

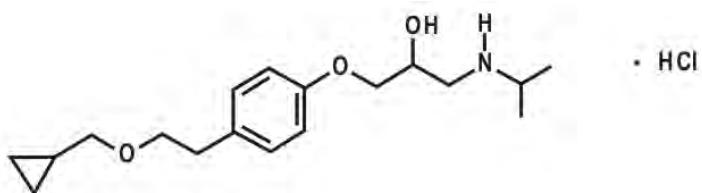
KerledexTM

(betaxolol hydrochloride and chlorthalidone)

DESCRIPTION

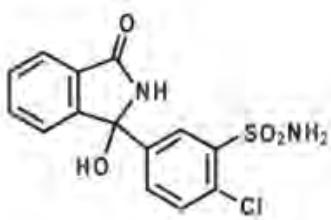
Kerledex (betaxolol hydrochloride and chlorthalidone) is a combination product indicated for the treatment of hypertension. It combines the activities of betaxolol hydrochloride, a β_1 -selective (cardioselective) adrenergic receptor blocking agent, with chlorthalidone, a monosulfamyl diuretic.

Betaxolol hydrochloride is chemically described as 2-propanol, 1-[4-[2-(cyclopropylmethoxy)ethyl] phenoxy]-3-[(1-methylethyl)amino]-,hydrochloride,(\pm). It has the following chemical structure:



Betaxolol hydrochloride is a water-soluble white crystalline powder with a molecular formula of C₁₈H₂₉NO₃ · HCl and a molecular weight of 343.9. It is freely soluble in water, ethanol, chloroform, and methanol, and has a pKa of 9.4.

Chlorthalidone, a monosulfamyl diuretic, differs chemically from thiazide diuretics in that a double-ring system is incorporated in its structure. It is 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzenesulfonamide with a molecular formula of C₁₄H₁₁ClN₂O₄S and a molecular weight of 338.76. It is practically insoluble in water, ether and chloroform; soluble in methanol; and slightly soluble in alcohol.



Kerledex is available as orally administered tablets containing 5 or 10 mg of betaxolol HCl and 12.5 mg of chlorthalidone (5/12.5; 10/12.5). Inactive ingredients include corn starch, hydroxypropyl methylcellulose, iron oxide colorant, lactose, magnesium stearate, polyethylene glycol 400, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY

Kerledex: Data supporting the efficacy of once-daily administration of Kerledex include those derived from five double-blind, randomized, controlled trials, involving a total of 1,146 patients. Two of these trials were concurrent placebo-controlled.

The first placebo-controlled trial was a factorial design, parallel fixed-dose study ($n = 408$). The study consisted of an initial 3 week double-blind period evaluating placebo, chlorthalidone 12.5 mg, and chlorthalidone 25 mg, followed by a second 3 week double-blind period in which betaxolol 5 mg, betaxolol 10 mg, or placebo was added to the medication received during the first period. Placebo-subtracted reductions in trough supine diastolic blood pressures (SDBP) in mmHg at endpoint were:

	Placebo	Betaxolol 5 mg	Betaxolol 10 mg
Placebo	0	- 5.0	- 7.3
Chlorthalidone 12.5 mg	-3.2	- 9.2	-10.4
Chlorthalidone 25 mg	-4.9	-11.1	-12.8

The second placebo controlled trial ($n = 261$) was a parallel, fixed-dose study with a 6 week double-blind treatment period. Patients were randomized to receive either placebo, betaxolol 10 mg, chlorthalidone 12.5 mg, or the combination betaxolol 10 mg/chlorthalidone 12.5 mg. Placebo-subtracted reductions in SDBP (mmHg) were:

betaxolol 10 mg	-6.7
chlorthalidone 12.5 mg	-4.6
betaxolol 10 mg/chlorthalidone 12.5 mg	-9.4

The results of these two studies demonstrate that the combination of betaxolol plus chlorthalidone has a greater effect than either of the individual components. The three nonconcurrent placebo controlled studies, each of which used betaxolol 20 mg, chlorthalidone 25 mg, and the combination of these treatments, support the superior antihypertensive efficacy of the combination of betaxolol plus chlorthalidone, when compared to either of its individual components.

Results of the factorial design study indicate that the administration of the low-dose combination (betaxolol 5 mg/chlorthalidone 12.5 mg) is associated with a lower incidence of hypokalemia than the same dose, or a higher dose, of chlorthalidone used alone. The incidence of hypokalemia (serum potassium < 3.5 mEq/L) as a percentage of randomized patients was:

	Placebo	Betaxolol 5 mg	Betaxolol 10 mg
Placebo	0%	2%	0%
Chlorthalidone 12.5 mg	23%	17%	11%
Chlorthalidone 25 mg	45%	28%	30%

Also in this study, the overall incidence of bradycardia (heart rate < 50 bpm) tended to be lower in patients whose treatment included the 5 mg dose (1.5%) of betaxolol than in those whose treatment included betaxolol 10 mg (3.7%). Regimens which combine low doses of betaxolol and chlorthalidone are less likely to be associated with dose-dependent adverse effects (eg,

hypokalemia, bradycardia) than higher doses of the individual components, while still achieving equal or greater reductions in blood pressure.

In a retrospective subgroup analysis of the data from the large factorial study, the blood pressure response and the effect on serum potassium levels were compared between white and black patients. In general, blacks and whites showed a greater decrease in blood pressure with the combination than either component alone. This is shown in the table below which provides reduction in SDBP (mmHg) from baseline for white and black subgroups in this trial.

	Placebo	Betaxolol 5 mg	Betaxolol 10 mg
Placebo			
White	– 6.3	–12.6	–14.4
Black	– 4.8	– 6.9	–10.0
Chlorthalidone 12.5 mg			
White	– 8.5	–15.5	–17.6
Black	–10.9	–13.8	–12.3
Chlorthalidone 25 mg			
White	–10.7	–16.8	–18.3
Black	–12.9	–15.6	–17.5

In white patients, adding betaxolol decreases the potassium loss associated with chlorthalidone (at any dose of chlorthalidone) and this potassium-sparing effect was seen at all doses of betaxolol. This effect was not observed in the subgroup of black patients.

Overall, in clinical trials involving betaxolol/chlorthalidone, the average change in serum potassium was approximately –0.26 mEq/L in subjects who received betaxolol 10 mg and chlorthalidone 12.5 mg. The average subject who received betaxolol 10 mg and chlorthalidone 25 mg experienced a reduction in serum potassium less than that experienced by the average subject receiving the same dose of chlorthalidone monotherapy.

Pharmacokinetics and metabolism: A clinical study conducted in normal volunteers indicates that the pharmacokinetic profiles of betaxolol and chlorthalidone, when administered concurrently, do not differ from the observations in the same subjects when each agent was administered alone.

Betaxolol: Betaxolol is a β_1 -selective (cardioselective) adrenergic receptor blocking agent that has weak membrane-stabilizing activity and no intrinsic sympathomimetic (partial agonist) activity. The preferential effect on β_1 receptors is not absolute, however, and some inhibitory effects on β_2 receptors (found chiefly in the bronchial and vascular musculature) can be expected at higher doses.

Pharmacokinetics and metabolism: In man, absorption of an oral dose of betaxolol is complete. There is a small and consistent first-pass effect resulting in an absolute bioavailability of $89 \pm 5\%$ that is unaffected by the concomitant ingestion of food or alcohol. Mean peak blood concentrations of 21.6 ng/ml (range 16.3 to 27.9 ng/ml) are reached between 1.5 and 6 (mean about 3) hours after a single oral dose, in healthy volunteers, of 10 mg of betaxolol. Peak

concentrations for 20-mg and 40-mg doses are 2 and 4 times that of a 10-mg dose and have been shown to be linear over the dose range of 5 to 40 mg. The peak-to-trough ratio of plasma concentrations over 24 hours is 2.7. The mean elimination half-life in various studies in normal volunteers ranged from about 14 to 22 hours after single oral doses and is similar in chronic dosing. Steady-state plasma concentrations are attained after 5 to 7 days with once-daily dosing in persons with normal renal function.

Betaxolol is approximately 50% bound to plasma proteins. It is eliminated primarily by liver metabolism and secondarily by renal excretion. Following oral administration, greater than 80% of a dose is recovered in the urine as betaxolol and its metabolites. Approximately 15% of the dose administered is excreted as unchanged drug, the remainder being metabolites whose contribution to the clinical effect is negligible.

Steady-state studies in normal volunteers and hypertensive patients found no important differences in betaxolol kinetics. In patients with hepatic disease, elimination half-life was prolonged by about 33%, but clearance was unchanged, leading to little change in AUC. Dosage reductions have not routinely been necessary in these patients. In patients with chronic renal failure undergoing dialysis, mean elimination half-life was approximately doubled, as was AUC, indicating the need for a lower initial dosage (5 mg) in these patients. The clearance of betaxolol by hemodialysis was 0.015 L/h/kg and by peritoneal dialysis, 0.010 L/h/kg. In one study (n = 8), patients with stable renal failure, not on dialysis, with mean creatinine clearance of 27 ml/min showed slight increases in elimination half-life and AUC, but no change in C_{max} . In a second study of 30 hypertensive patients with mild to severe renal impairment, there was a reduction in clearance of betaxolol with increasing degrees of renal insufficiency. Inulin clearance (mL/min/1.73 m²) ranged from 70 to 107 in 7 patients with mild impairment, 41 to 69 in 14 patients with moderate impairment, and 8 to 37 in 9 patients with severe impairment. Clearance following oral dosing was reduced significantly in patients with moderate and severe renal impairment (26% and 35%, respectively) when compared with those with mildly impaired renal function. In the severely impaired group, the mean C_{max} and the mean elimination half-life tended to increase (28% and 24%, respectively) when compared with the mildly impaired group. A starting dose of 5 mg is recommended in patients with severe renal impairment.

Studies in elderly patients (n = 10) gave inconsistent results but suggest some impairment of elimination, with one small study (n = 4) finding a mean half-life of 30 hours. A starting dose of 5 mg is suggested in older patients.

Pharmacodynamics: Clinical pharmacology studies have demonstrated the beta-adrenergic receptor blocking activity of betaxolol by (1) reduction in resting and exercise heart rate, cardiac output, and cardiac work load, (2) reduction of systolic and diastolic blood pressure at rest and during exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The β_1 selectivity of betaxolol in man was shown in three ways: (1) In normal subjects, 10- and 40-mg oral doses of betaxolol, which reduced resting heart rate at least as much as 40 mg of propranolol, produced less inhibition of isoproterenol-induced increases in forearm blood flow and finger tremor than propranolol. In this study, 10 mg of betaxolol was at least comparable to

50 mg of atenolol. Both doses of betaxolol, and the one dose of atenolol, however, had more effect on the isoproterenol-induced changes than placebo (indicating some β_2 effect at clinical doses) and the higher dose of betaxolol was more inhibitory than the lower. (2) In normal subjects, single intravenous doses of betaxolol and propranolol, which produced equal effects on exercise-induced tachycardia, had differing effects on insulin-induced hypoglycemia, with propranolol, but not betaxolol, prolonging the hypoglycemia compared to placebo. Neither drug affected the maximum extent of the hypoglycemic response. (3) In a single-blind crossover study in asthmatics ($n = 10$), intravenous infusion over 30 minutes of low doses of betaxolol (1.5 mg) and propranolol (2 mg) had similar effects on resting heart rate but had differing effects on FEV₁ and forced vital capacity, with propranolol causing statistically significant (10% to 20%) reductions from baseline in mean values for both parameters while betaxolol had no effect on mean values. While blood levels were not measured, the dose of betaxolol used in this study would be expected to produce blood concentrations, at the time of the pulmonary function studies, considerably lower than those achieved during antihypertensive therapy with recommended doses of betaxolol. In a randomized double-blind, placebo-controlled crossover (4X4 Latin Square) study in 10 asthmatics, betaxolol (about 5 or 10 mg IV) had little effect on isoproterenol-induced increases in FEV₁; in contrast, propranolol (about 7 mg IV) inhibited the response.

Consistent with its negative chronotropic effect, due to beta-blockade of the SA node, and lack of intrinsic sympathomimetic activity, betaxolol increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged.

Significant reductions in blood pressure and heart rate were observed 24 hours after dosing in double-blind, placebo-controlled trials with doses of 5 to 40 mg administered once daily. The antihypertensive response to betaxolol was similar at peak blood levels (3 to 4 hours) and at trough (24 hours). In a large randomized, parallel dose-response study of 5, 10, and 20 mg, the antihypertensive effects of the 5-mg dose were roughly half of the effects of the 20-mg dose (after adjustment for placebo effects) and the 10-mg dose gave more than 80% of the antihypertensive response of the 20-mg dose. The effect of increasing the dose from 10 mg to 20 mg was thus small. In other trials, there was little evidence of a greater antihypertensive response to 40 mg than to 20 mg. The maximum effect of each dose was achieved within 1 or 2 weeks. In comparative trials against propranolol, atenolol, and chlorthalidone, betaxolol appeared to be at least as effective as the comparative agent.

Betaxolol has been studied in combination with thiazide-type diuretics and the blood pressure effects of the combination appear additive. Betaxolol has also been used concurrently with methyldopa, hydralazine, and prazosin.

The mechanism of the antihypertensive effects of beta-adrenergic receptor blocking agents has not been established. Several possible mechanisms have been proposed, however, including: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic-neuronal sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity.

The results from long-term studies have not shown any diminution of the antihypertensive effect of betaxolol with prolonged use.

Chlorthalidone: Chlorthalidone is a diuretic with prolonged activity and low toxicity. The diuretic effect of the drug occurs within two hours of an oral dose and continues for 48 to 72 hours. Thiazides reduce the reabsorption of sodium and chloride in the first half of the distal convoluted tubule and a portion of the cortical ascending limb of the loop of Henle.

Pharmacokinetics and metabolism: In man, chlorthalidone has a mean plasma half-life of 40 hours following a 25 mg to 200 mg dose and an oral availability of approximately 64%. Approximately 65% of the intravenous dose is renally excreted unchanged and chlorthalidone has a reported volume of distribution of 3.9 L/Kg. Approximately 75% of the drug is bound to plasma proteins; 68% of the drug is bound to albumin. Due to the high affinity of chlorthalidone to erythrocyte carbonic anhydrase, red blood cells contain much higher levels of chlorthalidone than plasma. Data indicate that chlorthalidone crosses the placental barrier and appears in human milk.

INDICATIONS AND USAGE

Kerledex is indicated in the management of hypertension.

CONTRAINDICATIONS

Kerledex is contraindicated in patients with anuria, sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see *Warnings*). It is also contraindicated in patients with a known hypersensitivity to any of the individual components or other sulfonamide-derived drugs.

WARNINGS

Cardiac failure: Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and beta-adrenergic receptor blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe heart failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, beta-blockers should be administered cautiously. Both digitalis and beta-adrenergic receptor blocking agents slow AV conduction.

In patients without a history of cardiac failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of cardiac failure, discontinuation of Kerledex should be considered. In some cases Kerledex therapy can be continued while cardiac failure is treated with cardiac glycosides, additional diuretics, and other agents, as appropriate.

Renal and hepatic diseases and electrolyte disturbances: In patients with renal disease, chlorthalidone or related drugs may precipitate azotemia. Cumulative effects may develop in the presence of impaired renal function. If progressive renal impairment becomes evident, Kerledex therapy should be reappraised.

In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma. Kerledex should be used with caution in these patients.

Exacerbation of angina pectoris upon withdrawal: Abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease has been followed by exacerbations of angina pectoris and, in some cases, myocardial infarction has been reported. Therefore, such patients should be warned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of Kerledex is planned, it should be done gradually over about 2 weeks and the patient should be carefully observed. A beta-blocker should be reinstated, at least temporarily, if withdrawal symptoms occur.

Bronchospastic diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD NOT IN GENERAL RECEIVE BETA-BLOCKERS. Because of its relative β_1 selectivity (cardioselectivity), low doses of betaxolol may be used with caution in patients with bronchospastic disease who do not respond to or cannot tolerate alternative treatment. Since β_1 selectivity is not absolute and is inversely related to dose, the lowest possible dose of betaxolol should be used (5 to 10 mg once daily) and a bronchodilator should be made available.

Hypersensitivity reactions to chlorthalidone may occur in patients with a history of bronchial asthma or allergy (see *Precautions: Drug interactions*).

Anesthesia and major surgery: The necessity, or desirability, of withdrawal of a beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. While this might be of benefit in preventing arrhythmic response, the risk of excessive myocardial depression during general anesthesia may be increased and difficulty in restarting and maintaining the heart beat has been reported with beta-blockers. If treatment is continued, particular care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene, and it is prudent to use the lowest possible dose of betaxolol. Betaxolol, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists and its effect on the heart can be reversed by cautious administration of such agents (eg, dobutamine or isoproterenol—see *Overdosage*). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine 1 to 3 mg IV in divided doses.

Diabetes and hypoglycemia: Beta-blockers should be used with caution in diabetic patients. Beta-blockers may mask tachycardia occurring with hypoglycemia (patients should be warned of this), although other manifestations such as dizziness and sweating may not be significantly affected. Unlike nonselective beta-blockers, betaxolol does not prolong insulin-induced hypoglycemia.

During chlorthalidone administration insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism (eg, tachycardia). Abrupt withdrawal of beta-blockade might precipitate a thyroid storm; therefore, patients known or suspected of being thyrotoxic from whom betaxolol is to be withdrawn should be monitored closely.

Systemic lupus erythematosus: The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics, which are structurally related to chlorthalidone. However, systemic lupus erythematosus has not been reported following chlorthalidone administration.

PRECAUTIONS

General: Beta-adrenoceptor blockade can cause reduction of intraocular pressure. Since betaxolol hydrochloride is marketed as an ophthalmic solution for treatment of glaucoma, patients should be told that Kerledex may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure. Patients receiving beta-adrenergic blocking agents orally and beta-blocking ophthalmic solutions should be observed for potential additive effects either on the intraocular pressure or on the known systemic effects of beta-blockade.

In patients receiving chlorthalidone, hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia.

Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (eg, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements or foods with a high potassium content. The hypokalemic effect of chlorthalidone is dose-related.

Any chloride deficit during chlorthalidone therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency.

Frequently, therefore, more sensitive indicators than the serum potassium level are the serum bicarbonate and chloride concentrations. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Increases in serum glucose may occur in patients on chlorthalidone. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving chlorthalidone. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium even in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been

observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired hepatic or renal function: Betaxolol is primarily metabolized in the liver to metabolites that are inactive and then excreted by the kidneys; clearance is somewhat reduced in patients with renal failure but little changed in patients with hepatic disease. Dosage reductions have not routinely been necessary when hepatic insufficiency is present but patients should be observed. Patients with severe renal impairment and those on dialysis require a reduced dose.

Information for patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Kerledex therapy without the physician's advice.

Although cardiac failure rarely occurs in appropriately selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult a physician at the first sign or symptom of heart failure.

Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness. Patients should also be cautioned that taking alcohol can increase the chance of dizziness occurring. Patients should contact their physician if any difficulty in breathing occurs, and before surgery of any type. Patients should inform their physicians or dentists that they are taking Kerledex. Patients with diabetes should be warned that beta-blockers may mask tachycardia occurring with hypoglycemia.

Patients should inform their physicians if they have: 1) had an allergic reaction to chlorthalidone or other diuretics or have asthma; 2) kidney disease; 3) liver disease; 4) gout; 5) systemic lupus erythematosus; or 6) been taking other drugs such as cortisone, digitalis, lithium carbonate, or drugs for diabetes.

Patients should be cautioned to contact their physician if they experience any of the following symptoms of potassium loss: excess thirst, tiredness, weakness, drowsiness, restlessness, muscle pains or cramps, nausea, vomiting, increased heart rate or pulse, extra beats or irregular heart rhythms.

Laboratory tests: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Drug interactions:

Betaxolol: The following drugs have been coadministered with betaxolol and have not altered its pharmacokinetics: cimetidine, nifedipine, chlorthalidone, and hydrochlorothiazide. Concomitant

administration of betaxolol with the oral anticoagulant warfarin has been shown not to potentiate the anticoagulant effect of warfarin.

Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Kerledex plus a catecholamine depletor should, therefore, be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving Kerledex and clonidine concurrently, Kerledex should be discontinued slowly over several days before the gradual withdrawal of clonidine.

Literature reports suggest that oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function. Hypotension, AV conduction disturbances, and left ventricular failure have been reported in some patients receiving beta-adrenergic blocking agents when an oral calcium antagonist was added to the treatment regimen. Hypotension was more likely to occur if the calcium antagonist were a dihydropyridine derivative, eg, nifedipine, while left ventricular failure and AV conduction disturbances, including complete heart block, were more likely to occur with either verapamil or diltiazem.

Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Risk of anaphylactic reaction: Although it is known that patients on beta-blockers may be refractory to epinephrine in the treatment of anaphylactic shock, beta-blockers can, in addition, interfere with the modulation of allergic reaction and lead to an increased severity and/or frequency of attacks. Severe allergic reactions including anaphylaxis have been reported in patients exposed to a variety of allergens either by repeated challenge, or accidental contact, and with diagnostic or therapeutic agents while receiving beta-blockers. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Chlorthalidone: Medication such as digitalis may also influence serum electrolytes. Warning signs of electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, mental confusion, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine.

Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Lithium generally should not be given with diuretics because they reduce its renal clearance and increase the risk of lithium toxicity. Read package inserts for lithium preparations before use of such preparations with Kerledex.

Drug/Laboratory test interactions: Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Carcinogenesis, mutagenesis, impairment of fertility: *Betaxolol*: Lifetime studies with betaxolol HCl in mice at oral dosages of 6, 20, and 60 mg/kg/day (up to 90 X the maximum recommended human dose (MRHD) based on 60-kg body weight or 7.4 X MRHD based on body surface area) and in rats at 3, 12, or 48 mg/kg/day (up to 72 X MRHD, based on body weight, or 11.8 X MRHD based on body surface area) showed no evidence of a carcinogenic effect. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic. Betaxolol caused no adverse effects on fertility or general reproductive performance of male or female rats at doses up to 256 mg/kg/day (380 X MRHD, based on body weight; 62.9 X MRHD, based on body surface area).

Chlorthalidone: No information is available concerning the carcinogenic effects of chlorthalidone or its effects on fertility. Mutagenicity studies with chlorthalidone in mammalian cell assays demonstrated that the drug causes chromosomal aberrations when tested at high concentrations *in vitro* in the presence of hepatic metabolizing enzymes. The clinical significance of these findings has not been established.

Betaxolol and Chlorthalidone: The effects of the combination of betaxolol and chlorthalidone on carcinogenicity and impairment of fertility have not been assessed. The mutagenic effects of chlorthalidone do not appear to be altered by betaxolol.

Pregnancy: Pregnancy Category C. Reproduction and teratology studies were conducted with the combination betaxolol/chlorthalidone in rats and rabbits. No teratologic effects were noted at doses up to 540 times the MRHD (based on 60 kg body weight; or 88 X MRHD based on body area) in rats and up to 72 times the MRHD in rabbits (or 15.6 X MRHD based on body area). Embryotoxicity in the form of post-implantation loss (primarily embryonic resorption) was observed at doses 120 times the MRHD in the rat (or 20 X MRHD, based on body area) and at doses 72 times the MRHD in the rabbit (15.6 X MRHD, based on body area). There was no embryotoxicity at doses up to 6 times the MRHD in the rat (or 1 X MRHD, based on body area) and 24 times the MRHD in the rabbit (or 5.2 X MRHD, based on body area).

Betaxolol: In a study in which pregnant rats received betaxolol at doses of 4, 40, or 400 mg/kg, the highest dose (600 X MRHD based on body weight, 98 X MRHD based on body surface area) was associated with increased postimplantation loss, reduced litter size and weight, and an increased incidence of skeletal and visceral abnormalities, which may have been a consequence of drug-related maternal toxicity. Other than a possible increased incidence of incomplete descent of testes and sternebral reductions, betaxolol at 4 mg/kg/day and 40 mg/kg/day (60 X MRHD based on body weight; 9.8 X MRHD, based on body surface area) caused no fetal abnormalities. In a second study with a different strain of rat, 200 mg betaxolol/kg/day (300 X MRHD based on body weight, or 49 X MRHD based on body area) was associated with maternal toxicity and an increase in resorptions, but no teratogenicity. In a study in which pregnant rabbits received doses of 1, 4, 12 or 36 mg betaxolol/kg/day (54 X MRHD based on body weight, or 12 X MRHD based on body area), a marked increase in postimplantation loss occurred at the highest dose, but no drug-related teratogenicity was observed. The rabbit is more

sensitive to betaxolol than other species because of higher bioavailability resulting from saturation of the first-pass effect. In a peri- and postnatal study in rats at doses of 4, 32 and 256 mg betaxolol/kg/day (380 X MRHD based on body weight, or 62.8 X MRHD based on body area), the highest dose was associated with a marked increase in total litter loss within 4 days postpartum. In surviving offspring, growth and development were also affected.

Chlorthalidone: Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

There are no adequate and well-controlled studies in pregnant women. Kerledex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: Each component of Kerledex is excreted in human milk. Because of the potential for serious adverse reactions from Kerledex in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: Safety and efficacy in children have not been established.

Elderly patients: Betaxolol may produce bradycardia more frequently in elderly patients. In general, patients 65 years of age and older had a higher incidence rate of bradycardia (heart rate < 50 BPM) than younger patients in U.S. clinical trials. In a double-blind study in Europe, 19 elderly patients (mean age = 82) received betaxolol 20 mg daily. Dosage reduction to 10 mg or discontinuation was required for 6 patients due to bradycardia.

ADVERSE REACTIONS

Kerledex is usually well tolerated in properly selected patients. Discontinuation of therapy due to adverse events in U.S. controlled clinical trials was necessary in about 4% of patients receiving betaxolol in combination with chlorthalidone. The most frequent reasons for discontinuation were fatigue (1.1%) and bradycardia (0.9%). The following reasons for discontinuation of therapy were reported in 0.4% (2 patients each) of the 465 patients receiving the combination in U.S. controlled studies: myalgia, depression, insomnia, lethargy, palpitation, and elevated serum transaminase levels.

In controlled clinical trials, Kerledex has been evaluated versus placebo and/or its component monotherapies in doses of 5/12.5 mg, 5/25 mg, 10/12.5 mg, 10/25 mg, and 20/25 mg for treatment periods lasting 3 to 24 weeks. In these controlled studies, the most common adverse reactions to Kerledex were bradycardia, headache, dizziness, arthralgia, dyspepsia, and fatigue.

Kerledex adverse events with a 2% or greater frequency, and selected events with lower frequency, in these controlled studies are:

Kerledex

Body System/ Adverse Reaction	(n=465) 5/12.5– 20/25 mg q.d.	Placebo (n=199)	Betaxolol (n=306) 5–20 mg q.d.	Chlorthalidone (n=494) 12.5–25 mg q.d.
	(%)	(%)	(%)	(%)
Cardiovascular				
Bradycardia (heart rate < 50 BPM)	7.3	0	5.2	0.6
Edema	0.9	0.5	1.0	0.8
Central Nervous System				
Headache	4.5	8.0	5.2	4.9
Dizziness	3.9	3.5	4.6	4.9
Fatigue	3.4	2.5	3.9	5.1
Lethargy	1.9	0.5	3.3	2.4
Psychiatric				
Insomnia	0.6	0.5	1.0	1.6
Nervousness	0.4	1.0	0.7	1.2
Depression	0.4	0	0.7	0.2
Autonomic				
Impotence*	1.4	0.8	2.1	0.3
Metabolic				
Hypokalemia (serum K+ < 3.0 mEq/L)	2.4	0	0	5.1
Respiratory				
Dyspnea	1.1	0.5	1.3	0.4
Pharyngitis	0.6	0	2.0	0.8
Rhinitis	1.9	0	1.3	0.8
Upper respiratory infection	4.5	6.5	4.9	6.1
Gastrointestinal				
Dyspepsia	3.7	1.0	2.6	3.0
Nausea	1.1	1.0	1.3	0.8
Diarrhea	1.1	1.0	2.3	1.6
Musculoskeletal				
Arthralgia	3.7	1.5	2.6	5.1
Skin				
Rash	1.3	1.0	0.7	0.8

*Percentage based on number of males: Kerledex n=282; placebo n=131; betaxolol n=188; chlorthalidone n=311.

The following selected (potentially important) adverse events have been reported in patients receiving Kerledex at an incidence of less than 2.0% in U.S. controlled and long-term clinical studies. It is not known whether a causal relationship exists between Kerledex and these events, they are listed to alert the physician to a possible relationship.

Autonomic: flushing, sweating.

Body as a whole: allergy, chest pain, fever, malaise, pain.

Cardiovascular: angina pectoris, hypotension, palpitations, syncope.

Central and peripheral nervous system: asthenia, ataxia, dysphonia, migraine, neuralgia, numbness, paresthesia, twitching, vertigo.

Endocrine: sialadenitis.

Gastrointestinal: anorexia, constipation, dry mouth, dysphagia, gastroenteritis, increased appetite, mouth ulceration, rectal disorder, stomatitis, vomiting.

Hearing and vestibular: earache, tinnitus.

Hematologic: anemia, hyperhemoglobinemia, leucocytosis, lymphadenopathy.

Liver and biliary: cholecystitis, increased AST, increased ALT.

Metabolic and nutritional: diabetes mellitus, hypercalcemia, hyperglycemia, hyperlipemia, hyperuricemia, increased alkaline phosphatase, weight gain, weight loss.

Musculoskeletal: arthropathy, myalgia, neck pain, tendinitis.

Platelet, bleeding and clotting: purpura.

Psychiatric: amnesia, emotional lability, euphoria, decreased libido, hallucinations, hysteria, nightmares.

Reproductive: amenorrhea, dysmenorrhea, dyspareunia, epididymitis, menstrual disorder, ovarian disorder, prostatitis.

Respiratory: apnea, bronchitis, bronchospasm, cough, epistaxis, sinusitis.

Skin: follicular rash, photosensitivity, pruritus, skin disorders.

Special senses: dysgeusia.

Urinary: cystitis, dysuria, micturition disorder, polyuria, renal calculus, urethral disorder.

Vascular: cerebrovascular disorder, cold extremities (peripheral ischemia), leg cramps, phlebitis.

Vision: abnormal lacrimation, abnormal vision, conjunctivitis.

Other adverse events that have been reported with the individual components are listed by body system below:

Betaxolol: *Autonomic*: salivation; *Body as a whole*: rigors; *Cardiovascular*: arrhythmia, atrioventricular block, heart failure, hypertension, myocardial infarction, thrombosis; *Central and peripheral nervous system*: neuropathy, speech disorder, stupor, tremor; *Hearing and vestibular*: deafness, labyrinth disorders; *Hematologic*: thrombocytopenia; *Metabolic and nutritional*: acidosis, hypercholesterolemia, hyperkalemia, increased LDH, thirst; *Musculoskeletal*: muscle cramps; *Psychiatric*: abnormal thinking, impaired concentration, confusion; *Reproductive*: breast pain, breast fibroadenosis, Peyronie's disease; *Respiratory*: flu, pneumonia; *Special senses*: taste loss; *Skin*: alopecia, eczema, erythematous rash, hypertrichosis; *Urinary*: oliguria, proteinuria, abnormal renal function, renal pain; *Vascular*: intermittent claudication, thrombophlebitis; *Vision*: blepharitis, cataract, dry eyes, iritis, ocular hemorrhage, scotoma.

Potential adverse effects: Although not reported in clinical studies with betaxolol, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential adverse effects of betaxolol: *Central nervous system*: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium,

and decreased performance on neuropsychometric tests; *Allergic*: Fever combined with aching and sore throat, laryngospasm, respiratory distress; *Hematologic*: Agranulocytosis, thrombocytopenic purpura, and non-thrombocytopenic purpura; *Gastrointestinal*: Mesenteric arterial thrombosis, ischemic colitis; *Vascular*: Raynaud's phenomena.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with betaxolol during investigational use and extensive foreign experience. Dry eyes and skin rash, however, have been reported. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

Chlorthalidone: *Cardiovascular*: orthostatic hypotension; *Central and peripheral nervous system*: xanthopsia; *Gastrointestinal*: cramping, gastric irritation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; *Hematologic*: agranulocytosis, aplastic anemia, leukopenia, thrombocytopenia; *Dermatologic-Hypersensitivity*: urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis); *Miscellaneous*: glycosuria, muscle spasm, restlessness, weakness.

OVERDOSAGE

No specific information is available regarding overdosage with Kerledex in humans. Treatment is symptomatic and supportive.

Betaxolol: No specific information on emergency treatment of overdosage with betaxolol is available. The most common effects expected are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia. In one acute overdosage of betaxolol, a 16-year-old female recovered fully after ingesting 460 mg.

Chlorthalidone: Symptoms of chlorthalidone overdose include nausea, weakness, dizziness and disturbances of electrolyte balance.

The oral LD₅₀ of the betaxolol/chlorthalidone combination, administered in a ratio of 1:1.25, is 440 to 450 mg/kg in the mouse and 410 to 490 mg/kg in the rat.

In the case of overdosage, treatment with Kerledex should be stopped and the patient carefully observed. Hemodialysis or peritoneal dialysis does not remove substantial amounts of betaxolol. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Hypotension: In addition to the usual supportive measures (eg, fluid replacement), the use of sympathomimetic pressor drug therapy, such as dopamine, dobutamine, or norepinephrine may be required. In refractory cases of overdosage of other beta-blockers, the use of glucagon hydrochloride has been reported to be useful.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.

Acute cardiac failure: Conventional therapy including digitalis, diuretics, and oxygen should be instituted immediately.

Bronchospasm: Use a β_2 -agonist. Additional therapy with aminophylline may be considered.

Heart block (2nd- or 3rd-Degree): Use isoproterenol or a transvenous cardiac pacemaker.

Electrolyte imbalance: Supportive treatment, with appropriate electrolyte therapy, should be instituted and monitored.

DOSAGE AND ADMINISTRATION

Betaxolol is effective in the treatment of hypertension in once-daily doses of 5-20 mg, while chlorthalidone is effective in doses of 12.5-50 mg. In clinical trials of betaxolol/chlorthalidone combination therapy using betaxolol doses of 5-20 mg and chlorthalidone doses of 12.5-25 mg, the antihypertensive effects increased with increasing doses of either component.

The adverse effects of betaxolol are a mixture of dose-dependent phenomena (principally bradycardia) and dose-independent phenomena (eg, probably skin rash); those of chlorthalidone are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (eg, pancreatitis), the former much more common than the latter. Therapy with a combination of betaxolol and chlorthalidone will be associated with both sets of dose-independent adverse effects and to minimize these, it may be appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. On the other hand, regimens that combine low doses of betaxolol and chlorthalidone should produce minimal dose-dependent adverse effects, ie, bradycardia and decreases in serum potassium (see *Clinical Pharmacology*).

Therapy guided by clinical effect: A patient whose blood pressure is not adequately controlled with monotherapy using either betaxolol (usually 10-20 mg) or chlorthalidone may be switched to Kerledex 5/12.5 mg. Subsequent titration (14-day intervals) could add additional betaxolol, chlorthalidone, or both, using single entity products, Kerledex 5/12.5, or Kerledex 10/12.5 as appropriate.

Initial therapy: Antihypertensive therapy should be initiated with the lowest dose of Kerledex, one 5/12.5 mg tablet once daily. Subsequent titration (14-day intervals) may be carried out with Kerledex tablets up to the maximum recommended dose of 20/25 mg (two 10/12.5 mg tablets) once daily, as appropriate. Alternatively, the single entity products could be used for dose titration.

Replacement therapy: The combination may be substituted for the titrated individual components.

Cessation of therapy: If withdrawal of Kerledex therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed.

HOW SUPPLIED

Kerledex 5/12.5 (betaxolol HCl 5 mg and chlorthalidone 12.5 mg) tablets are oval, yellow, film coated, with KERLEDEX debossed on one side and 5221 on the other, supplied as:

<u>NDC Number</u>	<u>Size</u>
0025-5221-31	bottle of 100
0025-5221-34	carton of 100 unit dose

Kerledex 10/12.5 (betaxolol HCl 10 mg and chlorthalidone 12.5 mg) tablets are capsule-shaped, yellow, film coated, with KERLEDEX debossed on one side and 5231 on the other, supplied as:

<u>NDC Number</u>	<u>Size</u>
0025-5231-31	bottle of 100
0025-5231-34	carton of 100 unit dose

Store below 86°F (30°C) and protect from moisture.
Dispense in a tight container.

Caution: Federal law prohibits dispensing without prescription.

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Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

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