Measurements:

PEFR: The weekly average 30 minute post-morning dose improvement over the baseline value showed a dramatic increase from the single-blind placebo period (week 0) to the first dose of active pirbuterol treatment. This improvement continued to be maintained across time (12 weeks of therapy). The overall average improvement for pirbuterol was superior to that of metaproterenol (52.3 L/minute as compared to 22.4 L/minute respectively).

3. MULTIPLE DOSE, DOUBLE-BLIND, (3 MONTHS) PARALLEL COMPARISON OF PIRBUTEROL ACETATE AND METAPROTERENOL AEROSOLS. Dr. I.L. Bernstein 14-4

- | | |
|------------------------------|---|
| a. TYPE OF STUDY | A multiple-dose randomized double-blind comparative parallel study of pirbuterol acetate and metaproterenol aerosols. The duration was 12 weeks of double-blind therapy following a washout period of at least one week of placebo. |
| b. NUMBER OF PATIENTS | A total of 41 patients; 20 in the pirbuterol group and 21 in the metaproterenol group. |
| c. AGE AND SEX | Females (33 to 73 years)
Males (32 to 65 years) |
| d. DISEASE STUDIED | COPD (mild, moderate, and severe)

Extrinsic asthma: 13 (7 pirbuterol and 6 metaproterenol)

Intrinsic asthma: 15 (7 pirbuterol and 8 metaproterenol) |

Chronic bronchitis with or without emphysema: 13 (6 pirbuterol and 7 metaproterenol)

e. PURPOSE OF THE STUDY

To address the questions of chronic efficacy, tolerance development and safety of multiple doses of pirbuterol acetate aerosol.

f. DOSAGE

Pirbuterol 0.4 mg q.i.d.
Metaproterenol 1.3 mg q.i.d.

g. RESULTS

CVS: 12 lead EKGs did not show any drug-related abnormalities throughout the 12 weeks of therapy.

The analysis of ectopic beat counts (PVCs and PACs) showed no increase following administration of pirbuterol.

There was no clinically or statistically significant change in standing diastolic blood pressure or pulse rate after either pirbuterol or metaproterenol.

Side Effect: Five of 20 patients on pirbuterol reported 9 incidences of side effects. Three of 21 patients on metaproterenol reported 3 incidences. All side effects were mild or moderate. No patients in either drug group were discontinued from therapy because of the side effects.

Efficacy

Chronic Comparative Efficacy. Clinically there was no difference in efficacy between pirbuterol and metaproterenol. In one efficacy parameter (peak MEFR at week 12) pirbuterol showed a higher response than metaproterenol.

There was no statistically significant difference between the drugs except that average peak MEFR at weeks 2 to 12 nearly reached significance in favor of pirbuterol ($p = 0.08$) over metaproterenol.

Tolerance Development:

Subjective:

Patients' Self-Assessment. The results showed no statistically significant change ($p > 0.20$) in the average post-treatment values across time for either pirbuterol or metaproterenol. There was no deterioration over time.

Investigator's Global Evaluation. There was no indication of tolerance development to either pirbuterol or metaproterenol by this measure. For both treatments there was a continued improvement in response across time which was statistically significant ($p < 0.01$).

Objective:

Investigator's Spirometry Measurements:

FEV₁: Except for week 10, there was a clinically significant improvement in FEV₁, number of responders, peak, and AUC over time. 12/13 pirbuterol patients maintained their response over time. 13/15 metaproterenol patients maintained their response over time.

MEFR: As with FEV₁, there was no evidence of deterioration in number of responders and peak response over time.

Patients' Measurements:

PEFR: There was an improvement in the weekly average PEFR from week 0 to week 1 and this improvement was maintained over the 12 weeks of therapy.

4. MULTIPLE DOSE, DOUBLE-BLIND, (3 MONTHS) PARALLEL COMPARISON OF PIRBUTEROL ACETATE AND METAPROTERENOL AEROSOLS. Dr. H.M. Beumer, (Utrecht, The Netherlands) 21-8

- a. TYPE OF STUDY** A multiple-dose randomized double-blind comparative parallel study of pirbuterol acetate and metaproterenol aerosols. The duration was 12 weeks of double-blind therapy following a washout period of at least one week of placebo.
- b. NUMBER OF PATIENTS** A total of 38 patients; 19 in the pirbuterol group and 19 in the metaproterenol group.
- c. AGE AND SEX** All males (40 to 76 years)
- d. DISEASE STUDIED** COPD (all except one patient moderate in severity)
Extrinsic asthma: 12 (6 pirbuterol and 6 metaproterenol)
Intrinsic asthma: 12 (6 pirbuterol and 6 metaproterenol)
Chronic bronchitis: 14 (7 pirbuterol and 7 metaproterenol)
- e. PURPOSE OF THE STUDY** To address the questions of chronic efficacy, tolerance development and safety of multiple doses of pirbuterol acetate aerosol.
- f. DOSAGE** Pirbuterol 0.4 mg q.i.d.
Metaproterenol 1.3 mg q.i.d.
- g. RESULTS** CVS: 12 lead EKGs did not show any drug-related abnormalities throughout the 12 weeks of therapy.

An analysis of ectopic beat counts (PVCs and PACs) showed no evidence of a drug related effect for either compound.

Side Effects: There were no side effects associated with chronic pirbuterol therapy while two side effects were reported in the metaproterenol group — tremors and cough.

Efficacy

Chronic Comparative Efficacy. Clinically, metaproterenol achieved slightly higher values in MEFR peak and AUC at week 12 and across all clinic visits (weeks 3-12). None of these differences, however, reached statistical significance.

Tolerance Development:

Subjective Parameters:

Patients' Self-Assessments. The overall slopes of the average post-dose values for each patient reflect a slight decreasing trend across time; both drugs were similar in this respect. The trend was neither statistically ($p < 0.20$), nor clinically significant for either pirbuterol or metaproterenol.

Objective:

FEV₁: Both pirbuterol and metaproterenol effected clinically significant bronchodilation. There was no evidence of deterioration in efficacy across time in terms of number of patients responding and median peak improvement. There were no statistically significant differences in these responses between the two drugs.

MEFR: As with FEV₁, there was no evidence of deterioration in number of responders and median peak response for either drug.

PEFR: The average weekly improvement following the morning dose for pirbuterol remained constant across time; that for metaproterenol tended to decrease across time but did not reach statistical significance ($p > 0.10$). The difference between the two drug groups in this respect almost attained statistical significance ($p = 0.06$) in favor of pirbuterol.

**5. MULTIPLE DOSE, DOUBLE-BLIND, (3 MONTHS)
PARALLEL COMPARISON OF PIRBUTEROL ACETATE AND
METAPROTERENOL AEROSOLS. Dr. R. Schindl, (Linz,
Austria) 63-3.**

a. TYPE OF STUDY

A multiple-dose randomized double-blind comparative parallel study of pirbuterol acetate and metaproterenol aerosols. The duration was 12 weeks of double-blind therapy following a washout period of at least one week of placebo.

**b. NUMBER
OF PATIENTS**

A total of 36 patients; 18 in each of the pirbuterol and metaproterenol groups.

c. AGE AND SEX

Females: 5 (43-70 years)
Males (32-75 years)

d. DISEASE STUDIED

COPD (moderate and severe)

Extrinsic asthma: 12 (6 pirbuterol and 6 metaproterenol)

Intrinsic asthma: 12 (6 pirbuterol and 6 metaproterenol)

Chronic bronchitis: 12 (6 pirbuterol and 6 metaproterenol)

**e. PURPOSE OF
THE STUDY**

To address the questions of chronic efficacy, tolerance development and safety of multiple doses of pirbuterol acetate aerosol.

f. DOSAGE

Pirbuterol 0.4 mg q.i.d.
Metaproterenol 1.3 mg q.i.d.

g. RESULTS

CVS: 12 lead EKGs did not show any drug-related abnormalities throughout the 12 weeks of therapy.

Blood Pressure and Pulse Rate: Supine blood pressure and pulse rate showed no changes of clinical relevance.

Side Effects: Side effects were tolerated without interruption of dosage. The incidence was consistently higher in the metaproterenol than in the pirbuterol group, 17 and 11 respectively. For tremor and for tachycardia/palpitations, the difference reached statistical significance ($p < 0.05$) in favor of pirbuterol.

Efficacy

Chronic Comparative Efficacy. The two drugs were both clinically and statistically comparable in terms of all chronic efficacy measures.

Tolerance Development:

Subjective:

Patients' Self-Assessments. The weekly averaged values for each patient in the pirbuterol group showed some improvement in breathing for each week but this was not statistically significant ($p > 0.20$) across time. The metaproterenol data reflect some improvement in breathing for each week; however, there is evidence of significant ($p < 0.02$) overall deterioration in effect across time. The difference between pirbuterol and metaproterenol treated groups approaches statistical significance at $p = 0.053$ in favor of pirbuterol.

Investigator's Global Assessments. The average values for the patients in the pirbuterol group reflect improvement at each time point (weeks 3, 6, 9, and 12) and a tendency to increase across time (average 3.3 at week 3 and 2.7 at week 12). This tendency to increase across time was not statistically significant ($p > 0.10$).

However the average values for the metaproterenol group reflect statistically significant ($p < 0.02$) deterioration across time. The difference between the two groups is highly significant ($p < 0.005$) in favor of pirbuterol.

Investigator's Spirometry Measurements:

FEV₁: Both pirbuterol and metaproterenol effected clinically significant bronchodilation. There was no evidence of deterioration in efficacy across time in terms of number of patients responding and median peak improvement.

MMF: As with FEV₁, there was no evidence of deterioration in number of responders and median peak response for either drug.

GA₁₀: As with FEV₁ and MMF, there was no evidence of deterioration in number of responders and median peak response for either drug.

PEFR: The average weekly improvement over baseline for pirbuterol increased significantly ($p < 0.005$) across time; the average weekly values for metaproterenol also increased significantly ($p < 0.02$). The two groups did not differ to a significant degree.

C. Studies supportive of the adequate and well-controlled studies:

Nine single-blind, single-dose crossover studies and 15 open uncontrolled multiple dose studies provided supportive data on efficacy and safety. In the single dose studies, patients were randomized to pirbuterol, salbutamol and placebo aerosols in 8; in the remaining study patients received pirbuterol, fenoterol and placebo:

1. Study #21-6 Dr. Beumer (The Netherlands)

A single-blind, single dose, crossover trial of pirbuterol (0.2 and 0.4 mg), placebo and salbutamol (0.2 mg) in 12 patients with bronchial asthma.

Both doses of pirbuterol and the single dose of salbutamol effected clinically and statistically significant bronchodilator activity relative to placebo in FEV₁ and MEFR (peak and AUC responses).

There was no significant difference between 0.4 mg pirbuterol and 0.2 mg salbutamol. There was significance for 0.2 mg salbutamol over 0.2 mg of pirbuterol in FEV₁, peak and average response and in average MEFR.

Both active drugs had an onset of action within 5 minutes after administration and the duration of action was longer than 4 hours.

2. Study #28-2 Dr. Holten (Norway)

A single-blind, single dose, crossover trial of pirbuterol (0.2 and 0.4 mg), placebo and salbutamol (0.2 mg) in 20 patients with bronchial asthma and bronchial asthma associated with chronic bronchitis with or without emphysema.

Both doses of pirbuterol and the single dose of salbutamol effected statistically significant bronchodilator activity relative to placebo in FEV₁, peak average responses and number of responders and in MMF number of responders and average and peak responses. Only the 0.4 mg achieved significance in peak response against salbutamol. There were no statistically significant differences between the 2 active drugs in terms of the remaining efficacy parameters.

At the 90-minute evaluation point 85% of patients receiving 0.4 mg pirbuterol were still responding compared with 65% for 0.2 mg pirbuterol and salbutamol.

3. Study #60-2 Dr. Kok Jensen (Denmark)

A single blind, single dose, crossover trial of pirbuterol 0.2 and 0.4 mg, placebo and salbutamol 0.2 mg, in 11 patients with bronchial asthma, chronic bronchitis and bronchial asthma associated with chronic bronchitis.

Both doses of pirbuterol and the single dose of salbutamol showed clinically and statistically significant bronchodilator activity relative to placebo in FEV₁ and PEFR peak and average responses.

There were no statistically significant differences between the two active drugs.

A clinically significant response in FEV₁ and PEFR was highest in peak response for 0.2 mg salbutamol while the number of responders to 0.4 mg of pirbuterol and 0.2 mg of salbutamol were equal.

4. Study #68-1 Dr. J. Lulling (Belgium)

A single-blind, single dose, crossover study of pirbuterol 0.4 mg, placebo and salbutamol 0.2 mg, in 14 patients with intrinsic/extrinsic bronchial asthma and chronic bronchitis with asthma and or emphysema.

Pirbuterol 0.4 mg and salbutamol 0.2 mg effected clinically and statistically significant bronchodilator activity relative to placebo in FEV₁ and PEF_R number of responders, peak and average response. There were statistically significant differences between pirbuterol and salbutamol in favor of pirbuterol in peak and average FEV₁ response.

The onset of action for both drugs was within 5 minutes of administration with 75% of pirbuterol and 50% of salbutamol patients still responding at 4 hours post-dose.

5. Study #65-1 Dr. Schaanning (Norway)

A single-blind, single dose, crossover study of pirbuterol 0.2 and 0.4 mg, placebo and salbutamol 0.2 mg in 12 patients with bronchial asthma, chronic bronchitis, asthma associated with chronic bronchitis and chronic bronchitis associated with emphysema.

The effects of pirbuterol and the single dose of salbutamol were clinically and statistically significant relative to placebo in FEV₁ and MMF peak and average responses. There was no statistically significant difference between pirbuterol and salbutamol.

The onset of action for both active drugs was within 5 minutes of administration.

6. Study #63-2 Dr. Schindl (Austria)

A single-blind, single dose, crossover study of pirbuterol 0.2 mg and 0.4 mg, placebo and salbutamol 0.2 mg in 20 patients with bronchial asthma and chronic bronchitis.

Both doses of pirbuterol and the single dose of salbutamol showed clinically and statistically significant bronchodilator activity relative to placebo in FEV₁, MMF and GAV_{1g} onset, peak and AUC.

The clinically significant response among both active drugs was maximal after pirbuterol 0.4 mg in terms of FEV₁, MMF, and GAV_{1g} number of responders. The peak response in MMF and GAV_{1g} was also highest after 0.4 mg pirbuterol. The onset of activity for both active drugs was within 5 minutes of administration.

7. Study #61-3 Dr. Van der Straeten (Belgium)

A single-blind, single dose, crossover study of pirbuterol 0.4 mg, placebo and salbutamol 0.2 mg in 14 patients with bronchial asthma, chronic bronchitis and bronchial asthma associated with chronic bronchitis.

Both doses of pirbuterol and the single dose of salbutamol 0.2 mg produced clinically and statistically significant bronchodilator effects relative to placebo in FEV₁ and GAV_{1g} peak, average response and number of responders. A statistically significant difference in favor of 0.4 mg pirbuterol over 0.2 mg salbutamol was attained in peak FEV₁ response.

Clinically, both pirbuterol and salbutamol produced FEV₁ and GAV_{1g} responses which were superior to placebo. In general, response to pirbuterol was better than to salbutamol. In FEV₁, a higher percentage of patients responded to pirbuterol than to salbutamol (86% vs 71%) and effected a higher median peak improvement (45% vs 35%). In GAV_{1g} 93% of patients responded to salbutamol and 86% responded to pirbuterol while the median peak improvement favored pirbuterol over salbutamol (149% vs 108%). The onset of bronchodilator activity for the two drugs was at 5 minutes.

8. Study #74-1 Dr. Verstraeten (Belgium)

A single-blind, single dose, crossover study of pirbuterol 0.4 mg, placebo and salbutamol 0.2 mg in 12 patients with bronchial asthma and bronchial asthma associated with bronchitis and emphysema.

Relative to placebo statistical significance was achieved for pirbuterol in FEV₁; peak response, number of responders and average response. For salbutamol, only the average response reached significance ($p < .01$). There were no statistically significant differences in responses between pirbuterol and salbutamol.

The onset of bronchodilator activity for pirbuterol and salbutamol was at five minutes. However, a higher percentage of patients were still responding at 240 minutes to 0.4 mg pirbuterol (83%) than to salbutamol (55%).

9. Study #70-1 Dr. Ulmer (Germany)

A single-blind, single dose, crossover study of pirbuterol 0.2 mg and 0.4 mg, fenoterol 0.2 mg and placebo aerosols in 12 patients with chronic bronchitis and chronic bronchitis associated with emphysema.

Statistical significance ($p < 0.01$) was achieved for pirbuterol 0.4 mg against placebo in average post-dose improvement in airway resistance (RAW).

10. Fifteen Uncontrolled Studies

A total of 267 patients were included in 15 open multiple dose studies. Pirbuterol was administered in doses of 0.4 mg to 4 mg (mean 1.78 mg) for periods ranging between 1 day and 566 days (mean 2.6 months).

The data generated in these studies provided supportive evidence of efficacy and safety.

D. Safety

1. General Comments

Information on side effect profile, as well as on laboratory parameters and cardiovascular effects is provided by 365 patients in controlled single dose studies and 411 patients in multiple dose studies. Apart from dose ranging studies the doses employed were the proposed recommended doses of 0.2 - 0.4 mg (1-2 puffs).

The patients in multiple dose studies were exposed to drug for periods up to 566 days (mean 2.6 months).

In single dose studies pirbuterol was well tolerated. The side effect profile was comparable to that of comparative agents.

Pirbuterol was also well tolerated following multiple dose administration. In this respect it was comparable to metaproterenol.

Although total side effects were a little lower in the open studies compared with the comparative studies the qualitative distribution of side effects was comparable in the two sub-sets of data (Table 1).

Table 1
"Most Common Side Effects"

Double-blind Comparative and Open Titration Multiple Dose Studies

Drug	Total Patients	Tremors	CNS*	CVS**	Patients with Any Side Effects
Comparative Studies					
Pirbuterol	157	12 (7.6%)	34 (21.7%)	8 (5.1%)	59 (37.6%)
Metaproterenol	153	18 (11.8%)	24 (15.7%)	15 (9.8%)	54 (35.3%)
Open Studies					
Pirbuterol	267	13 (4.9%)	18 (6.7%)	6 (2.2%)	53 (19.9%)

*CNS = Nervousness, Headache, Insomnia

**CVS = Palpitations, Tachycardia

Overall incidence of side effects at the recommended doses of 0.2 and 0.4 mg was 2.3% and 1.9% respectively. The commonest side effects (0.3 - 0.6%) were those which related to the CNS (headache and nervousness) and a local effect (sore throat, bad taste).

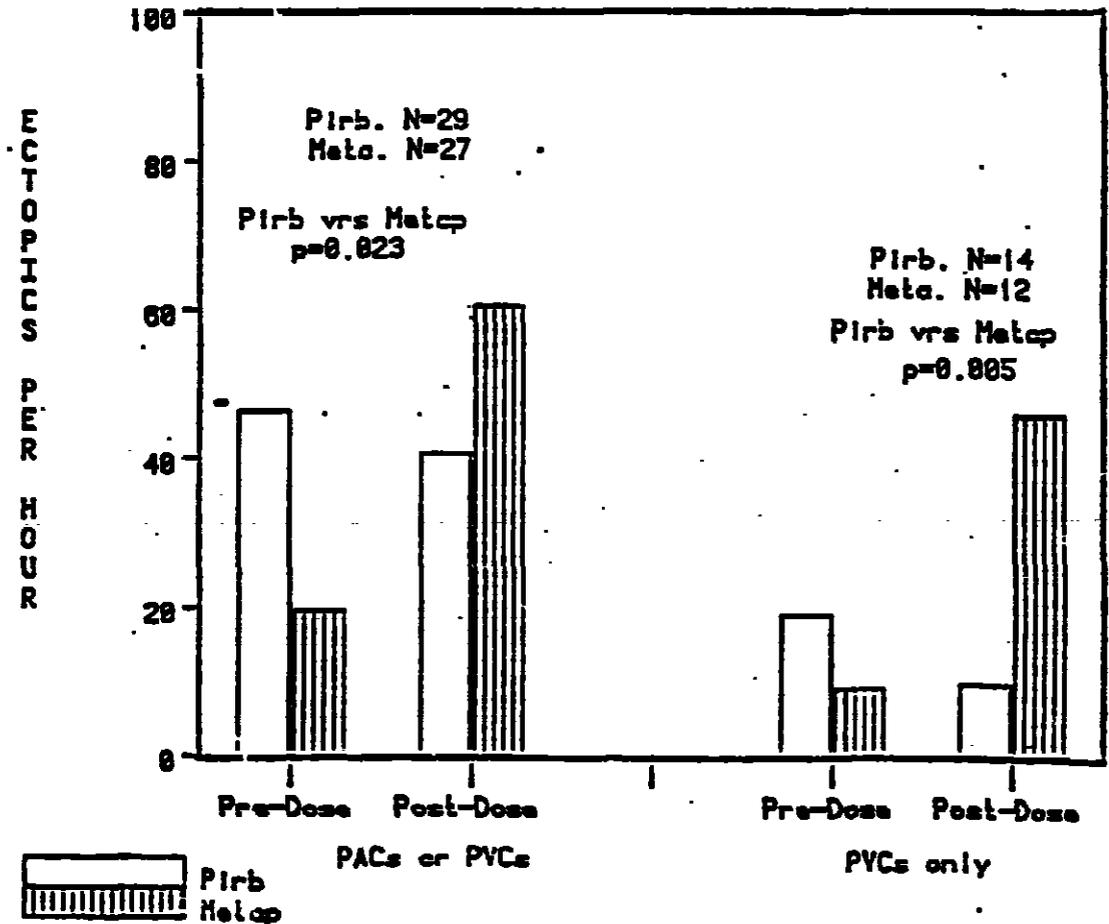
Selectivity:

At optimum single doses (0.2 and 0.4 mg) and the maximum recommended multiple dose regimen (0.4 mg q.i.d.), pirbuterol shows greater selectivity for beta₂ opposed to beta₁ receptors. Effective bronchodilation is achieved but without accompanying chronotropic effects (heart rate) or inotropic effects (force of cardiac contraction as measured by systolic time intervals). There is no evidence of a significant increase in systolic blood pressure. There is, however, evidence of a small decrease in diastolic blood pressure (beta₂ effect on peripheral vasculature).

The use of pirbuterol aerosol is not associated with the production or augmentation of ventricular ectopic activity (Figure 1).

Figure 1

Aver. Ectopics/Hour—Patients with Ectopics on EKG Tracings
All Multiple Dose Controlled Aerosol Studies Combined



2. Single Dose Studies

Subjective Side Effects: Side effects include those that were designated as definitely related to pirbuterol as well as those whose relationship to pirbuterol was considered uncertain. Only those side effects designated by the investigator as clearly not drug related were excluded. The overall incidence of side effects in all patients treated with single doses of pirbuterol ranging for 0.1 mg to 0.8 mg was between a low of 1.9% and a high of 12%. The percentage of side effects considered definitely related to pirbuterol was 1.6%. There was no dose related increase in incidence of side effects (Table 2). The incidence of side effects at the recommended doses of 0.2 and 0.4 mg was 2.3 and 1.9% respectively.

CNS: The most common side effects were central nervous system type: nervousness, headache, insomnia and irritability. The incidence of CNS side effects for pirbuterol 0.2 and 0.4 mg was 0.6% and 1.2% respectively, versus 3.4% for 1.3 mg metaproterenol, the main comparative agent used in the research program. The incidence of CNS side effects for 0.2 mg pirbuterol were no different from that reported after 0.2 mg of salbutamol; 1% and 0.7% respectively. In the placebo controlled studies the percent incidence of CNS side effects at the 0.2 and 0.4 mg optimum pirbuterol doses were 0.7% and 1.4% respectively, little different is the 1.2% experienced with placebo aerosol administration (Table 3).

Tremor: Tremor was not reported at the 0.2 and 0.4 mg doses but was reported at the 0.6 mg dose (2.8%); a dose higher than that recommended for clinical use (Table 3).

Subjective Cardiovascular Side Effects: Subjective cardiovascular side effects (palpitations and tachycardia) were rare (0.98%) and were experienced at the 0.2 mg dose. (Table 3.)

There was one incidence of palpitation in single dose studies that was definitely related to pirbuterol therapy. This occurred at a 0.2 mg dose level. Two other incidences occurred but their relationship to pirbuterol therapy (0.2 mg) was uncertain.

Electrocardiographic Evaluations: In the single dose studies a 12-lead EKG tracing was taken on test days prior to drug or placebo and 5 to 60 minutes post-drug. The majority of patients had their post-drug EKGs at 15-30 minutes. Baseline and post-drug EKG monitoring relative to placebo and various doses of pirbuterol was performed on 336 patients receiving single doses. These patients were derived from 18 studies (5 U.S. and 13 European). (Table 4.)

Rhythm Changes - Standard EKG Monitoring: For this purpose a detailed analysis was carried out on 137-patients from 7 studies with single doses of pirbuterol, metaproterenol, salbutamol or placebo. A detailed analysis sheet was completed for each patient for each test day with respect to pre- (or placebo) treatment tracings and the subsequent post- (or placebo) treatment tracings. The counts of ectopic beats (PVCs and PACs) was done for each strip, then the average of ectopic counts was calculated per minute. Table 5 displays the counts of patients with ectopic beats and the average number of these beats per minute (based only on those who showed at least one ectopic beat at any time) for baseline and post-drug readings during the four test days when pirbuterol 0.2 or 0.4 mg, metaproterenol, salbutamol or placebo was administered. From that table it can be concluded that pirbuterol 0.2 and 0.4 mg was no different from placebo or metaproterenol in percent of patients who developed ectopic beats. In addition the percent of patients who had ectopic beats before and after administration of 0.2 and 0.4 mg was not different. The above findings show that pirbuterol at the recommended doses of 0.2 and 0.4 mg has no adverse effect relative to ectopic beat formation.

Rhythm Changes - Continuous Holter Monitoring: In addition to the above analysis, two U.S. single dose studies included continuous Holter monitoring of patients:

In study #02-2, one 10 hour recording was started on each test day at 0 time up to 5 to 6 hours post-dose. Holter data on 14 patients, who completed Holter recording for all 4 test days, were subjected to statistical analysis. The results showed that there was no difference between placebo, pirbuterol 0.2 and 0.4 mg and metaproterenol 1.3 mg in overall average post-dose ectopic beats. In two patients the number of ectopic beats were highest on the day they received placebo. In addition, there was no difference between pirbuterol, metaproterenol and placebo in terms of frequency of ventricular premature beats (average grade).

In study #46-2 all 24 patients were followed for one hour before and 5 hours after the doses of active drugs or placebo. Additionally continuous Holter monitoring was available after isoproterenol on evaluation day. This allowed for a 3 way comparison of frequency of ectopic beats between pirbuterol, isoproterenol and placebo in terms of the average differences

between pre-dosing activity and post-dosing activity. There was an average tendency for patients to show a reduction of ectopic activity after pirbuterol and a slight increase in ectopic activity after placebo. This difference was nearly significant ($p < .10$). There is a greater tendency for patients to show an increase in ectopic activity after isoproterenol with the difference between that drug and pirbuterol reaching formal statistical significance ($p < 0.05$) for the number of VPB's per hour.

Blood Pressure and Pulse Rate: Data from 15 single dose studies (270 patients) in which two doses of pirbuterol, 0.2 and 0.4 mg, were administered in a randomized fashion with placebo are displayed in Table 6. Clinically significant changes in pulse rate or blood pressure were defined as changes of ≥ 10 beats/minute and ≥ 10 mmHg respectively. Using these definitions, standing pulse rate and diastolic blood pressure were analysed.

There was no difference between placebo and pirbuterol (0.2 and 0.4 mg) in terms of percent of patients who developed clinically significant increases in standing pulse rate and standing diastolic blood pressure after single dose administration. Approximately 25% of placebo or pirbuterol patients showed ≥ 10 mmHg decrease in diastolic blood pressure and 15-20% of placebo or pirbuterol patients showed ≥ 10 beats/minute increase in pulse rate.

The difference between these two groups (placebo and pirbuterol) did not reach statistical significance. (Table 6.)

TABLE 2

FENBUTEROL ACETATE AEROSOL SINGLE DOSE STUDIES SIDE EFFECT PROFILE						
Dose (mg) Number of Patients	.1 25	.2 50	.3 75	.4 100	.6 150	.8 200
CENTRAL NERVOUS SYSTEM						
Nervousness	0	0	0	1 (0.3%)	0	0
Dizziness	1 (4%)	2 (0.7%)	0	2 (0.6%)	0	0
Faintness	0	1 (0.3%)	0	0	0	0
Headache	0	0	1 (4%)	2 (0.6%)	0	0
Tremors	0	0	0	0	1 (2.8%)	0
Numbness in Extremities	1 (4%)	0	0	0	0	0
CARDIOVASCULAR						
Palpitations	0	3 (1%)	0	0	0	0
RESPIRATORY						
Breathlessness	1 (4%)	0	0	0	0	0
Cough, non-productive	0	1 (0.3%)	0	0	0	0
GASTROINTESTINAL						
Diarrhea	0	0	0	1 (0.3%)	0	0
Nausea	0	1 (0.3%)	0	0	0	0
EYE, EAR, NOSE, THROAT						
Vision, Blurred	0	0	0	1 (0.3%)	0	0
Throat, Sore	0	0	0	1 (0.3%)	0	0
Smell/taste change	0	0	0	1 (0.3%)	0	0
SKIN						
Itching	0	1 (0.3%)	0	0	0	0
Rash	0	2 (0.7%)	0	0	0	0
Number Patients with Side Effects	3	7	1	7	1	0
% Patients*	12.0%	2.3%	4.0%	1.9%	2.8%	0
Total Number Patients: 365						
# with Side Effects: 17 (4.7%)**						
# Discontinues: 0						

*Side Effects counted at first occurrence at each dose
**Represents number of patients who experienced any side effect

TABLE 3

PIRIBUTEROL ACETATE/COMPARATIVE DRUGS

SINGLE DOSE STUDIES*

ALL SINGLE DOSE STUDIES:

	<u>Dose</u>	<u># Pats</u>	<u>Tremor</u>	<u>CNS</u>	<u>CVS</u>	<u>Any S.E.</u>
<u>Pirbuterol</u>	.1	25	0	2 (8.0%)	0	3 (12.0%)
	.2	305	0	2 (0.7%)	3 (0.98%)	7 (2.3%)
	.3	25	0	1 (4.0%)	0	1 (4.0%)
	.4	362	0	3 (1.4%)	0	7 (1.9%)
	.6	36	1 (2.8%)	0	0	1 (2.8%)
	.8	25	0	0	0	0
<u>Placebo</u>	--	322	0	4 (1.2%)	0	5 (1.6%)

Salbutamol Single Dose Studies: 03-7, 03-8, 21-6, 28-2, 60-2, 61-3, 63-2, 65-1, 67-1, 68-1, 74-1

<u>Pirbuterol</u>	.2	101	0	1 (1.0%)	0	1 (1.0%)
	.4	156	0	0	0	1 (0.6%)
	.6	12	0	0	0	0
<u>Salbutamol</u>	.2	154	0	1 (0.7%)	0	1 (0.7%)
<u>D/S Placebo</u>	--	116	0	0	0	0

Metaproterenol Single Dose Studies: 02-2, 31-4, 47-1, 63-4, 66-1, 66-2, 96-1

<u>Pirbuterol</u>	.2	168	0	1 (0.6%)	3 (1.8%)	6 (3.6%)
	.4	170	0	2 (1.2%)	0	3 (1.8%)
<u>Metaproterenol</u>	1.3	149	0	3 (3.4%)	1 (0.7%)	8 (5.4%)
	1.5	24	0	0	0	0
<u>D/S Placebo</u>	--	170	0	4 (2.4%)	0	5 (2.9%)

Fenoterol Single Dose Study: 70-1

<u>Pirbuterol</u>	.2	12	0	0	0	0
<u>Fenoterol</u>	.4	12	0	0	0	0
<u>Placebo</u>	--	12	0	0	0	0

CNS = Nervousness, Dizziness, Faintness, Headache, Drowsiness/Sedation
CVS = Palpitations

* Incidence of Most Common Side Effects With Single Doses of B₂ Agonists i.e., Pirbuterol Acetate and Various Comparative Agents

TABLE 4

EKG EVALUATIONS

FIBUTEROL AEROSOL - 336 PATIENTS IN 18 SINGLE-DOSE STUDIES

Dose Mg	BASELINE		Abnormalities Disappeared	Unchanged	FOLLOW-UP Abnormalities Developed	Abnormalities Changed/Lessened	Abnormalities Due to Drug
	Diagnosis	No. Patients					
Placebo	Normal	185	—	184	1	—	—
	Abnormal	116	3	91	—	22	—
Fibu- terol 0.1	Normal	16	—	15	1	—	0
	Abnormal	9	0	9	—	0	0
0.2	Normal	133	—	130	3	—	0
	Abnormal	93	3	77	—	18	0
0.3	Normal	15	—	15	0	—	0
	Abnormal	10	0	10	—	0	0
0.4	Normal	191	—	187	4	—	0
	Abnormal	123	2	102	—	24	0
0.6	Normal	20	—	20	0	—	0
	Abnormal	16	0	14	—	2	0
0.8	Normal	17	—	16	1	—	0
	Abnormal	8	0	8	—	0	0

Eighteen of twenty single-dose studies are represented. The studies included are 02-2, 03-7, 03-8, 21-6, 31-4, 46-2, 47-1, 60-2, 63-2, 63-4, 65-1, 66-1, 66-2, 67-1, 68-1, 70-1, 74-1 and 36-1. There were no EKG's in study 20-2 or 41-3.

T Wave Changes, ST Segment Changes: All patients showing T wave abnormalities, ST segment abnormalities pre-drug or post drug or on both occasions were identified from the total single dose data base. There was no clear evidence of a drug induced effect on T wave and/or ST segment.

TABLE 5

PATIENTS IN SINGLE-DOSE STUDIES WITH SIX OR MORE ECTOPICS OBSERVED IN A DAY ON EKG STRIPS

Patient	Treatment	PVC's/Min		PAC's/Min	
		Pre-Drug	Post-Drug	Pre-Drug	Post-Drug
21-090-6	Placebo			1.386	0.000
	Pirb 0.2			1.997	0.000
	Pirb 0.4			2.882	0.000
	Salb 0.2			26.961	2.384
21-091-6	Salb 0.2			0.332	0.000
31-128-4	Placebo	0.000	6.307		
	Pirb 0.2	6.480	3.930		
	Pirb 0.4	0.000	1.098		
66-024-1	Placebo			0.000	0.596
	Pirb 0.4			0.192	2.439
	Pirb 0.4			0.000	0.071
	Metap 1.3			0.695	0.075
68-001-1	Placebo			0.079	0.000
	Pirb 0.4	0.314	0.000		
	Salb 0.2	3.585	0.000		
68-004-1	Pirb 0.4	0.190	0.040	0.950	0.278
	Salb 0.2			0.000	0.160
68-007-1	Placebo			0.098	0.056
	Pirb 0.4			1.341	0.212
	Salb 0.2			0.741	0.130

EXTRINSIC CARDIO-VASCULAR CHANGES BLIND ON ALL RANDOMIZED SINGLE DOSE CROSSOVER STUDIES FOLLOWING SINGLE DOSES OF TRIM

Study	Patients with 10 mmHg or Greater Prop. in Diastolic Blood Pressure						Patients with 10 or more Beats/minute Increase in Pulse Rate											
	Placebo		1/12 0.2 mg		1/12 0.4 mg		Placebo		1/12 0.2 mg		1/12 0.4 mg							
	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent						
55-1	4/23	17.4	-	-	6/24	25.0	0/23	0.0	-	-	1/23	4.3						
55-2	1/23	4.3	-	1/24	4.2	1/23	4.3	1/23	4.3	-	1/23	4.3						
31-4	10/23	43.5	10/24	41.7	15/24	62.5	3/23	13.0	4/24	16.7	5/24	20.8						
36-1	12/21	57.1	17/24	70.8	17/24	70.8	3/21	14.3	0/24	0.0	6/24	25.0						
02-2	7/23	30.4	5/24	20.8	1/24	4.2	15/23	65.2	8/24	33.3	6/24	25.0						
47-1	2/23	8.7	2/23	8.7	2/23	8.7	3/23	13.0	7/23	30.4	3/23	13.0						
48-2	6/24	25.0	4/24	16.7	4/24	16.7	4/24	16.7	4/24	16.7	6/24	25.0						
21-6	3/12	25.0	4/12	33.3	4/12	33.3	1/12	8.3	0/12	0.0	0/12	0.0						
28-2	2/20	10.0	2/20	10.0	5/20	25.0	6/20	30.0	4/20	20.0	1/20	5.0						
60-2	1/7	14.3	4/8	50.0	1/7	14.3	1/7	14.3	0/8	0.0	0/7	0.0						
68-1	1/12	8.3	-	-	2/12	16.7	0/12	0.0	0/12	0.0	0/12	0.0						
69-1	0/12	0.0	0/12	0.0	3/12	25.0	1/12	8.3	0/12	0.0	0/11	0.0						
63-2	4/20	20.0	1/20	5.0	2/20	10.0	5/20	25.0	3/20	15.0	3/20	15.0						
61-3	1/13	7.7	-	-	2/11	18.2	1/13	7.7	-	-	3/11	27.3						
74-1	1/12	8.3	-	-	1/12	8.3	1/12	8.3	-	-	1/12	8.3						
Overall	163/872	21.33	49/191	25.65	69/273	25.27	163/872	18.73	30/191	15.71	40/271	14.76						
Montel-Rosenbl vs Placebo							n = 0.983 p = 0.163						n = 0.499 p > 0.20					

TABLE 6

3. Multiple Dose Studies

The overall incidence of the most common side effects after pirbuterol 0.4 mg q.i.d. from five controlled studies of three months duration was: nervousness 24.8%, tremors 7.6%, dizziness 1.9%, headache 5.1%. Palpitations were reported at 2.5% and tachycardia = 3.2%. (Table 7.)

Of a total of 411 patients who participated in multiple dose studies; 9 were discontinued due to side effects. (Table 8.)

Subjective Cardiovascular Side Effects: Subjective feelings of palpitation and tachycardia (12 incidences) were reported in 10 of a total of 411 patients who were administered multiple doses of pirbuterol for periods ranging between 1 day and 18.8 months. Of those ten patients, 3 received doses of 0.4 mg 5 or 6 times per day.

Electrocardiograms: The electrocardiographic monitoring after multiple dose and long term administration of pirbuterol showed no drug related abnormalities. In the 3 month double-blind comparative trials, EKG monitoring of pirbuterol patients compared favorably with that seen with metaproterenol therapy. These results support those found after single dose administration.

Rhythm Changes: A detailed analysis was carried out on the 12 lead EKGs similar to that done in the single dose studies. For patients who showed one or more ectopic beats (PVCs or PACs) across all tracings taken throughout the 12 weeks of therapy, a count was taken, then the number of ectopic beats per minute was calculated. (Table 9.)

Five double-blind comparative studies were combined; this included a total of 143 patients on pirbuterol and 146 patients on metaproterenol. Only 29 patients from the pirbuterol group and 27 patients from the metaproterenol group showed PVCs or PACs.

14/29 pirbuterol patients and 12/27 metaproterenol patients had PVCs. The average pre-dose and post-dose combined PVCs and PACs and PVCs only were subjected to statistical analysis. Hypothesis testing was run on square roots of the average counts. There was statistically significant evidence that metaproterenol was associated with an increase in ectopic activity while pirbuterol was associated with a slight decrease in ectopic activity; this significance was seen for the combined PVCs and PACs as well as the PVCs only (Tables 10).

Pulse Rate and Blood Pressure: The single dose data indicated that, at doses of 0.2 mg and 0.4 mg, pirbuterol exerts a bronchodilator effect without significant beta-1 stimulation (chronotropic effect). No significant difference between pirbuterol and placebo was seen. Evidence of a beta-2 effect on the vasculature (fall in diastolic blood pressure) was seen at the same doses only in 15-20% of patients administered either pirbuterol or placebo.

Multiple dose data were also examined for effects on diastolic blood pressure and/or pulse rate after long term administration. Data from five, 3 month double-blind comparative trials were analysed. Blood

pressure and pulse rate readings were compared from pre-dose to 40 minutes post-dose at each 2 week visit for U.S. studies and each 3 week visit for European studies. Table 11 displays the average changes from baseline to 40 minutes post-dose in standing diastolic blood pressure and pulse rate. Although there was a statistically significant decrease in average standing diastolic blood pressure and pulse rate for patients on pirbuterol the actual changes from visit to visit were not clinically significant (< 10 mmHg and < 10 beats/minute). (Tables 11 and 12).

TABLE 7

MULTIPLE DOSE STUDIES SIDE EFFECT PROFILE		
REPRESENTS 157 PATIENTS (INCLUDES 8 MULTICENTER STUDIES, PROTOCOLS A & B AND STUDIES #14-4, 21-8, 63-3 RECEIVING ANY DOSE OF AEROSOL FIBUTEROL		
	TOTAL S.E. AT EACH DOSE	(COUNTS EACH PTS S.E. ONLY ONCE) TOTAL S.E. AT 1ST OCCURRENCE ONLY
NO. OF PATIENTS	157	157
MEAN DURATION OF THERAPY	84	84
CENTRAL NERVOUS SYSTEM		
Nervousness	39 (24.8%)	32 (20.4%)
Dizziness	3 (1.9%)	3 (1.9%)
Drowsiness	3 (1.9%)	1 (0.6%)
Headache	8 (5.1%)	8 (5.1%)
Other	3 (1.9%)	2 (1.3%)
TREMORS	12 (7.6%)	12 (7.6%)
CARDIOVASCULAR		
Palpitations	4 (2.5%)	3 (1.9%)
Tachycardia	5 (3.2%)	5 (3.2%)
Other	1 (0.6%)	1 (0.6%)
RESPIRATORY		
Chest Pain/Tightness	2 (1.3%)	2 (1.3%)
GASTROINTESTINAL		
Abdominal Pain/Cramps	1 (0.6%)	1 (0.6%)
Dry Mouth	5 (3.2%)	4 (2.5%)
Nausea	8 (5.1%)	7 (4.5%)
Other	9 (5.7%)	7 (4.5%)
SKIN		
Alopecia	1 (0.6%)	1 (0.6%)
MISCELLANEOUS		
Smell/Taste Change	1 (0.6%)	1 (0.6%)
Bruising	1 (0.6%)	1 (0.6%)

TABLE 8

FIRBUTEROL SIDE EFFECTS ALL 27 MULTIPLE DOSE STUDIES (411 PATIENTS)			
	NUMBER PATIENTS	PERCENT INCIDENCE	DISCONTINUED
Any Side Effect	112	27.3%	9 (2.2%)
Tremors	25	6.1%	1 (0.2%)
CNS	52	12.7%	1 (0.2%)
CVS	14	3.4%	2 (0.5%)

CNS Side Effects includes: insomnia, nervousness, headache

CVS Side Effects includes: palpitations, tachycardia

Nine patients discontinued are:

20-098-6	71-002-1
25-002-2	74-022-2
25-006-2	74-030-2
25-008-2	95-013-1
54-039-3	

TABLE 9

AVERAGE NUMBER OF STROKES/PATIENT SEEN ON EEG TRACINGS --- CONTROLLED MULTIPLE DOSE STUDIES

LEVITIMINOL

PATIENT	AVERAGE NO. OF PAC'S OR PVC'S PER MINUTE		AVERAGE NO. OF PVC'S OR PER MINUTE	
	PRE DOSE	POST DOSE	PRE DOSE	POST DOSE
47-343-2	1.654	2.107		
20-479-6	0.000	0.198	0.128	0.004
20-486-6	0.000	0.004	0.161	0.092
46-463-3	0.122	0.402		
49-406-3	0.220	2.840		
49-423-5	0.596	0.025	0.019	0.043
49-426-5	0.071	0.043		
32-415-1	0.019	0.081		
32-419-1	0.000	0.091	0.000	0.133
13-437-3	0.071	0.043	0.092	0.347
35-419-1	0.046	0.043		
35-420-1	0.092	0.043		
15-416-1	2.443	2.346		
21-507-8	0.003	0.152	0.068	0.228
21-519-8	0.293	0.327	1.181	7.045
21-521-8	0.351	5.142	0.000	0.171
21-525-8	0.021	0.171	0.061	0.031
21-528-8	0.000	0.031	0.061	0.748
32-403-2	0.061	0.748	0.079	0.079
13-505-3	0.051	0.099	0.000	0.222
20-401-6	0.000	0.228		
46-405-3	0.079	0.096		
14-405-4	0.000	0.000		
14-417-4	0.126	0.000		
14-451-4	1.400	0.085		
14-459-4	0.000	0.000		
14-477-4	0.262	0.000		

PLANTINOL

PATIENT	AVERAGE NO. OF PAC'S OR PVC'S PER MINUTE		AVERAGE NO. OF PVC'S PER MINUTE	
	PRE DOSE	POST DOSE	PRE DOSE	POST DOSE
14-099-4	0.672	0.160		
14-060-4	0.000	0.046		
14-064-4	0.129	0.190		
32-008-1	0.731	0.108	0.231	0.108
32-012-1	0.564	0.495		
32-014-1	0.159	0.287	0.079	0.073
15-100-3	0.039	0.052	0.673	0.572
20-098-6	1.051	0.903	0.000	0.000
20-090-6	0.038	0.356	0.038	0.356
20-091-6	0.033	0.356	0.033	0.000
13-076-3	0.082	0.000	0.082	
21-017-8	0.073	4.207		
21-019-8	1.305	6.398		
21-021-8	9.179	2.754	1.223	0.616
21-077-8	1.223	0.616	0.000	0.000
21-079-8	0.873	0.279	0.196	0.240
21-103-8	0.213	0.000		
21-119-8	0.213	0.279		
21-126-8	0.000	0.196	0.673	0.000
21-131-8	0.226	1.014		
63-042-3	1.259	0.000		
63-048-3	1.642	0.000		
63-070-3	0.000	1.196		
67-070-3	1.154	0.000	0.037	0.042
35-006-1	0.037	0.212	0.177	0.140
35-019-3	0.190	0.018	0.087	0.123
13-074-5	0.673	0.276	0.098	0.021
47-030-2	0.658	0.021		

MLP8108575.2 BMM/CLM/TV V13/10/85 P13/10/03

TABLE 10

ANALYSIS OF AVERAGE NUMBER OF HYPNOTIC/MINUTES DURING REM ON TWO TREATING CONTROLLED MULTIPLE DOME STUDIES

	HYPOSED				METHYLATED			
	NO. OF PATIENTS	OVERALL AVERAGE ACROSS PATIENTS		NO. OF PATIENTS	OVERALL AVERAGE ACROSS PATIENTS		PAIRED T-TEST SIG	TWO-SAMPLE T
		PRE-DOME	POST-DOME		PRE-DOME	POST-DOME		
All Samples (PAC's or PPG's)	29	0.774	0.681	27	0.328	1.145		
All Samples PPG's	29	0.643	0.547	27	0.306	0.755	2.512	0.019
PPG's	14	0.317	0.161	12	0.131	0.766		0.005
PPG's	14	0.475	0.301	12	0.270	0.506	2.391	0.056

TABLE 11

AVERAGE CHANGE IN STANDING DIASTOLIC BLOOD PRESSURE AND PULSE 0-40 MIN POST-DOSE
THREE U.S. MULTIPLE DOSE DOUBLE-BLIND STUDIES COMBINED

	WEEK OF STUDY					
	2	4	6	8	10	12
Diastolic B.P. (mmHg)						
Pirbuterol (N=116)	-1.217	-1.006	-0.412	-1.302	-0.578	-1.372
Metaprot. (N=102)	-1.777	-0.785	-1.584	0.050	0.115	0.081
Pulse Rate (Beats per minute)						
Pirbuterol (N=116)	-1.313	-0.702	-0.775	-0.519	-1.740	-3.629
Metaprot. (N=102)	-2.307	0.516	-3.675	-4.974	-4.596	-3.297

TABLE 12

AVERAGE EFFECTS OF MORTIER BONE ON DIASTOLIC BLOOD PRESSURE AND PULSE RATE DURING-BLIND MULTIPLE BONE STUDIES OF PINDROLOL AND METAPROLOL ALONE OR COMBINED

Researcher	No. of Studies	Overall Average Change Pre- to Post-Test		Number of Patients		Pooled Variance		95% Conf. Bounds			
		P/R	M/Sup	P/R	M/Sup	P/R	M/Sup	P/R	M/Sup	P/R	M/Sup
Standing	3	-1.275	-0.720	117	102	37.08	51.22	-0.340	0.446	-2.210	-1.085
Pulse Rate	5	-1.098	-2.018	155	157	79.95	79.08	-0.559	-0.754	-2.057	-3.243

VI. Approved Package Insert

A copy of the package insert is attached.

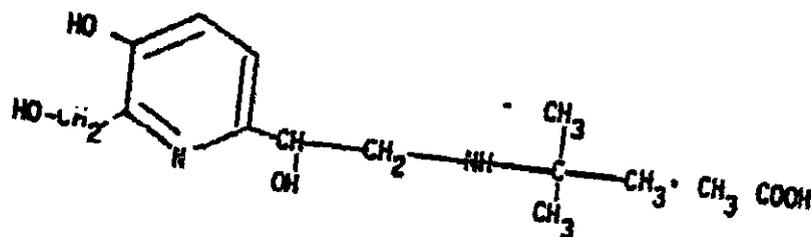
ANNOTATED PACKAGE INSERT

EXIREL[®] INHALER

(Pirbuterol Acetate)

Bronchodilator Aerosol
For Oral Inhalation Only

DESCRIPTION. The active component of EXIREL[®] Inhaler is a 6-[[[(1,1-dimethylethyl)amino]methyl]-3-hydroxy-2,6-pyridine-dimethanol monooctate salt, a relatively selective beta-adrenergic bronchodilator having the following chemical structure:



Pirbuterol acetate is the official generic name. Pirbuterol acetate is a white, crystalline powder which is very soluble in water. The molecular weight of pirbuterol acetate is 300.3 and its empirical formula is $C_{12}H_{20}N_2O_3 \cdot C_2H_4O_2$.

EXIREL[®] Inhaler is a metered-dose aerosol unit for oral inhalation. It is a fine-particle suspension of pirbuterol acetate in the propellant mixture of trichloromonofluoromethane and dichlorodifluoromethane, with sorbitan trioleate. It is formulated to deliver pirbuterol acetate equivalent to 200 mcg of pirbuterol per actuation from the mouthpiece. Each canister provides at least 300 inhalations.¹

CLINICAL PHARMACOLOGY. Pirbuterol is a beta-adrenergic receptor agonist which has been shown by in vitro and in vivo pharmacological studies in animals to exert a preferential effect on beta-₂ adrenergic receptors, specifically those located in the bronchial smooth muscle, uterus and vascular supply to skeletal muscles. It acts preferentially on pulmonary beta-₂ receptors as opposed to cardiac beta-₁ receptors. In this regard the data indicate that pirbuterol is 7.5 times more selective than albuterol.

It is postulated that beta-adrenergic stimulants cause many of their pharmacological effects by activation of adenylyclase, the enzyme which catalyzes the conversion of adenosine triphosphate to cyclic adenosine monophosphate, thus mediating cellular responses.

Pirbuterol causes complete relaxation of the guinea pig tracheal muscle in vitro which is the probable mechanism by which it antagonizes histamine, acetylcholine, and anaphylaxis - induced bronchospasm in vivo. Combining pirbuterol with either hydroxyzine or theophylline in the histamine aerosol test in animals results in an additive effect². Pirbuterol is longer acting than isoproterenol because it is an unlikely substrate for the cellular uptake processes for catecholamines or for catechol-O-methyltransferase.

PHARMACOKINETICS. As expected by extrapolation from oral data, systemic levels of pirbuterol are below the detection limit of about 5 ng/ml following inhalation of 400 to 800 mcg. Nevertheless, drug appears to be well absorbed, inasmuch as a mean of 51 percent of the dose is recovered in urine as pirbuterol plus its sulfate conjugate following administration by aerosol. This recovery does not change significantly over the dose range of 400 to 800 mcg and is not significantly different from that after oral administration of pirbuterol.³ The plasma half-life of about 2 hours measured after oral administration is probably also applicable to administration of pirbuterol by inhalation.

INDICATIONS AND USAGE. EXIREL[®] Inhaler is indicated for the relief of acute bronchospasm in patients with chronic reversible obstructive airway disease (extrinsic asthma, intrinsic asthma and chronic bronchitis/emphysema). Bronchodilator activity was manifested clinically

by an improvement in various pulmonary function parameters (FEV_1 , MMF, PEF, airway resistance [RAW] and conductance [GA/V_{tG}])⁴.

In controlled double-blind single dose clinical trials, the onset of improvement in pulmonary function occurred within 5 minutes, as determined by Forced Expiratory Volume in One Second (FEV_1). FEV_1 and MMF measurements also showed that maximum improvement in pulmonary function generally occurs 30-60 minutes following one or two (2) inhalations of pirbuterol (200 - 400 mcg) and that clinically significant improvement is maintained for at least 4 to 5 hours in most patients (the time at which the last observations were made). In four (4) single dose trials, 63/97, 66.9% patients showed a therapeutic response (defined by maintaining FEV_1 values 15% or more above baseline). This response was still apparent at 5 hours in 42/63 patients (66.7%). Continued effectiveness of pirbuterol was demonstrated over a 12-week period in controlled clinical trials. Chronic dosing is not associated with the development of tachyphylaxis/tolerance to the bronchodilator effect. In these studies, EXIREL[®] (pirbuterol acetate) was shown to be an effective bronchodilator with greater selectivity for beta-₂ as opposed to beta-₁ receptors. No limiting cardiac effects were observed over the recommended dose range.⁵

CONTRAINDICATIONS. EXIREL[®] Inhaler is contraindicated in patients with a history of hypersensitivity to sympathomimetic agents.

WARNINGS. As with other adrenergic aerosols, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. The exact cause of death is unknown, but cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

The contents of EXIREL[®] Inhaler are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

PRECAUTIONS. Although it has less effect on the cardiovascular system than isoproterenol at recommended dosages, pirbuterol is a sympathomimetic amine and as such should be used with caution in patients with cardiovascular disorders, including coronary insufficiency and hypertension, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

INFORMATION FOR PATIENTS. The action of EXIREL[®] Inhaler may last up to five hours and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without

medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking EXIREL[®] Inhaler, other inhaled medicines should not be used unless prescribed.

DRUG INTERACTIONS. Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with pirbuterol.

Beta-receptor blocking agents and pirbuterol inhibit the effect of each other.

USAGE IN PREGNANCY. As with any medication, pirbuterol should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS. Data is not available on the excretion of pirbuterol in breast milk. In the absence of such data, it must be assumed that excretion occurs.

USAGE IN PEDIATRICS. EXIREL[®] Inhaler is not presently recommended for patients under the age of 12 years due to insufficient clinical data in this pediatric age group.

INHALATION TOXICOLOGY. Inhalation studies, designed to deliver daily doses of 200, 400 and 800 mcg pirbuterol base/kg/day, representing approximately 10, 20 and 40 times the maximum anticipated daily human dose level (200 mcg x 6), to rats for one month, to dogs and monkeys for six months and to rats

and rabbits in Segment II teratology studies, were free of adverse effects.⁶ These experiments were carried out by multiple actuations of the pirbuterol acetate (200 mcg/puff) aerosol canisters developed for clinical use.

CARCINOGENESIS AND MUTAGENESIS. Pirbuterol administered in the diet to rats for 24 months and to mice for 18 months was free of carcinogenic activity.⁶

Pirbuterol showed no evidence of mutagenic potential in a battery of in vitro and host-mediated microbial (Ames) assays for point mutation, and in in vivo tests for somatic cytogenetic or germ cell (dominant lethal) effects following acute and subacute treatment.⁶

REPRODUCTION AND TERATOLOGY. Animal reproductive studies in rats at oral doses up to 300 mg/kg (250 times the maximum recommended human daily dose) and in rabbits at oral doses up to 100 mg/kg (83 times the maximum recommended human daily dose) have shown no adverse effects on reproductive behavior, fertility, litter size, peri- and postnatal viability or fetal development⁶. Only in rabbits at the highest dose level given (300 mg/kg - which corresponds to 250 times the maximum recommended human daily dose) were abortion and fetal mortality observed.

There was no evidence of teratogenic activity in either species.

ADVERSE REACTIONS. The incidence of adverse reactions to pirbuterol is based on clinical trials involving 761 patients, 400 of those received

multiple doses over long-term periods (mean duration is 2.5 months and the range is 1 to 566 days).

The following were the adverse reactions reported more frequently than 1 in 100 at the optimum dose of 0.4 mg q.i.d.

Incidence greater than 1%:

Central nervous system:	Nervousness	6.9%
	Headache	2.0%
	Dizziness	1.2%
Cardiovascular:	Palpitations	1.7%
	Tachycardias	1.2%
Respiratory:	Cough	1.2%
Gastrointestinal:	Nausea	1.7%

Incidence less than 1% (causal relationship probable):

The following adverse reactions occurred less frequently than 1 in 100.

The probability exists that there is a causal relationship between pirbuterol and these reactions:

Central Nervous System:	depression, anxiety, confusion, insomnia, weakness, hyperkinesia, syncope
-------------------------	---

Cardiovascular: hypotension, skipped beats

Gastrointestinal: dry mouth, glossitis, abdominal pain/cramps, anorexia, diarrhea, stomatitis

Ear, Nose and Throat: smell/taste changes, sore throat

Dermatological: rash

Other: numbness in extremities, alopecia, bruising, fatigue, edema, weight gain, flushing

Incidence of less than 1% (causal relationship unknown):

Other adverse reactions were reported with a frequency of less than 1 in 100 but a causal relationship between pirbuterol and the reaction could not be determined.

Central Nervous System: headache, nervousness, migraine, insomnia

Gastrointestinal: anorexia, nausea

Respiratory: productive cough, wheeze

Dermatological: dermatitis, rash

The adverse reactions of pirbuterol are similar in nature to those of other sympathomimetic agents, although the incidence of certain cardiovascular effects is less with pirbuterol.

OVERDOSAGE. The symptoms of overdosage are essentially those of excessive beta-stimulation, together with any of the symptoms listed under adverse reactions, i.e. nervousness, headache, tremor, dry mouth, palpitations, nausea, dizziness, fatigue, malaise and insomnia.⁷

Treatment consists of discontinuation of pirbuterol together with appropriate symptomatic therapy.

The oral LD₅₀ in male and female rats and mice was greater than 2000 mg base/kg. The aerosol LD₅₀ was not determined.⁶

DOSAGE AND ADMINISTRATION. The usual oral dose for adults and children 12 years and older is one inhalation (0.2 mg) or two inhalations (0.4 mg) repeated at 4-6 hour intervals depending upon response.⁸

If asthma is severe, or attacks are frequent, a 0.4 mg dose is recommended. A total daily dose of 12 actuations should not be exceeded.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

HOW SUPPLIED. EXIREL[®] Inhaler is supplied in pressurized aluminum canisters. Each actuation delivers pirbuterol acetate equivalent to 200 mcg of pirbuterol from the mouthpiece. It is supplied with an oral adapter and patient's instructions.⁹

Store between 15° and 30°C (59° to 86°F).

ANNOTATED PACKAGE INSERT

EXIREL[®] INHALER

Annotation Page

1. Section 2-3. A. Chemistry
2. Section 2-3. D. 1. Pharmacology
3. Section 2-3. D. 2. Metabolism

Section 2-3. E. CLINICAL STUDIES

3. Single Dose Studies; Study #46-2, D. Tashkin, M.D.
4. Section 2-3. E. 9. Overall Results and Conclusions d. Effectiveness
Double-blind-placebo
Study #46-2, and
Double-blind comparative - placebo and
Metaproterenol
FEV₁ and/or PEF; Studies #02-2, 47-1, 31-4, 96-1, 66-2, 66-1,
21-6, 28-2, 60-2, 68-1, 65-1, 63-2,
74-1.
GA/Vtg: Studies #31-4, 63-2 and 61-3.
MEFR: Study #21-6.

PEFR: Studies #60-2, 68-1.

RAW: Study #70-1.

5. Section 2-3. E. 9. Overall Results and Conclusions d. Effectiveness
 - Double-blind-placebo
 - #46-2 and
 - Double-blind comparative-placebo and Metaproterenol
 - Studies #02-2, 47-1, 31-4, 96-1, 66-2, 66-1 and
 - Multiple-dose studies:
 - Double-blind comparative vs. Metaproterenol
 - Studies #13-5, 47-2, 32-1, 35-1, 09-5, 46-3,
 - 15-1, 20-6, 14-4, 21-8, 63-3.
6. Section 2-3. D. 3. Safety Evaluation Studies
7. Section 2-3. E. 9. Overall Results and Conclusions
 - e. Safety
8. Section 2-3. E. 9. Overall Results and Conclusions
 - d. Effectiveness - Claim
9. Section 7. Composition of Drug