HIGHLIGHTS OF PRESCRIBING INFORMATION

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

QBRELIS (lisinopril) oral solution
Initial US Approval: 1988

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue QBRELIS as soon as possible. (5.1)**
- **Drugs that act directly on the rennin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

---------- INDICATIONS AND USAGE ----------

QBRELIS is an angiotensin converting enzyme (ACE) inhibitor indicated for:

- Treatment of hypertension in adults and pediatric patients 6 years of age and older (1.1)
- Adjunct therapy for heart failure (1.2)
- Treatment of Acute Myocardial Infarction (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

- Hypertension: Initial adult dose is 10 mg once daily. Titrate up to 40 mg daily based on blood pressure response. Initiate patients on diuretics at 5 mg once daily. (2.1)
- Pediatric patients with glomerular filtration rate > 30 mL/min/1.73m^2: Initial dose in patients 6 years of age and older is 0.07 mg per kg (up to 5 mg total) once daily. (2.1)
- Heart Failure: Initiate with 5 mg once daily. Increase dose as tolerated to 40 mg daily. (2.2)
- Acute Myocardial Infarction (MI): Give 5 mg within 24 hours of MI followed by 5 mg after 24 hours, then 10 mg once daily. (2.3)
- Renal Impairment: For patients with creatinine clearance ≥ 10 mL/min and ≤ 30 mL/min, halve usual initial dose. For patients with creatinine clearance < 10 mL/min or on hemodialysis, the recommended initial dose is 2.5 mg. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

Oral solution: 1 mg/mL (3)

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

- Angioedema or a history of hereditary or idiopathic angioedema (4)
- Hypersensitivity (4)
- Co-administration of aliskiren with QBRELIS in patients with diabetes (4, 7.4)

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

- Angioedema: Discontinue QBRELIS; provide appropriate therapy and monitor until resolved. (5.2)
- Renal impairment: Monitor renal function periodically. (5.3)
- Hypotension: Patients with other heart or renal diseases have increased risk, monitor blood pressure after initiation. (5.4)
- Hyperkalemia: Monitor serum potassium periodically. (5.5)
- Cholestatic jaundice and hepatic failure: Monitor for jaundice or signs of liver failure. (5.6)

---------- ADVERSE REACTIONS ----------

Common adverse reactions (events 2% greater than placebo) by use:

- Hypertension: headache, dizziness and cough (6.1)
- Heart Failure: hypotension and chest pain (6.1)
- Acute Myocardial Infarction: hypotension (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Silvergate Pharmaceuticals, Inc., at 1-855-379-0383 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Diuretics: Excessive drop in blood pressure (7.1)
- NSAIDS: Increased risk of renal impairment and loss of antihypertensive efficacy (7.3)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension and hyperkalemia (7.4)
- Lithium: Symptoms of lithium toxicity (7.5)
- Gold: Nitritoid reactions have been reported (7.6)

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

- Lactation: Advise not to breastfeed (8.2)
- Race: Less antihypertensive effect in Blacks than non-Blacks (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue QBRELIS as soon as possible *[see Warnings and Precautions (5.1)]*.**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus *[see Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

1.1 Hypertension

QBRELIS is indicated for the treatment of hypertension in adult patients and pediatric patients 6 years of age and older to lower blood pressure. Lowering blood pressure lowers the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs from a variety of pharmacologic classes and with different mechanisms of action have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in Black patients, and many antihypertensive drugs have additional approved indications and effects

(e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

QBRELIS may be administered alone or with other antihypertensive agents *[see Clinical Studies (14.1)]*.

1.2 Heart Failure

QBRELIS is indicated to reduce signs and symptoms of systolic heart failure *[see Clinical Studies (14.2)]*.

1.3 Reduction of Mortality in Acute Myocardial Infarction

QBRELIS is indicated for the reduction of mortality in treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Hypertension

Adults

Initial Therapy in adults: The recommended initial dose is 10 mg taken orally once a day. Adjust dosage as needed according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose. Doses up to 80 mg per day have been used but do not appear to give greater effect.

Use with diuretics in adults

If blood pressure is not controlled with QBRELIS alone, a low dose of a diuretic may be added (e.g., hydrochlorothiazide, 12.5 mg). After the addition of a diuretic, it may be possible to reduce the dose of QBRELIS.

The recommended starting dose in adult patients with hypertension taking diuretics is 5 mg once per day.

Pediatric Patients 6 years of age and older with hypertension

For pediatric patients with glomerular filtration rate > 30 mL/min/1.73m^2, the recommended starting dose is 0.07 mg per kg (up to 5 mg total) taken orally once daily. Dosage should be adjusted according to blood pressure response up to a maximum of 0.61 mg per kg (up to 40 mg) once daily. Doses above 0.61 mg per kg (or in excess of 40 mg) have not been studied in pediatric patients *[see Clinical Pharmacology (12.3)]*.

QBRELIS is not recommended in pediatric patients less than 6 years of age or in pediatric patients with glomerular filtration rate < 30 mL/min/1.73m^2 *[see Use in Specific Populations (8.4) and Clinical Studies (14.1)]*.

2.2 Heart Failure

The recommended starting dose for QBRELIS, when used with diuretics and (usually) digitalis as adjunctive therapy for systolic heart failure, is 5 mg taken orally once daily. The recommended starting dose in these patients with hyponatremia (serum sodium < 130 mEq/L) is 2.5 mg once daily. Increase as tolerated to a maximum of 40 mg once daily.

Diuretic dose may need to be adjusted to help minimize hypovolemia, which may contribute to hypotension *[see Warnings and Precautions (5.4), and Drug Interactions (7.1)]*. The appearance of hypotension after the initial dose of QBRELIS does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

2.3 Reduction of Mortality in Acute Myocardial Infarction

Initiation

In hemodynamically stable patients within 24 hours of the onset of symptoms of acute myocardial infarction, give QBRELIS 5 mg orally, followed by 5 mg after 24 hours, and then 10 mg once daily. Dosing should continue for at least six weeks. In patients with a low systolic blood pressure (≤ 120 mmHg and > 100 mmHg) during the first 3 days after the infarct initiate therapy with 2.5 mg once daily *[see Warnings and Precautions (5.4)]* and titrate up based on tolerability.

Maintenance

The usual maintenance dose is 10 mg once daily. If hypotension (systolic blood pressure ≤ 100 mmHg) occurs during maintenance treatment, give 5 mg once daily with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure < 90 mmHg for more than 1 hour) QBRELIS should be withdrawn.

2.4 Dose in Patients with Renal Impairment

No dose adjustment of QBRELIS is required in patients with creatinine clearance > 30 mL/min. In patients with creatinine clearance ≥ 10 mL/min and ≤ 30 mL/min, reduce the initial dose of QBRELIS to half of the usual recommended dose, i.e., hypertension, 5 mg once daily; systolic heart failure, 2.5 mg once daily and acute myocardial infarction, 2.5 mg once daily. Up titrate as tolerated to a maximum of 40 mg daily. For patients on hemodialysis or creatinine clearance < 10 mL/min, the recommended initial dose is 2.5 mg once daily *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

QBRELIS oral solution is available in a 150 mL bottle containing 1 mg/mL of lisinopril solution. QBRELIS oral solution is a clear to slightly opalescent liquid.

4 CONTRAINDICATIONS

QBRELIS is contraindicated in patients with:

- a history of angioedema or hypersensitivity related to previous treatment with an angiotensin converting enzyme inhibitor
- hereditary or idiopathic angioedema

Do not co-administer aliskiren with QBRELIS in patients with diabetes *[see Drug Interactions (7.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue QBRELIS as soon as possible *[see Use in specific Populations (8.1)]*.

5.2 Angioedema and Anaphylactoid Reactions

Angioedema

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx, including some fatal reactions, have occurred in patients treated with angiotensin converting enzyme inhibitors, including lisinopril, at any time during treatment. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. QBRELIS should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms of angioedema has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor *[see Contraindications (4)]*. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients.

Patients receiving coadministration of an ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.

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