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APPLICATION NUMBER:

19-835

OFFICE DIRECTOR MEMO

DIVISION DIRECTOR'S MEMORANDUM

Date: November 8, 2007

To: NDA 22-155 Zyrtec Syrup
NDA 19-835/S-022 Zyrtec Tablets
NDA 21-150/S-007 Zyrtec-D 12 Hour Extended Release Tablets
NDA 21-621/S-005 Zyrtec Chewable Tablets

From: Sally Seymour, MD
Acting Division Director, Division of Pulmonary and Allergy Products

Applicant: Pfizer, Inc. / McNeil Consumer Healthcare

Executive Summary

This is a Divisional Memorandum from the Division of Pulmonary and Allergy Products (DPAP) recommending the Approval of the partial over the counter (OTC) switch of Zyrtec (cetirizine) and a full switch of Zyrtec D (cetirizine/pseudoephedrine).

McNeil Consumer Healthcare submitted an NDA and three efficacy supplements to support a partial OTC switch of cetirizine (Zyrtec) and a full OTC switch of cetirizine/pseudoephedrine (Zyrtec D). Cetirizine is currently approved as a prescription product for:

- seasonal allergic rhinitis (SAR) in patients $\geq$ 2 years and older
- perennial allergic rhinitis (PAR) in patients $\geq$ 6 months and older, and
- chronic idiopathic urticaria (CIU) in patients $\geq$ 6 months and older.

Cetirizine/pseudoephedrine is currently approved as a prescription product for the nasal and non-nasal symptoms of SAR and PAR in patients 12 years and older.

The Applicant proposes taking cetirizine OTC for the SAR and PAR indications in patients 2 years and older and the CIU indication in patients 6 years and older. Thus, the CIU indication in children 6 months to less than 6 years of age and the PAR indication in children 6 months to less than 2 years of age will remain prescription status. The applicant proposes taking cetirizine/pseudoephedrine OTC for the SAR/PAR indications in patients 12 years of age and older; thus, there will be no prescription indications remaining. The OTC indication for SAR/PAR is the "temporary relief of symptoms of hay fever or other upper respiratory allergies" and for CIU is "the relief of hives."

The safety and efficacy of cetirizine and cetiririze/PSE have been previously established to support the prescription indications. Cetirizine has an extensive safety database that does not suggest a safety concern with regards to the OTC switch with the caveat that the OTC labeling should carry sedation language/precautions. At a joint meeting in May 2001, the Nonprescription and Pulmonary-Allergy Drugs Advisory Committees concluded that cetirizine demonstrates a risk/benefit profile suitable for an OTC antihistamine. In DPAP's opinion, because of the extensive pre-approval and post-approval database for cetirizine, no new clinical studies are required to support the

proposed OTC switch. Therefore, no new efficacy and safety studies were conducted for the proposed OTC switch of cetirizine and cetirizine/PSE.

Although the DPAP recommendation is Approval, there are two issues regarding this OTC switch that warrant further discussion: the safety and efficacy of cetirizine in the pediatric population and

Safety and Efficacy in Pediatric Population

Cetirizine was approved for SAR and PAR in adults and adolescents 12 years and older in December 1995 based upon the results of clinical studies. Cetirizine was approved for SAR and PAR in children 6-11 years of age in September 1996 and children 2 to 5 years of age in May 1998. The approval of cetirizine for children less than 12 years of age was based upon extrapolation of efficacy from the adult and adolescent population as well as pharmacokinetic and safety data in pediatric patients as described below.

To support SAR and PAR indications in adults, typically large clinical studies are necessary to establish efficacy due to the subjective nature of the primary efficacy variable, which is usually a variation of the total nasal symptom score (TNSS). For the pediatric population, demonstration of efficacy in clinical studies can be difficult due to the subjective nature of the primary efficacy variable and the fact that often surrogates (parents/guardians) are grading the symptoms of the child. DPAP considers the pathophysiology of allergic rhinitis and the role of antihistamines in the treatment of allergic rhinitis to be well understood and to be sufficiently similar in children and adults to allow extrapolation of efficacy results obtained from adult studies to pediatric populations. Therefore, extrapolation of efficacy from adults/adolescents was used to support SAR and PAR indications for cetirizine in pediatric patients. Extrapolation of efficacy is consistent with the 1994 Final Pediatric Labeling Rule, which states the following:

> "The rule explicitly recognizes that controlled clinical studies to support pediatric use need not be carried out in pediatric patients where the course of the disease and the effects of the drug are sufficiently similar in children and adults to permit extrapolation from the adult effectiveness data to pediatric patients. In these cases, controlled clinical studies in adults together with pharmacokinetic and adverse reaction data in pediatric patients may be sufficient to establish pediatric safety and effectiveness."

When data is extrapolated from adults/adolescents to pediatrics, the amount of clinical data in pediatric patients necessary to support approval can vary from program to program. For cetirizine, multiple clinical safety and efficacy studies and pharmacokinetic studies in pediatric patients were conducted by the Applicant. The primary purpose of these studies was to provide information regarding the appropriate dose (pharmacokinetic data) and safety information in the pediatric population. While efficacy was measured in the clinical studies, efficacy variables in pediatric SAR/PAR studies are often used as a measure of compliance to assure adequacy of adverse event monitoring. However, some of the studies numerically favored cetirizine and thus provided additional support for the efficacy of cetirizine. The extrapolation of efficacy from adults and primary safety and

pharmacokinetic data obtained from pediatric studies provided the basis of approval for cetirizine for SAR and PAR in pediatric patients.

While the above discussion focused on the SAR and PAR indications, the same process was used to support the CIU indication in pediatric patients. Extrapolation of efficacy from adults in addition to safety and pharmacokinetic data were the basis of approval of cetirizine for CIU in pediatric patients.

The indications for SAR, PAR and CIU, in layman's terms, already exist in the OTC market. DPAP believes the existing data for prescription cetirizine for SAR, PAR, and CIU demonstrate that efficacy has been established for these indications. Cetirizine has an extensive safety database and the safety profile is similar to other antihistamine products that are legally available without a prescription. This combination of efficacy and safety are sufficient to support the OTC switch of cetirizine and therefore, we recommend Approval of the applications.

Another issue worth discussion is the Applicant's proposal to seek a specific [redacted] claim as an OTC indication. DPAP believes that this indication is not warranted and does not recommend the adoption of such language as an OTC indication for drug facts labeling. The terms [redacted] are not scientifically recognized clinical conditions and these terms are not used as indications in the prescription labeling.

We acknowledge that the terms [redacted] are included in some patient package inserts and the Division of Drug Marketing, Advertising, and Communications (DDMAC) has allowed these terms for use in advertising. However, DPAP does not believe that the Agency should endorse these terms by allowing their use as an OTC indication.

The monograph language that is used for OTC antihistamines is intended to cover the SAR and PAR indications. Therefore, allowing OTC cetirizine to have a unique indication [redacted], suggests an artificial distinction between cetirizine and the other OTC antihistamines that is not necessarily supported.

While the Zyrtec prescription label includes specific allergens (e.g. ragweed, grass, etc.) in the indication section, including specific allergens is no longer standard in prescription labels since the medication is assumed to be effective for all allergens regardless of the allergens studied in the clinical trials and this type of wording may be removed in future labeling supplements and will not be allowed in future approved labeling.

In summary, DPAP recommends that the terms [redacted] and the use of the specific allergens not be included as part of the OTC indication.

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/s/

Sally Seymour
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MEDICAL OFFICER
Acting Division Director