QBRELIS- lisinopril solution
Praxis, LLC

QBRELIS (lisinopril) oral solution

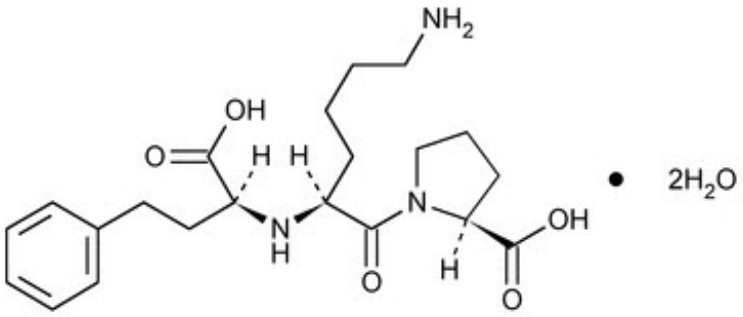
10 OVERDOSAGE

Following a single oral dose of 20 g/kg no lethality occurred in rats, and death occurred in one of 20 mice receiving the same dose. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Lisinopril can be removed by hemodialysis *[see Clinical Pharmacology (12.3)]* .

11 DESCRIPTION

Lisinopril is an oral long-acting angiotensin converting enzyme (ACE) inhibitor. Lisinopril is a synthetic peptide derivative that is manufactured as a dihydrate and is chemically described as 1-[N^2-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate. Its molecular formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$ and its structural formula is:



Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.52 (for dihydrate). It is soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol.

QBRELIS (lisinopril), 1 mg/mL, is a ready-to-use aqueous formulation. Each 1 mL of the oral solution contains 1.09 mg of lisinopril dihydrate, which is equivalent to 1 mg of lisinopril as the active ingredient and the following inactive ingredients: purified water, xylitol, sodium citrate, citric acid, sodium benzoate, and either hydrochloric acid or sodium hydroxide which may be added for pH adjustment. The solution is clear to slightly opalescent. The pH of the solution ranges from 4.3 to 5.1. QBRELIS is supplied as 150 mL of the solution packaged in a 150-mL round, white, opaque, high-density polyethylene (HDPE) bottle with a white, polypropylene, child-resistant closure with a heat induction layered inner seal.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lisinopril inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15% of patients had increases greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L. In the same study, patients treated with lisinopril and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mEq/L; approximately 4% of patients had increases greater than 0.5 mEq/L and approximately 12% had a decrease greater than 0.5 mEq/L *[see Clinical Studies (14.1)]* . Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of QBRELIS remains to be elucidated.

While the mechanism through which QBRELIS lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, QBRELIS is antihypertensive even in patients with low-renin hypertension. Although lisinopril was antihypertensive in all races studied, Black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-Black patients.

Concomitant administration of lisinopril and hydrochlorothiazide further reduced blood pressure in Black and non-Black patients and any racial differences in blood pressure response were no longer evident.

12.2 Pharmacodynamics

Hypertension

Adult Patients: Administration of lisinopril to patients with hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients *[see Warnings and Precautions (5.4)]* . When given together with thiazide-type diuretics, the blood pressure lowering effects of the two drugs are approximately additive.

In most patients studied, onset of antihypertensive activity was seen at one hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses; however, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6

hours after dosing.

The antihypertensive effects of lisinopril are maintained during long-term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure, or a significant increase in blood pressure compared to pretreatment levels.

Non-Steroidal Anti-Inflammatory Agents

In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of lisinopril alone were compared lisinopril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

12.3 Pharmacokinetics

Adult Patients: QBRELIS is bioequivalent to lisinopril tablets under fasted and fed conditions.

Following oral administration of lisinopril tablets, peak serum concentrations of lisinopril occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Food does not alter the bioavailability of lisinopril tablets. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Upon multiple dosing, lisinopril exhibits an effective half-life of 12 hours.

Lisinopril does not appear to be bound to other serum proteins. Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large intersubject variability (6-60%) at all doses tested (5-80 mg). The absolute bioavailability of lisinopril is reduced to 16% in patients with stable NYHA Class II-IV congestive heart failure, and the volume of distribution appears to be slightly smaller than that in normal subjects. The oral bioavailability of lisinopril in patients with acute myocardial infarction is similar to that in healthy volunteers.

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 mL/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged *[see Dosage and Administration (2.4)]* . Lisinopril can be removed by hemodialysis.

*Pediatric Patients:*The pharmacokinetics of lisinopril were studied in 29 pediatric hypertensive patients between 6 years and 16 years with glomerular filtration rate > 30 mL/min/1.73 m^2. After doses of 0.1 to 0.2 mg per kg, steady state peak plasma concentrations of lisinopril occurred within 6 hours and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults. The typical value of lisinopril oral clearance (systemic clearance/absolute bioavailability) in a child weighing 30 kg is 10 L/h, which increases in proportion to renal function.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg per kg per day (about 56 or 9 times* the maximum recommended daily human dose, based on body weight and body surface area, respectively). There was no evidence of carcinogenicity when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg per kg per day (about 84 times* the maximum recommended daily human dose). This dose was 6.8 times the maximum human dose based on body surface area in mice.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an *in vitro*alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an *in vitro*test in Chinese hamster ovary cells or in an *in vivo*study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg per kg per day of lisinopril. This dose is 188 times and 30 times the maximum human dose when based on mg/kg and mg/m ^{2}, respectively.

Studies in rats indicate that lisinopril crosses the blood brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the fetuses.

*Calculations assume a human weight of 50 kg and human body surface area of 1.62 m ^{2}.

14 CLINICAL STUDIES

14.1 Hypertension

Two dose-response studies utilizing a once-daily regimen were conducted in 438 mild to moderate hypertensive patients not on a diuretic. Blood pressure was measured 24 hours after dosing. An antihypertensive effect of lisinopril was seen with 5 mg of lisinopril in some patients. However, in both studies blood pressure reduction occurred sooner and was greater in patients treated with 10, 20 or 80 mg of lisinopril than patients treated with 5 mg of lisinopril.

In controlled clinical studies of patients with mild to moderate hypertension, patients were treated with lisinopril 20-80 mg daily, hydrochlorothiazide 12.5-50 mg daily or atenolol 50-200 mg daily; and in other studies of patients with moderate to severe hypertension, patients were treated with lisinopril 20-80 mg daily or metoprolol 100-200 mg daily. Lisinopril demonstrated superior reductions of systolic and diastolic compared to hydrochlorothiazide in a population that was 75% Caucasian. Lisinopril was approximately equivalent to atenolol and metoprolol in reducing diastolic blood pressure, and had somewhat greater effects on systolic blood pressure.

Lisinopril had similar blood pressure reductions and adverse effects in younger and older (> 65 years) patients. It was less effective in reducing blood pressure in Blacks

than in Caucasians.

In hemodynamic studies of lisinopril in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of lisinopril, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

In patients with renovascular hypertension lisinopril has been shown to be well-tolerated and effective in reducing blood pressure *[see Warnings and Precautions (5.3)]* .

*Pediatric Patients:*In a clinical study involving 115 hypertensive pediatric patients 6 to 16 years of age, patients who weighed < 50 kg received either 0.625, 2.5 or 20 mg of lisinopril once daily and patients who weighed ≥ 50 kg received either 1.25, 5, or 40 mg of lisinopril once daily. At the end of 2 weeks, lisinopril lowered trough blood pressure in a dose-dependent manner with antihypertensive efficacy demonstrated at doses > 1.25 mg (0.02 mg per kg). This effect was confirmed in a randomized withdrawal phase, where the diastolic pressure rose by about 9 mmHg more in patients randomized to placebo than compared to patients who remained on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, and race. In this study, lisinopril was generally well-tolerated.

In the above pediatric study, lisinopril was given either as tablets or in a suspension for those children who were unable to swallow tablets or who required a lower dose than is available in tablet form.

14.2 Heart Failure

Two placebo controlled, 12-week clinical studies compared the addition of lisinopril up to 20 mg daily to digitalis and diuretics alone. The combination of lisinopril, digitalis and diuretics reduced the following signs and symptoms of heart failure: edema, rales, paroxysmal nocturnal dyspnea and jugular venous distention. In one of the studies, the combination of lisinopril, digitalis and diuretics reduced orthopnea, presence of third heart sound and the number of patients classified as NYHA Class III and IV; and improved exercise tolerance. A large (over 3000 patients) survival study, the ATLAS Trial, comparing 2.5 and 35 mg of lisinopril in patients with systolic heart failure, showed that the higher dose of lisinopril had outcomes at least as favorable as the lower dose.

During baseline-controlled clinical trials, in patients with systolic heart failure receiving digitalis and diuretics, single doses of lisinopril resulted in decreases in pulmonary capillary wedge pressure, systemic vascular resistance and blood pressure accompanied by an increase in cardiac output and no change in heart rate.

14.3 Acute Myocardial Infarction

The Gruppo Italiano per lo Studio della Sopravvienza nell'Infarto Miocardico (GISSI-3) study was a multicenter, controlled, randomized, unblinded clinical trial conducted in 19,394 patients with acute myocardial infarction (MI) admitted to a coronary care unit. It was designed to examine the effects of short-term (6 week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (6 week) mortality and on long-

term death and markedly impaired cardiac function. Hemodynamically-stable patients presenting within 24 hours of the onset of symptoms were randomized, in a 2 x 2 factorial design, to six weeks of either 1) lisinopril alone (n=4841), 2) nitrates alone (n=4869), 3) lisinopril plus nitrates (n=4841), or 4) open control (n=4843). All patients received routine therapies, including thrombolytics (72%), aspirin (84%), and a beta blocker (31%), as appropriate, normally utilized in acute myocardial infarction (MI) patients.

The protocol excluded patients with hypotension (systolic blood pressure ≤ 100 mmHg), severe heart failure, cardiogenic shock, and renal dysfunction (serum creatinine > 2 mg per dL and/or proteinuria > 500 mg per 24 h). Patients randomized to lisinopril received 5 mg within 24 hours of the onset of symptoms, 5 mg after 24 hours, and then 10 mg daily thereafter. Patients with systolic blood pressure less than 120 mmHg at baseline received 2.5 mg of lisinopril. If hypotension occurred, the lisinopril dose was reduced or if severe hypotension occurred lisinopril was stopped *[see Dosage and Administration (2.3)]* .

The primary outcomes of the trial were the overall mortality at 6 weeks and a combined end point at 6 months after the myocardial infarction, consisting of the number of patients who died, had late (day 4) clinical congestive heart failure, or had extensive left ventricular damage defined as ejection fraction ≤ 35% or an akinetic-dyskinetic [A-D] score ≥ 45%. Patients receiving lisinopril (n=9646), alone or with nitrates, had an 11% lower risk of death (p=0.04) compared to patients who did not receive lisinopril (n=9672) (6.4% vs. 7.2%, respectively) at six weeks. Although patients randomized to receive lisinopril for up to six weeks also fared numerically better on the combined end point at 6 months, the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography, and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomized to 6 weeks of lisinopril, preclude any conclusion about this end point.

Patients with acute myocardial infarction, treated with lisinopril, had a higher (9.0% versus 3.7%) incidence of persistent hypotension (systolic blood pressure < 90 mmHg for more than 1 hour) and renal dysfunction (2.4% versus 1.1%) in-hospital and at six weeks (increasing creatinine concentration to over 3 mg per dL or a doubling or more of the baseline serum creatinine concentration) *[see Adverse Reactions (6.1)]* .

16 HOW SUPPLIED/STORAGE AND HANDLING

QBRELIS (lisinopril), 1 mg/mL, is supplied as 150 mL of a clear to slightly opalescent, colorless aqueous oral solution with a sweet taste in a 150-mL high-density polyethylene (HDPE) bottle with a child-resistant cap (NDC 52652-3001-1).

Store at controlled room temperature 20°C-25°C (68°F-77°F) [see USP] in a tightly closed container. Protect from freezing and excessive heat.

17 PATIENT COUNSELING INFORMATION

Pregnancy: Tell female patients of childbearing age about the consequences of exposure to QBRELIS during pregnancy. Discuss treatment options with women planning to become pregnant. Tell patients to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema may occur at any time during treatment with angiotensin converting enzyme inhibitors, including QBRELIS. Tell patients to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Tell patients to report light-headedness especially during the first few days of therapy. If actual syncope occurs, tell the patient to discontinue the drug until they have consulted with the prescribing physician.

Tell patients that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; advise patients accordingly.

Hyperkalemia: Tell patients to consult their physician prior to using salt substitutes containing potassium.

Hypoglycemia: Tell diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor to monitor for hypoglycemia closely, especially during the first month of combined use *[see Drug Interactions (7.2)]* .

Leukopenia/Neutropenia: Tell patients to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of leukopenia/neutropenia.

Manufactured for:
Azurity Pharmaceuticals, Inc.
Woburn, MA 01801 USA

Patent: https://azurity.com/patents

This product’s label may have been updated. For current Full Prescribing Information, please visit Qbrelis.com

PI100073.05 Rev. 4/2023

PRINCIPAL DISPLAY PANEL - Bottle Label

NDC 52652-3001-1

Qbrelis ®
(lisinopril)

Oral Solution
1 mg/mL

READY TO USE

150 mL
azurity™
pharmaceuticals
Rx Only

Each 1 mL contains
1 mg of lisinopril.

Usual Dose:
See prescribing information.

Store at room temperature
20° - 25°C (68° - 77°F)
Avoid freezing and excessive heat.
Keep container tightly closed.

KEEP THIS AND ALL
MEDICATIONS OUT OF THE
REACH OF CHILDREN

P/N 141146

Manufactured for:
Azurity Pharmaceuticals, Inc.
Wilmington, MA 01887 USA

Lot:
Exp:

QBRELIS

lisinopril solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59368-406
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LISINOPRIL (UNII: E7199S1YWR) (LISINOPRIL ANHYDROUS - UNII:7Q3P4BS2FD)	LISINOPRIL	1 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
WATER (UNII: 059QF0KO0R)	
XYLITOL (UNII: VCQ006KQ1E)	
SODIUM CITRATE, UNSPECIFIED FORM (UNII: 1Q73Q2JULR)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:59368-406-01	150 mL in 1 BOTTLE; Type 0: Not a Combination Product	08/29/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208401	08/29/2016	

Labeler - Praxis, LLC (016329513)

Establishment

Name	Address	ID/FEI	Business Operations
Praxis, LLC		016329513	manufacture(59368-406) , label(59368-406) , pack(59368-406)

Revised: 1/2023

Praxis, LLC