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**WARNER
LAMBERT**

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November 20, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: Docket No. 76N-052H Cold, Cough, Allergy, Bronchodilator, and
Antiasthmatic Drug Products for Over-the-Counter Human Use;**
**SUBJECT: Reopening of the Administrative Record for Antihistamine Drug
Products**

Dear Sir or Madam:

These comments are submitted by Warner-Lambert Consumer Healthcare (Warner-Lambert) in response to the Food and Drug Administration (FDA) reopening the administrative record for over-the-counter (OTC) antihistamine drug products, as published in the Federal Register on August 25, 2000. The reopening of the record provides for the acceptance of comments on recommendations by the public concerning the use of these products to relieve symptoms of sneezing and runny nose due to the common cold.

Warner-Lambert supports the agency's current belief that OTC antihistamine active ingredients effectively relieve cold symptoms in populations of consumers and should remain viable for that use. To this end, we are submitting to the Docket the results of a comparative *in vitro* receptor binding assay conducted in cloned human cell lines. This data was originally submitted to Docket 76N-052H in October 1997 to support the efficacy of diphenhydramine hydrochloride for relief of runny nose and sneezing in the common cold. We are resubmitting the data at this time because a recent (October 3, 2000) index listing of this Docket did not list this submission.

The comparative *in vitro* receptor binding assay was conducted in a cloned human cell lines using diphenhydramine hydrochloride, chlorpheniramine maleate and clemastine fumarate. The results showed a similarity in receptor binding affinity for human histamine H₁ receptor (vs. chlorpheniramine maleate) and human muscarinic M₁, M₂, M₃, M₄ and M₅ receptors (vs. clemastine fumarate). Given the previously established efficacy of clemastine fumarate and chlorpheniramine maleate for the indication of relief of runny nose and sneezing in the common cold, a comparison of the receptor binding data for histaminic and muscarinic receptors of the three antihistamines evaluated provides data specific to diphenhydramine

76N-052H

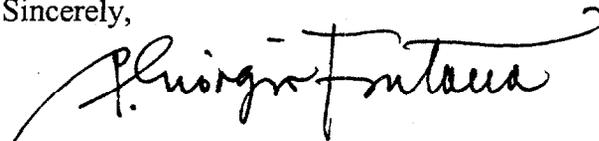
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hydrochloride for a labeled indication for runny nose and sneezing associated with the common cold.

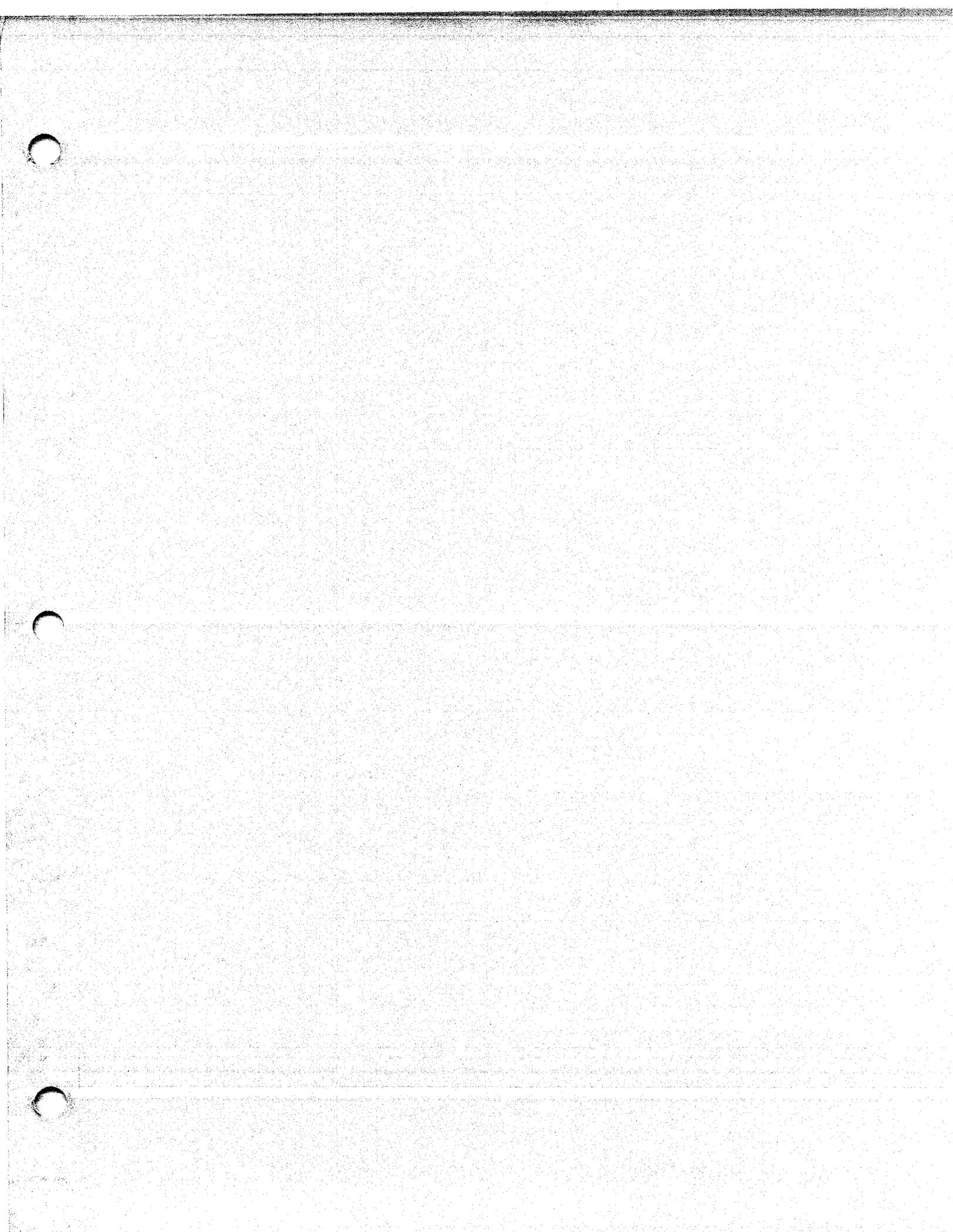
As per the August 25, 2000 Federal Register notice, we have enclosed three copies of our comments incorporating one volume. Please feel free to contact Dr. P. Giorgio Fontana (973-385-3416) or Mr. Hans Knapp (973-385-7250) with any questions on this matter.

This submission contains Confidential/ Trade Secret Information to which all claims of privilege and confidentiality are asserted in both statutory and common law. Further dissemination may only be made with the express written permission of Warner-Lambert Consumer Healthcare.

Sincerely,



P. Giorgio Fontana, Ph.D., Senior Director
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Warner-Lambert Consumer Healthcare



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**WARNER
LAMBERT**

October 14, 1997

Mr. Michael Kennedy
Director, OTC Drug Policy Staff
CDER: Office of Drug Evaluation V
Food and Drug Administration
HFD 560
9201 Corporate Blvd.
Rockville, MD 20850

Re: Docket No. 76N-052H;
Docket Title: OTC Antihistamines
Subject of Submission: Diphenhydramine HCl
Support of Indications of Relief of Runny Nose and Sneezing in the
Common Cold

Dear Mr. Kennedy:

Reference is made to the Warner-Lambert Consumer Healthcare submission to your office dated January 24, 1997 and to a subsequent telephone conversation of January 30, 1997. As you may remember, the January 24, 1997 submission was a data package in preparation for the scheduled February 13, 1997 meeting between Warner-Lambert and FDA to discuss the indication of relief of runny nose and sneezing in the common cold for diphenhydramine hydrochloride.

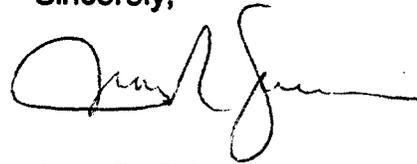
On January 30, 1997, you contacted Warner-Lambert and requested that the scheduled meeting be postponed until such time that the administrative record for OTC antihistamine drug products could be temporarily reopened for submission of new data. At that time you offered to place the January 24 submission in the docket. Warner-Lambert declined your invitation and requested that we be allowed to reevaluate the submission to remove any confidential information prior to it being placed in the docket.

At this time Warner-Lambert is submitting a revised copy of the January 24, 1997 submission to the OTC Antihistamine docket (76N-052H). A desk copy of the

submission is included for your review. The changes made were minor and were intended to improve the overall flow of the information being presented. We are also forwarding a fully revised desk copy and 18 additional copies of the revisions only to Babette Merritt for updating the above referenced pre-meeting data package previously distributed by Ms. Merritt within FDA.

Warner-Lambert would welcome the opportunity to answer any additional questions or concerns which will aid in the resolution of this important issue. Please feel free to contact either Hans Knapp or myself with any questions or concerns which you would like to pursue. Mr. Knapp can be reached at 201-540-7250. My direct telephone number is 201-540-6705.

Sincerely,



Jean R. Grieve
Sr. Director, Regulatory Affairs

cc:

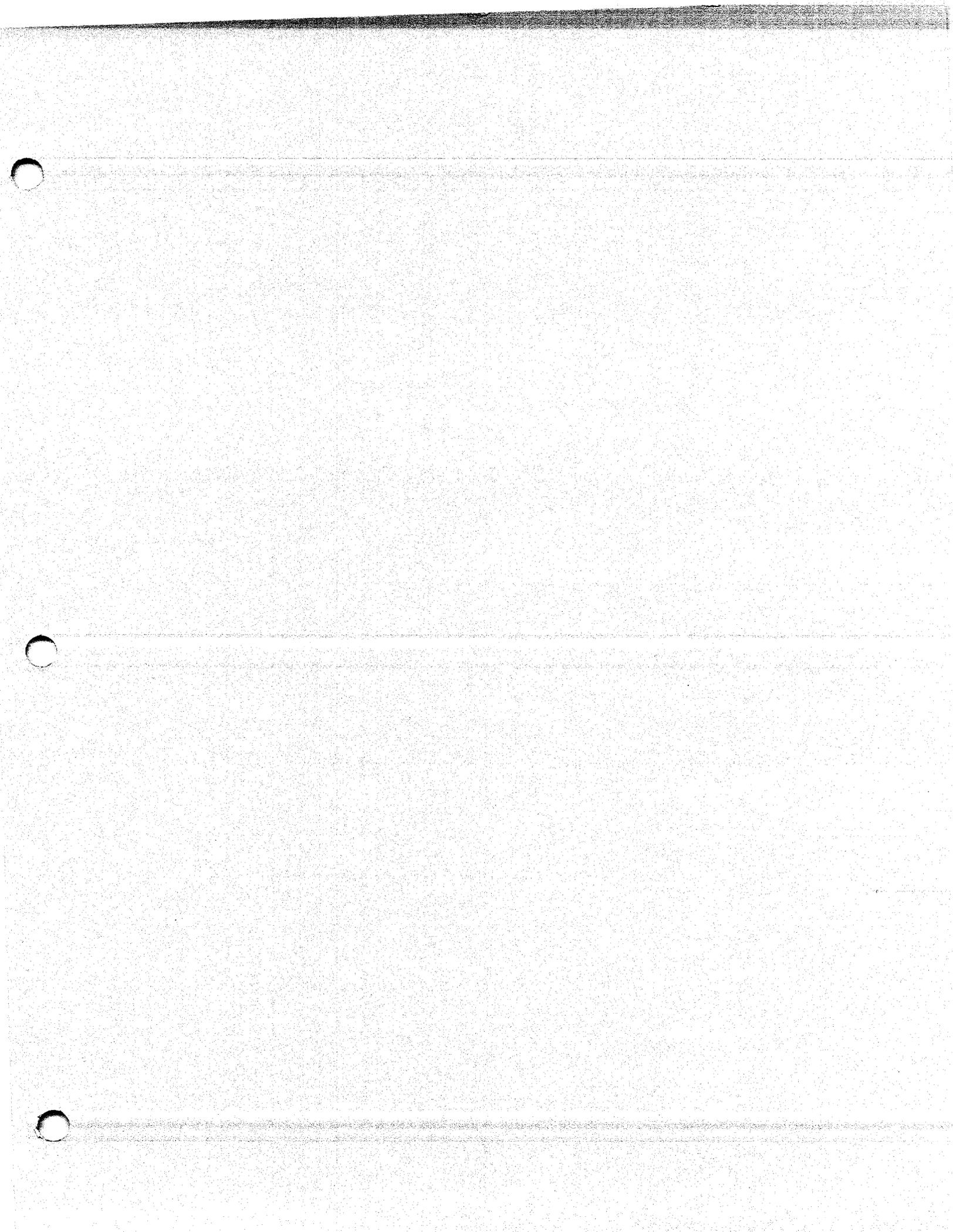
B. Merritt (attachments: annotated text, 18 copies of revised text; complete desk copy)

Warner-Lambert Consumer Healthcare
Morris Plains, New Jersey

DOCKET NO. 76N-052H
DOCKET TITLE: OTC ANTIHISTAMINES

Diphenhydramine HCl
Support of Indications of Relief of Runny Nose
and Sneezing in the Common Cold

October 14, 1997



Diphenhydramine HCl

Relief of Runny Nose and Sneezing in the Common Cold

The efficacy of OTC monograph antihistamines for the relief of runny nose and sneezing due to a common cold was the subject of a joint meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee on November 16, 1995. Although the joint committee recommended that these claims be approved for chlorpheniramine maleate and doxylamine succinate based on a meta-analysis of available study information, they recommended that the analysis not be extrapolated to the remainder of the OTC monograph antihistamines for this common cold indication. The lack of efficacy data for these antihistamines for the indication as well as the uncertainty over the mechanism of action of the antihistamines, were cited as the reasons for the recommendation. The joint committee could not agree on and did not recommend what data would be needed to support a runny nose and sneezing efficacy claim for these antihistamines for the common cold.

Warner-Lambert Consumer Healthcare is the manufacturer and marketer of BENADRYL® OTC cold and allergy products which contain the active ingredient diphenhydramine HCl.* We are interested in obtaining monograph status for the use of diphenhydramine HCl for the OTC indication of relief of runny nose and sneezing in the common cold. In response to the November 15, 1995 joint advisory committee's discussions and recommendations to the FDA, Warner-Lambert has assembled literature references, expert opinion and *in vitro* receptor binding study results to demonstrate the pharmacologic activity and clinical effectiveness of diphenhydramine HCl in runny nose and sneezing secondary to the common cold.

Regulatory History

The public record for OTC monograph antihistamines was initiated with the publication of the Advanced Notice of Proposed Rulemaking (ANPR) for Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products (41 FR 38312; September 9, 1976). However, the indication for relief of "runny nose and sneezing due to the common cold" for OTC antihistamine drug products was not proposed by FDA until publication of the Tentative Final Monograph for OTC Antihistamines (50 FR 2200; January 15, 1985). Specifically, the Agency stated in the Tentative Final Monograph:

"Because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted for chlorpheniramine allow Category I status for these claims to be extended to all Category I antihistamine active ingredients. Accordingly, an indication for the temporary relief of runny nose and sneezing associated with the common cold has been added to proposed 341.72(b) of this tentative final monograph." (50 FR 2200 at 2204)

More specifically, the FDA stated:

“...because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted on chlorpheniramine allow an indication for treating the symptoms of runny nose and sneezing when associated with the common cold to be extended to all Category I antihistamine active ingredients.” (50 FR 2200 at 2212)

With the publication of the Final Monograph for OTC Antihistamine Drug Products (57 FR 58356; December 9, 1993), the agency questioned whether the pharmacologic effects of older Category I ingredients were characteristic of newer antihistamine drugs and whether the cold claims of these older antihistamines could be extended to these newer drugs.^b FDA stated that the issue of extrapolation of the chlorpheniramine data was under review and deferred a final conclusion concerning the use of antihistamines for the relief of runny nose and sneezing associated with the common cold. This action left intact the Tentative Final Monograph for OTC Antihistamine Drug Products (50 FR 2200; January 15, 1985) in which FDA proposed Category I status for the claim:

"Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing associated with the common cold".

Subsequent to this and in further support of the efficacy of antihistamines for relief of runny nose and sneezing due to the common cold, the agency performed a meta-analysis of efficacy data of chlorpheniramine and doxylamine.

In a November 16, 1995 joint meeting, members of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee were asked to consider whether a statistical compilation of the results of various clinical studies of chlorpheniramine and doxylamine (the "meta-analysis") supported the efficacy of these antihistamines for the relief of runny nose and sneezing due to the common cold. The joint committees voted unanimously that the meta-analysis supported the efficacy of chlorpheniramine and doxylamine for the temporary relief of runny nose and sneezing due to the common cold.

The joint committees were also asked to consider whether the results of the meta-analysis could be used to extrapolate efficacy (for the relief of runny nose and sneezing due to the common cold) to the remainder of the monograph antihistamines. Following much discussion, the joint committees voted against the extrapolation of the efficacy data from the meta-analysis of chlorpheniramine and doxylamine to the remainder of the monograph antihistamines. Support for this position was based on the lack of available efficacy data for monograph antihistamines as well as uncertainty over the mechanism of action of the antihistamines.

FDA requested guidance from the joint committees on how the lack of efficacy data for the various OTC monograph antihistamines could be addressed. The joint committees could not reach a consensus as to what, if any, additional testing was needed. Dr. Randy Juhl (Chairman, Nonprescription Drugs Advisory Committee) commented "the likelihood of your getting efficacy studies to the level that we've just reviewed earlier in the day on all of these is slim to

none.”^c Dr. John Jenne (Pulmonary-Allergy Drugs Advisory Committee) stated: “But it seems to me that the alternative to this statement, i.e., insisting that all of these do studies like the one we’ve seen, is an impossible demand...”^d Drs. Richard Ahrens^e and Lynn Taussig^f, both of the Pulmonary-Allergy Drugs Advisory Committee, expressed opinions that effectiveness data is needed to support the cold indication, i.e., the data can not be extrapolated from chlorpheniramine maleate and doxylamine succinate.

Dr. Juhl questioned whether there could be reasonable surrogates (e.g., antihistamine binding potency, or anticholinergic potency or binding) for effectiveness data. Again, although there was considerable discussion, the joint committees could not reach agreement on what, if any, additional tests would be acceptable.

FDA has not yet commented on the committees' recommendation against extrapolation of the data for chlorpheniramine and doxylamine to the other monograph antihistamines.

Marketplace Experience

Diphenhydramine HCl is a classic H₁ receptor antagonist with anticholinergic activity. It has combined Rx and OTC marketplace experience of over fifty years and is generally recognized as safe and effective for allergy-related and cold-related symptoms when used according to label directions. Warner-Lambert markets several diphenhydramine-based products under the BENADRYL brand name that are labeled with an indication for the relief of cold symptoms. Based on the most recent usage study (April 1994 - March 1995), 18% of total BENADRYL sales volume, 7.7 million packages per year, is used when consumers have a cold. One-third of the BENADRYL liquid sales volume is used for treating cold symptoms, particularly among children. Professional treatment of the common cold and related upper respiratory diseases (excluding allergic rhinitis) also includes antihistamines. During the period October 1994 through September 1995, physicians recommended or prescribed an oral antihistamine 2.9 MM times for the common cold or upper respiratory infection. During this period, BENADRYL was specifically mentioned by name by physicians 175M times for cold-related disorders.⁵ Such marketplace statistics demonstrate the consumer's acceptance of the product, and by extension, diphenhydramine HCl, as a treatment for labeled common cold symptomatic conditions.

Technical Assessment

The “first generation” antihistamines, of which diphenhydramine, clemastine and chlorpheniramine are members, are H₁ antagonists which share a common molecular core. Diphenhydramine hydrochloride, a classic H₁ antagonist, is a member of the ethanolamine class of antihistamines. Clemastine fumarate (Tavist®) is also included within this class. Chlorpheniramine maleate, another classical H₁ antagonist, is a member of the alkylamine class of antihistamines.

Antihistamine-containing products are frequently used as treatment for the common cold. The clinical efficacy of OTC H₁ histamine receptor blockers in the symptomatic treatment of the common cold has been shown with statistical significance by the published and unpublished

clinical trials on doxylamine succinate and published data on chlorpheniramine, clemastine, and other antihistamines. Diphenhydramine shares the actions and uses of other proven antihistamines.

First generation (classic) antihistamines, as a class, have been reported to produce clinical benefits for runny nose and sneezing associated with the common cold via two possible mechanisms. First, through intrinsic anticholinergic activity that produces a "drying" effect by blocking parasympathetic innervation of the nasal mucous and serous glands in the mucosa and a direct effect on the centrally mediated sneezing reflex.¹ Secondly, through blocking increased amounts of histamine caused by virally induced degranulation of upper respiratory tract mast cells.²

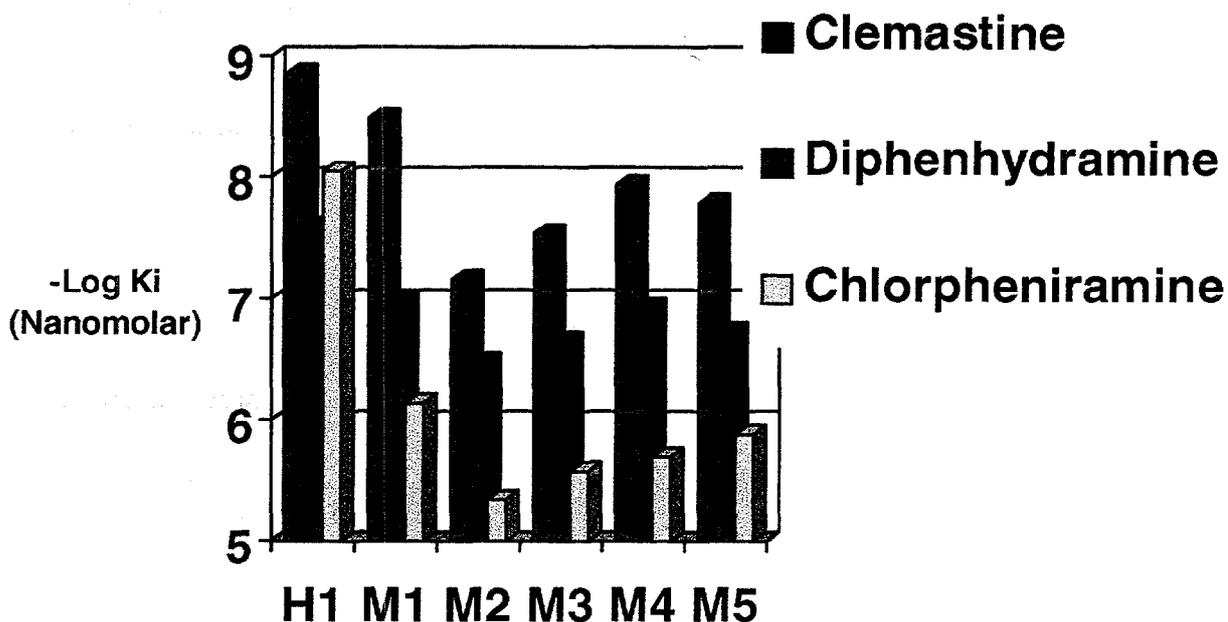
Warner-Lambert concluded that it may be reasonable to evaluate the clinical efficacy of antihistamines by evaluating their effect in the muscarinic and histaminic receptors thought to be responsible for their action. In fact, as early as 1971, the literature indicated that diphenhydramine displayed substantial atropine-like activity, as assessed by a bioassay system. In the past couple of decades, diphenhydramine-like drugs, which were shown to have antimuscarinic activities causing clinical effects, were evaluated for their affinities for various receptors. For example, Kubo et al demonstrated that in general, the ethanolamines (diphenhydramine as prototype) were potent H₁-receptor antagonists and possessed significant antimuscarinic activity.³ Further, there is evidence of correlation between *in vivo* H₁ receptor binding in human brain vs. binding in animal (guinea pig) brain. Yanai et al measured H₁ receptor occupancy in the human brain via positron emission tomography (PET) after administration of single doses of commonly used antihistamines. PET data from human brain were essentially compatible with data on H₁ receptor occupancy in the guinea pig brain as determined by an *in vivo* binding technique.⁴

We have recently completed studies to extend these observations through quantitative receptor binding assays of both histaminic and muscarinic receptors. It was important to determine if similarities existed between clemastine fumarate, chlorpheniramine maleate and diphenhydramine as well as to determine the appropriate receptor activity in human tissues. Clemastine and chlorpheniramine were chosen as comparators because they are molecularly similar to diphenhydramine and data exist to show their clinical efficacy for runny nose and sneezing in the common cold. Prior to execution of this comparative receptor binding study utilizing human cell lines, a pilot study was completed evaluating the affinity and selectivity of binding of diphenhydramine HCl vs. chlorpheniramine at histamine H₁ and muscarinic M₁, M₂ and M₃ receptors.

The results of the pilot receptor binding assay are detailed in Attachment B.⁵ Briefly, the affinity and selectivity of binding of diphenhydramine and chlorpheniramine were evaluated *in vitro* at histamine H₁ and muscarinic M₁, M₂ and M₃ receptors. The results showed similar inhibition/affinity at the receptors tested for diphenhydramine and the reference compound. No selectivity was apparent.

The results of the definitive receptor binding assay are detailed in Attachment C.⁶ Chlorpheniramine, clemastine and diphenhydramine were tested in M₁, M₂, M₃, M₄, and M₅ human muscarinic receptor subtypes and in human H₁ histamine receptor assays. The results of this study showed that all three compounds had similar receptor binding activity at the H₁ histamine and M₁-M₅ muscarinic subtypes.

As illustrated in the following graph, the affinity of diphenhydramine for the histamine H₁ receptor was closest to that of chlorpheniramine while the affinity at the muscarinic receptors was similar to that for clemastine.



This figure presents a summary of the radioligand competition data. Because the affinities of the compounds for the various receptors span several log orders of magnitude, the K_i values have been transformed to -log K_i values. Thus, the higher the affinity for a particular receptor type, the larger the number. What can be readily appreciated from the graph is the fact that affinity of diphenhydramine for all the muscarinic receptor types lies between that of clemastine and chlorpheniramine. The affinity of diphenhydramine for the histamine H₁ receptor is closest to that of chlorpheniramine. If one compares the muscarinic affinities of diphenhydramine and clemastine, *relative to their histamine receptor affinity*, one finds that the receptor selectivity profile for diphenhydramine and clemastine is quite similar.

Summary

There are several key points to consider in the evaluation of the pharmacologic activity and clinical effectiveness of diphenhydramine HCl in runny nose and sneezing secondary to rhinovirus infection.

- There is a core molecular structure common to H₁ antagonists and an expected common biological/pharmacological response from them in man.⁷
- Both diphenhydramine and clemastine are aminoalkyl ethers (ethanolamines), with comparable antihistaminic and anticholinergic activity, and similar duration of pharmacologic action.⁸
- Diphenhydramine, clemastine, and chlorpheniramine have high affinity and selectivity for histamine H₁ receptors, with diphenhydramine also having affinities at the muscarinic receptor subtypes and receptor selectivities intermediate between those of clemastine and chlorpheniramine.⁶
- The relief provided by OTC antihistamines to cold sufferers for the specific symptoms of runny nose and sneezing is approximately the same magnitude as the relief provided by antihistamines to allergy sufferers.¹

In addition, Mullol et al, utilizing human nasal provocation techniques in volunteers and exploring explant cultures of human inferior turbinate nasal mucosa *in vitro*, demonstrated that muscarinic stimulation by methacholine induced significant glandular secretion both *in vivo* and *in vitro*.⁹ The same investigators also showed that M₁ and M₃ muscarinic receptor subtypes regulate mucus glycoprotein secretion from human nasal mucosa *in vitro* and suggest that the M₃ receptor has the predominant effect.¹⁰ Affinity for these receptors by muscarinic antagonists would be expected to produce inhibition of mucus secretion. Thus, this demonstrates a correlation between direct actions on cells and clinical relevance.

In conclusion, Warner-Lambert believes that sufficient data exist to support the clinical efficacy of diphenhydramine hydrochloride for runny nose and sneezing in the common cold. Those data include:

- the similarity in receptor binding affinity for human histamine H₁ receptor (vs. chlorpheniramine) and human muscarinic M₁, M₂, M₃, M₄, and M₅ receptors (vs. clemastine),
- similar inhibition/affinity for diphenhydramine and chlorpheniramine in guinea pig ileum muscarinic M₁, M₂, and M₃, receptors and histamine H₁ receptors. Selectivity was not apparent,
- the similarity in chemical structure to clemastine fumarate and chlorpheniramine maleate, and,
- a direct correlation between muscarinic receptors and human nasal mucus secretions.

Similar affinity, inhibition, selectivity and chemical structure of these compounds lends itself to the hypothesis of similar clinical efficacy.

Warner-Lambert believes that in the context of the November 15, 1995 joint advisory committee meeting discussions, the expert opinion, scientific review, and comparative *in vitro* receptor binding data in cloned human cell lines presented in this submission, there are appropriate supportive data to establish the efficacy of diphenhydramine HCl as a symptomatic treatment for runny nose and sneezing in the common cold. Given the previously established efficacy of clemastine fumarate and chlorpheniramine maleate for the indication, a comparison of the receptor binding data for histaminic and muscarinic receptors of the three antihistamines evaluated provides data specific to diphenhydramine HCl for a label indication for runny nose and sneezing associated with the common cold.

Endnotes

^a Diphenhydramine is indicated for relief of cold symptoms in several products including Benadryl®, Contac® Day & Night Cold/Flu (SmithKline Beecham Consumer Healthcare) and Maximum Strength Tylenol® Flu Nighttime (McNeil Consumer Products). [Source: 1997 Physicians Desk Reference for Nonprescription Drugs, Medical Economics Company, Montvale, NJ.]

^b "Recently, the agency has been evaluating applications requesting prescription-to-OTC switch for drug products containing antihistamines. Some have included labeling for use in the common cold without direct support from clinical studies. The requested claim is based on similarity of pharmacologic action to the other antihistamines included in the tentative final monograph for OTC antihistamine drug products, in which the agency proposed common cold claims based on clinical studies for chlorpheniramine maleate and the similarity of pharmacologic action of all the other monograph antihistamines (50 FR 2216). However, the agency has concerns whether the pharmacologic effects of older Category I ingredients that it considered previously as providing relief of common cold symptoms are characteristic of newer antihistamine drugs. The agency is presently evaluating whether data on chlorpheniramine maleate for this use should be extrapolated to other antihistamines included in this final monograph or any other antihistamines that may be switched from prescription to OTC status. Also, the agency is aware that there is controversy within the scientific community as to whether antihistamines are effective in treating symptoms of the common cold. Before completing this aspect of the rulemaking, the agency wishes to evaluate more recent clinical studies as well as the older data concerning the effectiveness of antihistamines in treating symptoms of the common cold." (57 FR 58356 at 58357)

^c Ibid, page 301.

^d Ibid, page 279.

^e Ibid, page 277.

^f Ibid, page 280.

^g National Drug and Therapeutic Index data for 12 months ending September 1995. Source: IMS Audit Data.

References

1. Soller, W.R., Nonprescription Drug Manufacturers Association (NDMA). Submission to Docket No.: 78N-052H Cold, Cough, Allergy, Bronchodilator and Antihistaminic Drug Products for Over-the-Counter Human Use. June 15, 1992.
2. Smith, T.F. and L.K. Remigio. Histamine in Nasal Secretions and Serum may be Elevated during Viral respiratory Tract Infection. Int. Archo. Allergy Appl. Immuno. 1982;67:380-383.
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4. Yanai, K., et al. Positron Emission Tomographic Study of Central Histamine H₁ Receptor Occupancy in Human Subjects Treated with Epinastine, a Second Generation Antihistamine. Methods Find Exp. Clin. Pharmacol. 1995;17:64-69.
5. Data on file, Warner-Lambert Company, 1996. **SEE ATTACHMENT B**
6. Data on file, Warner-Lambert Company, 1997. **SEE ATTACHMENT C**
7. Nichols, D.E., Ph.D., Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN. Personal Communication: Characterization of the Pharmacology of Diphenhydramine and other H₁ Antagonists by Radioligand Competition Studies. **SEE ATTACHMENT A**
8. Ziment, I. In: Respiratory Pharmacology and Therapeutics. Philadelphia, WB Saunders, 1978.
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Note: References 1 and 9 not included in copies of the enclosed references.

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