HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KARBINAL® ER safely and effectively. See full prescribing information for KARBINAL® ER.

Karbinal® ER (carbinoxamine maleate) extended-release oral suspension
Initial U.S. Approval: 1953

----------RECENT MAJOR CHANGES----------
Contraindications, Nursing Mothers (4) Removed 3/2021

----------INDICATIONS AND USAGE----------
Karbinal ER (carbinoxamine maleate) extended-release oral suspension is an H_1 receptor antagonist indicated for adults and pediatric patients 2 years of age and older for the symptomatic treatment of:

- Seasonal and perennial allergic rhinitis (1)
- Vasomotor rhinitis (1)
- Allergic conjunctivitis due to inhalant allergens and foods (1)
- Mild, uncomplicated allergic skin manifestations of urticaria and angioedema (1)
- Dermatographism (1)
- As therapy for anaphylactic reactions *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled (1)
- Amelioration of the severity of allergic reactions to blood or plasma (1)

----------DOSAGE AND ADMINISTRATION----------
Adults and Adolescents 12 years of age and older (2.3):
7.5 mL to 20 mL (6 to 16 mg) every 12 hours
Pediatric patients 2-11 years of age (approximately 0.2 to 0.4 mg/kg/day) (2.4):
2 to 3 years – 3.75 mL to 5 mL (3 to 4 mg) every 12 hours
4 to 5 years – 3.75 mL to 10 mL (3 to 8 mg) every 12 hours
6 to 11 years – 7.5 mL to 15 mL (6 to 12 mg) every 12 hours

----------DOSAGE FORMS AND STRENGTHS----------
Extended-release oral suspension: 4 mg carbinoxamine maleate per 5 mL (3)

----------CONTRAINDICATIONS----------

- Children younger than 2 years of age (4)
- Patients with known hypersensitivity to the drug or any of the inactive ingredients (4)
- Monoamine oxidase inhibitors (MAOI) (4)

----------WARNINGS AND PRECAUTIONS----------

- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring complete mental alertness such as driving or operating machinery. (5.2)
- Anticholinergic actions: Use with caution in patients with increased intraocular pressure, narrow angle glaucoma, hyperthyroidism, cardiovascular disease, hypertension, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction. (5.3)
- Contains sodium metabisulfite, a sulfite that may cause anaphylaxis including life-threatening or less severe asthmatic episodes in susceptible individuals. (5.4)

----------ADVERSE REACTIONS----------
Most common adverse reactions are: sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, and thickening of bronchial secretions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Aytu Therapeutics, LLC at 1-855-298-8246 or FDA at 1-800-FDA-1088 or *ww.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Monoamine oxidase inhibitors (MAOIs): Prolong and intensify the anticholinergic (drying) effects. (4 and 7)
- Alcohol and CNS depressants (hypnotics sedatives, tranquilizers, etc.): Avoid concomitant use due to additive adverse effects. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)
- Contraindicated in children younger than 2 years of age. (4 and 8.4)
- May cause sedation or excitation in young children. (8.4)
- May cause dizziness, sedation, and hypotension in elderly patients. Start elderly patients on lower doses and observe closely for confusion and over-sedation. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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- Seasonal and perennial allergic rhinitis
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- Allergic conjunctivitis due to inhalant allergens and foods
- Mild, uncomplicated allergic skin manifestations of urticaria and angioedema
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- Amelioration of the severity of allergic reactions to blood or plasma

2 DOSAGE AND ADMINISTRATION

2.1 Overview

The dosage of Karbinal ER should be individualized based on the severity of the condition and the response of the patient. Start with lower doses and increase as needed and tolerated.

2.2 Administration

Administer Karbinal ER by the oral route only. Measure Karbinal ER with an accurate milliliter measuring device. A household teaspoon is not an accurate measuring device and could lead to overdosage. A pharmacist can provide an appropriate measuring device and can provide instructions for measuring the correct dose.

2.3 Recommended Dosage for Adults and Adolescents 12 years of age and older:

7.5 mL to 20 mL (6 mg to 16 mg) every 12 hours administered orally

2.4 Recommended Dosage for Pediatric Patients 2 to 11 years of age (approximately 0.2 to 0.4 mg/kg/day):

2 to 3 years: 3.75 mL to 5 mL (3 mg to 4 mg) every 12 hours administered orally

4 to 5 years: 3.75 mL to 10 mL (3 mg to 8 mg) every 12 hours administered orally

6 to 11 years: 7.5 mL to 15 mL (6 mg to 12 mg) every 12 hours administered orally

3 DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension: 4 mg carbinoxamine maleate per 5 mL

4 CONTRAINDICATIONS

Karbinal ER is contraindicated in:

- children younger than 2 years of age because deaths have been reported in this age group *[see Warnings and Precautions (5.1)]*.
- patients who are hypersensitive to carbinoxamine maleate or any of the inactive ingredients in Karbinal ER *[see Warnings and Precautions (5.4)]*.
- patients who are taking monoamine oxidase inhibitors (MAOI) *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pediatric Mortality

Deaths have been reported in children less than 2 years of age who were taking carbinoxamine-containing drug products; therefore, Karbinal ER is contraindicated in children younger than 2 years of age.

5.2 Somnolence and Impaired Mental Alertness

Karbinal ER may produce marked drowsiness and impair the mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Advise patients to avoid engaging in hazardous tasks requiring mental alertness and motor coordination after ingestion of Karbinal ER. Avoid concurrent use of Karbinal ER with alcohol or other central nervous system depressants because additional impairment of central nervous system performance may occur.

5.3 Concomitant Medical Conditions

Karbinal ER has anticholinergic (atropine-like) properties and, therefore, should be used with caution in patients with: increased intraocular pressure, narrow angle glaucoma, hyperthyroidism, cardiovascular disease, hypertension, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, or pyloroduodenal obstruction.

5.4 Allergic Reactions due to Sulfites, including Anaphylaxis

Karbinal ER contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic individuals.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Somnolence and Impaired Mental Alertness *[see Warnings and Precautions (5.2)]*
- Allergic Reactions due to Sulfites, including Anaphylaxis *[see Warnings and Precautions (5.4)]*

The most frequent adverse reactions include: sedation, sleepiness, dizziness, disturbed coordination, epigastic distress, and thickening of bronchial secretions. In clinical use, younger children and older adults may be particularly sensitive to adverse reactions *[see Pediatric Use (8.4) and Geriatric Use (8.5)]*.

The following adverse reactions, listed by body system, have been identified in case reports and during the use of carbinoxamine in observational studies. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

Cardiovascular: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Central Nervous System: Fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, constipation.

Hematologic: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Laboratory: Increase in uric acid levels.

Respiratory: Tightness of chest and wheezing, nasal stuffiness.

Urogenital: Urinary frequency, difficult urination, urinary retention, early menses.

7 DRUG INTERACTIONS

- Do not use Karbinal ER in patients who are taking monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic (drying) effects of antihistamines.
- Avoid use of Karbinal ER with alcohol and other CNS depressants (hypnotics sedatives, tranquilizers, etc.) due to additive effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published data over decades of use of antihistamines, including carbinoxamine, have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. However, published data specifically evaluating the risk of carbinoxamine were not found. Animal reproductive studies have not been conducted with carbinoxamine maleate.

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 risks of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Based on the physical properties of carbinoxamine, it is likely that carbinoxamine is present in breastmilk. There are published reports of drowsiness and irritability in infants exposed to antihistamines via breast milk. There are post-marketing reports of deaths in children under 2 years of age exposed to carbinoxamine by oral administration. There are no available data on the effects on milk production. It is not recommended to breastfeed during treatment with Karbinal ER *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]*.

8.4 Pediatric Use

Karbinal ER is contraindicated in pediatric patients younger than 2 years of age because deaths have been reported in this patient population who were taking carbinoxamine-containing drug products *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

The safety and effectiveness of Karbinal ER in pediatric patients aged 2 years and older have been established and is based on demonstration of bioequivalence to the immediate-release reference product *[see Clinical Pharmacology (12.3)]*. Carbinoxamine may diminish mental alertness or produce sedation in children. Paradoxical reactions with excitation are more likely in younger children.

8.5 Geriatric Use

Karbinal ER may cause dizziness, hypotension, confusion, or over-sedation in the elderly. Start elderly patients on lower doses and observed closely.

10 OVERDOSAGE

Overdosage with carbinoxamine may cause central nervous system depression or stimulation, hallucinations, convulsions, and death. Atropine-like signs and symptoms – dry mouth; fixed, dilated pupils; flushing; and gastrointestinal symptoms may also occur.

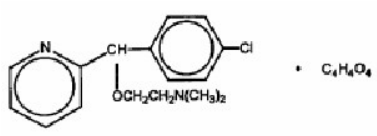
The treatment of overdosage consists of discontinuation of Karbinal ER and institution of symptomatic and supportive therapy. Vital signs (including respiration, pulse, blood pressure, and temperature) and EKG

should be monitored. Induction of vomiting is not recommended. Activated charcoal should be given and gastric lavage should be considered after ingestion of a potentially life-threatening amount of drug. In the presence of severe anticholinergic effects, physostigmine may be useful. Vasopressors may be used to treat hypotension.

11 DESCRIPTION

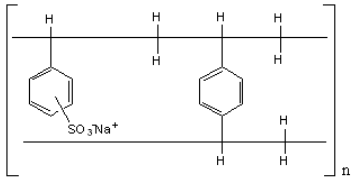
Each 5 mL of Karbinal ER extended-release oral suspension contains carbinoxamine complexed with polistirex equivalent to 4 mg carbinoxamine maleate and the following inactive ingredients: citric acid anhydrous, strawberry-banana flavor, glycerin, high fructose corn syrup, methylparaben, modified food starch, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sulfonate, sucrose, triacetin, and xanthan gum.

Carbinoxamine maleate is freely soluble in water. The chemical name is 2-[(4-chlorophenyl)-2-pyridinylmethoxy]-*N*, *N*-dimethylethanamine (Z)-2-butenedioate (1:1), which has the following structure:



$C_{16}H_{19}ClN_2O \cdot C_4H_4O_4$ MW = 406.86

The drug-polistirex complex is formed with the active ingredient (carbinoxamine maleate, USP) and sodium polystyrene sulfonate, USP, which has the following structure:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carbinoxamine is an H_1 receptor antagonist (antihistamine) that exhibits anticholinergic (drying) and sedative properties.

Antihistamines compete with histamine for receptor sites on effector cells.

12.3 Pharmacokinetics

Karbinal ER after single-dose administration of 16 mg was bioequivalent to the reference carbinoxamine immediate-release oral solution after the administration of two doses of 8 mg six hours apart under fasting conditions. The carbinoxamine mean (SD) peak plasma concentration (C_{max}) was 28.7 (5.3) ng/mL at 6.7 hours after Karbinal ER administration. The plasma half-life of carbinoxamine was 17.0 hours. There was no effect of food on the pharmacokinetic parameters.

Karbinal ER after multiple-dose administration of 16 mg every 12 hours for 8 days was bioequivalent to the reference carbinoxamine immediate-release oral solution after multiple-dose administration of 8 mg every 6 hours. The mean (SD) steady-state C_{max} was 72.9 (24.4) ng/mL at 5.6 hours after Karbinal ER administration. Carbinoxamine mean (SD) minimum plasma concentration at steady-state was 51.8 (20.3) ng/mL.

13 NONCLINCAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to determine the possible effects of carbinoxamine on carcinogenesis, mutagenesis, and fertility.

14 CLINICAL STUDIES

The effectiveness and safety of Karbinal ER is based on demonstration of bioequivalence to the immediate-release reference product *[see Pharmacokinetics (12.3)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Karbinal ER extended-release oral suspension contains 4 mg carbinoxamine maleate per 5 mL. It is a light beige to tan viscous suspension with strawberry banana flavor and is supplied as follows:

NDC 27808-046-02 bottles of 10 fl oz (300 mL)

NDC 27808-046-03 bottles of 16 fl oz (480 mL)

Store at 25ºC (77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF). [See USP Controlled Room Temperature].

Dispense in tight, light-resistant container with child-resistant closure.

17 PATIENT COUNSELING INFORMATION

Administration

Advise patients to measure Karbinal ER with an accurate milliliter measuring device. A household teaspoon is not an accurate measuring device and could lead to overdosage *[see Dosage and Administration (2.2)]*.

Activities Requiring Mental Alertness

Advise patients to use caution when driving a motor vehicle or operating machinery. Karbinal ER may produce marked drowsiness and impair the mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery *[see Warnings and Precautions (5.2)]*.

Alcohol, Sedatives, and Tranquilizers

Advise patients to avoid the use of alcoholic beverages, sedatives, and tranquilizers while taking Karbinal ER because additional reduction in mental alertness may occur *[see Warnings and Precautions (5.2) and Drug Interactions (7)]*.

MAOIs

Advise patients to not use MAOIs while taking Karbinal ER. MAOIs may prolong and intensify the anticholinergic (drying) effects *[see Contraindications (4) and Drug Interactions (7)]*.

Lactation

Advise women that breastfeeding is not recommended during treatment with Karbinal ER *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.2)]*.

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