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EXECUTIVE SUMMARY

ABBREVIATIONS

AE	Adverse Event
BID	Twice Daily
CDER	Center for Drug Evaluation and Research
NDA	New Drug Application
OTC	Over-The-Counter
OPDRA	Office Of Post-Marketing Drug Assessment
QD	Once Daily
SAE	Serious Adverse Event
WR	Written Request
AERS	Adverse Event Reporting System

RESUMI

This document summarizes an extensive review of worldwide safety information related to loratadine, fexofenadine, and cetirizine that was conducted by the CDER OTC Switch Review Team in response to a Citizen Petition requesting that these drugs be switched to OTC status. The primary objective of this review was to determine whether there are safety concerns associated with loratadine, fexofenadine, or cetirizine that might preclude their appropriate use in the OTC marketplace. This review did not focus on issues related to effectiveness of these agents in the OTC setting, since there is a long history of OTC marketing of antihistamines. A summary of the safety data for each drug derived from the work-group's review is provided.

BACKGROUND

Allergic rhinitis and related conditions are generally considered amenable to self-diagnosis and self-treatment. Antihistamines as a class have a long history of OTC availability and use in these indications, with correct usage guided by "OTC monograph labeling" (21 CFR 341.72). The efficacy of this class of drug products and the appropriateness of antihistamines in general for OTC marketing is not in question. However, as with all drugs, the currently marketed OTC

antihistamines are associated with adverse effects. The most commonly reported adverse effect of currently marketed OTC antihistamines is sedation. This adverse effect is addressed as a warning in the OTC monograph and in product labeling.

The sedation that is characteristic of the older antihistamines is a well-recognized, subjectively reported, dose-related adverse effect. Cognitive and task-performance impairment are also adverse effects of these drugs, however, these effects are not as easily identified and quantified as sedation. Clinical trials demonstrating cognitive impairment on complex tasks such as simulated driving in persons receiving currently marketed OTC antihistamines are common in the peer-reviewed medical literature (see, for example, [1 - 3] and the references cited therein).

Over the past decade, newer antihistamines have been developed with a specific intent of trying to limit or eliminate sedation as an adverse effect. The antihistamines that are the subject of this safety review have been associated with fewer reports of sedation as compared to the older OTC antihistamines, and in clinical trials the frequency of sedation in patients treated with these drugs is generally only slightly in excess of that seen in patients treated with placebo. When approved in the United States, loratadine, fexofenadine, and cetirizine were considered to be new molecular entities and as a precaution, pending the availability of a more extensive safety database, they were each approved as prescription-only products. This regulatory pathway has led a situation in which the antihistamines that are most associated with sedation are widely available OTC, while the antihistamines that less likely to be associated with sedation are available by prescription only.

The FDA has historically adopted a conservative approach to approval of OTC marketing for new drugs and in particular new molecular entities. A decision to approve a new drug for OTC marketing has generally been deferred until a time at which the accumulated postmarketing safety data are adequate to allow a more accurate assessment of the true safety of the drug, and to allow a more complete assessment of whether the drug can be used safely by consumers without the oversight of a physician or other caregiver. The merit of this conservative approach is exemplified by the regulatory history of two other "non-sedating" antihistamines: terfenadine (Seldane) and astemizole (Hismanal). These drugs were initially approved in the U.S. as prescription drugs. Seldane, in particular, was later considered for OTC status. However, within the first several years of marketing of these drugs, a serious safety concern related to cardiac arrhythmias was what eventually resulted in these drugs being withdrawn from the U.S. market.

In July 1998, Dr. Robert Seidman, as a representative of Blue Cross of California, filed a Citizen Petition requesting that the Agency remove the

prescription-dispensing requirements of section 503(b)(1)(C) of the Federal Food, Drug and Cosmetic Act for three of the newer generation antihistamine single ingredient products and two combination antihistamine-decongestant products/formulations containing the active moieties loratadine, fexofenadine, and cetirizine. The drug products that are the subject of the Citizen Petition are summarized in the table below. The petitioner argued, in part, that the newer antihistamines were as safe or safer than the currently marketed OTC antihistamines and should be marketed OTC to make them more readily available to consumers. (NOTE: Not all currently approved products that contain loratadine, fexofenadine, and cetirizine are mentioned in the Citizen Petition or in the table. Other approved products include loratadine (Claritin) syrup, ceterizine (Zyrtec) syrup, loratadine (Claritin RediTabs) rapidly disintegrating tablets, and fexofenadine (Allegra) multiple strength tablets. However, these products have been included in the safety review and would be considered as part of any Agency response to the Citizen Petition.)

APPROVED FORMULATIONS CONTAINING THE ACTIVE MOIETIES
LORATADINE, FEXOFENADINE, OR CETIRIZINE REFERENCED IN THE
CITIZEN PETITION

<u>Drug Product</u>	<u>Drug Substance and Dose</u>	<u>NDA</u>	<u>Sponsor</u>
Allegra Capsules	Fexofenadine 60 mg	20-625	Aventis
Allegra-D Extended Release Tablets	Fexofenadine 60 mg Pseudoephedrine 120 mg	20-786	Aventis
Claritin Tablets	Loratadine 5 mg	19-658	Schering
Claritin-D 12 Hour Extended Release Tablets	Loratadine 5 mg Pseudoephedrine 120 mg	19-670	Schering
Claritin-D 24 Hour Extended Release Tablets	Loratadine 10 mg Pseudoephedrine 240 mg	20-470	Schering
Zyrtec Tablets	Cetirizine 5 mg	19-835	Pfizer

The safety review summarized in this document was conducted in response to the Citizen Petition to help the Agency to formulate an appropriate response to the actions requested by the petitioner.

REVIEW STRATEGY

The data for this review were primarily derived from three sources: the NDA safety databases for loratadine, fexofenadine, and cetirizine, the spontaneous reporting system (AERS) database, and the published literature. Information from two additional source documents, one from the Canadian drug regulatory authorities, and one from the National Transportation Safety Board (NTSB), were also incorporated into the review. In addition, public comments made at the FDA-OTC Part 15 Hearing held on June 28, 2000 (*see below*), that were relevant to this issue were also considered.

The existing NDA clinical reviews for the approved drug products were surveyed to determine whether potentially relevant information not previously described in the approved product labeling was available for any one of these three moieties. Due to a prior full review by FDA, the primary NDA data were not further re-examined. In conjunction with the fexofenadine evaluation, information regarding the closely related molecule, terfenadine, was also reviewed. Terfenadine was a pro-drug that was rapidly converted in the body to form fexofenadine, which was responsible for the majority of the effectiveness of orally administered terfenadine. While terfenadine's cardiac toxicity is widely known, a comprehensive review of terfenadine's non-cardiac adverse event profile was expected to add substantially to information available for the safety evaluation of fexofenadine.

The AERS database was extensively searched, with concentration of review efforts on AE's that appeared to be most serious or life threatening. A review of the published literature was also conducted to determine whether there were additional safety data available that were not reflected in any of the other databases reviewed.

A general review of the safety profile of the currently marketed OTC antihistamines was also undertaken. It is important to emphasize that the review of these older antihistamines was not intended to be comprehensive, or to suggest that there may be safety issues pertinent to the continued marketing of these products in this country, OTC or otherwise. Rather, the goal was to examine whether the known pharmacological properties of the earlier generation, OTC antihistamines were predictive of, and of value in identifying, potential safety issues not presently associated with the three newer products in question. The limitations of the review of the safety profile of the currently marketed OTC antihistamines are discussed at the beginning of that section.

LORATADINE

There are five approved formulations of loratadine:

NDA 19-658: Loratadine 10 mg (Claritin) tablets, approved April, 1993.

NDA 20-704: Loratadine Zydis (Claritin RediTabs), approved December, 1993.

NDA 19-670: Loratadine 5 mg/pseudoephedrine 120 mg (Claritin-D 12 Hour Extended Release tablets, approved November, 1994.

NDA 20-470: Loratadine 10 mg/pseudoephedrine 240 mg (Claritin-D 24 Hour Extended Release) tablets, approved August, 1996.

NDA 20-641: Loratadine 10 mg/10 mL (Claritin) Syrup, approved October, 1996.

The single ingredient Claritin tablet products are currently labeled for use in children age 6 years and above. Claritin Syrup was recently approved (September 26, 2000) for use in children down to age 2 years. The two Claritin-D formulations are approved for use in adults and children 12 years of age and older.

The NDA reviews for the single ingredient loratadine formulations showed that at the labeled dose of 10 mg once daily, the most commonly reported events from placebo-controlled clinical trials included headache, dry mouth, and somnolence (8% for loratadine vs. 6% for placebo vs. 22% for clemastine⁴ 1 mg BID). Other safety information in the prescription package insert of potential relevance in an OTC setting include recommendations for dosing adjustment in renal failure (because of reduced loratadine clearance) and avoidance of the combination loratadine- pseudoephedrine products (Claritin-D) in patients with cardiac disease as well as hepatic insufficiency. Clinical pharmacology studies reported in the package insert and conducted in normal volunteers revealed no evidence of QT_c prolongation at doses of loratadine up to four times the labeled dose. Drug interaction studies reported in the package insert have demonstrated increased plasma loratadine and descarboethoxyloratadine⁵ levels associated with coadministration of erythromycin, cimetidine, and ketoconazole. No significant effects on the QT_c interval were observed in these studies.

As of April, 2000, the AERS database contained 4081 adverse event reports in association with products containing loratadine, including 55 reports with death as an outcome. The most prevalent event categories were for "drug ineffectiveness," "drug interaction," "headache," and "palpitations." Among the serious events, three categories were identified as potential areas of concern: ventricular arrhythmias and sudden death, seizures, and hepatotoxicity. These adverse events are further evaluated below.

There were a total of 86 cases of ventricular arrhythmias, including 16 deaths, reported in association with loratadine use. Careful review of these reports by

FDA staff revealed that there were confounding factors present in the majority of cases that precluded a definitive conclusion that loratadine was causally related to the reported adverse event. These confounding factors included use of concomitant medications that might be associated with arrhythmias and pre-existing cardiovascular disease. It remains unclear whether concomitant cardiovascular disease is predictive of an arrhythmic event in association with loratadine or simply reflects the type of patient more likely to have been prescribed loratadine, given the known association of other “non-sedating” antihistamines (i.e, terfenadine and astemizole) with ventricular arrhythmias.

There were a total of 43 cases of seizures reported in association with loratadine use. Careful review of these reports by FDA staff suggested that a causal association with loratadine was possible or likely in 26 of the cases. Seizures are currently included as an adverse event in the loratadine prescription package insert. A review of the professional labeling of several currently marketed OTC antihistamines suggests that as a class, antihistamine products may rarely be associated with seizures.

Rare occurrences of liver-related events have been reported, including abnormal hepatic function, jaundice, hepatitis, and hepatic necrosis, and are currently included in the loratadine prescription package insert. In AERS, there were a total of 103 cases of hepatic injury reported in association with loratadine use. Of these, there were five cases of hepatic failure, of which four required liver transplantation. Careful review of these reports by FDA staff revealed that there were confounding factors in 3 of the 5 cases of hepatic failure that precluded a definitive conclusion that loratadine was causally related. These confounding factors included use of concomitant medications that might be associated with liver failure and recent foreign travel. To further evaluate the potential association between loratadine and hepatic failure, OPDRA reviewers undertook substantial efforts to establish a comparative background rate for occurrence of hepatic failure, which is known to occur “spontaneously” (i.e., without an identifiable cause) and which is not uncommonly reported in association with use of a wide variety of drugs. The reporting rate for hepatic failure in association with use of loratadine was several fold lower than the calculated background rate of hepatic failure (i.e., 1 per million person years). In considering these data, it is important to remember that underreporting of adverse events is a well recognized limitation of spontaneous reporting systems. Although there is no clear causal relationship between loratadine use and the occurrence of hepatic failure, the possibility that loratadine use may very rarely result in hepatic failure cannot be excluded.

Soon after approval and marketing of Claritin-D 24 Hour Extended Release Tablets in 1996, numerous reports of tablets becoming lodged in the patient's esophagus were received. Some of these cases were serious in nature and required endoscopic removal of the tablet, which had adhered tightly to the esophageal mucosa. This problem was thought to be related to the tablet coating and possibly the shape and size of the tablet. The tablet coating and

shape were changed in December 1998. No such serious adverse events have been reported for the new formulation.

A careful review of the published literature for loratadine did not provide additional insight regarding the primary areas of safety concern, nor did it identify new adverse events that were not observed in the other safety databases.

For loratadine, a report prepared by the Therapeutic Products Programme of the Bureau of Licensed Products Assessment (Canadian regulatory authorities) dated June 22, 2000 was reviewed by the FDA review team.⁶ This document was prepared as part of an ongoing, comprehensive surveillance inquiry of all newer generation antihistamines presently marketed in Canada. A safety analysis of loratadine was included in this report, with the focus primarily being on cardiovascular risk. The data reviewed in the report included global safety data submitted by the drug sponsor, including all Canadian domestic as well as foreign adverse event reports, published case reports and clinical trials, and any new scientific information relevant to a benefit-risk assessment. The current marketing status of loratadine in Canada as well as internationally was also reviewed. A summary of the findings and conclusions of this report are provided below.

Loratadine was first marketed in February, 1988 in Belgium. Approval was granted in June, 1988 in Canada, where it became a non-prescription product in December, 1989. As of March, 1999, loratadine in some formulation had been approved and marketed in 94 countries worldwide, including in 17 as a non-prescription product. With the exception of the switch to non-prescription status in 1989, no significant regulatory action related to safety has been taken regarding loratadine in Canada since its approval.

The most commonly reported cardiac-related adverse events in the databases reviewed in the Canadian report were palpitations and/or tachycardia. There were cases of documented cardiac arrhythmias, although most were confounded by concomitant medications and underlying cardiac disease. The report noted that loratadine does not significantly block HERG potassium channels under the same *in vitro* conditions in which terfenadine has been shown to block these important channels that are involved in cardiac repolarization. Therefore, the authors of this report concluded that a causal association of loratadine with ventricular arrhythmias was unlikely, both from a clinical as well as a scientific standpoint.

On the other hand, new information regarding the *in vitro* affinity of loratadine for an atrial ion channel was discussed in the report. Although considered very preliminary, the possibility that a primary atrial tachycardia could be triggered under certain rare conditions was discussed as an explanation for the confirmed cases of atrial arrhythmia in the database. The authors of this report concluded that these data alone could not support a labeling change.

After careful consideration of the available data, the Canadian regulatory authorities recommended a risk management plan for loratadine. Specifically, the loratadine product monograph would be updated to include “tachycardia” under “Adverse Reactions,” the adverse event databases would continue to be closely monitored by both the sponsor as well as the regulators, and the sponsor would be required to formally investigate the confounders “concomitant medications” and “underlying cardiac disease” on the cardiovascular safety of this drug product. Loratadine would remain a nonprescription product in Canada.

In conclusion, a thorough review of all available safety data for loratadine failed to identify conclusive evidence of a causal relationship between use of loratadine and serious adverse events. Potential safety signals were noted for ventricular arrhythmias and liver failure; however, as described above, the data are inconclusive and suggest that if such events were causally-related to loratadine, they are extremely unusual. A potential association between loratadine use and seizures was observed, consistent with information contained in the current package insert, and likely consistent with a class effect.

FEXOFENADINE

NDA 20-625 for Allegra capsules (fexofenadine 60 mg) was approved on July 31, 1996. Since then, two additional NDA's for drug products containing the drug substance fexofenadine have been approved, Allegra-D tablets (with the decongestant, pseudoephedrine: NDA 20-786, approved December, 1997) and Allegra multiple strength tablets (fexofenadine 30, 60, and 180 mg: NDA 20-872, approved February, 2000). Single ingredient formulations of fexofenadine are approved for use in adults and in children age 6 years and older. The combination of fexofenadine and pseudoephedrine (Allegra-D) is approved for use in adults and children 12 years of age and older.

The original reviews for these fexofenadine NDAs were assessed with respect to their safety findings. Overall, the placebo-controlled clinical trials included data from over 2000 patients age 12 years to adult. Adverse experiences occurring at a frequency of greater than >1.0% and which were more common in fexofenadine-treated patients compared to placebo included viral infection, nausea, dysmenorrhea, drowsiness (0.9% for placebo BID vs. 1.3 % for Allegra 60 mg BID), dyspepsia, and fatigue. Adverse experiences reported from Allegra-D trials reflected the contribution of the pseudoephedrine component. These adverse events noted in the preapproval clinical trials are adequately described in the “Adverse Experiences” section of the label for each of these drug products.

A literature review revealed no case reports or citations describing unique or unexpected adverse events not already included in product labeling, or covered adequately by review of the AERS post-marketing database.

As of April 5, 2000, there were a total of 1768 adverse event reports in the AERS database associated with use of fexofenadine, 360 of which had a serious outcome and 18 of which resulted in death. The in-depth review of these data focused primarily on events that were serious and/or potentially life threatening. These included reports of ventricular arrhythmias and sudden death, seizures, and drug interactions.

A total of 39 cases of ventricular arrhythmias, including 11 deaths have been reported in association with use of fexofenadine. A detailed review of these cases by FDA staff revealed that evaluation of a majority of the total cases and 8 of the 11 deaths were confounded by a history of cardiac disease and/or use of one or more concomitant medication possibly associated with arrhythmias in the affected individual. Concomitant drugs included drugs that belong to classes known to be associated with prolongation of the QT_c, in particular cisapride, macrolides, or antifungals. A definite causal association between use of fexofenadine and ventricular arrhythmias was not supported by the data; however, the possibility of such rare events cannot be excluded.

A total of 30 cases of seizures associated with the use of fexofenadine were included in the AERS database. A detailed review of these cases by FDA staff revealed 17 cases of new onset seizures or increase in seizure frequency that were possibly associated with fexofenadine, by generally accepted epidemiological criteria. Seizure as an adverse event of fexofenadine use is not listed in the current approved package insert.

A careful review of reports of possible drug-drug interactions associated with fexofenadine disclosed 9 reports of cardiac dysrhythmia associated with the co-administration of fexofenadine plus a macrolide antibiotic. The cause of the arrhythmia in these cases remains unexplained. Although clinical pharmacology studies have demonstrated that coadministration of a macrolide antibiotic or an azole antifungal increases plasma fexofenadine levels, elevated plasma fexofenadine levels have not been shown to have a significant effect on QT_c. Conversely, fexofenadine has not been shown to increase plasma macrolide or azole levels, a mechanism by which QT_c prolongation might occur.

Three cases of coagulation abnormalities have been reported following co-administration of fexofenadine and warfarin. The mechanism of a possible drug interaction is unclear, although alteration of protein binding is one possibility.

Fexofenadine is the active metabolite of terfenadine, but lacks the pro-drug's ability to inhibit the main subunit of the HERG potassium channel *in vitro*, which is felt to be the primary mechanism responsible for cardiac arrhythmias

associated with terfenadine use. As the sole active metabolite of terfenadine, fexofenadine is predicted to have a non-cardiac adverse events profile reflective of terfenadine, and to be safe from a cardiac perspective. A full safety review of terfenadine, excluding cardiac events, was therefore conducted by DPADP to supplement the available post-marketing data available for fexofenadine.

As of 20 March 2000, there were a total of 6,186 adverse event reports associated with the use of terfenadine in the AERS database. Many of the serious adverse events and deaths could be ascribed to cardiovascular causes, the consequence of toxicity unique to terfenadine and unlikely to be relevant for fexofenadine. Alopecia was the 2nd most common non-cardiac AE, and review of individual cases argues for a causal relationship to the drug. Alopecia has also been reported in association with fexofenadine use. There were 113 reports of seizures/convulsions associated with use of terfenadine. As noted above, seizures have also been reported to occur in association with fexofenadine use, as they have with most first generation antihistamines.

Review of the medical literature for terfenadine retrieved a total of 1095 references over 25 years (1975 – 2000). Review of the adverse events associated with the use of terfenadine reported in the medical literature generally mirrored the known cardiac toxicity of terfenadine and otherwise complemented the AERS/SRS search. No unique or unexpected adverse events attributable to terfenadine were reported in the medical literature.

In conclusion, a detailed review of all available safety data for fexofenadine did not reveal conclusive evidence of a causal association between fexofenadine use and serious and/or life threatening adverse events. A possible association between fexofenadine use and seizures was noted and this is not currently reflected in the package insert. A potential signal of ventricular arrhythmias in association with fexofenadine use was detected, however, the data were inconclusive and the known pharmacologic properties of fexofenadine argue against a causal link.

CETIRIZINE

Cetirizine is an active metabolite of hydroxyzine, a currently marketed prescription antihistamine. In clinical trials cetirizine has been associated with somnolence at a rate slightly greater than that seen with placebo (13.7% in adults, 4.2% in children at a dose of 10 mg).

There are two approved formulations of cetirizine:

NDA 19-835: Cetirizine 5 mg (Zyrtec) tablets, approved December, 1995.

NDA 20-346: Cetirizine 1 mg/1 mL (Zyrtec Syrup), approved September, 1996.

Cetirizine tablets are currently labeled for use in adults and children age 12 years and above at a dose of 5 to 10 mg once daily. Cetirizine Syrup is approved for use in children down to age 2 years. Approved dosing for children age 6 to 11 years is 5 to 10 mg once daily and for children age 2 to 5 years is 2.5 mg (2.5 ml Zyrtec Syrup) once daily.

The NDA reviews for these cetirizine formulations showed that at the labeled dose of 10 mg once daily, the most commonly reported events from placebo-controlled clinical trials included somnolence (13.7% for cetirizine vs. 6.3% for placebo), fatigue (5.9% vs. 2.6%), and dry mouth (5.0% vs. 2.3%). The frequency of reported psychiatric disorders after administration of cetirizine was twice that of placebo (18% compared to 9%) in placebo-controlled studies in adults. There was no gender difference.

A total of four clinical pharmacology studies were conducted prior to approval to ascertain the potential effect of cetirizine on cardiac repolarization, specifically QT_c. There was no evidence of QT_c prolongation in three of these studies at doses up to six times the labeled dose of 10 mg for up to 7 days. A fourth study showed a 9.1 msec increase in QT_c with cetirizine (ketoconazole alone showed an increase of 8.3 msec in the same study, the co-administration of the two was associated with a QT_c of 17.4 msec). The validity of this finding has been questioned due to the absence of a known PK interaction between cetirizine and ketoconazole, the absence of preclinical data demonstrating an impact of cetirizine on QT_c, and concerns about the reproducibility of this finding. There was no evidence of ECG changes supportive of a QT_c effect in either the adult or the pediatric phase 3 controlled clinical trials conducted for product approval.

Additional drug-drug interaction studies have disclosed no significant impact of coadministration of ketoconazole or the macrolide antibiotics erythromycin or azithromycin on cetirizine levels.

Other safety information from the approved package insert of potential relevance in an OTC setting include recommendations for dosing adjustment in patients with renal failure and hepatic insufficiency, and in geriatric patients (each because of reduced clearance of cetirizine in that patient population).

As of March, 2001, the AERS database contained a total of 3096 adverse event reports in association with products containing cetirizine. The most prevalent event categories were "drug ineffective" and adverse event terms encoding psychiatric events. Specifically, 39.3% of adverse reaction reports (n = 1216) for cetirizine included one or more nervous system or psychiatric terms. These included sedation (306), headache (107), insomnia (98), syncope (54), agitation (49), nervousness (48), convulsions (44), confusion (41), anxiety (40), paresthesia (38), tremor (38), abnormal dreams (37), depersonalization (34), malaise (34), depression (32), hyperkinetic syndrome (27), abnormal thinking (26), loss of consciousness (25), and hallucinations (23). There were 16 deaths,

four of which were possibly attributable to a primary nervous system or psychiatric event. One patient committed suicide when he became confused, depressed and had hallucinations after taking cetirizine.

Among the serious events, three categories were identified as potential areas of concern: convulsions/seizures, ventricular arrhythmias, and thrombocytopenia.

As of April 2000, there were 16 reports of new onset seizures temporally related to cetirizine administration. In 11 other cases, there was exacerbation of seizures after initiating treatment with cetirizine. Data are incomplete, but there was a positive dechallenge in 13 patients and a positive rechallenge in 4 patients, suggestive of causality.

As of April 2000, there were 27 cases of ventricular arrhythmias, sudden cardiac death and QT prolongation temporally associated with cetirizine administration. About 50% of the patients had pre-existing cardiac disease or were taking a concomitant medication that could prolong the QT interval. Four patients were taking a medication that could induce an arrhythmia in a patient with pre-existing QT prolongation. Torsades de pointes was reported in 3 patients and ventricular tachycardia in 6 patients. Asymptomatic prolongation of the QT interval was noted in 4 patients and symptomatic prolongation in 6 patients. There were 5 fatalities in this group. The majority of these patients were adult women. In four patients, the event occurred the same day that treatment with cetirizine was initiated. Based on a careful review of these cases by FDA it appears that a causal relationship may be present between cetirizine and cardiac arrhythmias, however, the data are by no means conclusive.

There were 11 cases of thrombocytopenia possibly associated with cetirizine. Seven cases were domestic and four were non-US. Seven of these cases were reported solely as thrombocytopenia, the remainder as ITP, TTP, or pancytopenia. The lowest platelet count reported was 1000, with three of the four cases reporting nadir levels less than 10,000. The outcomes include one death and seven patients that were hospitalized. Cetirizine and hydroxyzine have known cross-reactivity with the piperazines, and thrombocytopenia associated with piperazines has been reported in the literature. Based on a careful review of these data by FDA staff it appears that there may be a causal relationship between cetirizine and rare reports of thrombocytopenia; however, the data are not conclusive.

The published literature did not provide additional insight regarding the primary areas of safety concern.

In conclusion, an extensive review of adverse event reports associated with use of cetirizine revealed possible associations between cetirizine and sedation, neuropsychiatric events, including seizures, cardiac arrhythmias, and thrombocytopenia. There is a preponderance of neuropsychiatric adverse events,

particularly sedation, which may exceed the rate of reporting of similar events for loratadine and fexofenadine. The data are inconclusive with regard to a causal relationship between cetirizine and arrhythmias and thrombocytopenia.

OTC ANTIHISTAMINES

Additional review was conducted of the safety experience with currently available OTC antihistamines other than known sedating effects. The review focused not only on the primary areas of interest for the newer generation antihistamines (seizures, cardiac and hepatic toxicity, thrombocytopenia, and metabolic interactions) but also screened for the occurrence of other potential events of interest.

There are 13 antihistamines marketed under the OTC monograph system, first established in 1976: brompheniramine, chlorcyclizine, chlorpheniramine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine (2 salts), doxylamine, phenindamine, pheniramine, pyrillamine, thonzylamine and triprolidine. Some of these compounds are also marketed under NDAs, as extended release formulations or higher strength products. Another first generation antihistamine, clemastine, was switched from prescription to OTC status in 1992 (NDAs 17-661 and 18-298). These antihistamines represent several structural classes: the ethanolamine, propylamine and piperazine derivatives. In general, these products are labeled for use in children as young as 6 years. The professional labeling intended for health practitioners and not for the general public provides information for dosing several of these antihistamines down to the age of 2 years.

Since the clinical data supporting the monograph and/or the original approval of each of the NDAs is over 20 years old, the NDAs were not reviewed for safety information. A full search of the AERS and SRS databases was also considered impractical due to the number of moieties and volume of reports, the anticipated age of these reports and consequently the difficulty accessing them, and the predominance of consumer-generated reports in the database. A search of the published literature was able to circumvent a few of these problems (see below).

A search of the AERS database for cases of liver failure associated with any of the OTC antihistamines located a total of 19 reports. Attribution was confounded by the concomitant administration of acetaminophen. Only three cases could be remotely associated with the antihistamine (one case each for clemastine, chlorpheniramine and diphenhydramine).

The published literature was reviewed first for any concerns in the event categories highlighted during reviews of the newer generation antihistamines, then for safety profile in general. The OTC class was searched as a whole, then the specific agents - brompheniramine, chlorpheniramine, clemastine and diphenhydramine, based on their predominance in the marketplace.

Overall, the most common adverse effects of the first generation antihistamines were sedation and anticholinergic events such as dry mouth and urinary retention. The latter are particularly problematic for elderly patients who may have co-morbid conditions such as glaucoma or prostatic hypertrophy. Class labeling provides warnings regarding these events, as well as against the use of these agents with alcohol and sedative drugs or when driving a motor vehicle or operating heavy machinery. It has been a long held belief that first generation antihistamines may reduce the volume and cause thickening of bronchial secretions, thus the current class labeling contains warnings regarding use in patients with emphysema or chronic bronchitis.

Less common events include paradoxical excitation, characterized by restlessness and insomnia. Although the labeling identifies this event as more common in children, it has been reported in adults, particularly among geriatric patients. A recent survey of elderly, ambulatory men and women (60-92 years; N=47) who were self-medicating with OTC antihistamines for insomnia reported that agitation/restlessness was experienced by 21% of the respondents.⁷ Other side effects reported by this group included dry mouth (47%), daytime somnolence (28%), memory problems (19%), urinary retention (17%), constipation (17%), and headaches (13%). On average, the patients surveyed in this group had two concurrent medical conditions (range 0-6) and were taking 4 concomitant medications (range 0-10). The problem of polypharmacy and drug interactions with the first generation antihistamines is covered briefly below.

Other less frequent events that were not considered to be life-threatening have included acute dystonic reactions with dexbromphenamine⁸, rash and urticaria (especially diphenhydramine, multiple references).

Serious and life-threatening reactions with the OTC antihistamines have been described in the literature, including paranoid psychosis and hallucinations with triprolidine,^{9,10,11} rhabdomyolysis with doxylamine¹² and diphenhydramine¹³, seizures with brompheniramine¹⁴ and others¹⁵, and pyloric stenosis associated with maternal use of triprolidine.¹⁶ First generation antihistamines have as a class been associated with rare cases of agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia and pancytopenia¹⁵ Although any adverse event is likely to be under-reported, these serious hematologic reactions are even more prone to this. Correct attribution is not only hindered by the time lag between exposure and the development of symptoms, but also by the attitudes of patients themselves, who may not regard these products as true “drugs” because of their OTC availability.

Inadvertent diphenhydramine overdose is not uncommon, particularly when oral and topical products are combined on a patient with cutaneous lesions (e.g. chicken pox/varicella; multiple references). Presentation resembles atropine overdose, with mydriasis, tachycardia, fever, urinary retention, visual and

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auditory hallucinations, dry mouth and skin, ataxia, and seizures all reported. Autopsy findings described in lethal overdoses include pulmonary and visceral edema. Three of the four cases described in a recent review were characterized by cardiomegaly and marked myocardial fibrosis, suggesting underlying cardiac dysfunction may predispose an individual to a lethal outcome in an overdose situation.¹⁷

Adverse hepatic events have not been reported to be associated with the use of these antihistamines in AERS to any significant extent, and no notable cases were found in the literature for the relevant moieties. Information regarding the metabolic pathways of these antihistamines is scant, although clemastine, chlorpheniramine and diphenhydramine have been described as substrates and inhibitors of the P450 isoenzyme CYP2D6. While it has been suggested that these agents may be capable of producing clinically relevant interactions at therapeutic plasma concentrations, specific interactions have not been identified.¹⁸

Recently, the potential for cardiac toxicity and CNS effects, particularly the potential to lower seizure threshold, have been studied primarily for diphenhydramine. This moiety has been found to possess $K_{V(r)}$ channel-blocking properties and it is suggested that administration to individuals who are poor metabolizers or concomitantly using other inhibitors of CYP2D6, may predispose to cardiac or seizure events.¹⁹ While cardiac events have been described very rarely in the literature, and are commonly attributed to the anticholinergic activity of first generation agents, seizures have been more commonly described, particularly in cases of overdosage (see above).

Overall, although generally accepted as appropriate OTC drugs, the first generation antihistamines agents possess a number of safety concerns, some of which are serious, in addition to their widely recognized sedative and cognition-impairing properties. It is not surprising that CNS events predominate for these older antihistamines, given that these agents readily cross the blood-brain barrier. Anticholinergic events are also common, another property predicted by their pharmacology. Both of these types of adverse reactions are less common in the newer generation products.

Although the occurrence rates of adverse events attributable to the OTC antihistamines cannot be directly compared to those of loratadine, fexofenadine, or cetirizine due to the many confounders already discussed, these three products may offer certain safety advantages over the currently available first generation antihistamines, primarily with regard to sedation and cognition. This is not to malign to currently available OTC antihistamines, many of which are labeled as OTC sleep aids, but to acknowledge that a choice of appropriately labeled drug products in the OTC marketplace can be expected to aid the consumer to tailor product selection to one most appropriate to the intended use.

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