CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211415Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 13, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 211415
Product Name and Strength:	Quzyttir (cetirizine hydrochloride) injection, 10 mg/mL
Applicant/Sponsor Name:	JDP Therapeutics, Inc.
FDA Received Date:	August 9, 2019
OSE RCM #:	2019-10-2
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on August 9, 2019 for Quzyttir. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container label and carton labeling for Quzyttir (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are a response to our previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Vee S. Label and Labeling Review for Quzyttir (NDA 211415). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 01. RCM No.: 2019-10-1.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
08/13/2019 12:08:38 PM

IDALIA E RYCHLIK
08/13/2019 02:04:23 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 5, 2019

To: Renee Kleris, Clinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Susan Rhee, Regulatory Project Manager, DPARP

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Quzyttir (cetirizine) injection, for intravenous use

NDA: 211415

In response to DPARP's consult request dated January 24, 2019, OPDP has reviewed the proposed prescribing information (PI) and carton and container labels for the original NDA submission for Quzyttir (cetirizine) injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on July 31, 2019, and are provided below.

Carton and Container Labels: OPDP has reviewed the attached proposed carton and container labels received by electronic mail from DPARP on August 5, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
08/05/2019 03:11:05 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 1, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 211415
Product Name and Strength:	Quzyttir (cetirizine hydrochloride) injection, 10 mg/mL
Applicant/Sponsor Name:	JDP Therapeutics, Inc.
FDA Received Date:	July 29, 2019
OSE RCM #:	2019-10-1
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 29, 2019 for Quzyttir. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container label and carton labeling for Quzyttir (Appendix A) to determine if it is acceptable from a medication error perspective. We reviewed the original container label and carton labeling submitted in our previous label and labeling review.[a] However, our recommendations were not conveyed to JDP Therapeutics prior to the Applicant submitting the revised labeling.

2 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. We provide recommendations for the Applicant in Section 3.

[a] Rychlik, I. Label and Labeling Review for Quzyttir (NDA 211415). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 22. RCM No.: 2019-10.

3 RECOMMENDATIONS FOR JDP THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Carton Labeling and Container Label)

a. Package type statement is incomplete and competes for readability with the Proprietary name. As accurately defined package type statement is necessary to identify how the medication should be safely handled and used. This statement should be located away from other important product information to enhance readability of all information. Delete the statement "(b) (4)" above the product's proprietary name. Revise the statement "(b) (4)" to read "Single-Dose Vial – Discard Unused Portion".

b. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Carton Labeling

a. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)" to read "Recommended Dosage: See prescribing information."

C. Container Label

a. Net volume statement competes for prominence with more important information on the PDP. Net quantity statement interferes with the readability of other important information (e.g. proprietary name, established name, strength, route of administration) on the PDP. This may lead to wrong dose errors. Decrease the font size and un-bold the net quantity statement to reduce the prominence of the statement as compared to more important product information on the PDP. Consider relocating the statement to the bottom half of the label.

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/s/

SARAH K VEE
08/01/2019 09:06:47 AM

IDALIA E RYCHLIK
08/01/2019 09:58:57 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Memo

Date:	July 3, 2019
Reviewers:	Jill K Logan, PharmD, BCPS Division of Pharmacovigilance I (DPV-I) Kelly Harbourt, PharmD, BCCCP DPV-I
Team Leader:	Lisa Harinstein, PharmD, BCCCP Safety Evaluator Team Leader DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Quzyttir (cetirizine)
Subject:	Overdose
Application Type/Number:	NDA 211415
Applicant/Sponsor:	JDP Therapeutics
OSE RCM #:	2019-1202

****This document contains proprietary American Association of Poison Control Centers data obtained by FDA under contract. This data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology. All product codes must be redacted for public release. ****

1 INTRODUCTION

The purpose of this consult memo is for the Division of Pharmacovigilance I (DPV-I) to provide the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) an analysis of postmarketing cases of supratherapeutic cetirizine exposures in the FDA Adverse Event Reporting System (FAERS) database, medical literature, and the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS). DPARP requested this analysis to inform their review of a 505(b)(2) New Drug Application (NDA 211415) for intravenous (IV) cetirizine.

1.1 BACKGROUND

Antihistamine medications targeting the H_1 histamine receptor are common medications used for a variety of indications such as allergies, urticaria, anaphylactic reactions, and motion sickness.[1] Cetirizine, the major metabolite of hydroxyzine, is a second-generation H_1 antihistamine agent. Cetirizine was approved for use in oral formulations in 1995 and became available as an over-the-counter product in 2007.[2] Currently, an IV formulation of cetirizine (proposed brand name of Quzyttir) has been submitted under the 505(b)(2) regulatory pathway by JDP Therapeutics for the indication of acute urticaria in patients 6 months of age and older.

H_1 antihistamines are typically divided into two classes: first-generation and second-generation. First-generation H_1 antihistamines are lipophilic and are capable of crossing the blood brain barrier.[3] Second-generation agents are peripherally selective and do not penetrate into the central nervous system (CNS) well because of their hydrophilicity and other pharmacologic differences.[3] As a result, sedation is more frequently associated with first-generation agents. Appendix A compares the clinical effects of first- and second-generation H_1 antihistamines. If approved, IV cetirizine will be the only second-generation H_1 antihistamine available for IV administration.

Clinical guidelines for the treatment of acute urticaria designates H_1 antihistamines as the "cornerstone of therapy" for acute presentations.[4] The application under review submitted clinical trial data from healthy adult volunteers for safety, tolerability, and pharmacokinetic (PK) outcomes of IV cetirizine as well as clinical trial data from adult patients comparing IV cetirizine to IV diphenhydramine (a first-generation H_1 antihistamine) to support the indication of acute urticaria. The sponsor suggests that IV cetirizine will provide clinical benefit over IV diphenhydramine when treating acute urticaria (b) (4) .[2] This application, however, has not submitted new pediatric studies.

On June 6, 2019, DPARP consulted DPV-I requesting an analysis of postmarketing data to see if there are any cases of cetirizine overdose that might provide more information to help support approval of IV cetirizine in the pediatric population given the limited PK data submitted within the NDA for IV cetirizine. DPV-I was initially requested to focus on pediatric overdose cases. On June 18, 2019, DPARP met with DPV-I to discuss and clarify the consult. Specifically, DPARP requested an analysis of all pediatric and adult cases reporting administration of a one-time dose of greater than 60 mg of cetirizine. This dose cut-off was chosen based on results of a

thorough QT study which did not result in a significant effect on QT prolongation in adults given 60 mg of oral cetirizine (see Section 1.2 for additional information).

1.2 SUPRATHERAPEUTIC CETIRIZINE EXPOSURE RISK

The potential for supratherapeutic cetirizine concentrations, defined as blood concentrations exceeding those achieved with therapeutic administration of oral cetirizine at approved doses (see Table 1), or overdoses of cetirizine may occur with the approval of the IV product. Possible situations leading to the development of supratherapeutic exposures or overdoses of cetirizine include (1) potential dosing errors caused by the concentration difference in the product under review (10 mg/mL) versus the currently available oral syrup (1 mg/mL), (2) the possible confusion with H_1 antihistamine dosing or frequency, and (3) differences of PK properties at the proposed therapeutic IV dose such as the higher maximum concentration (Cmax) reached with the IV versus oral cetirizine administration demonstrated in adult PK studies.[5]

Table 1. Cetirizine Dosing by Age and Route

Age	Proposed IV Dose[6]	Approved Oral Dose[7]
Adults 12 years and older	10 mg daily	5 or 10 mg daily
6 to 11 years	5 or 10 mg daily	5 or 10 mg daily
6 months to 5 years	2.5 mg daily	2.5 or 5 mg daily OR 2.5 mg every 12 hours

Additionally, an effect of age on cetirizine PKs has been demonstrated. A PK comparison of cetirizine administration in children versus adults has shown a significantly shorter half-life in the pediatric population when compared with adults.[8] These findings have been confirmed in a retrospective analysis of pooled clinical trial data of 112 children ages 0.5-12 years, suggesting that pediatric dosing recommendations call for smaller but more frequent cetirizine dosing to achieve similar therapeutic concentrations in pediatric patients when compared with adult dosing.[9] As a result, children receiving a usual dose every 24 hours may be exposed to supratherapeutic cetirizine concentrations during the early portion of the dosing interval.

Reassuringly, the safety of cetirizine is supported by its long availability on the market. Single doses up to 60 mg of oral cetirizine have been studied in adult males at the time of initial approval when assessing the impact of cetirizine on cardiac adverse events.[7] Cetirizine, and similar agents, have been associated with a high degree of safety—specifically cetirizine does not appear to have cardiac adverse effects in severe overdose, and it is associated with a low level of sedation when compared to the first-generation H_1 antihistamines.[10] A review on the safety of antihistamines in children states that *in vitro* and *in vivo* study results suggest that intentional and unintentional cetirizine intoxication would result in few adverse events.[10]

Two published cases demonstrating the relative safety of cetirizine overdose in children are described below; both are included in the Agreed Pediatric Assessment Plan and one is also included in Zyrtec labeling.[5,7]

- A published case from Great Brittan in 1997 described an 18-month-old boy who accidentally ingested 180 mg of cetirizine by drinking the cetirizine study solution.[11] He was admitted to the hospital, and vomiting was induced with syrup of ipecac 75 minutes after cetirizine ingestion. After ipecac administration, the patient became slightly

agitated and was reported to be "running around the ward in a lively manner" for approximately 2 hours. It was reported that all other vital and neurologic signs remained stable with no episodes of arrythmia or electrocardiographic abnormalities. Blood concentrations of cetirizine confirmed the ingestion.

- An English-language abstract summarizing a case published in Danish in 1998 described a 4-year-old boy who accidentally ingested 60 mg of cetirizine.[12] Vomiting was induced 90 minutes after ingestion because of severe drowsiness, and he was hospitalized for observation. He was reported to have fully recovered after 5-6 hours without any further treatment and electrocardiographic monitoring was reported as normal.

1.3 REGULATORY HISTORY

Zyrtec (cetirizine oral products);

- December 8, 1995: Cetirizine tablets approved for adults and children 12 years of age and older for seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU).
- September 27, 1996: Cetirizine syrup (1 mg/mL) approved for adults and children 6-11 years of age for SAR, PAR, and CIU.
- May 15, 1998: Cetirizine tablets and syrup approved for adults and children 2-5 years of age for SAR, PAR, and CIU.
- August 10, 2001: Cetirizine 5 mg combination product with pseudoephedrine 120 mg approved for adults and children 12 years of age and older for the relief of nasal and non-nasal symptoms associated with SAR and PAR.
- October 21, 2002: Cetirizine tablets and syrup approved for the relief of symptoms associated with SAR, PAR, or CIU in adults and children 6 months of age and older.
- November 16, 2007: Cetirizine approved for nonprescription use in adults and children 2 years of age and older for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat.
- November 3, 2013: Approval of cetirizine oral syrup was withdrawn. Cetirizine tablets and oral syrup remain available as an over-the-counter product for adults and children 2 years of age and older.

Quzyttir (cetirizine IV); NDA 211415

- February 2, 2014: An Investigational New Drug (IND) application was opened for IV cetirizine
- November 18, 2015: The FDA agreed to the Pediatric Assessment Plan including the following information:[5]
    - "For the proposed cetirizine injection, the NDA's safety profile of the adult population will be based on the pivotal phase III study, the previous pilot phase III, the injection PK studies, and the large amount of safety data from Zyrtec."
    - "The pediatric safety is supported by safety data from Zyrtec oral product's pediatric studies, and by PK extrapolated from the injection's adult data and from Zyrtec oral product's pediatric data."
- December 7, 2018: An NDA was received by the FDA for IV cetirizine.

1.4 PROPOSED PRODUCT LABELING

Submitted draft safety-related labeling of Quzyttir (cetirizine IV), updated November 2018 is summarized below.[6]

> CONTRAINDICATIONS
> Known hypersensitivity to cetirizine, levocetirizine, or hydroxyzine
>
> WARNINGS AND PRECAUTIONS
> Somnolence/Sedation: Exercise caution when driving a car or operating potentially dangerous machinery
>
> ADVERSE REACTIONS
> The most common adverse reactions (incidence > 2%) are somnolence, fatigue, dry mouth, pharyngitis, dizziness (b) (4)

2 METHODS AND MATERIALS

2.1 CASE SELECTION CRITERIA

FAERS and Medical Literature
Reports retrieved from FAERS and published literature were screened for a description of the dosage received by the patient.[a] Per DPARP's consult request, we included reports as a case if they described a patient who ingested greater than 60 mg of cetirizine within a 2-hour timeframe.

AAPCC-NPDS Line Listing
All reports were included for a high-level overview.

2.2 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of Search	June 19, 2019
Time Period of Search	All reports through June 18, 2019
Search Type	Drug Safety Analytics Dashboard Quick Search
Product Terms	Product Active Ingredient: Cetirizine hydrochloride
MedDRA Search Terms (Version 22.0)	Preferred Terms: Accidental exposure to product, Accidental exposure to product by child, Accidental overdose, Accidental poisoning, Completed suicide, Depression suicidal, Drug abuse, Inappropriate schedule of product administration, Intentional overdose, Intentional product misuse, Intentional self-injury, Medication error, Overdose, Poisoning, Poisoning deliberate, Suicidal behavior, Suicide attempt, Suspected suicide, Suspected suicide attempt, Systemic toxicity
* See Appendix B for a description of the FAERS database.	

[a] Dose screening strategy: Dosing ranges (e.g., 5-10 tablets) were recorded as the higher dose, solid oral dosage forms were assumed to be 10 mg unless otherwise specified, liquid oral dosage forms were assumed to be 1 mg/mL unless otherwise specified, doses occurring over a prolonged timeframe (e.g., 70 mg over 48 hours) or where the ingestion timeframe was not assessable were excluded.

2.3 LITERATURE SEARCH

DPV-I searched the medical literature with the strategy described in Table 3.

Table 3. Literature Search Strategy	
Date of Searches	June 28, 2019
Query 1	
Database	PubMed@FDA
Search Terms	("Cetirizine"[Mesh]) AND "Drug Overdose"[Mesh]
Years Included in Search	All years included
Limitation	English language only
Query 2	
Database	Embase
Search Terms	'cetirizine'/exp AND 'drug overdose'/exp AND 'case report'/exp
Years Included in Search	All years included
Limitations	English language only

2.4 AAPCC-NPDS SEARCH STRATEGY

To assess the effect of supratherapeutic cetirizine exposures in pediatric patients, DPV-I searched NPDS **Version 17.1.0** database using the search strategy described in Table 4. Product codes for cetirizine were obtained using Micromedex Tox & Drug Product Lookup and searched by the active ingredient "cetirizine". The search was restricted to closed cases of human exposure calls involving cetirizine products only (single substance) to exclude other potential confounders such as concomitant medications or effects of other substances found in combination products.

Exposure calls received by Poison Control Centers (PCCs) are managed by healthcare professionals with specialized toxicology training. PCC professionals are trained to assess toxicology cases, triage patients to the most appropriate level of care, provide care recommendations, and to obtain follow up information on toxicologic emergencies.

Table 4. NPDS Search Strategy*	
Date of Search	June 13, 2019
Time Period of Search	January 1, 2000, through December 31, 2018
Type of Search	Case Log (Product Code)
Search Restrictions	Minimum Age: 0 years Maximum Age: 18 years Age Estimate categories: <=5 yrs, 6-12 yrs, Teen, Unknown child (<=19 yrs) Call type: Exposure Case status: Closed Species: Human Product Type: Contains at least one Single Substance Only: Yes Route: Ingestion
Clinical Effects	Related only

Table 4. NPDS Search Strategy*	
Exposure Product	Cetirizine
Product codes†	See Appendix C for full list of product codes
Reason for Exposure	Unintentional - General, Unintentional - Environmental, Unintentional - Occupational, Unintentional - Therapeutic error, Unintentional - Misuse, Unintentional - Bite / sting, Unintentional - Food poisoning, Unintentional - Unknown, Intentional - Suspected suicide, Intentional - Misuse, Intentional - Abuse, Intentional – Unknown
Outcome	Minor effect; Moderate effect; Major effect; Death; Death, Indirect report
Report Names	Case Log (Product Code) – Aggregate Counts Per Year Case Log (Product Code) – Demographics Listing (Relational) Case Log (Product Code) – Route Listing (Relational) Case Log (Product Code) – Scenario Listing (Relational) Case Log (Product Code) – Therapy Listing (Relational) Case Log (Product Code) – Clinical Effect Listing (Relational) Case Log (Product Code) – Substance Listing (Relational)

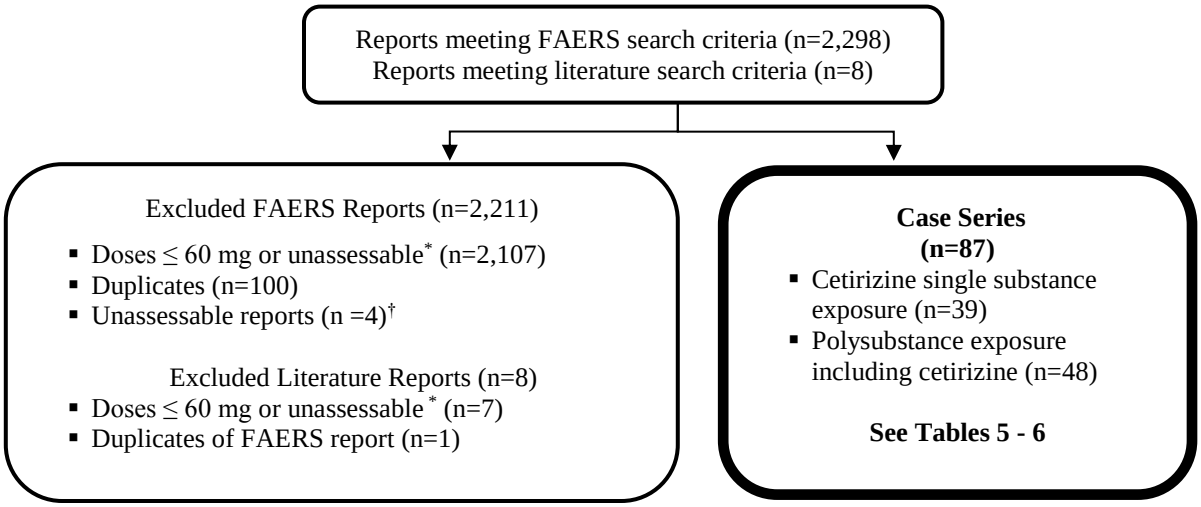
* See Appendix D for a description of the NPDS database.
† Product codes were obtained from Micromedex by searching Tox & Drug Product Lookup for active ingredients "cetirizine".

3 RESULTS

3.1 FAERS AND LITERATURE CASE SELECTION

The FAERS search retrieved 2,298 reports and the literature search retrieved 8 reports. After applying the case selection criteria in Section 2.1 and accounting for duplicate reports, 87 cases were included in the case series describing supratherapeutic cetirizine exposures (see Figure 1). Of note, the published case from Great Brittan described in Section 1.2 was identified in the FAERS search and included in the case series.

Figure 1. FAERS and Literature Case Selection



* Dosing unassessable includes reports describing an unknown dose, route of administration other than oral, unclear administration timing or total dose administered over a prolonged period, reports describing no cetirizine administration, reports not including an individual patient, and reports describing the use of the Japanese cetirizine dry syrup (12.5 mg of cetirizine hydrochloride per 1 gram of product).

† Unassessable reports include those with an unclear adverse event described (n=2), cetirizine dose possibly incorrectly reported (n=1), or a social medial report with unclear information (n=1).

Table 5 summarizes the 87 FAERS cases of supratherapeutic cetirizine exposure for this case series.

Appendix E contains a line listing of the 87 cases in this case series.

Table 5. Descriptive Characteristics of Supratherapeutic Cetirizine Exposure Cases in this FAERS Case Series, Received by FDA through June 18, 2019 (N=87)

	All Cetirizine Exposures (n=87)	**Cetirizine Single Substance Exposure (n=39)**	**Polysubstance Exposure Including Cetirizine (n=48)**
Age, years, median (range)	22.2 (1.5-81),	19.8 (1.5-81),	23 (2.6-75)
All reports describing age, n	76	31	45
0 to < 6 years	8	7	1
6 to < 12 years	3	3	0
12 to < 18 years	13	3	10
18 years and older	52	18	34
Sex, n (%)			
Male	25 (28.7)	16 (41.0)	9 (18.8)
Female	60 (69.0)	22 (56.4)	38 (79.1)
Not reported	2 (2.3)	1 (2.6)	1 (2.1)

Table 5. Descriptive Characteristics of Supratherapeutic Cetirizine Exposure Cases in this FAERS Case Series, Received by FDA through June 18, 2019 (N=87)			
	All Cetirizine Exposures (n=87)	**Cetirizine Single Substance Exposure (n=39)**	**Polysubstance Exposure Including Cetirizine (n=48)**
Reason for supratherapeutic exposure, n (%)			
Intentional	57 (65.5)	15 (38.5)	42 (87.5)
Unintentional	17 (19.5)	16 (41.0)	1 (2.1)
Not reported	13 (15)	8 (20.5)	5 (10.4)
Concomitant substances per case, n, median (range)*			3 (1-17), n=46
Frequently reported concomitant substance, n (%)†			
Non-steroidal anti-inflammatory drugs			20 (41.7)
Antihistamines			15 (31.3)
Acetaminophen			13 (27.1)
Antibiotics			13 (27.1)
Opioid agonists			7 (14.6)
Antidepressants (excluding tricyclics)			7 (14.6)
Alcohol			7 (14.6)
Benzodiazepines			6 (12.5)
Antipsychotics			5 (10.4)
Pseudoephedrine			5 (10.4)
Sedative hypnotics			3 (6.3)
Stimulants			3 (6.3)
Serious outcome, n (%)‡	75 (86.2)	28 (71.8)	47 (97.9)
Death	3 (3.4)	1 (2.6)	2 (4.2)
Life-threatening	6 (6.9)	0 (0.0)	6 (12.5)
Hospitalized	48 (55.2)	17 (43.6)	31(64.6)
Required intervention	1 (1.1)	1 (2.6)	0 (0.0)
Other	38 (43.7)	15 (38.5)	23 (47.9)
Report year, n (%)			
1996-2000	10 (11.5)	6 (15.4)	4 (8.3)
2001-2005	14 (16.1)	7 (17.9)	7 (14.6)
2006-2010	12 (13.8)	4 (10.3)	8 (16.7)
2011-2015	19 (21.8)	8 (20.5)	11 (22.9)
2016-2019	32 (36.8)	14 (35.9)	18 (37.5)
Country, n (%)			
Domestic	28 (32.2)	24 (61.5)	4 (8.3)
Foreign	59 (67.8)	15 (38.5)	44 (91.7)

* Two polysubstance exposure cases reported "many" concomitant medications without further specification.

† Cases may report more than one concomitant substance. Other notable concomitant substances included bleach (n=1), aluminum phosphide (n=1), and beta blockers (n=1). The list of concomitant substances is non-inclusive.

‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case may have more than one serious outcome.

Reviewer comment: Less than half (44.8%, 39/87) of the cases involved exposure to cetirizine only; the remaining cases (55.2%, 48/87) involved polysubstance exposures including cetirizine

and most resulted from intentional use (87.5%, 42/48). Agents concomitantly ingested within the polysubstance exposure group included those with significant safety risks (such as acetaminophen, aspirin, and benzodiazepines). Additionally, the polysubstance exposure cases were associated with a higher proportion of serious outcomes (97.9%, 47/48) compared to cetirizine only cases (71.8%, 28/39), and many of the serious adverse events can be attributed to these concomitant agents. For example, of the three cases reporting death, two were from the polysubstance exposure group; one possibly overdosed on rodenticide and died from aluminum phosphide poisoning, and the other death occurred after a massive overdose of venlafaxine (24,150 mg—life-threatening cardiovascular toxicities are associated with doses greater than 8,000 mg[13]) with concomitant cetirizine (300 mg) and meloxicam (270 mg).

Approximately one-third (24/87) of the cases involved pediatric patients less than 18 years of age (see Table 7 for details of the pediatric single substance cetirizine overdoses); pediatric patients 0 to less than 12 years of age mostly ingested cetirizine only (10/13), whereas most of the children >12 years of age ingested multiple substances including cetirizine (10/11). More females than males are reported within our case series, particularly within the polysubstance exposure category.

Table 6 summarizes the dosing reported within the case series as well as the reported adverse events associated with the product ingestion.

Table 6. Dosing and Adverse Events Associated with Supratherapeutic Cetirizine Exposure in this FAERS Case Series, Received by FDA through June 18, 2019 (N=87)

	All Cetirizine Exposures (n=87)	**Cetirizine Single Substance Exposure (n=39)**	**Polysubstance Exposure Including Cetirizine (n=48)**
Cetirizine dose, mg, median (range)*	120 (65-800)	130 (70-800)	115 (65-540)
Cetirizine exposures reporting symptoms, n (%)	65 (74.7)	27 (69.2)	38 (77.6)
Dose, mg, median (range)	150 (70-800)	180 (70-800)	140 (70-540)
Cetirizine exposure reporting no symptoms, n (%)	22 (25.3)	12 (30.8)	10 (20.8)
Dose, mg, median (range)	100 (65-300)	110 (70-300)	100 (65-200)
Neurologic adverse event, n (%)†	44 (50.6)	18 (46.2)	26 (54.2)
Somnolence/fatigue	21 (24.1)	13 (33.3)	8 (1.7)
Depressed level of consciousness/coma	14 (16.1)	1 (2.6)	13 (27.1)
Speaking/moving difficulty or slowness	12 (13.8)	5 (1.3)	7 (14.6)
Agitation	5 (5.7)	1 (2.6)	4 (8.3)
Seizure	4 (4.6)	1 (2.6)	3 (6.3)
Headache	1 (1.1)	1 (2.6)	0 (0.0)
Cardiac adverse event, n (%)†	18 (20.7)	5 (12.8)	13 (27.1)
Tachycardia	11 (12.6)	4 (10.3)	7 (14.6)
Cardiac arrest	3 (3.4)	1 (2.6)	2 (4.2)
Hypertension	3 (3.4)	0 (0.0)	3 (6.3)
Hypotension	3 (3.4)	1 (2.6)	2 (4.2)
Other	3 (3.4)	0 (0.0)	3 (6.3)‡
Bradycardia	2 (2.3)	1 (2.6)	1 (2.1)

Table 6. Dosing and Adverse Events Associated with Supratherapeutic Cetirizine Exposure in this FAERS Case Series, Received by FDA through June 18, 2019 (N=87)

	All Cetirizine Exposures (n=87)	Cetirizine Single Substance Exposure (n=39)	Polysubstance Exposure Including Cetirizine (n=48)
Gastrointestinal adverse event, n (%)†	16 (18.4)	3 (7.7)	13 (27.1)
Abdominal pain	8 (9.2)	1 (2.6)	7 (14.6)
Nausea/vomiting	7 (8.0)	2 (5.1)	5 (10.4)
Decreased motility/constipation	3 (3.4)	0 (0.0)	3 (6.3)
Bloody diarrhea	1 (1.1)	1 (2.6)	0 (0.0)
Anorexia	1 (1.1)	0 (0.0)	1 (2.1)
Respiratory compromise, n (%)	4 (4.6)	0 (0.0)	4 (8.3)
Other adverse event, n (%)	17 (19.5)	8 (20.5)§	9 (18.8)‖

* Dose in mg was calculated on the following assumptions: reports in mg were assessed as reported, reports in volume were assumed to be 1 mg/mL concentration (ounces were assumed to be 30 mL, tablespoons were assumed to be 15 mL, teaspoons were assumed to be 5 mL), reports as dosage forms (e.g., tablets) were assumed to be 10 mg/dosage form. Dose reported as "g", "L", "lbs", "mcg", "mouthfuls", or "taste/lick/drop" were not included in the dose calculation. Dosages reported as ranges were recorded at the highest possible dose.

† A case may have more than one adverse event reported.

‡ Other cardiac adverse events include AV block (n=1), T-wave inversion (n=1), and shortened PR interval (n=1).

§ Other adverse events in the single substance exposure group include hypokalemia (n=2), dry throat and nose (n=1), mydriasis (n=1), methemoglobinemia (n=1), elevated CPK (n=1), blurry vision (n=1), and feeling "unwell" (n=1).

‖ Other adverse events in the polysubstance exposure group include liver failure (n=1), hypoglycemia and respiratory alkalosis (n=1), mild increase in transaminases (n=1), muscle cramping and rash (n=1), increased serum creatinine (n=1), metabolic acidosis with bleeding diathesis (n=1), dry mouth with urinary problems (n=1), increased lactate with dark urine (n=1), and hypokalemia (n=1).

Reviewer comment: The median cetirizine dose of 120 mg within this case series represents a greater than 10-fold overdose for adult patients, and despite these supratherapeutic doses, approximately 25% (22/87) of the identified patients did not report any adverse events. Of the cases reporting adverse events, the median dose was 150 mg corresponding to a 15-fold overdose in adult patients and a 30-fold overdose for pediatric patients. No dose threshold was able to be identified above which all patients developed adverse events, however, precise dose reporting was not available for all cases and limitations exist with any dose estimation strategy. Neurologic adverse events were the most frequently reported adverse events for all groups, however, the severity of these adverse events was higher in the polysubstance exposure group (e.g., depressed level of consciousness) than in the single substance exposure group (e.g., somnolence). Other serious adverse events, such as respiratory compromise, were only reported in the polysubstance group and were not associated with cetirizine single substance exposures. Additionally, many of the adverse events reported within the single substance cetirizine group, such as somnolence, nausea, and abdominal pain, are within the known adverse event profile of therapeutic doses of cetirizine.

With cetirizine single-substance exposure, a solitary case resulting in death was reported which included symptoms of depressed level of consciousness, hypotension, bradycardia, and seizures. Additionally, a case of methemoglobinemia was identified within the single-substance cetirizine exposure group. These cases are described below.

FAERS Case# 5689337, serious outcome—death and other medically serious outcome, Poland, 2004:[14] This published case describes an 18-year-old female patient with a 2-year history of anorexia nervosa (body mass index of 17 kg/m^2) who committed suicide with a cetirizine overdose. The patient ingested 270 mg of cetirizine. She had been treated with cetirizine therapeutically for 4 years for allergic rhinitis prior to the event. Three hours after her cetirizine ingestion, she presented to a treatment facility and was found to be hypotensive (blood pressure of 70/40 mmHg), bradycardic (heart rate of 36-40/min), and to have a decreased level of consciousness. Her laboratory values were significant for a metabolic acidosis (pH=7.13) and hypokalemia (3.1 mmol/L). The patient's condition progressed 30 minutes after presentation (3 hours 30 minutes after ingestion) with the development of generalized convulsive attacks and respiratory failure requiring mechanical ventilation. She was treated with crystalloid infusions, maximum doses of vasopressors (dopamine, dobutamine, norepinephrine), atropine, and "temporary endocavitary electrostimulation" without hemodynamic improvement. After two hours of treatment (5 hours after ingestion), the patient developed ventricular tachycardia which progressed to ventricular fibrillation and cardiac arrest. The patient was unable to be resuscitated. Of note, no QT interval prolongation was observed in echocardiographic evaluations. The authors attributed the fatal outcome to the combination of the cetirizine with underlying electrolyte, metabolic, and endocrine disturbances associated with anorexia nervosa.

Reviewer comment: This case describes a patient who had a fatal outcome after ingestion of a 27-fold overdose of cetirizine without any concomitant substances reported. Because cetirizine is a highly protein bound drug (mean plasma protein binding of 93%),[7] diseases of malnutrition with low albumin levels may lead to an increased free cetirizine concentration when ingested. In the setting of the case described above, this could result in further increasing the effects of the cetirizine overdose. This case demonstrates that cetirizine, with its typically benign adverse effect profile, may result in serious adverse events and death in the setting of massive overdose in patients with underlying risk factors—such as anorexia nervosa.

FAERS Case# 16295987, serious outcome—hospitalization, United States, 2019:[15] This case, published as a poster presentation, describes an 18-year-old female patient with a past medical history of anxiety and depression who ingested 10-16 tablets of 10 mg cetirizine (160 mg maximum dose) for allergy relief of abdominal pain. At the time of emergency department presentation, she was tremulous and anxious. Laboratory values were significant for a low serum bicarbonate (19 mmol/L), high serum creatinine (1.2 mg/dL), high bilirubin (1.9 mg/dL), and her arterial blood oxygen saturation on room air was reported to be normal. Serum tests for acetaminophen and aspirin were found to be normal. Urine tests for illicit drugs and pregnancy were negative. After approximately 4-5 hours, she developed cyanosis without respiratory distress and a pulse oximetry reading of 75% on her left hand and 85% on her forehead. Her oxygen level did not show improvement when treated with 4 L/minute oxygen supplementation via nasal cannula. An arterial blood gas resulted in a methemoglobin level of 38%. She responded to treatment with methylene blue and ascorbic acid. Further workup did not identify underlying causes of methemoglobinemia and the author attributed the cause of methemoglobinemia to the cetirizine overdose.

Reviewer comment: This case describes methemoglobinemia possibly related to cetirizine overdose. This case demonstrates that adverse events of cetirizine overdose may be unexpected

when compared to the adverse event profile of the drug. A supplementary search of FAERS for cetirizine and methemoglobinemia did not retrieve additional cases of this drug-event pair.[b]

Table 7 describes pediatric single substance cetirizine overdoses by age, identified within the FAERS database.

Table 7. Dosing and Adverse Events for Pediatric Cetirizine Single Substance Exposures in this FAERS Case Series, Received by FDA through June 18, 2019 (N=13)

	Ages 0 to < 6 years (n=7)	**Ages 6 to <12 years (n=3)**	**Ages 12 to <18 years (n=3)**
Cetirizine dose, mg, median (range)*	110 (90-180)	100 (90-150)	300 (200-300)
Cetirizine exposures reporting symptoms, n	6	1	3
Cetirizine exposures reporting no symptoms, n	1	2	0
Neurologic adverse event, n†	4	0	3
Somnolence/fatigue	3	0	3
Speaking/moving difficulty or slowness	1	0	1
Agitation	1	0	0
Tachycardia, n	1	0	0
Nausea/vomiting, n	0	1	0
Other adverse event, n	2‡	0	0

* Dose in mg was calculated on the following assumptions: reports in mg were assessed as reported, reports in volume were assumed to be 1 mg/mL concentration (ounces were assumed to be 30 mL, tablespoons were assumed to be 15 mL, teaspoons were assumed to be 5 mL), reports as dosage forms (e.g., tablets) were assumed to be 10 mg/dosage form. Dose reported as "g", "L", "lbs", "mcg", "mouthfuls", or "taste/lick/drop" were not included in the dose calculation. Dosages reported as ranges were recorded at the highest possible dose.
† A case may have more than one adverse event reported.
‡ Other adverse events include mydriasis (n=1) and feeling "unwell" (n=1).

Reviewer comment: Pediatric single substance cetirizine overdose cases reported adverse events consistent with the adverse reaction profile of cetirizine (somnolence, fatigue, nausea) or reported adverse events of little clinical significance. For example, a case reported that a 2-year-old boy possibly drank an estimated dose of 100 mg of liquid cetirizine and developed tachycardia (heart rate unspecified) and dilated pupils. The patient was brought to brought to the emergency department (ED), treated with charcoal, and his symptoms resolved within 6-7 hours. Follow up was obtained from the ED physician who stated that the incident was "not that big of a deal" and that "no adverse effects were reported from the examination." In the youngest age range, the median reported dose of 110 mg is equivalent to a 22-fold overdose which appears to have been tolerated with minimal adverse events.

[b] A supplemental FAERS search was performed on July 3, 2019 for all reports through July 2, 2019 for the Product Active Ingredients of Cetirizine Hydrochloride, Hydroxyzine pamoate, and Hydroxyzine hydrochloride with the Preferred Term Methaemoglobinemia. The search resulted identified 24 reports: 18 reports with cetirizine, all of which are duplicates of FAERS Case# 16295987; and 6 reports with hydroxyzine where the methemoglobinemia was attributed to other concomitant drugs (n=4) or were duplicate reports (n=2).

3.2 AAPCC-NPDS

The NPDS search yielded (b) (4) reports using the search strategy described in Table 4. Table 8 provides the descriptive characteristics of the NPDS reports retrieved. For the purposes of this review, narrative case descriptions were not included and therefore a case-level analysis was not performed.

(b) (4)

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(b) (4)

4 DISCUSSION

Cases identified in FAERS describing single substance cetirizine overdoses (> 60 mg ingested within 2 hours) suggest a mild adverse event profile. Of the single substance cetirizine FAERS cases, approximately 30% did not describe an adverse event or symptom associated with the overdose (reporting a median exposure of 110 mg, an 11-fold overdose for adult patients). Of the cases that did describe an adverse event, the dose of cetirizine was higher (median of 180 mg for single substance cetirizine exposures, an 18-fold overdose for adult patients) suggesting the possibility that adverse events may be more likely as the dose increases, however, no dosing threshold for adverse event development was identifiable from the reported cases. The most frequently reported adverse events in this cohort were somnolence and lethargy, known effects of cetirizine. Furthermore, somnolence and lethargy were the most commonly reported adverse events in the pediatric population (single substance cetirizine exposures) and no clinically significant adverse events were reported in this group with reported doses ranging from 90 to 300 mg. However, patients with underlying risk factors, such as anorexia nervosa or electrolyte imbalances, have the potential to develop serious and clinically significant adverse events with massive cetirizine overdoses as described in the single case of an 18-year-old female with anorexia who committed suicide with a 27-fold overdose of cetirizine. Additionally, our case series identified a case of methemoglobinemia associated with cetirizine overdose, an event that is outside the known adverse event profile of the drug. A supplementary search of the FAERS database for cases of methemoglobinemia with cetirizine did not identify additional cases of this drug-event pair. Patients within our case series who had polysubstance exposures had a higher likelihood of reporting an adverse event associated with a serious outcome, such as requiring hospitalization. It is possible that this increased severity may be attributed to the concomitant product, but it is also possible that cetirizine may contribute to adverse events when combined with other substances.

Many reports of single substance cetirizine exposures were identified in pediatric patients within the NPDS database. Of these reports, the majority described acute exposures (b) (4)%) defined as occurring over a period of 8 hours or less. Additionally, approximately (b) (4)% of the cohort reported doses of 60 mg or greater. Overall, the most frequently reported adverse event, which was also identified in the FAERS case series, were the known adverse events of drowsiness and lethargy. Some cases reported adverse events with the potential for concern, such as tachycardia. Like the FAERS data, adverse events of potential concern were reported at higher doses (where dosing information was available). For example, reports describing tachycardia that contained cetirizine dose information described a (b) (4)fold overdose associated with this adverse event. Importantly (b) (4)% of the (b) (4) reports identified in the NPDS database described a medical outcome of "minor effect" illustrating the relative safety of cetirizine exposures. Furthermore, no cases reported an outcome of death.

When comparing the results from FAERS and NPDS, it is important to acknowledge differences between the patient populations. For example, the FAERS cases included all age groups and all cetirizine exposures over 60 mg within 2 hours, regardless of concomitant substance exposures. FAERS cases not including dosing information were not included in our review. On the other

hand, the NPDS search was limited to pediatric patients with single substance exposures but included all dosages (including those with missing information) of cetirizine and all timeframes of exposure. For NPDS, acute exposure was defined as occurring within 8 hours whereas this was limited to 2 hours for our FAERS cases. Despite these differences, the results from the two data sources were similar in terms of adverse events reported and clinical severity, particularly when comparing the single substance cetirizine exposure cohort from the FAERS case series to the NPDS reports. These findings support the relative safety of cetirizine.

Limitations of both FAERS and NPDS should be taken into consideration when making conclusions based upon the presented data. Both databases rely upon spontaneous reporting and cannot be used to calculate the incidence of adverse events associated with cetirizine exposures. Spontaneous adverse event reports frequently are missing complete information. Therefore, it is possible that serious adverse events were not reported or were not adequately described within a report to make an adequate assessment. Furthermore, single substance cetirizine exposures are referred to throughout the review, however, knowledge of concomitant substance exposures rely upon accurate reporting of all substances involved.

5 CONCLUSION

Overall, DPV-I did not identify any new patterns of unexpected events with supratherapeutic cetirizine exposures; the most frequently reported events were expected based on the known safety profile of cetirizine at approved doses (such as lethargy, somnolence). However, underlying risk factors, increasing cetirizine doses, and polysubstance exposures may place patients at risk for more serious outcomes.

6 REFERENCES

1. Hilal-Dandan R, Brunton LL. Histamine, Bradykinin, and Their Antagonists. Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2e. New York, NY: McGraw-Hill Education; 2016.
2. Kleris R. Medical officer filing review. NDA 211415. Quzyttir (cetirizine). December 7, 2018. DARRTS.
3. Gosselin S. Antihistamines and Decongestants. In: Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS, eds. Goldfrank's Toxicologic Emergencies, 11e. New York, NY: McGraw-Hill Education; 2019.
4. The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. Joint Task Force on Practice Parameters. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2000;85:521-44.
5. Chowdhury B. Agreed Initial Pediatric Study Plan-greement. IND 107689. November 18, 2015. DARRTS.
6. Quzyttir (cetirizine IV) [DRAFT Package Insert]. JDP Therapeutics Inc., Lansdale, PA. Revised 11/2018. GlobalSubmit Review.
7. Zyrtec (cetirizine) [Package Insert]. Pfizer Labs, New York, NY. Revised August 2003. GlobalSubmit Review.
8. Desager JP, Dab I, Horsmans Y, Harvengt C. A pharmacokinetic evaluation of the second-generation H1-receptor antagonist cetirizine in very young children. Clinical pharmacology and therapeutics 1993;53:431-5.
9. Pitsiu M, Hussein Z, Majid O, Aarons L, de Longueville M, Stockis A. Retrospective population pharmacokinetic analysis of cetirizine in children aged 6 months to 12 years. British journal of clinical pharmacology 2004;57:402-11.
10. Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. Drug safety 2001;24:119-47.
11. Ridout SM, Tariq SM. Cetirizine overdose in a young child. The Journal of allergy and clinical immunology 1997;99:860-1.
12. Hansen JJ, Feilberg Jorgensen NH. [Accidental cetirizine poisoning in a four-year-old boy]. Ugeskrift for laeger 1998;160:5946-7.
13. Venlafaxine Hydrochloride [Contained in: Effexor]. Toxicology-Range of Toxicity: Venlafaxine and related agents. (Accessed July 2, 2019, at https://www.micromedexsolutions.com/micromedex2/librarian/CS/9D4946/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/358428/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=922260&contentSetId=100&title=Venlafaxine+Hydrochloride&servicesTitle=Venlafaxine+Hydrochloride&brandName=Effexor#.)
14. Chodorowski Z, Sein Anand J, Kujawska H. [Fatal suicidal intoxication with cetirizine in patient with anorexia--a case report]. Przeglad lekarski 2004;61:433-4.
15. Grillo M, Hong J, Kosuri S, Kumar K, Verma R. Is cetirizine a risk factor for drug induced methemaglobinemia? Pediatric Blood and Cancer 2019;66:S235.

7 APPENDICES

7.1 APPENDIX A. EFFECTS OF H_1 ANTIHISTAMINES

Effects of H_1 Antihistamines[3]		
Effects and Clinical Results	**First-generation**	**Second Generation**
Mast cell histamine inhibition • Decreased itching • Decreased vascular permeability • Vasodilation	Therapeutic	Therapeutic
Calcium channel blockade • Decreased mediator release	Therapeutic	Therapeutic
CNS antihistamine receptor occupancy • Sedation • Impaired psychomotor performance	Market effect in therapeutic and overdose	Minimal or no effect reported with cetirizine in overdose
CNS serotonin receptor antagonism • Increased appetite • Weight gain	Occurs in therapeutic dose; no significance in overdose	No effect
Peripheral muscarinic receptor antagonism • Dry mucosa • Decreased peristalsis • Urinary retention • Sinus tachycardia • Mydriasis	Marked effect in overdose; minimal effect can occur at therapeutic doses	Minimal or no effect
Central muscarinic receptor antagonism • Agitation • Delirium • Hallucinations	Marked effect in overdose	No effect
Alpha-adrenergic receptors • Dizziness • Hypotension	Marked effect in overdose; minimal effect can occur at therapeutic doses	No effect
Cardiac sodium and potassium channel blockers • Prolonged QRS complex • Prolonged QT interval	Marked effect in overdose on sodium channel	Minimal or no effect at therapeutic doses (except terfenadine, astemizole on potassium channels)
Source: Adapted from Goldfrank's Toxicologic Emergencies, 11e.		

7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. U.S. PRODUCT CODES FOR CETIRIZINE SINGLE SUBSTANCE PRODUCTS

Micromedex Product Codes

NOTE: These product codes must be redacted for public release

(b) (4)

8.4 APPENDIX D. NATIONAL POISON DATA SYSTEM (NPDS)

The National Poison Data System (NPDS) is a database managed by the American Association of Poison Control Centers (AAPCC) and derived from a nationwide network of Poison Control Centers (PCCs) that receives calls from individuals, healthcare professionals, and other interested persons regarding exposures to prescription drugs, over-the-counter medications as well as unapproved products. Within NPDS, calls for exposures may result in documentation of an event, provision of information, or advice regarding medical management, and AAPCC staff managing these calls undergo training in the efforts to standardize documentation across centers.

Documentation of calls includes detail on the drug(s), patient characteristics, route of exposure, reported reasons for exposure, level of care received (e.g. admitted to critical care unit vs. treated and released), medical outcomes (e.g., death, no effect) and other more curated variables, such as "relatedness" of the reported exposure to the outcomes of interest. Reasons for use are categorized into groups by AAPCC, and include such categories as "intentional", "unintentional," the former encompassing the subgroups of intentional misuse, abuse, suspected suicide or unknown intent.

PCC call data should not be interpreted as representing the complete incidence of national exposures or cases of misuse/abuse related to any substance. These data only capture events if the exposure resulted in a call to a PCC. PCC data rely on information electively shared by patients and healthcare personnel, and most substance classification is based on history alone and does not involve any biologic confirmation. Reported exposures may be unconfirmed ingestions, i.e., the product may not have been ingested at all by the patient. Drug exposures resulting in unattended or out-of-hospital death are unlikely to generate a call to a PCC, and therefore, fatal poisonings are expected to be substantially under-reported in PCC call data. Follow-up and medical outcomes are not available for all calls. It is possible that changes in PCC rates in part reflect changes in public and professional awareness of the risks associated with specific drugs, and awareness of the abuse potential of a drug among call center personnel could also increase the likelihood of an exposure being coded as intentional abuse. Call rates may also be influenced by general changes in use of PCCs over time. AAPCC is not able to completely verify the accuracy of every report made to member centers.

8.4 APPENDIX E. FAERS LINE LISTING OF SUPRATHERAPEUTIC CETIRIZINE EXPOSURE CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	All Outcome(s)*
Single Substance Exposures									
1	06/16/2008	6722990	1	2008010443	Non-expedited	26.00	Male	USA	OT
2	02/07/2018	14499437	1	US-PERRIGO-16US023193	Non-expedited	66.95	Female	USA	
3	01/02/2013	8992968	2	US-JNJFOC-20121213306	Expedited		Male	USA	HO
4	04/01/2019	16144472	3	BE-JNJFOC-20190400217	Expedited	27.00	Female	BEL	HO, OT
5	02/15/2019	15967740	1	US-PERRIGO-18US007314	Non-expedited	48.00	Female	USA	
6	02/15/2019	15967472	1	US-PERRIGO-18US012706	Non-expedited	54.00	Female	USA	
7	08/15/2013	9460825	3	JP-JNJFOC-20130805955	Expedited	81.00	Male	JPN	HO, OT
8	08/02/2017	13826208	1	US-PERRIGO-16US022268	Non-expedited	2.59	Female	USA	
9	09/12/2017	13958992	1	US-JNJFOC-20170809045	Non-expedited	6.00	Male	USA	
10	03/09/1998	3022752	6	9804651	Expedited	2.33	Male	USA	RI, OT
11	04/17/2008	6630536	1	2008009339	Expedited	3.00	Male	AUS	OT
12	02/01/2005	5734754	2	2005017269	Expedited	7.00	Male	POL	HO
13	09/26/2011	8170561	1	USA/USA/11/0021286	Expedited		Female	USA	OT
14	07/08/1997	3051322	1	9711676	Non-expedited	4.00	Male	USA	OT
15	07/08/1997	3051325	1	9711675	Non-expedited	5.00	Male	USA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	All Outcome(s)*
16	08/09/2002	3830162	1	2002002540	Expedited	21.00	Female	DEU	HO
17	02/06/2018	14492620	2	US-JNJFOC-20171234577	Non-expedited	69.00	Female	USA	
18	04/01/2018	14702203	1	US-JNJFOC-20180325033	Non-expedited		Female	USA	
19	10/24/2018	15544368	1	US-JNJFOC-20180933665	Non-expedited		Male	USA	
20	08/07/2015	11355052	1	US-JNJFOC-20150715295	Non-expedited		Male	USA	
21	12/28/2012	8990644	2	US-JNJFOC-20121211885	Expedited	10.00	Male	USA	HO
22	05/10/2019	16295987	2	US-STRIDES ARCOLAB LIMITED-2019SP003942	Expedited	18.00	Female	USA	HO
23	01/08/2010	7240474	2	GB-JNJCH-2010000196	Expedited	1.50	Male	GBR	HO
24	09/08/2015	11469686	1	US-JNJFOC-20150803324	Non-expedited	2.00	Female	USA	
25	11/27/2002	3873026	1	2002061549	Expedited	12.00	Female	CHE	HO
26	06/13/2016	12460878	1	IT-TEVA-666994ACC	Expedited	19.83	Female	ITA	HO
27	12/13/2013	9752064	2	DE-JNJFOC-20131207815	Expedited	23.81	Female	DEU	OT
28	11/19/2003	4038277	1	2003116911	Expedited	36.00	Female	DEU	HO
29	01/10/1997	5521322	1	9619184	Non-expedited	38.00	Female	USA	OT
30	07/19/2017	13767493	1	US-JNJFOC-20170711127	Expedited		Male	USA	HO
31	07/31/2017	13816506	1	US-JNJFOC-20170504704	Non-expedited		Not Reported	USA	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	All Outcome(s)*
32	11/22/2004	5689337	3	2004091192	Expedited	18.00	Female	POL	DE, OT
33	07/11/2012	8687816	1	USA/USA/12/0024945	Expedited	13.00	Female	USA	OT
34	10/06/1997	3070700	1	9720495	Expedited	15.00	Female	USA	HO, OT
35	06/28/1996	5422890	1	9604229	Non-expedited	39.00	Female	USA	OT
36	11/19/2003	4036358	1	2003116913	Expedited		Male	DEU	HO
37	05/13/2002	3793625	3	A209856	Expedited	26.00	Female	FRA	HO
38	04/12/2017	13430849	4	GR-JNJFOC-20170407137	Expedited	37.00	Male	GRC	HO, OT
39	05/06/2010	7379367	1	IN-JNJCH-2010010298	Expedited	28.00	Female	IND	HO
Polysubstance exposures									
40	08/26/2011	8108723	1	JP-JNJFOC-20110811391	Expedited		Not Reported	JPN	OT
41	12/21/2012	8979690	1	BE-JNJFOC-20121210391	Expedited	Adult	Female	BEL	HO
42	09/01/2010	7569861	1	DE-JNJCH-2010019518	Expedited	20.00	Female	DEU	OT
43	09/04/2008	6748005	1	DE-JNJCH-2008022573	Expedited	30.92	Female	DEU	OT
44	09/09/2016	12729114	2	IT-TEVA-690331ACC	Expedited	44.42	Female	ITA	OT
45	04/23/2018	14789662	2	IN-TORRENT-00001690	Expedited	40.00	Female	IND	DE, HO, OT
46	11/09/1998	3163123	1	9836430	Expedited	15.00	Female	USA	HO
47	05/30/2019	16374841	2	IT-JNJFOC-20190529620	Expedited	22.00	Male	ITA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	All Outcome(s)*
48	12/04/2001	6592271	1	A127282	Expedited	14.00	Female	FRA	HO
49	10/12/1999	5733904	1	9941293	Expedited	2.58	Female	BEL	HO
50	09/05/2014	10434441	3	IT-PFIZER INC-2014245551	Expedited	26.00	Female	ITA	HO
51	02/04/2011	7799993	1	DE-JNJCH-2011002744	Expedited	22.41	Female	DEU	OT
52	06/18/1996	5415302	1	9605238	Expedited	15.00	Female	USA	HO, OT
53	06/22/2017	13679504	1	CZ-SA-2017SA110208	Expedited	17.00	Female	CZE	HO, LT
54	03/27/2001	3633309	1		Direct	23.00	Male	USA	HO
55	05/22/2006	6057540	2	2006063976	Expedited	42.00	Male	DEU	HO, OT
56	02/20/2003	3911193	2	2003005470	Expedited	55.00	Male	NLD	HO
57	05/14/2004	4145233	2	GBWYE623805MAR04	Expedited	58.00	Male	GBR	DE
58	04/25/2019	16239549	1	PHHY2019SE094027	Expedited	15.00	Female	SWE	HO
59	12/28/2016	13070264	1	IT-JNJFOC-20161219210	Expedited	20.00	Female	ITA	OT
60	07/06/2017	13724830	1	CZ-MYLANLABS-2017M1040419	Expedited	21.00	Female	CZE	LT
61	10/08/2012	8827362	2	DE-JNJFOC-20121003461	Expedited	21.00	Female	DEU	HO, OT
62	10/10/2018	15481022	2	IT-JNJFOC-20181004102	Expedited	25.00	Female	ITA	HO
63	05/29/2013	9324814	2	2013AP005382	Expedited	32.00	Female	ITA	OT
64	06/11/2013	9341368	2	IT-JNJFOC-20130604243	Expedited	51.43	Female	ITA	HO, OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	All Outcome(s)*
65	02/26/1998	6252185	1	JAGER-37770	Expedited	16.00	Female	DEU	HO
66	10/17/2016	12855495	2	SE-BAUSCH-BL-2016-024904	Expedited	22.00	Female	SWE	HO
67	09/30/2004	5824193	2	2004018823	Expedited	28.00	Female	DEU	HO
68	12/28/2016	13069343	3	FR-JNJFOC-20161221929	Expedited	17.14	Male	FRA	HO
69	11/08/2010	7660482	1	DE-JNJFOC-20101007773	Expedited	19.00	Female	DEU	OT
70	01/19/2006	5971244	1	2006-DE-00104GD	Expedited	19.00	Female	Norway	HO, LT
71	09/15/2017	13976875	5	PHHY2017IT133922	Expedited	51.48	Female	ITA	HO, OT
72	03/17/2015	10920576	9	PHHY2015CH030129	Expedited	28.00	Female	CHE	HO, LT, OT
73	01/21/2019	15847028	1	DE-ROCHE-2244537	Expedited	21.00	Female	DEU	OT
74	06/07/2011	7976780	2	JP-JNJFOC-20110600927	Non-expedited	15.00	Female	JPN	HO
75	05/23/2017	13573685	11	IT-PFIZER INC-2017221255	Expedited	28.00	Female	ITA	HO, OT
76	08/02/2016	12613603	1	IT-ACTAVIS-2016-16881	Expedited	66.54	Male	ITA	HO
77	05/30/2003	5865301	2	2003-05-3818	Expedited	36.00	Female	DEU	HO
78	12/30/2014	10682597	3	IT-ACTAVIS-2014-27676	Expedited	38.52	Female	ITA	OT
79	09/30/2003	6453567	1	2003039172	Expedited	26.00	Male	GBR	HO
80	12/04/2009	7294225	1	2009028909	Expedited	23.00	Female	DEU	HO, OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	All Outcome(s)*
81	05/18/2016	12383009	1	IT-MYLANLABS-2016M1019923	Expedited	14.00	Female	ITA	HO, OT
82	07/09/2008	6704276	1	2008015102	Expedited	75.00	Female	DEU	HO
83	03/17/2006	6016908	1	2006034952	Expedited	15.00	Female	DEU	OT
84	08/31/2018	15339250	1	IT-DSJP-DSE-2018-138483	Expedited	19.00	Male	ITA	LT
85	09/08/2011	8127216	1	DE-PFIZER INC-2011207073	Expedited	43.00	Female	DEU	OT
86	02/16/2016	12079568	3	FR-PFIZER INC-2016079585	Expedited	28.00	Female	FRA	HO, LT
87	07/31/2017	13816857	1	US-JNJFOC-20170701873	Non-expedited		Female	USA	

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, RI=Required Intervention, OT=Other medically significant

8.5 APPENDIX F. NPDS CASES WITH CLINICALLY CONCERNING CLINICAL EFFECTS RELATED TO CETIRIZINE EXPOSURE

(b) (4)

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MONICA MUNOZ
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 22, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 211415
Product Name and Strength:	Quzyttir (cetirizine hydrochloride) injection, 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	JDP Therapeutics, Inc.
FDA Received Date:	December 7, 2018, February 14, 2019
OSE RCM #:	2019-10
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Sarah K. Vee, PharmD.

1 REASON FOR REVIEW

As part of the approval process for Quzyttir (cetirizine hydrochloride) injection, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the proposed Quzyttir Prescribing Information (PI), carton and container labels for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

Cetirizine hydrochloride, was initially approved in 1996 as a second-generation antihistamine; it is currently marketed in several oral dosage forms and approved for the relief of symptoms associated with allergic rhinitis and chronic urticaria.

On December 7, 2018, JDP Therapeutics Inc. submitted a 505 (b)(2) New Drug Application (NDA 211415) for cetirizine hydrochloride injection for the treatment of acute urticaria for patients 6 months of age and older; the listed drug product is Zyrtec (cetirizine HCl), NDA 019835.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D- N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), carton and container labels, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Prescribing Information – General Issues			
1.	Use of confusing symbols (e.g., ">", "<" and "-") throughout the PI.	These symbols may be mistaken as opposite of intended.	Replace the symbols "<", "≥" and "-" with their intended meanings to prevent misinterpretation and confusion.
2.	The package type term (injection vs. (b) (4)) is inconsistent throughout the PI.	Inconsistent with Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use.	We defer to Office of Pharmaceutical Quality (OPQ) to add the appropriate package type term throughout the PI.
Highlights of Prescribing Information & Full Prescribing Information – Section 2 Dosage and Administration			
1.	Omission of a unit of measure after each numeric dose value.	Not including a unit of measure (e.g. mg) after each numeric dose designation may lead to wrong dose errors.	Include a unit of measure after each numeric dose value. (i.e. 5 mg to 10 mg vs. 5 to 10 mg)

Table 3. Identified Issues and Recommendations for JDP Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label(s) and Carton Labeling			
1.	The established name lacks prominence commensurate with the proprietary name.	As currently presented the established name is not at least half the size of the proprietary name, this decreases its readability and may lead to wrong drug errors.	Increase the prominence of the established name considering all pertinent factors, including typography, layout, contrast, and other printing features in

Table 3. Identified Issues and Recommendations for JDP Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			accordance with 21 CFR 201.10(g)(2).
2.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3.	NDC number is denoted by a placeholder.	Similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug.	Submit proposed NDC number. Ensure that the container label of one unit and the carton labeling of 25 units have different NDC package codes (last 2 digits of the NDC).
Container Label(s)			
1.	Net volume statement competes for	Net quantity statement interferes with the	Decrease the font size and un-bold the net quantity

Table 3. Identified Issues and Recommendations for JDP Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	prominence with more important information on the PDP.	readability of other important information (e.g. proprietary name, established name, strength, route of administration) on the PDP. This may lead to wrong dose errors.	statement to reduce the prominence of the statement as compared to more important product information on the PDP. Consider relocating the statement to the bottom half of the label.
2.	Package type has been omitted.	The package type is necessary to identify how the medication should be safely handled and used.	Revise the statement "(b) (4) " to read "Single-Dose Vial – Discard Unused Portion".
Carton Labeling			
1.	Net quantity statement is incomplete.	Per 21 CFR 201.51 Declaration of net quantity of contents, the declaration of net quantity of contents shall express an accurate statement of the quantity of the contents of the package.	Revise to read: 25 x 1 mL vials
2.	Package type statement is incomplete and competes for readability with the Proprietary name.	As accurately defined package type statement is necessary to identify how the medication should be safely handled and used. This statement should be located away from other important product information to enhance readability of all information.	Delete the statement "(b) (4) " above the product's proprietary name. Revise the statement "(b) (4) " to read "Single-Dose Vial – Discard Unused Portion".
3.	As currently presented the LOT number is omitted.	Lot number statement is required on the immediate container AND carton labeling when there is	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest

Table 3. Identified Issues and Recommendations for JDP Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		sufficient space per 21 CFR 201.10(i)(1)	saleable unit (usually the carton) display a human-readable and machine-readable (2D data matrix barcode) product identifier. Ensure the lot number is clearly differentiated from the expiration date on the label.

5 CONCLUSION

Our evaluation of the proposed Quzyttir Prescribing Information, carton and container labels identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to JDP Therapeutics, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Quzyttir that JDP Therapeutics, Inc. submitted on December 7, 2018, and the listed drug (LD).

Table 2. Relevant Product Information for Quzyttir and the Listed Drug

Product Name	**Quzyttir**	**Zyrtec (cetirizine HCl)[a]**
Initial Approval Date	n/a	12/08/1995
Active Ingredient	cetirizine hydrochloride	
Indication	Acute urticaria	• relief of symptoms associated with seasonal allergic rhinitis in adults and children 2 years of age and older. • relief of symptoms associated with perennial allergic rhinitis in adults and children 6 months of age and older. • treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older.
Route of Administration	Intravenous	oral
Dosage Form	injection	Tablet, Oral Solution
Strength	10 mg/mL	5 mg, 10 mg
Dose and Frequency	• Adults and adolescents 12 years and older: 10 mg • Children 6 to 11 years: 5 mg or 10 mg • Children 2 to 5 years: 2.5 mg • Children 6 months to less than 2 years: 2.5 mg (b) (4)	Adults and Patients 6 to 12 years old: 5 mg to 10 mg once daily Patients 2 to 5 years old: 2.5 mg to 5 mg once daily Patients 6 months to less than 2 years:

[a] Zyrtec [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 FEB 1. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

		2.5 mg once daily; 12 to 23 months may increase to 5 mg daily.
How Supplied	2 mL amber glass vial with 1 mL fill	• Bottles of 100 count white, film-coated, rounded-off rectangular shaped tablets containing 5 mg or 10 mg cetirizine hydrochloride • 120 mL or 1-pint amber bottles containing colorless to slightly yellow banana-grape flavor syrup (1 mg/mL).
Storage	20°-25°C (68°-77°F) excursions permitted to 15°-30°C (59°-86°F)	
Container Closure	n/a	

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Quzyttir labels and labeling submitted by JDP Therapeutics, Inc..

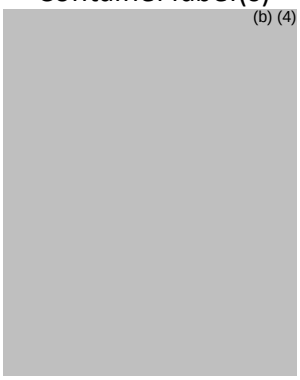
- Container label(s) received on December 7, 2018
- Carton labeling received on February 14, 2019
- Prescribing Information (Image not shown) received on December 7, 2018

F.2 Label and Labeling Images

Prescribing Information (Image not shown)

\\cdsesub1\evsprod\nda211415\0001\m1\us\114-labeling\draft-pi.pdf

Container label(s)



Carton labeling

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/22/2019

TO: Division of Pulmonary, Allergy and Rheumatology Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 211415

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The clinical inspection was conducted in December 2017 and the analytcial inspection was conducted in (b) (4), which falls within the surveillance interval. The inspections were conducted under the following submissions: (b) (4).

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the outcome of the previous inspections and the rationale described above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Algorithme Pharma, Inc.	1200 Beaumont Avenue, Mount-Royal, Quebec, Canada
Analytical	(b) (4)	

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