

Quzyttir®

Cetirizine HCl Injection 10 mg/mL



Coding and Reimbursement Guide

QUZYTTIR® (cetirizine hydrochloride injection), 10mg/mL for intravenous use

INDICATION AND USAGE

Quzyttir is a histamine-1 (H_1) receptor antagonist indicated for the treatment of acute urticaria in adults and children 6 months of age and older

Limitations of Use: QUZYTTIR is not recommended in pediatric patients <6 years of age with impaired renal or hepatic function.

IMPORTANT SAFETY INFORMATION

Contraindications: Known hypersensitivity to QUZYTTIR or any of its ingredients, to levocetirizine, or hydroxyzine.

Please see additional Important Safety Information on back cover and accompanying full Prescribing Information.

TerSera Therapeutics LLC is committed to providing you with detailed information to assist you in submitting for reimbursement for Quzyttir. This Coding and Reimbursement Guide has been developed to provide you with information regarding:

- Essential Coding Considerations
- Sample Claim Forms
- Important Product Information
- Reimbursement Support Resources

Information about Quzyttir access and reimbursement support resources, for both providers and patients, is available through TerSera SupportSource. Contact them at **1-855-686-8725**, Monday-Friday, 9 AM-6 PM ET, about any reimbursement-related questions or concerns.



Disclaimer

Third-party reimbursement is affected by many factors. This document and the information and assistance provided by TerSera SupportSource are presented for informational purposes only. They do not constitute reimbursement or legal advice. TerSera SupportSource does not promise or guarantee coverage, levels of reimbursement, or payment. Similarly, all CPT and HCPCS codes are supplied for informational purposes only and represent no statement, promise, or guarantee, expressed or implied, by TerSera or its third-party service providers that these codes will be appropriate or that reimbursement will be made. The fact that a drug, device, procedure, or service is assigned a HCPCS code and a payment rate does not imply coverage by the Medicare program, but indicates only how the product, procedure, or service may be paid if covered by the Medicare program. Laws, regulations, and policies concerning reimbursement are complex and are updated frequently. Accordingly, the information may not be current or comprehensive. TerSera and its third-party service providers strongly recommend you consult your payer for its most current coverage, reimbursement, and coding policies. TerSera and its third-party service providers make no representations or warranties, expressed or implied, as to the accuracy of the information provided. In no event shall the third-party service providers or TerSera, or their employees or agents, be liable for any damages resulting from or relating to any information provided by, or accessed to or through, TerSera SupportSource. All HCPs and other users of this information agree that they accept responsibility for the use of this program.

Ordering Through Specialty Distributors

Quzyttir®
Cetirizine HCl Injection
10 mg/mL



**Carton containing 25 single-use vials
(10mg/mL cetirizine hydrochloride)**

10 digit NDC 70720-100-25
11 digit NDC* 70720-0100-25

**Carton containing 1 single-use vial
(10mg/mL cetirizine hydrochloride)**

10 digit NDC 70720-100-10
11 digit NDC* 70720-0100-10

*Payers may require the submission
of an 11-digit NDC on healthcare claim forms.

Authorized Specialty Distributors

Name	Customer Service	Order Times
Hospitals		
Cardinal Specialty	Oncology: 877-453-3972 Other Specialties: 866-300-3838	Monday-Friday 8 AM-7 PM ET
CuraScript SD Specialty Distribution	877-599-7748	Monday-Friday 8:30 AM-7 PM ET
McKesson Plasma and Biologics	877-625-2566	Monday-Friday 9 AM-7:30 PM ET
Oncology Supply	800-633-7555	Monday-Friday 9 AM-8 PM ET
Clinics		
Besse Medical	800-543-2111	Monday-Thursday 8:30 AM-7 PM ET, Friday 8:30 AM-5 PM ET
Cardinal Specialty	Oncology: 877-453-3972 Other Specialties: 866-300-3838	Monday-Friday 8 AM-7 PM ET
CuraScript SD Specialty Distribution	877-599-7748	Monday-Friday 8:30 AM-7 PM ET
McKesson Specialty	Oncology: 800-482-6700 Specialties: 855-477-9800	Monday-Friday 7 AM-4 PM ET
Metro Medical	800-768-2002	Monday-Friday 8 AM-8 PM ET
Oncology Supply	800-633-7555	Monday-Friday 9 AM-8 PM ET

Hospital Outpatient and Ambulatory Surgical Center Setting

Sample Medicare Claim Form: CMS-1450 Form (Hospital Outpatient)

Hospital Outpatient Claims (CMS-1450)¹

The Form CMS-1450, also known as the UB-04, is a uniform institutional provider bill suitable for use in billing multiple third-party payers. It is the basic form prescribed by CMS for the Medicare and Medicaid programs for claims from hospitals, including HOPDs. Because it serves many payers, a particular payer may not need some data elements. For detailed guidance on completing the CMS-1450 items, please see the Medicare Claims Processing Manual, Pub. 100-04, Chapter 25, available at: <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c25.pdf>

CMS Discarded Drug Policy^{2,3}

When a physician, hospital or other provider or supplier must discard the remainder of a single-use vial or other single-use package after administering a dose/quantity of the drug or biological to a Medicare patient, the program provides payment for the amount of drug or biological discarded as well as the dose administered, up to the amount of the drug or biological as indicated on the vial or package label. Medicare contractors require the modifier JW to identify unused drugs or biologicals from single-use vials or single-use packages that are appropriately discarded. This modifier, billed on a separate claim line, supports payment for the amount of discarded drug or biological. For example, a single-use vial that is labeled to contain 100 units of a drug has 95 units administered to the patient and 5 units discarded. The 95-unit dose is billed on one line, while the discarded 5 units is billed on another line accompanied by the JW modifier. Both line items will be processed for payment. Providers must record the discarded amounts of drugs and biologicals in the patient's medical record.

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				5 FED. TAX NO.		6 STATEMENT COVERS PERIOD FROM _____ THROUGH _____	
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Hospital Outpatient and Ambulatory Surgical Center Setting

Sample Medicare Claim Form: CMS-1450 Form (Hospital Outpatient)

Quzyttir®
Cetirizine HCl Injection
10 mg/mL

1

Fields 42 and 43^{4,5}

Enter the appropriate revenue codes and descriptions corresponding to HCPCS codes in field 44. Other revenue codes may be acceptable and may vary by location.

2

Field 44^{3,4}

Enter the appropriate HCPCS and CPT codes. The HCPCS code for QUZYTIR (cetirizine hydrochloride injection) is J1201. Please note that for billing purposes, the NDC field requires 11 digits. Please refer to page 3 for the appropriate NDCs. These NDCs are consistent with the Redbook and First DataBank listings.

One or more of the following modifiers may be relevant to Quzyttir billing and are required by Medicare (Modifier on CMS-1450, Box 44):

25

Description: Significant, separately identifiable evaluation and management (E/M) service by the same physician or other qualified healthcare professional on the same day of the procedure or other service.

Indication:

- Patient requires distinct E/M service in addition to the infusion procedure
- Must be substantiated by documentation that supports the relevant criteria for the reported service

JW

Drug amount discarded/not administered to any patient

- Applies only to the unused drug that is discarded after applicable dose has been administered from a single-use vial
- Append the modifier to the drug code on a line separate from that reporting the administered dose

PO

Excepted services provided at an off-campus, outpatient provider-based department of a hospital

- To be reported on each claim line for excepted services furnished in an off-campus, provider-based department of a hospital and billed on an institutional claim⁴

PN

Non-exceptioned service provided at an off-campus, outpatient, provider-based department of a hospital

- To be reported on each claim line for non-exceptioned services furnished in an off-campus provider-based department of a hospital and billed on an institutional claim

JG

Drug or biological acquired with 340B Drug Pricing Program Discount

- Must be reported by providers that are NOT excepted from the 340B payment policy
- To be reported on the same claim line as the drug HCPCS code for all 340B acquired drugs

TB

Drug or biological acquired with 340B Drug Pricing Program Discount, reported for informational purposes

3

Field 46

Enter the number of units administered. J1201 has a billable unit per 0.5 mg.

DOSAGE AND ADMINISTRATION⁶

For intravenous administration only. Recommended dosages: • Adults and adolescents ≥ 12 years of age and older: 10 mg • Children 6 to 11 years: 5 mg or 10 mg • Children 6 months to 5 years: 2.5 mg.

Recommended dosage regimen is once every 24 hours as needed for acute urticaria.

4

Field 74

Enter the appropriate ICD-10-CM diagnosis code. Additional diagnosis codes may apply.

5

Field 80

Billing with a specific HCPCS code enables faster payment through electronic billing. Manual billing may still be required in certain circumstances. In those cases it may be necessary to provide the following information for payment: The NDC, quantity of the drugs administered (expressed in unit of measure applicable to the drug or biological), and the date the drug was administered to the patient.

Independent Clinic Setting

Sample Medicare Claim Form: CMS-1500 Form (Physician Office)

Physician Office Claims (CMS-1500)⁷

The Form CMS-1500 is the basic form prescribed by CMS for the Medicare and Medicaid programs for claims from suppliers and non-institutional providers that qualify for a waiver from the Administrative Simplification Compliance Act (ASCA) requirement for electronic submission of claims. It has also been adopted by the TRICARE Program. For detailed guidance on completing the CMS-1500 items, please see the Medicare Claims Processing Manual, Pub. 100-04, Chapter 26, available at: <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c26.pdf>

CMS Discarded Drug Policy

- Payment for discarded amounts of drug/biological applies only to single-use vials or packages
- Multi-use vials are not subject to payment for discarded amounts
- Discarded amounts of drugs/biologicals must be recorded in the patient's medical record
- Medicare contractors require the JW modifier; other payer policies may vary

As of April 1, 2014, version 02/12 is required.

REFERENCES

1. Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 25: Completing and Processing the Form CMS-1450 Data Set. <https://www.cms.gov/Regulations-and-Guidance/Manuals/Downloads/clm104c25.pdf>
2. Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 12: Physicians/Non-Physician Practitioners. <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c12.pdf>
3. Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 17: Drugs and Biologicals. <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c17.pdf>

4. Centers for Medicare & Medicaid Services. 2020 Alpha Numeric HCPCS File. <https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Alpha-Numeric-HCPCS-Items/2020-Alpha-Numeric-HCPCS-File>
5. Noridian Healthcare Solutions. Revenue Codes. <https://med.noridian-medicare.com/web/jea/topics/claim-submission/revenue-codes>
6. Quzyttir Prescribing Information: <https://documents.tersera.com/quzyttir/QuzyttirPrescribingInformation.pdf>
7. Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 26: Completing and Processing the Form CMS-1500 Data Set. <https://www.cms.gov/Regulations-and-Guidance/Manuals/Downloads/clm104c26.pdf>

Independent Clinic Setting

Sample Medicare Claim Form: CMS-1500 Form (Physician Office)

Quzyttir®
Cetirizine HCl Injection
10 mg/mL

1

Field 19²⁻⁵

Billing with a specific HCPCS code enables faster payment through electronic billing. Manual billing may still be required in certain circumstances. In those cases it may be necessary to provide the following information (see line 19) for payment: Specific drug information, i.e., drug name, NDC, dosage, strength, and route of administration. Please note that for billing purposes, the NDC field requires 11 digits. Please refer to Page 3 for the appropriate NDCs. These NDCs are consistent with the Red Book and First DataBank listings.

2

Field 21

Enter the appropriate ICD-10-CM diagnosis code. Additional diagnosis codes may apply.

3

Field 24, Column D

Enter the appropriate HCPCS codes and CPT codes.

The HCPCS code for QUZYTTIR (cetirizine hydrochloride injection) is J1201. Quzyttir is an IV injection and therefore likely included in Commercial Payers' injection and infusion policy. Please check your local payers' coverage and coding guidelines.

25 (Modifier on CMS-1500) (Box 24D)

Description: Significant, separately identifiable evaluation and management (E/M) service by the same physician or other qualified healthcare professional on the same day of the procedure or other service.

Indication:

- Patient requires distinct E/M service in addition to the infusion procedure
- Must be substantiated by documentation that supports the relevant criteria for the reported service

JW (Modifier on CMS-1500) (Box 24D)

Drug amount discarded/not administered to any patient

- Applies only to the unused drug that is discarded after applicable dose has been administered from a single-use vial
- Append the modifier to the drug code on a line separate from that reporting the administered dose

PO (Modifier on CMS-1500) (N/A to Box 24D)

Excepted services provided at an off-campus, outpatient provider-based department of a hospital

- To be reported on each claim line for excepted services furnished in an off-campus, provider-based department of a hospital and billed on an institutional claim

PN (Modifier on CMS-1500) (N/A to Box 24D)

Non-excepted service provided at an off-campus, outpatient, provider-based department of a hospital

- To be reported on each claim line for non-excepted services furnished in an off-campus provider-based department of a hospital and billed on an institutional claim

JG (Modifier on CMS-1500) (N/A to Box 24D)

Drug or biological acquired with 340B Drug Pricing Program Discount

- Must be reported by providers that are NOT excepted from the 340B payment policy
- To be reported on the same claim line as the drug HCPCS code for all 340B acquired drugs

TB (Modifier on CMS-1500) (N/A to Box 24D)

Drug or biological acquired with 340B Drug Pricing Program Discount, reported for informational purposes

4

Field 24, Column G

Enter the number of units administered. J1201 has a billable unit per 0.5 mg.

DOSAGE AND ADMINISTRATION⁶

For intravenous administration only. Recommended dosages: • Adults and adolescents ≥ 12 years of age and older: 10 mg • Children 6 to 11 years: 5 mg or 10 mg • Children 6 months to 5 years: 2.5 mg.

Recommended dosage regimen is once every 24 hours as needed for acute urticaria.

Patient Assistance

Quzyttir®
Cetirizine HCl Injection
10 mg/mL



If your patients need help with the cost of their co-pay, the Quzyttir Co-pay Program may help. Eligible* patients could lower their co-pay to as little as \$25.

- Patients can be reimbursed up to \$300 per claim on up to 4 claims per year
- Program allows a 60-day lookback prior to enrollment to give your patients time to understand their co-pay obligations
- Patients can get reimbursed by submitting proof of payment and a simple one-page form

* For eligible commercially insured patients, the card carries a maximum of \$300 per claim and a maximum of 4 claims per calendar year. Patients are not eligible if prescriptions are paid by any state or federally funded program, including, but not limited to, Medicare or Medicaid, Medigap, VA or DOD or Tricare, or where prohibited by law.

Indication and Important Safety Information QUZYTTIR® (cetirizine hydrochloride injection), 10mg/mL for intravenous use

INDICATION AND USAGE

QUZYTTIR is indicated for the treatment of acute urticaria in adults and children 6 months of age and older.

Limitations of Use: QUZYTTIR is not recommended in pediatric patients <6 years of age with impaired renal or hepatic function.

IMPORTANT SAFETY INFORMATION

Contraindications: Known hypersensitivity to QUZYTTIR or any of its ingredients, to levocetirizine, or hydroxyzine.

Warnings and Precautions: The occurrence of somnolence/sedation has been reported in some patients. Advise patients to exercise due caution when driving, or when operating potentially dangerous machinery. Avoid concurrent use of QUZYTTIR with alcohol or other CNS depressants because additional reduction in alertness and additional impairment of CNS performance may occur.

Adverse Reactions: The most common adverse reactions (incidence <1%) with QUZYTTIR are dysgeusia, headache, paresthesia, presyncope, dyspepsia, feeling hot, and hyperhidrosis.

The most common adverse reactions (incidence ≥2%) with chronic dosing of oral cetirizine hydrochloride in adults are somnolence, fatigue, dry mouth, pharyngitis, and

dizziness. Adverse reactions observed in pediatric patients with chronic use of oral cetirizine hydrochloride are headache, pharyngitis, abdominal pain, coughing, somnolence, diarrhea, epistaxis, bronchospasm, nausea, and vomiting.

For more information, please see the accompanying full Prescribing Information for QUZYTTIR.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use QUZYTIR™ safely and effectively. See full prescribing information for QUZYTIR™.

QUZYTIR™ (cetirizine hydrochloride injection), for intravenous use

Initial U.S. Approval: 1995

INDICATIONS AND USAGE

QUZYTIR™ is a histamine-1 (H₁) receptor antagonist indicated for the treatment of acute urticaria in adults and children 6 months of age and older (1)

Limitations of Use:

Not recommended in pediatric patients less than 6 years of age with impaired renal or hepatic function (1)

DOSAGE AND ADMINISTRATION

For intravenous administration only (2)

Recommended dosages:

- Adults and adolescents ≥ 12 years of age and older: 10 mg (2.1)
- Children 6 to 11 years: 5 mg or 10 mg (2.2)
- Children 6 months to 5 years: 2.5 mg (2.3)

Recommended dosage regimen is once every 24 hours as needed for acute urticaria (2)

DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL cetirizine hydrochloride (3)

CONTRAINDICATIONS

Known hypersensitivity to cetirizine hydrochloride or any of its ingredients, levocetirizine, or hydroxyzine (4)

WARNINGS AND PRECAUTIONS

Somnolence/Sedation: Exercise caution when driving a car or operating potentially dangerous machinery (5.1)

ADVERSE REACTIONS

The most common adverse reactions (incidence less than 1%) with QUZYTIR are dysgeusia, headache, paresthesia, presyncope, dyspepsia, feeling hot, and hyperhidrosis.

Most common adverse reactions (incidence equal to or greater than 2%) with use of oral cetirizine hydrochloride are somnolence, fatigue, dry mouth, pharyngitis, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, call TerSera Therapeutics LLC at 1-844-334-4035 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

QUZYTIR™ is indicated for the treatment of acute urticaria in adults and children 6 months of age and older.

Limitations of use:

QUZYTIR™ is not recommended in pediatric patients less than 6 years of age with impaired renal or hepatic function.

2 DOSAGE AND ADMINISTRATION

QUZYTIR is a single use injectable product for intravenous administration only. The recommended dosage regimen is once every 24 hours as needed for treatment of acute urticaria. Administer QUZYTIR as an intravenous push over a period of 1 to 2 minutes. QUZYTIR is not recommended in pediatric patients less than 6 years of age with impaired renal or hepatic function [see *Pediatric Use (8.4)*].

2.1 Adults and adolescents 12 years of age and older

The recommended dosage is 10 mg administered by intravenous injection.

2.2 Children 6 to 11 years of age

The recommended dosage is 5 mg or 10 mg depending on symptom severity administered by intravenous injection.

2.3 Children 6 months to 5 years of age

The recommended dosage is 2.5 mg administered by intravenous injection.

3 DOSAGE FORMS AND STRENGTHS

QUZYTIR is a sterile, clear, colorless, non-pyrogenic, isotonic aqueous solution of cetirizine hydrochloride for intravenous injection; supplied in 2 mL size amber glass vials for single use. Each 2 mL size amber glass vial contains 1 mL drug solution with 10 mg cetirizine hydrochloride (equivalent to 8.42 mg of cetirizine).

4 CONTRAINDICATIONS

The use of QUZYTIR is contraindicated in patients with a known hypersensitivity to cetirizine hydrochloride or any of its ingredients, levocetirizine, or hydroxyzine.

5 WARNINGS AND PRECAUTIONS**5.1 Somnolence/Sedation**

In clinical trials with QUZYTIR and cetirizine hydrochloride tablets, the occurrence of somnolence/sedation has been reported in some patients. Exercise due caution when driving a car or operating potentially dangerous machinery. Avoid concurrent use of QUZYTIR with alcohol or other CNS depressants because additional reduction in alertness and additional impairment of CNS performance may occur.

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is described elsewhere in the labeling:

- **Somnolence/Sedation** [see *Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Oral cetirizine hydrochloride

The following adverse reactions associated with the use of oral cetirizine hydrochloride were identified in clinical trials.

In clinical trials in patients 12 years and older the most common adverse reactions to oral cetirizine hydrochloride occurring with a 2% or greater incidence and greater than placebo were somnolence (14%), fatigue (6%), dry mouth (5%), pharyngitis (2%), and dizziness (2%). In clinical trials in children 6 to

11 years of age with oral cetirizine hydrochloride the most common adverse reactions occurring with a 2% or greater incidence and greater than placebo were headache, pharyngitis, abdominal pain, coughing, somnolence, diarrhea, epistaxis, bronchospasm, nausea, and vomiting. Somnolence appeared to be dose related. Adverse reactions reported in placebo-controlled trials with oral cetirizine hydrochloride in pediatric patients 2 to 5 years were qualitatively similar in nature and generally similar in frequency to those reported in trials with children 6 to 11 years of age. In placebo-controlled trials of pediatric patients 6 to 24 months of age, the incidences of adverse experiences were similar in the oral cetirizine hydrochloride and placebo treatment groups in each trial. In a trial of 1 week duration in children 6 to 11 months of age patients who received oral cetirizine hydrochloride exhibited greater irritability/fussiness than patients on placebo. In a trial of 18 months duration in patients 12 months and older, insomnia occurred more frequently in patients who received oral cetirizine hydrochloride compared to patients who received placebo.

QUZYTIR

The safety data of QUZYTIR was evaluated in a randomized, double-blind, single-dose, non-inferiority study comparing QUZYTIR to intravenous diphenhydramine in 262 adults with acute urticaria.

The adverse reactions with QUZYTIR occurred at an incidence of less than 1% and include: dyspepsia, feeling hot, dysgeusia, headache, paresthesia, presyncope, and hyperhidrosis.

An additional randomized, double-blind, single dose study was conducted in 33 adults which showed similar safety results.

Sedation

Subject-rated sedation scores were assessed at baseline, 1 hr, and/or 2 hrs, and/or "Readiness for Discharge". Sedation was rated on a 0 to 3 scale (0 = none, to 3 = severe) with lower sedation scores indicating less sedation. Subjects in the QUZYTIR treatment group reported less sedation at all time points compared to subjects treated with diphenhydramine.

7 DRUG INTERACTIONS

No clinically significant drug interactions with oral cetirizine hydrochloride, the active ingredient in QUZYTIR, have been found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. There was a small decrease in the clearance of oral cetirizine hydrochloride caused by a 400-mg dose of theophylline; it is possible that larger theophylline doses could have a greater effect [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy****Risk Summary**

There are no adequate and well-controlled studies in pregnant women with cetirizine hydrochloride the active ingredient in QUZYTIR. In animal reproduction studies, there was no evidence of fetal harm with administration of cetirizine hydrochloride by the oral route to pregnant mice, rats, and rabbits, during the period of organogenesis, at doses that were 45 times and higher than the maximum recommended human dose (MRHD) in adults. In rats treated during late gestation and the lactation period, cetirizine hydrochloride had no effects on pup development at oral doses up to approximately 30 times the MRHD in adults. In mice treated during late gestation and the lactation period, cetirizine hydrochloride administered by the oral route to the dams had no effects on pup development at a dose that was approximately 10 times the MRHD in adults; however, lower pup weight gain during lactation was observed at a dose that was 45 times the MRHD in adults (See Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20% respectively.

Data

Animal Data: In embryofetal development studies conducted in mice, rats, and rabbits, cetirizine hydrochloride, administered during the period of organogenesis, was not teratogenic at doses up to 45, 220, and 260 times the MRHD, respectively (on a mg/m² basis with maternal oral doses up to 96, 225, and 135 mg/kg).

In a prenatal and postnatal development (PPND) study conducted in mice, cetirizine hydrochloride was administered at oral doses up to 96 mg/kg/day from gestation day 15 through lactation day 21. Cetirizine hydrochloride lowered pup body weight gain during lactation at an oral dose in dams that was approximately 45 times the MRHD (on a mg/m² basis with a maternal oral dose of 96 mg/kg/day); however, there were no effects on pup weight gain at an oral dose in dams that was approximately 10 times the MRHD (on a mg/m² basis with a maternal oral dose of 24 mg/kg/day). In a PPND study conducted in rats, cetirizine hydrochloride was administered at oral doses up to 180 mg/kg/day from gestation day 17 to lactation day 22. Cetirizine hydrochloride did not have any adverse effects on rat dams or offspring development at doses up to approximately 30 times the MRHD (on a mg/m² basis with a maternal oral dose of 30 mg/kg/day). Cetirizine hydrochloride caused excessive maternal toxicity at an oral dose in dams that was approximately 180 times the MRHD (on a mg/m² basis with a maternal oral dose of 180 mg/kg/day).

8.2 Lactation**Risk Summary**

Cetirizine hydrochloride has been reported to be present in human breast milk. In mice and beagle dogs, studies indicated that cetirizine hydrochloride was excreted in milk (See Data). When a drug is present in animal milk, it is likely the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for QUZYTIR and any potential adverse effects on the breastfed child from QUZYTIR or from the underlying maternal condition.

Data

Animal Data: Cetirizine hydrochloride was detected in the milk of mice. No adverse developmental effects on pups were seen when cetirizine hydrochloride was administered orally to dams during lactation at a dose that was approximately 10 times the MRHD in adults [See Use in Specific Populations (8.1)]. Studies in beagle dogs indicated that approximately 3% of the dose of cetirizine hydrochloride was excreted in milk. The concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk.

8.4 Pediatric Use

The safety and efficacy of QUZYTIR have been established in patients 6 months to 17 years of age. The efficacy of QUZYTIR for the treatment of acute urticaria down to 6 months of age is based on extrapolation of the efficacy of QUZYTIR in adults with acute urticaria [See Clinical Studies (14)] and supported by pharmacokinetic data with oral cetirizine hydrochloride in patients 6 months to 17 years of age. Based upon the known PK profile of oral cetirizine hydrochloride, the exposure of IV cetirizine hydrochloride in pediatric patients (6 months to 17 years of age) is expected to be similar to the exposure of IV cetirizine hydrochloride in adults at the labeled doses. Extrapolation of efficacy is based on the likelihood that the disease course, pathophysiology and the drug's effect are similar between these two populations.

The safety of QUZYTIR in children 6 months to 17 years of age is supported by safety information from placebo-controlled clinical trials with oral cetirizine

hydrochloride (the active ingredient in QUZYTIR) in patients 6 months of age and older [see Adverse Reactions (6)]. QUZYTIR demonstrates a higher C_{max} compared to oral cetirizine hydrochloride in adults [See Clinical Pharmacology (12.3)]. As QUZYTIR is indicated for an acute condition administered in a medically supervised setting, the safety for higher C_{max} in children 6 months to less than 18 years of age is supported by the safety data from the clinical trial with IV cetirizine hydrochloride in adults [see Adverse Reactions (6)] and available safety information from pediatric overdose cases.

Because of the absence of pharmacokinetic and safety information for cetirizine hydrochloride in children below 6 years of age with impaired renal or hepatic function, the use of QUZYTIR in this impaired patient population is not recommended [see Dosage And Administration (2)].

The safety and efficacy of QUZYTIR in patients less than 6 months of age has not been established.

8.5 Geriatric Use

In clinical trials with QUZYTIR, 18 patients were 65 years and older, and 6 patients were 75 years and older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In clinical trials with cetirizine hydrochloride oral tablets, 186 patients were 65 years and older, and 39 patients were 75 years and older. No overall differences in safety were observed between these patients and younger patients.

With regard to efficacy, the clinical trials with cetirizine hydrochloride oral tablets and QUZYTIR did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients.

8.6 Hepatic Impairment

No dosage adjustment is required in patients with hepatic impairment. Monitor for antihistaminic side effects in this patient population [See Clinical Pharmacology (12.3)].

8.7 Renal Impairment

No dosage adjustment is required in patients with moderate and severe renal impairment and in patients on dialysis. Monitor for antihistaminic side effects in this patient population [see Clinical Pharmacology (12.3)].

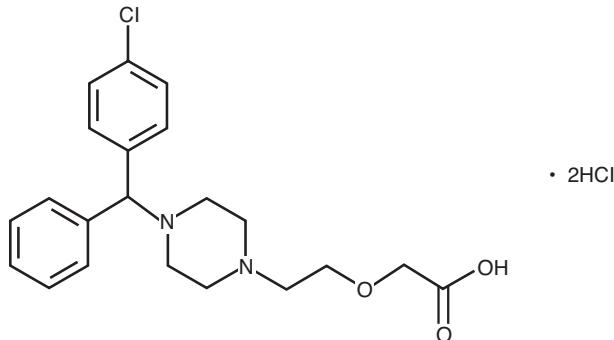
10 OVERDOSAGE

Cases of adult and pediatric patients with overdoses of only oral cetirizine hydrochloride have been reported, some of which resulted in adverse reactions. Adult overdose cases involved patients 18 to 81 years of age receiving oral cetirizine hydrochloride doses of 70 mg to 800 mg (7 to 80 times the maximum recommended dosage of 10 mg/day in adults). The most commonly reported adverse reactions were somnolence and fatigue. Other reported adverse reactions included tachycardia, abdominal pain, nausea, and vomiting. Pediatric overdose cases involved patients 18 months to 15 years of age receiving oral cetirizine hydrochloride doses of 90 mg to 300 mg (9 to 72 times the maximum age recommended dose). The adverse reactions reported included: somnolence, difficulty walking, agitation/irritability, hard to swallow/articulate clearly, tachycardia, vomiting, mydriasis, and elevated creatinine phosphokinase.

If overdose with QUZYTIR occurs, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to cetirizine hydrochloride. Cetirizine hydrochloride is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

11 DESCRIPTION

Cetirizine hydrochloride, the active component of QUZYTIR, is a selective histamine-1 (H1) receptor antagonist. The chemical name is (±)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy]acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of $C_{21}H_{25}ClN_2O_3 \bullet 2HCl$. The molecular weight is 461.82 and the chemical structure is shown below:



Cetirizine hydrochloride is a white, crystalline powder and is water soluble. QUZYTIR is a sterile, clear, colorless, non-pyrogenic, isotonic solution for intravenous injection. Each mL of QUZYTIR injection contains 10 mg cetirizine hydrochloride (equivalent to cetirizine 8.42 mg) and 6.5 mg sodium chloride, USP to adjust solution tonicity, in water for injection, USP. QUZYTIR is supplied in 2 mL size amber glass vials for single use. Each 2 mL size amber glass vial contains 1 mL drug solution with 10 mg cetirizine hydrochloride (10 mg/mL). QUZYTIR's pH is maintained between 4.5 to 6.5 with sodium hydroxide and/or hydrochloric acid as needed. The osmolality of QUZYTIR injection is between 255 to 340 mOsmol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cetirizine hydrochloride, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H1-receptors. The antihistaminic activity of cetirizine hydrochloride has been clearly documented in a variety of animal and human models. In vivo and ex vivo animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies however, dry mouth was more common with cetirizine hydrochloride than with placebo. In vitro receptor binding studies have shown no measurable affinity for receptors other than H1 receptors.

12.2 Pharmacodynamics

Studies in 69 adult normal volunteers (aged 20 to 61 years) showed that cetirizine hydrochloride oral tablets at doses of 5 and 10 mg strongly inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg oral dose occurred within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persisted for at least 24 hours. Cetirizine hydrochloride tablets at doses of 5 and 10 mg also strongly inhibited the wheal and flare caused by intradermal injection of histamine in 19 pediatric volunteers (aged 5 to 12 years) and the activity persisted for at least 24 hours. In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of cetirizine hydrochloride oral tablets was found. In 10 infants 7 to 25 months of age who received 4 to 9 days of cetirizine hydrochloride in an oral solution (0.25 mg/kg bid), there was a 90% inhibition of histamine-induced (10 mg/mL) cutaneous wheal and 87% inhibition of the flare 12 hours after administration of the last dose. The clinical relevance of this suppression of histamine-induced wheal and flare response on skin testing is unknown.

The effects of intradermal injection of various other mediators or histamine releasers were also inhibited by oral cetirizine hydrochloride, as was response to a cold challenge in patients with cold-induced urticaria. In mildly asthmatic subjects, cetirizine hydrochloride oral tablets at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20-mg dose. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by cetirizine hydrochloride oral tablets at a dose of 20 mg.

Cardiac Electrophysiology

In four clinical studies in healthy adult males, no clinically significant mean increases in QTc were observed in subjects treated with cetirizine hydrochloride oral tablets. In the first study, a placebo-controlled crossover trial, cetirizine hydrochloride oral tablets were given at doses up to 60 mg per day, 6 times the maximum clinical dose, for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, cetirizine hydrochloride oral tablets 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with cetirizine hydrochloride alone. In the third trial, also a crossover study, cetirizine hydrochloride oral tablet 20 mg and ketoconazole (400 mg per day) were given alone and in combination. Cetirizine caused a mean increase in QTc of 9.1 msec from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, equal to the sum of the individual effects. Thus, there was no significant drug interaction on QTc with the combination of cetirizine and ketoconazole. In the fourth study, a placebo-controlled parallel trial, cetirizine hydrochloride oral tablet 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with cetirizine hydrochloride 20 mg alone or in combination with azithromycin.

In a four-week clinical trial in pediatric patients aged 6 to 11 years, results of randomly obtained ECG measurements before treatment and after 2 weeks of treatment showed that cetirizine hydrochloride oral tablet 5 or 10 mg did not increase QTc versus placebo. In a one week clinical trial (N=86) of cetirizine hydrochloride oral syrup (0.25 mg/kg bid) compared with placebo in pediatric patients 6 to 11 months of age, ECG measurements taken within 3 hours of the last dose did not show any ECG abnormalities or increases in QTc interval in either group compared to baseline assessments. Data from other studies where cetirizine hydrochloride oral was administered to patients 6-23 months of age were consistent with the findings in this study.

The effects of cetirizine hydrochloride on the QTc interval at doses higher than 10 mg have not been studied in children less than 12 years of age.

12.3 Pharmacokinetics

In a single dose crossover study in healthy volunteers under fasting conditions, cetirizine reached a mean C_{max} of 495 ng/mL and 1344 ng/mL following single dose intravenous (IV) administration of 5 mg and 10 mg, respectively, injected over a period of 1 to 1.5 minutes. Peak concentrations were reached at 0.06 hour (range 0.03 to 0.07 hour) and 0.03 hour (range 0.03 to 2.00 hour) for cetirizine hydrochloride 5 mg and 10 mg IV injection, respectively. The mean systemic exposure ($AUC_{0-\infty}$) for cetirizine hydrochloride 5 mg and 10 mg IV injection was 1318 ng·hr/mL and 2746 ng·hr/mL, respectively. The $AUC_{0-\infty}$ for cetirizine hydrochloride 10 mg oral tablet in the study was 2651 ng·hr/mL.

Absorption

Following oral administration of tablets or syrup in adults, cetirizine was rapidly absorbed with a time to maximum concentration (T_{max}) of approximately 1 hour. When healthy volunteers were administered multiple doses of cetirizine hydrochloride (10 mg oral tablets once daily for 10 days), a mean peak plasma concentration (C_{max}) of 311 ng/mL was observed and there was no accumulation. Cetirizine pharmacokinetics were linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of cetirizine exposure (AUC) but T_{max} was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food when cetirizine hydrochloride was administered orally.

Distribution

The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed.

Elimination

The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

Metabolism

Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

Excretion

A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism.

Specific Populations

Geriatric Patients: Following a single, 10-mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

Pediatric Patients: When pediatric patients aged 7 to 12 years received a single, 5-mg oral cetirizine hydrochloride capsule, the mean C_{max} was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults. In pediatric patients aged 2 to 5 years who received 5 mg oral tablets of cetirizine hydrochloride, the mean C_{max} was 660 ng/mL. Based on cross-study comparisons, the weight-normalized apparent total body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter in this pediatric population than in adults. In pediatric patients aged 6 to 23 months who received a single dose of 0.25 mg/kg cetirizine hydrochloride oral solution (mean dose 2.3 mg), the mean C_{max} was 390 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 304% greater and the elimination half-life was 63% shorter in this pediatric population compared to adults. The average $AUC_{(0-t)}$ in children 6 months to less than 2 years of age receiving the maximum dose of cetirizine hydrochloride oral solution (2.5 mg twice a day) is expected to be two-fold higher than that observed in adults receiving a dose of 10 mg cetirizine hydrochloride oral tablets once a day.

Male and Female Patients: The effect of gender of cetirizine pharmacokinetics has not been adequately studied.

Racial or Ethnic Groups: No race-related difference in the kinetics of cetirizine has been observed.

Patients with Renal Impairment: The kinetics of cetirizine were studied following multiple, oral, 10-mg daily doses of cetirizine hydrochloride for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min). The pharmacokinetics of oral cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Patients on hemodialysis ($n = 5$) given a single, 10-mg oral dose of cetirizine hydrochloride had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

The pharmacokinetics of IV cetirizine has not been evaluated in patients with renal impairment.

Patients with Hepatic Impairment: Sixteen patients with chronic liver diseases (hepatocellular, cholestatics, and biliary cirrhosis), given 10 or 20 mg of cetirizine hydrochloride as a single oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects.

The pharmacokinetics of IV cetirizine has not been evaluated in patients with hepatic impairment.

Drug Interaction Studies

No interactions were observed in pharmacokinetic interaction studies conducted with oral cetirizine hydrochloride and pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine hydrochloride (20 mg oral tablets once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine hydrochloride administration.

13 NONCLINICAL TOXICOLOGY**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility****Carcinogenesis**

In a 2-year carcinogenicity study in rats, cetirizine hydrochloride was not carcinogenic at dietary doses up to 20 mg/kg (approximately 20, 10, 25, and 6 times the MRHDs in adults, children 6 to 11 years of age, children 2 to 5 years of age, and children 6 months to less than 2 years of age, respectively, on a mg/m² basis). In a 2-year carcinogenicity study in mice, cetirizine hydrochloride caused an increased incidence of benign hepatic tumors in males at a dietary dose of 16 mg/kg (approximately 8, 4, 9, and 2 times the MRHDs in adults, children 6 to 11 years of age, children 2 to 5 years of age, and children 6 months to less than 2 years of age, respectively, on a mg/m² basis). No increased incidence of benign hepatic tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2, 1, 2, and 0.5 times the MRHDs in adults, children 6 to 11 years of age, children 2 to 5 years of age, and children 6 months to less than 2 years of age, respectively, on a mg/m² basis). The clinical significance of these findings during long-term use of QUZYTIR is not known.

Mutagenesis

Cetirizine hydrochloride was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and *in vivo* micronucleus test in rats.

Impairment of Fertility

Fertility and reproductive performance were unaffected in male and female mice and rats that received cetirizine hydrochloride at oral doses up to 64 and 200 mg/kg/day, respectively (approximately 30 and 190 times the MRHD in adults on a mg/m² basis).

14 CLINICAL STUDIES

The safety and efficacy of QUZYTIR for the treatment of acute urticaria was demonstrated in a randomized, active-controlled, double-blind, single dose, multicenter (US and Canada), parallel group trial in 262 patients 18 years of age and older presenting to Emergency Departments or Urgent care Centers (NCT02935699). Subjects were treated with 10 mg of QUZYTIR or 50 mg diphenhydramine injection. Patients with acute urticaria with or without other diseases were enrolled, including patients with concomitant angioedema. The majority of the patients were Caucasian (48%) and female (63%) with a mean age of 39 years.

The primary efficacy endpoint was the change from baseline in patient-rated pruritus score assessed 2 hrs post treatment for the intent-to-treat (ITT) population. Pruritus was graded on a severity score of 0 to 3 with 0 = no pruritus, 1 = mild, 2 = moderate, and 3 = severe. The trial was non-inferiority design with the pre-specified non-inferiority margin of 0.50 for the difference between treatment groups. Two key secondary efficacy outcome measures: (i) the need to return to any ED or clinic after patient discharge, and (ii) time spent at the treatment center (time from treatment administration to readiness for discharge) were adjusted for multiplicity.

Result for the change from baseline in the pruritus scores are shown in Table 1. The difference between treatment groups excluded the pre-specified non-inferiority margin, i.e. the lower bound of the 95% confidence interval for the difference of diphenhydramine minus QUZYTIR did not include – 0.50. The primary efficacy data are presented in Table 1.

Table 1. Primary Efficacy Endpoint: Patient-rated Pruritus Score Change from Baseline at 2 hrs (using LOCF); ITT population

	Diphenhydramine injection 50 mg (N = 135)	QUZYTIR injection 10 mg (N = 127)	Adjusted Difference between treatment (95% CI)
Baseline: mean (SD)	2.19 (0.748)	2.20 (0.727)	
Change from Baseline: mean (SD)	–1.50 (0.984)	–1.61 (0.944)	0.06 (-0.28, 0.40)*
LOCF: last observation carried forward; ITT: intent-to-treat			

* Since the lower bound of the 95% CI for the treatment difference was > -0.50, effectiveness of QUZYTIR injection was demonstrated to be non-inferior to the effectiveness of diphenhydramine injection. The treatment difference and 95% CI were obtained from a generalized linear mixed-effects model. The model consisted of the change from baseline at 2 hours as the dependent variable and site, treatment and site-by-treatment interaction as the fixed effect.



QUZYTIR™ is a trademark of TerSera Therapeutics LLC or its affiliates.

Manufactured by: Pfizer Rocky Mount, NC 27801

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