HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Jenloga safely and effectively. See full prescribing information for Jenloga.

JENLOGA (clonidine hydrochloride) tablets
Initial U.S. Approval: 1974

----------INDICATIONS AND USAGE----------
Jenloga is a central alpha-2 adrenergic agonist indicated for the treatment of hypertension. Jenloga may be used alone or concomitantly with other antihypertensive agents. (1)

----------DOSAGE AND ADMINISTRATION----------
- Initial dose: One 0.1 mg tablet at bedtime. (2.1)
- Increase by 0.1 mg at weekly intervals up to 0.6 mg daily in divided doses (morning and bedtime) to achieve desired blood pressure lowering. (2.1)
- Patients with renal impairment: Uptitrate slowly. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
0.1 mg tablets (3)

----------CONTRAINDICATIONS----------
Known serious hypersensitivity to clonidine. (4)

----------WARNINGS AND PRECAUTIONS----------
- Withdrawal: Sudden cessation may result in agitation, tremor, rapid rise in blood pressure, especially after administration of higher doses or continuation of concomitant beta-blocker treatment. When discontinuing Jenloga, reduce the dose gradually over 2 to 4 days. If discontinuing in a patient also receiving a beta-blocker, withdraw the beta-blocker several days before the gradual discontinuation of Jenloga. (5.1)
- Allergic reactions: In patients who have developed localized contact sensitization or other allergic reaction to clonidine in a transdermal system, substitution of oral clonidine may be result in generalized skin rash, urticaria, or angioedema. (5.2)
- Use in patients with vascular disease, cardiac conduction disease, or chronic renal failure: Monitor carefully and uptitrate slowly. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 5%): dry mouth, fatigue, dizziness, headache, nausea, somnolence, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Addrenex Pharmaceuticals, Inc. at 1-919-941-0800 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Sedating drugs: Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. (7.1)
- Tricyclic antidepressants: May reduce the hypotensive effect of clonidine, necessitating an increase in clonidine dose. (7.2)
- Drugs known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers, beta-blockers): Use with caution due to potential for additive effects such as bradycardia and AV block. (7.3)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Avoid use in a nursing woman. (8.3)
- Pediatric use: Safety and effectiveness in pediatric patients below the age of eighteen have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2009

FULL PRESCRIBING INFORMATION: CONTENTS *

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Jenloga is indicated for the treatment of hypertension. Jenloga may be used alone or concomitantly with other antihypertensive agents.

2 DOSAGE AND ADMINISTRATION

Jenloga is a modified-release tablet formulation of clonidine hydrochloride. While it is dosed twice a day, the same as the immediate-release clonidine formulation, it is not to be used interchangeably with the immediate-release formulation. Substitution may necessitate further dose adjustment based upon tolerability or blood pressure response.

2.1 Recommended Dose

Adjust the dose of Jenloga according to the patient's individual blood pressure response. Initiate treatment with one 0.1 mg tablet at bedtime. Increase the dose in increments of 0.1 mg per day at weekly intervals, if necessary, until the desired response is achieved. Doses above 0.1 mg per day should be divided and taken at morning and bedtime. If morning and bedtime doses are not equal, the bedtime dose should be the larger of the two.

Jenloga was studied at doses of 0.2 to 0.6 mg per day, with little or no therapeutic benefit seen for the 0.6 mg dose over the 0.4 mg dose *[see Clinical Studies (14)]*. Doses of Jenloga higher than 0.6 mg per day (0.3 mg twice daily) were not evaluated in clinical trials and are not recommended.

2.2 Dosing in Renal Impairment

Start at 0.1 mg per day and uptitrate slowly. Monitor patients carefully to prevent excessive blood pressure lowering or bradycardia. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental Jenloga following dialysis.

3 DOSAGE FORM AND STRENGTHS

Jenloga is available as 0.1 mg tablets (white, round, standard convex with “651” debossed on one side).

4 CONTRAINDICATIONS

Do not use Jenloga in patients with known serious hypersensitivity to clonidine (e.g., rash or angioedema) *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Withdrawal

Sudden interruption of treatment with oral clonidine has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. Rare instances of hypertensive encephalopathy, cerebrovascular accidents, and death have been reported after clonidine withdrawal. Sudden cessation of Jenloga treatment in the 0.2 to 0.6 mg per day range resulted in reports of headache, tachycardia, nausea, flushing, warm feeling, brief lightheadedness, tightness in chest, and anxiety, although rebound hypertension as assessed by ambulatory blood pressure monitoring (ABPM) was not noted.

The likelihood of reactions to discontinuation of clonidine therapy appears to be greater after administration of higher doses or continuation of concomitant beta-blocker treatment, and special caution is therefore advised in these situations. An excessive rise in blood pressure following discontinuation of clonidine hydrochloride therapy can be reversed by administration of oral clonidine hydrochloride or by intravenous phentolamine.

When discontinuing therapy with Jenloga, reduce the dose gradually over 2 to 4 days to minimize withdrawal symptomatology. If therapy is to be discontinued in patients receiving a beta-blocker and Jenloga concurrently, withdraw the beta-blocker several days before the gradual discontinuation of Jenloga. Instruct patients not to discontinue therapy without consulting a physician.

5.2 Allergic Reactions

In patients who have developed localized contact sensitization to a clonidine transdermal system, substitution of oral clonidine therapy may result in the development of a generalized skin rash.

In patients who develop an allergic reaction from a clonidine transdermal system, substitution of oral clonidine may elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

5.3 Use in Patients with Vascular Disease, Cardiac Conduction Disease, or Chronic Renal Failure

Uptitrate slowly in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

5.4 Perioperative Use

Continue administration of Jenloga to within four hours of surgery and resume as soon as possible thereafter. Carefully monitor blood pressure during surgery and make additional measures to control blood pressure readily available if required.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in detail elsewhere in the labeling:

- Withdrawal *[see Warnings and Precautions (5.1)]*
- Allergic reactions *[see Warnings and Precautions (5.2)]*

6.1 Jenloga Clinical Trials Experience

Table 1 displays the most common treatment-emergent adverse reactions (ARs) reported by more than one patient in the mild to moderate hypertension study. The incidence of ARs progressively increased with increasing doses and was notably less in the 0.2 mg per day treatment group compared with the 0.4 mg per day and 0.6 mg per day treatments groups. The majority of ARs were mild. ARs of moderate severity occurred in 6 patients and included two reports each of insomnia and dry mouth. One patient (0.4 mg per day group) experienced symptomatic sinus bradycardia two weeks after initiating study drug. This event was the only severe AR, the only serious AR, and the only AR that led to discontinuation of study drug. Because the number of subjects is small and the duration of exposure short, no inferences regarding differences in adverse events between Jenloga and other clonidine formulations is warranted.

Table 1 Incidence of Treatment-Emergent Adverse Reactions by Dosing Group Reported by at least Two Patients in the Safety Population

Adverse Reaction	Treatment Group							
	0.2 mg per day (N=12)		0.4 mg per day (N=15)		0.6 mg per day (N=15)		Total (N=42)	
	N	%	N	%	N	%	N	%
At least one AR reported	5	42	10	67	12	80	27	64
Dry Mouth	0	0	8	53	8	53	16	38
Fatigue	2	17	4	27	4	27	10	24
Dizziness	0	0	3	20	2	13	5	12
Headache	1	8	1	7	2	13	4	10
Nausea	1	8	1	7	1	7	3	7
Somnolence	0	0	1	7	1	7	2	5
Insomnia	0	0	0	0	2	13	2	5

6.2 Experience with Immediate-Release Clonidine

Most adverse reactions are mild and tend to diminish with continued therapy. The most frequent (which also appear to be dose-related) are dry mouth (approximately 40%), ; drowsiness (approximately 33%), ; dizziness (approximately 16%), ; constipation and sedation (approximately 10% each).

The following less frequent adverse reactions have also been reported in patients receiving immediate-release clonidine, but in many cases patients were receiving concomitant medication and a causal relationship has not been established.

Body as a Whole: Fatigue, fever, headache, pallor, weakness, and withdrawal syndrome. Also reported were a weakly positive Coombs' test and increased sensitivity to alcohol.

Cardiovascular: Bradycardia, congestive heart failure, electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias), orthostatic symptoms, palpitations, Raynaud's phenomenon, syncope, and tachycardia. Cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Central Nervous System (CNS): Agitation, anxiety, delirium, delusional perception, hallucinations (including visual and auditory), insomnia, mental depression, nervousness, other behavioral changes, paresthesia, restlessness, sleep disorder, and vivid dreams or nightmares.

Dermatological: Alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria.

Gastrointestinal: Abdominal pain, anorexia, constipation, hepatitis, malaise, mild transient abnormalities in liver function tests, nausea, parotitis, pseudo-obstruction (including colonic pseudo-obstruction), salivary gland pain, and vomiting.

Genitourinary: Decreased sexual activity, difficulty in micturition, erectile dysfunction, loss of libido, nocturia, and urinary retention.

Hematologic: Thrombocytopenia.

Metabolic: Gynecomastia, transient elevation of blood glucose or serum creatine phosphokinase, and weight gain.

Musculoskeletal: Leg cramps and muscle or joint pain.

Oro-otolaryngeal: Dryness of the nasal mucosa.

Ophthalmological: Accommodation disorder, blurred vision, burning of the eyes, decreased lacrimation, and dryness of eyes.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted with Jenloga. The following have been reported with other oral formulations of clonidine.

7.1 Sedating Drugs

Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates, or other sedating drugs.

7.2 Tricyclic Antidepressants

In patients taking clonidine and a tricyclic antidepressant concomitantly, the hypotensive effect of clonidine may be reduced, necessitating an increase in the clonidine dose.

7.3 Drugs Known to Affect Sinus Node Function or AV Nodal Conduction

Monitor heart rate in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction, *e.g.,* digitalis, calcium channel blockers and beta-blockers. Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concomitantly with diltiazem or verapamil.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Oral administration of clonidine HCl to pregnant rabbits during embryo/fetal organogenesis, at doses up to 80 mcg/kg/day (human equivalent dose 26 mcg/kg/day), produced no evidence of teratogenic or embryotoxic potential. In pregnant rats, however, doses as low as 15 mcg/kg/day (HED 2.4 mcg/kg/day) were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating and throughout gestation. Increased resorptions were not associated with treatment at the same or higher dose levels (up to 150 mcg/kg/day (HED 24 mcg/kg/day)) when treatment of the dams was restricted to gestation days 6-15. Increases in resorptions were observed in both mice and rats at 500 or more mcg/kg/day (HED 80 mcg/kg/day for rats and 40 mcg/kg/day for mice) when the animals were treated on gestation days 1-14.

8.3 Nursing Mothers

Clonidine hydrochloride is excreted in human milk and should generally not be administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of eighteen have not been established.

8.5 Patients with Renal Impairment

The initial dosage should be based on the degree of impairment. Monitor patients carefully for hypotension and bradycardia, and titrate to higher doses cautiously. Because only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

10 OVERDOSAGE

In a clonidine overdose, hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability, and miosis. The frequency of CNS depression may be higher in children than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma, and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure. As little as 0.1 mg of clonidine has produced signs of toxicity in children.

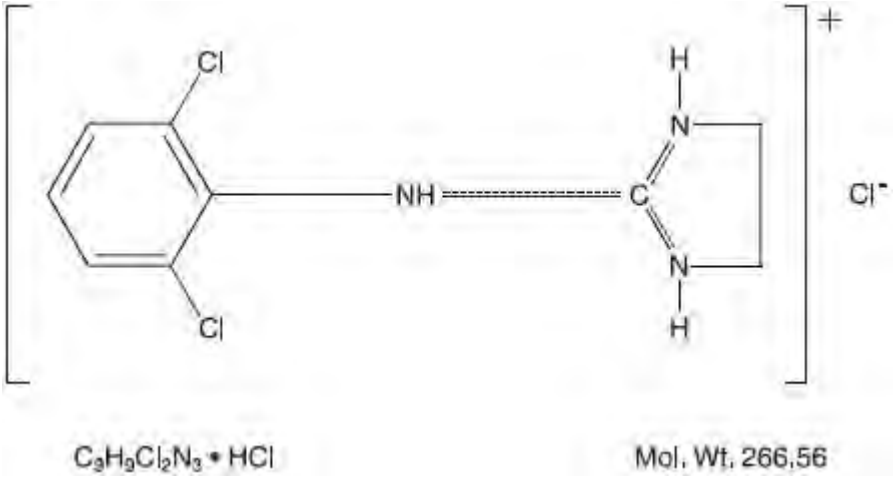
There is no specific antidote for clonidine overdosage. Gastric lavage may be indicated following recent and/or large ingestions. Administration of activated charcoal and/or a cathartic may be beneficial. Because clonidine overdosage may result in the rapid development of CNS depression administration of ipecac syrup to induce vomiting is not recommended. Supportive care may include atropine sulfate for bradycardia, intravenous fluids and/or vasopressor agents for hypotension and vasodilators for hypertension. Naloxone may be a useful adjunct for the management of clonidine-induced respiratory depression, hypotension or coma; monitor blood pressure as the administration of naloxone has occasionally resulted in paradoxical hypertension. Dialysis is not likely to significantly enhance the elimination of clonidine.

The largest overdose reported to date involved a 28-year-old male who ingested 100 mg of clonidine hydrochloride powder. This patient developed hypertension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. The patient fully recovered after intensive treatment. Plasma clonidine levels were 60 ng/mL after 1 hour, 190 ng/mL after 1.5 hours, 370 ng/mL after 2 hours, and 120 ng/mL after 5.5 and 6.5 hours. In mice and rats, the oral LD50 of clonidine is 206 and 465 mg/kg, respectively.

11 DESCRIPTION

Jenloga (clonidine hydrochloride) is a centrally acting alpha-2 adrenergic agonist available as 0.1 mg modified-release tablets for oral administration. Each 0.1 mg tablet is equivalent to 0.087 mg of the free base.

The inactive ingredients are sodium lauryl sulfate, lactose monohydrate, hypromellose type 2208, partially pregelatinized starch, colloidal silicon dioxide, and magnesium stearate. Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The following is the structural formula:



$C_9H_9Cl_2N_3 \cdot HCl$ Mol. Wt. 266.56

Clonidine hydrochloride is an odorless, bitter, white, crystalline substance soluble in water and alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clonidine stimulates alpha-adrenoceptors in the brain stem. This action results in reduced sympathetic outflow from the central nervous system and decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

12.2 Pharmacodynamics

With immediate-release clonidine, blood pressure declines within 30 to 60 minutes after an oral dose, the maximum decrease occurring within 2 to 4 hours. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact; therefore, orthostatic symptoms are mild and infrequent. These studies also show a reduction (15% to 20%) of cardiac output in the supine position with no change in the peripheral resistance. At a 45° tilt, there is a smaller reduction in cardiac output and a decrease of peripheral resistance. During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal hemodynamic response to exercise.

Tolerance to the antihypertensive effect of clonidine may develop in some patients.

Other studies in patients taking immediate-release clonidine have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines. The exact relationship of these pharmacologic actions to the antihypertensive effect of clonidine has not been fully elucidated.

Clonidine acutely stimulates growth hormone release in both children and adults, but does not produce a chronic elevation of growth hormone with long-term use.

12.3 Pharmacokinetics

Following oral administration of Jenloga, peak clonidine levels are reached in 4 to 7 hours, and the plasma half-life averages 13 hours. The absorption of clonidine from Jenloga is not affected by food. Following oral administration of the immediate-release formulation, about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours and about 50% of the absorbed dose is metabolized in the liver.

The half-life of clonidine from the immediate-release formulation increases up to 41 hours in patients with severe impairment of renal function. Although studies of the effect of renal impairment and studies of clonidine excretion have not been performed with Jenloga, results are likely to be similar to those of the immediate-release formulation.

The peak to trough ratio (Cmax/Cmin) of clonidine, following repeat dosing with Jenloga, ranges from 1.4 to 1.5. The plasma concentrations of clonidine increased proportionately with increase in dose over 0.1 mg – 0.6 mg twice daily.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Clonidine HCl was not carcinogenic when administered in the diets of rats (up to 132 weeks of exposure) at doses as high as 1620 mcg/kg/day in males (human equivalent dose: 260 mcg/kg/day) and 2040 mcg/kg/day in females (HED 324 mcg/kg/day) or the diets of mice (up to 78 weeks of exposure) at doses as high as 2500 mcg/kg/day (HED 203 mcg/kg/day). There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity. Fertility of male or female rats was unaffected by clonidine HCl doses as high as 150 mcg/kg/day (HED 24 mcg/kg/day). In a separate experiment, fertility of female rats appeared to be adversely affected at dose levels of 500 and 2000 mcg/kg/day (HED 80 and 324 mcg/kg/day, respectively).

13.2 Occular Toxicity

In several studies with oral clonidine hydrochloride, a dose-dependent increase in the incidence and severity of spontaneous retinal degeneration was seen in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys showed a concentration of clonidine in the choroid. In combination with amitriptyline, clonidine hydrochloride administration led to the development of corneal lesions in rats within 5 days.

In view of the retinal degeneration seen in rats, eye examinations were performed during clinical trials in 908 patients before, and periodically after, the start of clonidine therapy. In 353 of these 908 patients, the eye examinations were carried out over periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmological findings were recorded and, according to specialized tests such as electroretinography and macular dazzle, retinal function was unchanged.

14 CLINICAL STUDIES

Jenloga was studied in a single-dose pharmacokinetic study in healthy subjects *[see Clinical Pharmacology (12.3)]* and in a one-month pharmacokinetic/pharmacodynamic (PK/PD) study in patients with mild to moderate hypertension.

In the PK/PD study, 12-15 mild-moderate hypertensive patients per treatment group were randomized to Jenloga 0.2, 0.4 or 0.6 mg per day in two equal doses (morning and evening). Ambulatory measurements of blood pressure and heart rate were done at baseline and on day 26 of dosing. The changes from baseline in ambulatory measurements of blood pressure and heart rate for the different doses at day 26 are shown below.

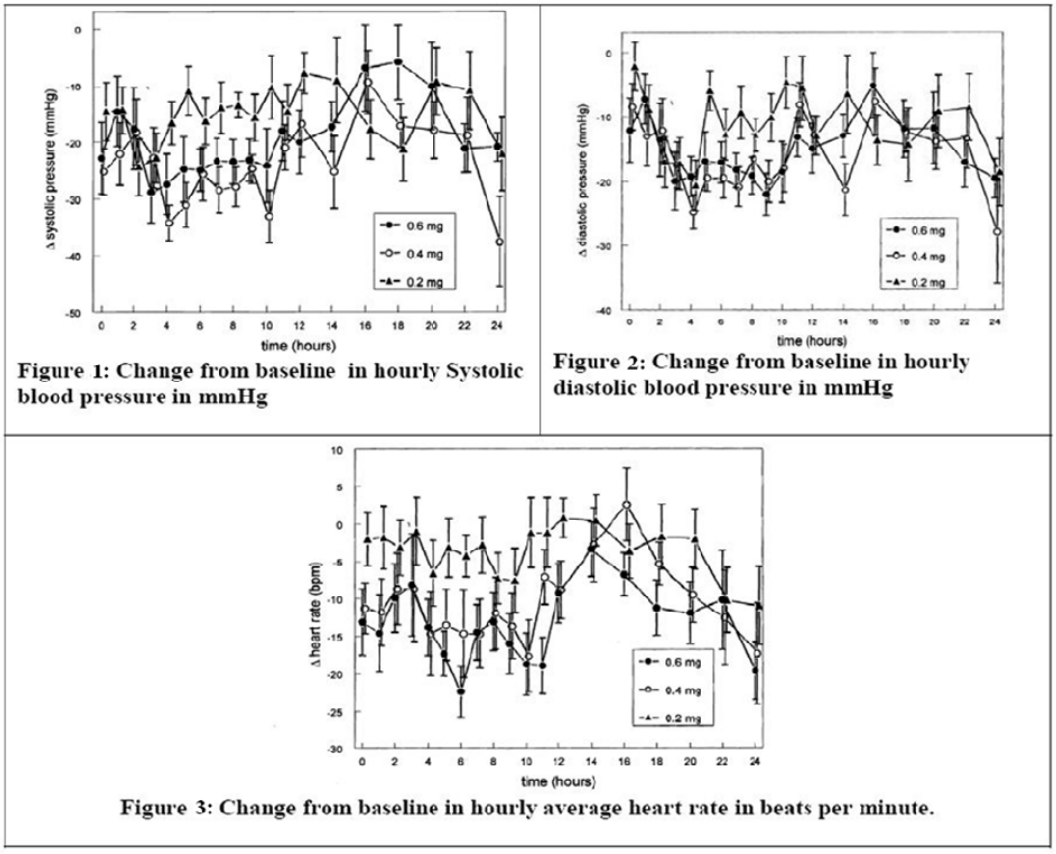


Figure 1: Change from baseline in hourly Systolic blood pressure in mmHg

Figure 2: Change from baseline in hourly diastolic blood pressure in mmHg

Figure 3: Change from baseline in hourly average heart rate in beats per minute.

16 HOW SUPPLIED/STORAGE AND HANDLING

Jenloga tablets are white, round, standard convex with “651” debossed on one side, supplied in bottles containing 60 (NDC 59630-651-60) or 180 tablets (NDC 59630-651-18).

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

17.1 Dosing

Advise patients to start treatment with an evening dose of 0.1 mg. If morning and evening doses are not equal, then the evening dose should be the larger of the two.

17.2 Risk of Withdrawal

Advise patients not to discontinue Jenloga abruptly without discussing with a physician.

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