CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203202Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NORTHERA™ (droxidopa) safely and effectively. See full prescribing information for NORTHERA.

NORTHERA (droxidopa) capsules, for oral use
Initial U.S. Approval: 2014

WARNING: SUPINE HYPERTENSION
See full prescribing information for complete boxed warning.
Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA *[see Warnings and Precautions (5.1)]*

----------INDICATIONS AND USAGE----------
NORTHERA is indicated for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been demonstrated. The continued effectiveness of NORTHERA should be assessed periodically. (1)

----------DOSAGE AND ADMINISTRATION----------
- Starting dose is 100 mg three times during the day (2.1)
- Titrate by 100 mg three times daily, up to a maximum dose of 600 mg three times daily (2.1)
- Take consistently with or without food (2.1)
- To reduce the potential for supine hypertension, elevate the head of the bed and give the last dose at least 3 hours prior to bedtime (2.1)
- Take NORTHERA capsule whole (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- 100 mg , 200 mg and 300 mg capsules (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- NORTHERA can cause supine hypertension and may increase cardiovascular risk if supine hypertension is not well-managed. (5.1)
- Hyperpyrexia and confusion (5 2)
- May exacerbate symptoms in patients with existing ischemic heart disease, arrhythmias, and congestive heart failure (5.3)
- Allergic reactions (5.4)

----------ADVERSE REACTIONS----------
Headache, dizziness, nausea, hypertension, and fatigue (greater than 5%) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Chelsea Therapeutics, Inc. 1-855-351-2879 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Use of DOPA decarboxylase inhibitors may require dose adjustments for NORTHERA (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Nursing Mothers: Choose nursing or NORTHERA (8.3)
- Patients with Renal Impairment: Dosing recommendations cannot be provided for patients with GFR less than 30 mL/min (8.6)

See 17 for Patient Counseling Information

Revised: 02/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SUPINE HYPERTENSION

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA *[see Warnings and Precautions (5.1)]*

1. INDICATIONS AND USAGE

NORTHERA is indicated for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) caused by primary autonomic failure [Parkinson's disease (PD), multiple system atrophy and pure autonomic failure], dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been established. The continued effectiveness of NORTHERA should be assessed periodically.

2. DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose of NORTHERA is 100 mg, taken orally three times daily: upon arising in the morning, at midday, and in the late afternoon at least 3 hours prior to bedtime (to reduce the potential for supine hypertension during sleep). Administer NORTHERA consistently, either with food or without food. Take NORTHERA capsule whole. Titrate to symptomatic response, in increments of 100 mg three times daily every 24-48 hours up to a maximum dose of 600 mg three times daily (i.e., a maximum total daily dose of 1800 mg).

Monitor supine blood pressure prior to initiating NORTHERA and after increasing the dose.

Patients who miss a dose of NORTHERA should take their next scheduled dose.

3. DOSAGE FORMS AND STRENGTHS

NORTHERA capsules are available in 100 mg, 200 mg, and 300 mg strengths as specified below.

- 100 mg: Hard gelatin capsules with "Northera" on the white body and "100" on the light blue cap
- 200 mg: Hard gelatin capsules with "Northera" on the white body and "200" on the light yellow cap
- 300 mg: Hard gelatin capsules with "Northera" on the white body and "300" on the light green cap

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Supine Hypertension

NORTHERA therapy may cause or exacerbate supine hypertension in patients with NOH. Patients should be advised to elevate the head of the bed when resting or sleeping. Monitor blood pressure, both in the supine position and in the recommended head-elevated sleeping position. Reduce or discontinue NORTHERA if supine hypertension persists. If supine hypertension is not well-managed, NORTHERA may increase the risk of cardiovascular events.

5.2 Hyperpyrexia and Confusion

Postmarketing cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported with NORTHERA use during post-marketing surveillance in Japan. Observe patients carefully when the dosage of NORTHERA is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes. The early diagnosis of this condition is important for the appropriate management of these patients.

5.3 Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure

NORTHERA may exacerbate existing ischemic heart disease, arrhythmias and congestive heart failure. Careful consideration should be given to this potential risk prior to initiating therapy in patients with these conditions.

5.4 Allergic Reactions

This product contains FD+C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD+C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

6. ADVERSE REACTIONS

The following adverse reactions with NORTHERA are included in more detail in the Warnings and Precautions section of the label:

- Supine Hypertension *[see Warnings and Precautions (5.1)]*
- Hyperpyrexia and Confusion *[see Warnings and Precautions (5.2)]*
- May exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety evaluation of NORTHERA is based on two placebo-controlled studies 1-2 weeks in duration (studies 301 and 302), one 8-week placebo-controlled study (study 306) and two long-term open label extension studies (studies 303 and 304). In the placebo-controlled studies, a total of 485 patients with Parkinson's disease, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy were randomized and treated, 245 with NORTHERA and 240 with placebo *[see Clinical Trials (14)]*.

Placebo-Controlled Experience

The most commonly observed adverse reactions (those occurring at an incidence of greater than 5% in the NORTHERA group and with at least a 3% greater incidence in the NORTHERA group than in the placebo group) in NORTHERA-treated patients during the three placebo-controlled trials were headache, dizziness, nausea, hypertension. The most common adverse reactions leading to discontinuation from NORTHERA were hypertension or increased blood pressure and nausea.

Table 1: Most Common Adverse Reactions Occurring More Frequently in the NORTHERA Group

	Study 301 and Study 302 (1-2 Weeks Randomized Treatment)		**Study 306 (8-10 Week Randomized Treatment)**	
	Placebo (N=132) n (%)	**NORTHERA (N=131) n (%)**	**Placebo (N=108) n (%)**	**NORTHERA (N=114) n (%)**
Headache	4 (3.0)	8 (6.1)	8 (7.4)	15 (13.2)
Dizziness	2 (1.5)	5 (3.8)	5 (4.6)	11 (9.6)
Nausea	2 (1.5)	2 (1.5)	5 (4.6)	10 (8.8)

Hypertension	0	2 (1.5)	1 (0.9)	8 (7.0)

Note: n=number of patients. Table displays adverse reactions that were reported in greater than 5% of patients in the NORTHERA group and with at least a 3% greater incidence in the NORTHERA group than in the placebo group.

Long-Term, Open-Label Trials with NORTHERA
In the long-term open label extension studies, a total of 422 patients, mean age 65 years, were treated with NORTHERA for a mean total exposure of approximately one year. The commonly reported adverse events were falls (24%), urinary tract infections (15%), headache (13%), syncope (13%), and dizziness (10%).

7. DRUG INTERACTIONS

7.1 Drugs that Increase Blood Pressure

Administering NORTHERA in combination with other agents that increase blood pressure (e.g., norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension.

7.2 Parkinson's Medications

Dopa-decarboxylase inhibitors may require dose adjustments for NORTHERA.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
There are no adequate and well controlled trials in pregnant women.

Following consecutive oral administration at doses of 60, 200, and 600 mg/kg/day to pregnant Sprague Dawley rats, increased incidences of lower body weight and occurrence of undulant rib were noted in fetuses, but they were slight and spontaneously reversed after birth. Based on dose per unit body surface area, these three doses correspond to approximately 0.3, 1 and 3 times, respectively, the maximum recommended total daily dose of 1800 mg in a 60 kg patient. Shortening of the gestation period was observed in rats at 600 mg/kg/day. Low incidences of renal lesions (cysts, indentations or renal pelvic dilation) were observed on the surface of the kidneys of female rats treated with droxidopa during the period of fetal organogenesis. No other potentially teratogenic effects have been observed in rats or rabbits.

8.3 Nursing Mothers

Choose nursing or NORTHERA. In rats, droxidopa is excreted in breast milk, and when the drug was administered to the nursing dams during the period of lactation, reduced weight gain and reduced survival were observed in the offspring.

8.4 Pediatric Use

The safety and effectiveness of NORTHERA in pediatric patients have not been established.

8.5 Geriatric Use

A total of 197 patients with symptomatic NOH aged 75 years or above were included in the NORTHERA clinical program. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Renal Impairment

NORTHERA and its metabolites are primarily cleared renally. Patients with mild or moderate renal impairment (GFR greater than 30 mL/min) were included in clinical trials and did not have a higher frequency of adverse reactions. Clinical experience with NORTHERA in patients with severe renal function impairment (GFR less than 30 mL/min) is limited.

10 OVERDOSAGE

10.1 Symptoms

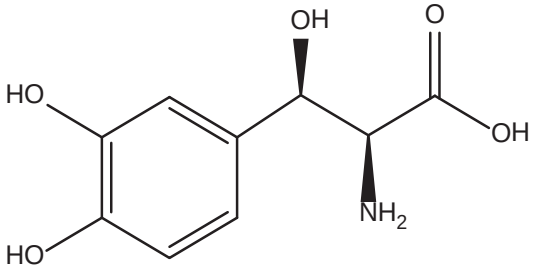
There was one case of overdose reported during post-marketing surveillance in Japan. The patient ingested 7700 mg of NORTHERA and experienced a hypertensive crisis that resolved promptly with treatment.

10.2 Treatment

There is no known antidote for NORTHERA overdosage. In case of an overdose that may result in an excessively high blood pressure, discontinue NORTHERA and treat with appropriate symptomatic and supportive therapy. Counsel patients to remain in a standing or seated position until their blood pressure drops below an acceptable limit.

11 DESCRIPTION

NORTHERA capsules contain droxidopa, which is a synthetic amino acid precursor of norepinephrine, for oral administration. Chemically, droxidopa is (–)-threo-3-(3,4-Dihydroxyphenyl)-L-serine. It has the following structural formula:



Droxidopa is an odorless, tasteless, white to off-white crystals or crystalline powder. It is slightly soluble in water, and practically insoluble in methanol, glacial acetic acid, ethanol, acetone, ether, and chloroform. It is soluble in dilute hydrochloric acid. It has a molecular weight of 213.19 and a molecular formula of $C_9H_{11}NO_5$. NORTHERA capsules also contain the following inactive ingredients: mannitol, corn starch, and magnesium stearate. The capsule shell is printed with black ink. The black inks contain Shellac glaze, ethanol, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol, and ammonium hydroxide. The capsule shell contains the following inactive ingredients: 100 mg - gelatin, titanium dioxide, FD & C Blue No. 2, Black and red iron oxide; 200 mg – gelatin, titanium dioxide, FD & C Blue No. 2, black and yellow iron oxide; 300 mg – gelatin, titanium dioxide, FD&C Blue No. 1, FD & C Yellow No. 5 (tartrazine) and FD & C Red No. 40. NORTHERA capsules differ in size and color by strength *[see Dosage Forms and Strengths (3)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action of NORTHERA in the treatment of neurogenic orthostatic hypotension is unknown. NORTHERA is a synthetic amino acid analog that is directly metabolized to norepinephrine by dopa-decarboxylase, which is extensively distributed throughout the body. NORTHERA is believed to exert its pharmacological effects through norepinephrine and not through the parent molecule or other metabolites. Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction. NORTHERA in humans induces small and transient rises in plasma norepinephrine.

12.2 Pharmacodynamics

Peak droxidopa plasma concentrations are associated with increases in systolic and diastolic blood pressures. Droxidopa has no clinically significant effect on standing or supine heart rates in patients with autonomic failure.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with NORTHERA at single oral doses up to 2,000 mg, as shown

in a dedicated thorough QT study.

12.3 Pharmacokinetics

Absorption
Peak plasma concentrations (C_{max}) of droxidopa were reached by 1 to 4 hours post-dose (mean of approximately 2 hours) in healthy volunteers. High-fat meals have a moderate impact on droxidopa exposure with C_{max} and area under the plasma concentration-time curve (AUC) decreasing by 35% and 20% respectively. The C_{max} was delayed by approximately 2 hours with a high-fat meal.

Distribution
Pre-clinical studies suggest that droxidopa can cross the blood brain barrier. Droxidopa exhibits plasma protein binding of 75% at 100 ng/mL and 26% at 10,000 ng/mL. The estimated apparent volume of distribution of droxidopa is about 200 L in humans.

Metabolism
The metabolism of droxidopa is mediated by catecholamine pathway and not through the cytochrome P450 system. Droxidopa is initially converted to methoxylated dihydroxyphenylserine (3-OM-DOPS), a major metabolite, by catechol-O-methyltransferase (COMT), to norepinephrine by DOPA decarboxylase (DDC), or to protocatechualdehyde by DOPS aldolase. After oral dosing in humans, plasma norepinephrine levels peak within 3 to 4 hours but are generally very low (less than 1 ng/mL) and variable with no consistent relationship with dose. The contribution of the metabolites of droxidopa other than norepinephrine to its pharmacological effects is not well understood.

Excretion
The mean elimination half-life of droxidopa is approximately 2.5 hours in humans. The major route of elimination of droxidopa and its metabolites is via the kidneys in both animals and in humans. Studies in animals showed that ~75% of the radiolabeled dose was excreted in urine within 24 hours of oral dosing.

Special Populations
There are no clinically relevant effects of age, body mass index or sex on the pharmacokinetics of droxidopa. A population pharmacokinetic analysis suggests that hepatic function, assessed by aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin, did not influence the exposure to droxidopa. The controlled clinical trials included patients with mild to moderate renal impairment. No dose adjustments are required in patients with mild to moderate renal impairment.

Drug Interactions
No dedicated drug-drug interaction studies were performed for droxidopa. Patients in the Phase 3 trials with NORTHERA received concomitant levodopa/carbidopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors and other medications used to treat Parkinson's Disease. Carbidopa, a peripheral dopa-decarboxylase inhibitor, could prevent the conversion of NORTHERA to norepinephrine outside of the central nervous system (CNS). Patients taking NORTHERA with L-DOPA/dopa-decarboxylase inhibitor combination drugs had decreased clearance of NORTHERA, an increase in exposure (AUC) to droxidopa of approximately 100%, and an increase in exposure to 3-OM-DOPS of approximately 50%. However, in clinical trials, it was found that the decreased clearance was not associated with a significant need for a different treatment dose or increases in associated adverse events. Dopamine agonists, amantadine derivatives, and MAO-B inhibitors do not appear to affect NORTHERA clearance, and no dose adjustments are required.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have been conducted at dosages up to 1000 mg/kg/day in mice and up to 100 mg/kg/day in rats with no indication of carcinogenic effects. Based on dose per unit body surface area, these two doses correspond to approximately 3 and 0.5 times, respectively, the maximum recommended total daily dose of 1800 mg in a 60 kg patient. Droxidopa was clastogenic in Chinese hamster ovary cells (chromosome aberration

assay), but was not mutagenic in bacteria (Ames assay), and was not clastogenic in a mouse micronucleus assay.

Studies in rats show that droxidopa has no effect on fertility.

13.2 Animal Toxicology and Pharmacology

Rats and mice treated for 52 and 80 weeks, respectively, at doses similar to human doses (100-300 mg/kg/day for rats and 300-1000 mg/kg/day for mice) had increased incidences of renal and cardiac lesions (rats and mice) and deaths (rats only). No signs of toxicity were observed in monkeys or dogs given droxidopa for 13 weeks at doses 32 times (3000 mg/kg/day) and 37 times (2000 mg/kg/day), respectively, the maximum recommended total daily dose of 1800 mg in a 60 kg patient, when based on body surface area.

14 CLINICAL STUDIES

14.1 Studies in Neurogenic Orthostatic Hypotension

Clinical studies (described below) examined the efficacy of NORTHERA in the short-term (1 to 2 weeks) and over longer-term periods (8 weeks; 3 months). Studies 301 and 306B showed a treatment effect of NORTHERA at Week 1, but none of the studies demonstrated continued efficacy beyond 2 weeks of treatment.

Study 306B was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study in patients with symptomatic NOH and Parkinson's disease. Patients entering the study were required to have a decrease of at least 20 mmHg or 10 mmHg, respectively, in systolic or diastolic blood pressure, within 3 minutes after standing, as well as symptoms associated with neurogenic orthostatic hypotension. The study had an initial dose titration period that lasted up to 2 weeks in which patients received placebo or 100 to 600 mg of NORTHERA three times daily, followed by an 8-week treatment period.

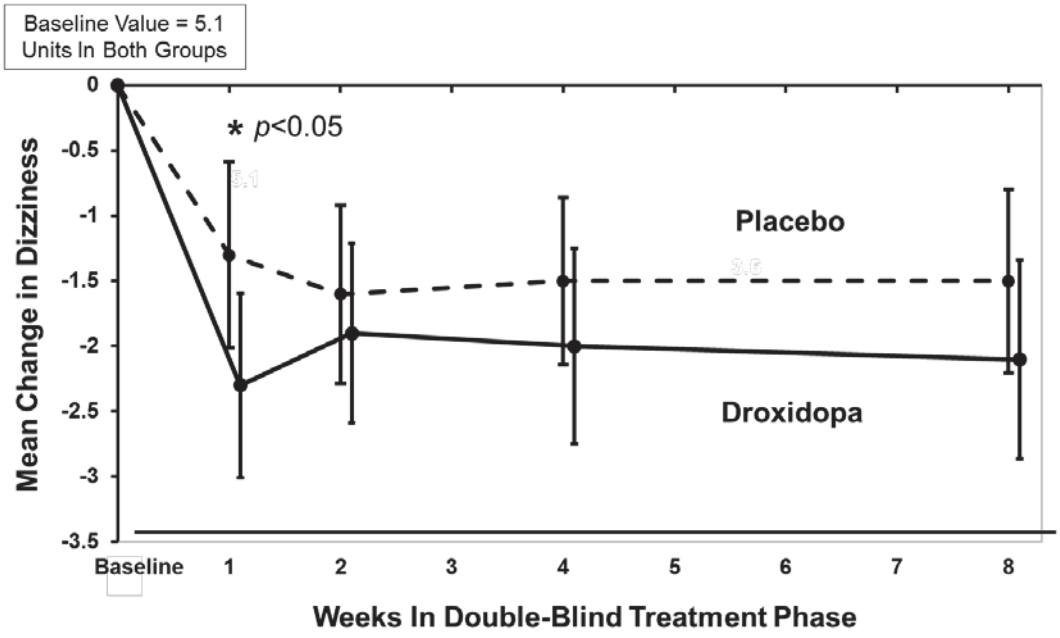
Efficacy was measured using the OHSA Item #1 score ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") at Week 1, in patients who had completed titration and 1 week of maintenance therapy.

A total of 171 patients were enrolled, and 147 patients were included in the efficacy analysis. The mean age was 72 years, and patients were mostly Caucasian. During the study, 94% of placebo treated patients and 88% on NORTHERA were taking dopa-decarboxylase inhibitors; 17% of placebo-treated patients and 26% on NORTHERA were taking fludrocortisone. There were more premature discontinuations in the NORTHERA group (28%) than in the placebo group (20%).

In both groups, the mean baseline dizziness score was 5.1 on an 11-point scale. At Week 1, patients showed a statistically significant mean 0.9-unit decrease in dizziness with NORTHERA versus placebo ($p = 0.028$), but the effect did not persist beyond Week 1. The data at all time points are shown in Figure 1.

Patients receiving NORTHERA also had a greater increase, compared to placebo, in the Week 1 lowest standing systolic blood pressure within 3 minutes after standing (5.6 mmHg; $p = 0.032$).

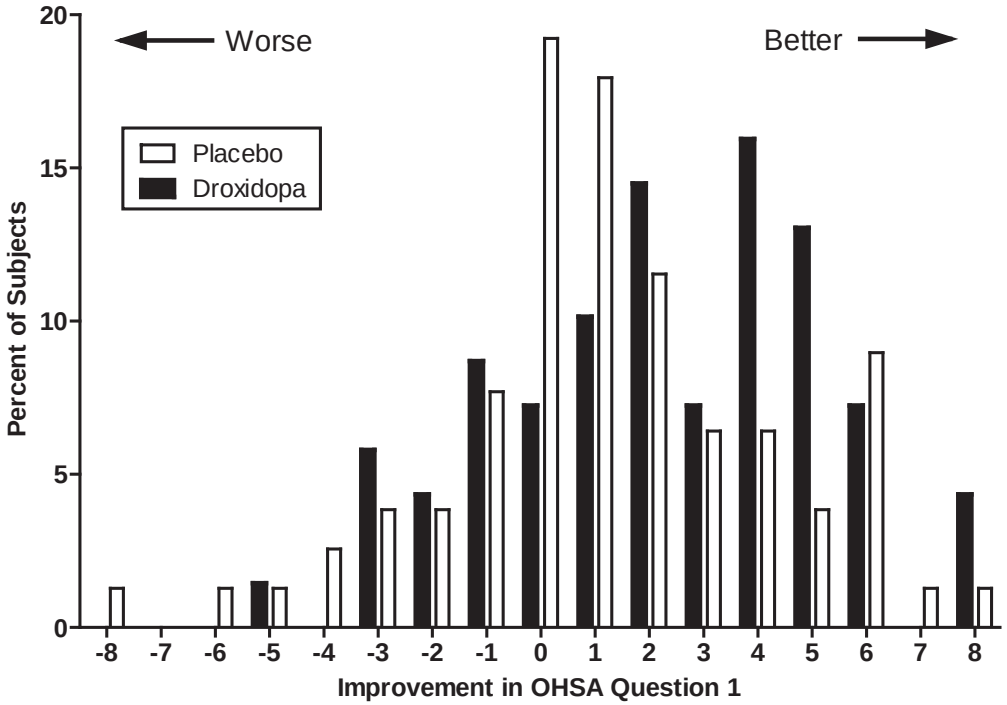
Figure 1. Mean Change in OHSA Item 1 score by week in Study 306B



Note: The graph is based on observed data only. The error bars are the 95% confidence interval of the mean change from baseline in OHSA Item 1 scores.

Figure 2. Distribution of Patients by Change in OHSA Item 1, Baseline to Week 1, in Study 306B

Figure 2 shows the distribution of changes from Baseline to Week 1 in the OHSA Item #1 score. Overall the figure shows that patients treated with NORTHERA improved more than those treated with placebo.



Study 301 was a multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group study in patients with symptomatic neurogenic orthostatic hypotension. The study included an initial open-label dose titration period, a 7-day washout period, and a randomized double-blind 7-day treatment period. To be eligible for enrollment, patients were required to have a decrease in systolic or diastolic blood pressure of at least 20 or 10 mmHg, respectively, within 3 minutes after standing. The study was enriched, such that only patients who had been identified as 'responders' during the titration period were randomized to NORTHERA or placebo. To be considered a responder, a patient had to demonstrate improvement on the OHSA Item #1 score by at least 1 point, as well as an increase in systolic blood pressure of at least 10 mmHg post-standing, during the open-label dose titration period. Patients who dropped out during the titration period because of side effects or other reasons were also not included in the double-blind portion of the study.

Patients had a primary diagnosis of Parkinson's Disease (n=60), pure autonomic failure (n=36), or multiple system atrophy (n=26). The mean age was 60 years, and most were Caucasian. 45% of patients were taking dopa-decarboxylase inhibitors, and 29% were taking fludrocortisone.

Efficacy was measured using the Orthostatic Hypotension Questionnaire (OHQ), a patient reported outcome that measures symptoms of NOH and their impact on the patient's ability to perform daily activities that require standing and walking. The OHQ includes OHSA Item #1 as one of several components. A statistically significant treatment effect was not demonstrated on OHQ (treatment effect of 0.4 unit, p-value=0.19).

The mean baseline dizziness score on OHSA Item #1 ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") was 5.2 units on an 11-point scale. At Week 1 of treatment, patients showed a mean 0.7 unit decrease in dizziness with NORTHERA versus placebo (p=0.06).

Study 302 (n=101) was a placebo-controlled 2-week randomized withdrawal study of NORTHERA in patients with symptomatic NOH. Study 303 (n=75) was an extension of studies 301 and 302, where patients received their titrated dose of NORTHERA for 3 months and then entered a 2-week randomized withdrawal phase. Neither study showed a statistically significant difference between treatment arms on its primary endpoint. Considering these data, the effectiveness of NORTHERA beyond 2 weeks is uncertain, and patients should be evaluated periodically to determine whether NORTHERA is continuing to provide a benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NORTHERA capsules are supplied in the following dosage strengths:

100 mg: Hard gelatin, size 3 capsule, with an opaque light blue cap and an opaque white body, printed with "Northera" on the body and "100" on cap, filled with a white to light brown powder.

200 mg: Hard gelatin, size 2 capsule, with an opaque light yellow cap and an opaque white body, printed with "Northera" on body and "200" on cap, filled with a white to light brown powder.

300 mg: Hard gelatin, size 1 capsule, with an opaque light green cap and an opaque white body, printed with "Northera" on body and "300" on cap, filled with a white to light brown powder.

100 mg 90-count bottle (NDC code# 76320-100 90)

200 mg 90-count bottle (NDC code# 76320-200-90)

300 mg 90-count bottle (NDC code# 76320-300-90)

16.2 Storage and Handling

NORTHERA capsules should be stored at room temperature, 20°C-25°C (68°F-77°F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Elevations in Blood Pressure

Counsel patients that NORTHERA causes elevations in blood pressure and increases the risk of supine hypertension, which could lead to strokes, heart attacks and death. Instruct patients to rest and sleep in an upper-body elevated position and monitor blood pressure. Instruct patients how to manage observed blood pressure elevations. To reduce the risk of supine hypertension, in addition to raising the upper body, the late afternoon dose of NORTHERA should be taken at least three hours before bedtime.

Concomitant Treatments

Counsel patients about the concomitant use of drugs to treat other conditions that may have an additive effect with NORTHERA *[see Drug Interactions (7)]*.

Pregnancy

Counsel patients to consult a physician if they are nursing, pregnant, or planning to become pregnant while taking NORTHERA.

Food

Patients should take NORTHERA the same way each time, either with food or without food.

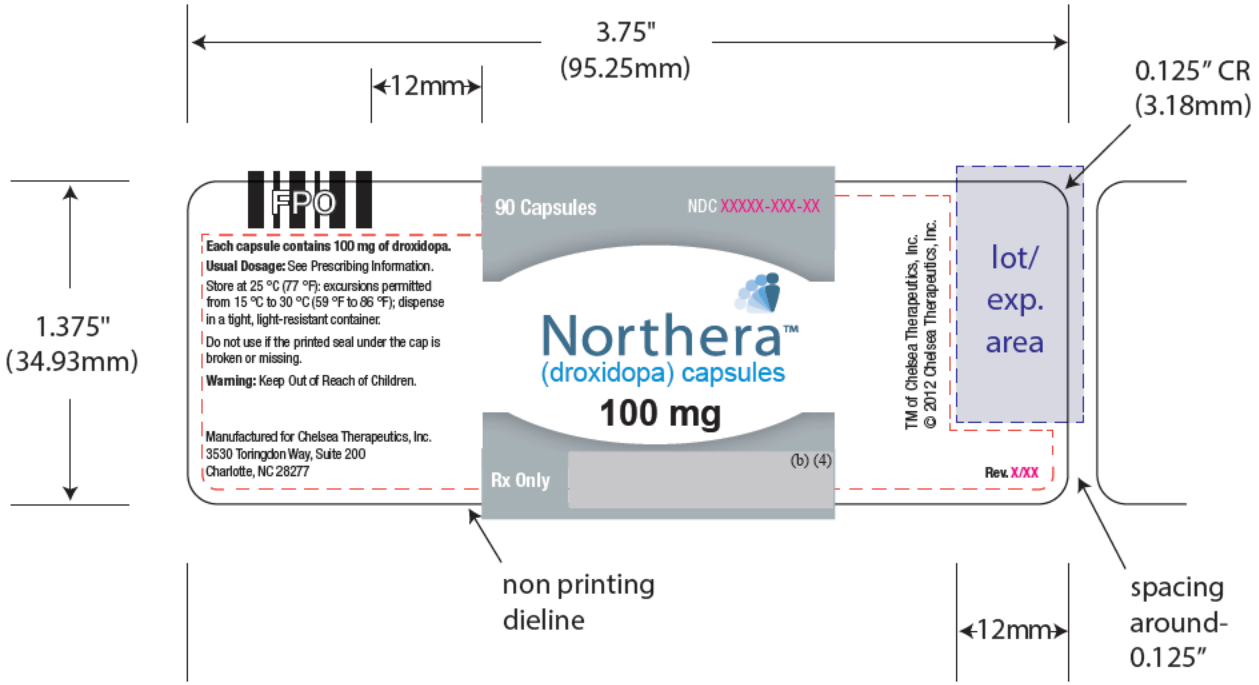
Missed Dose

If a dose is missed, patients should take the next dose at the regularly scheduled time and should not double the dose.

Manufactured for:

Charlotte, NC 28277

(b) (4)


3.75"
(95.25mm)
12mm
0.125" CR
(3.18mm)
1.375"
(34.93mm)
FPO
Each capsule contains 100 mg of droxidopa.
Usual Dosage: See Prescribing Information.
Store at 25 °C (77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F); dispense in a tight, light-resistant container.
Do not use if the printed seal under the cap is broken or missing.
Warning: Keep Out of Reach of Children.
Manufactured for Chelsea Therapeutics, Inc.
3530 Toringdon Way, Suite 200
Charlotte, NC 28277
90 Capsules
NDC XXXXX-XXX-XX
Northera™
(droxidopa) capsules
100 mg
Rx Only
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© 2012 Chelsea Therapeutics, Inc.
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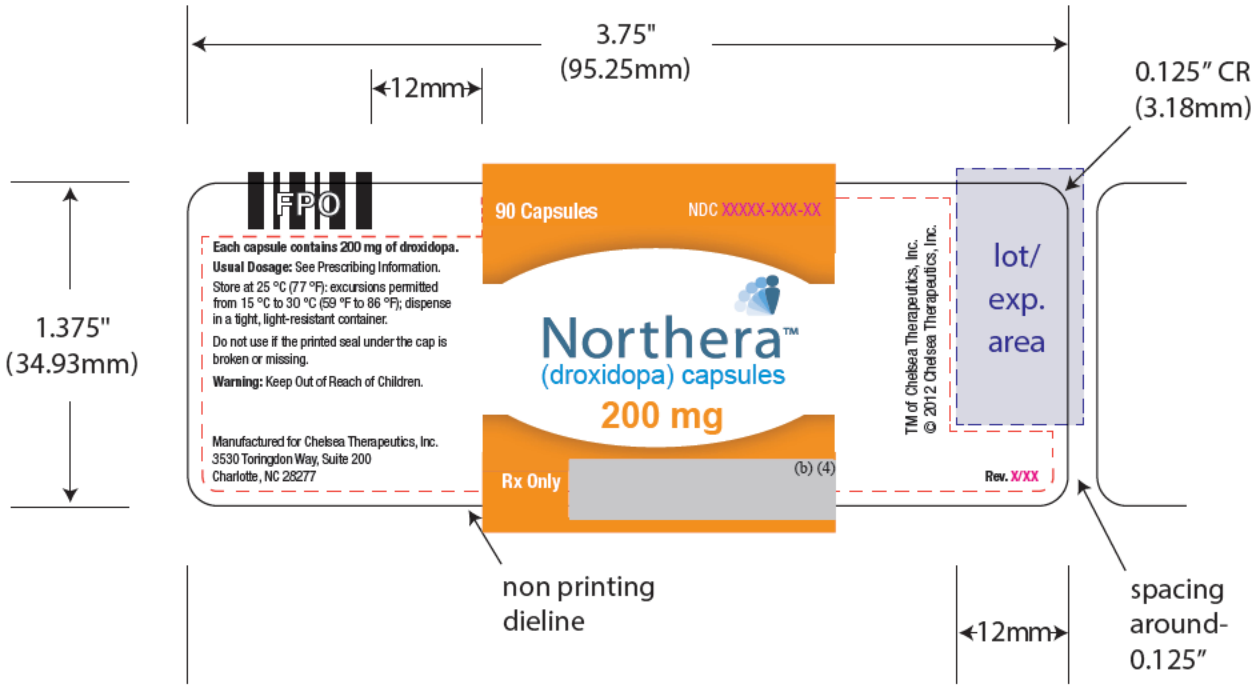
3.75"
(95.25mm)
12mm
0.125" CR
(3.18mm)
1.375"
(34.93mm)
FPO
Each capsule contains 200 mg of droxidopa.
Usual Dosage: See Prescribing Information.
Store at 25 °C (77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F); dispense in a tight, light-resistant container.
Do not use if the printed seal under the cap is broken or missing.
Warning: Keep Out of Reach of Children.
Manufactured for Chelsea Therapeutics, Inc.
3530 Toringdon Way, Suite 200
Charlotte, NC 28277
90 Capsules
NDC XXXXX-XXX-XX
Northera™
(droxidopa) capsules
200 mg
Rx Only
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TM of Chelsea Therapeutics, Inc.
© 2012 Chelsea Therapeutics, Inc.
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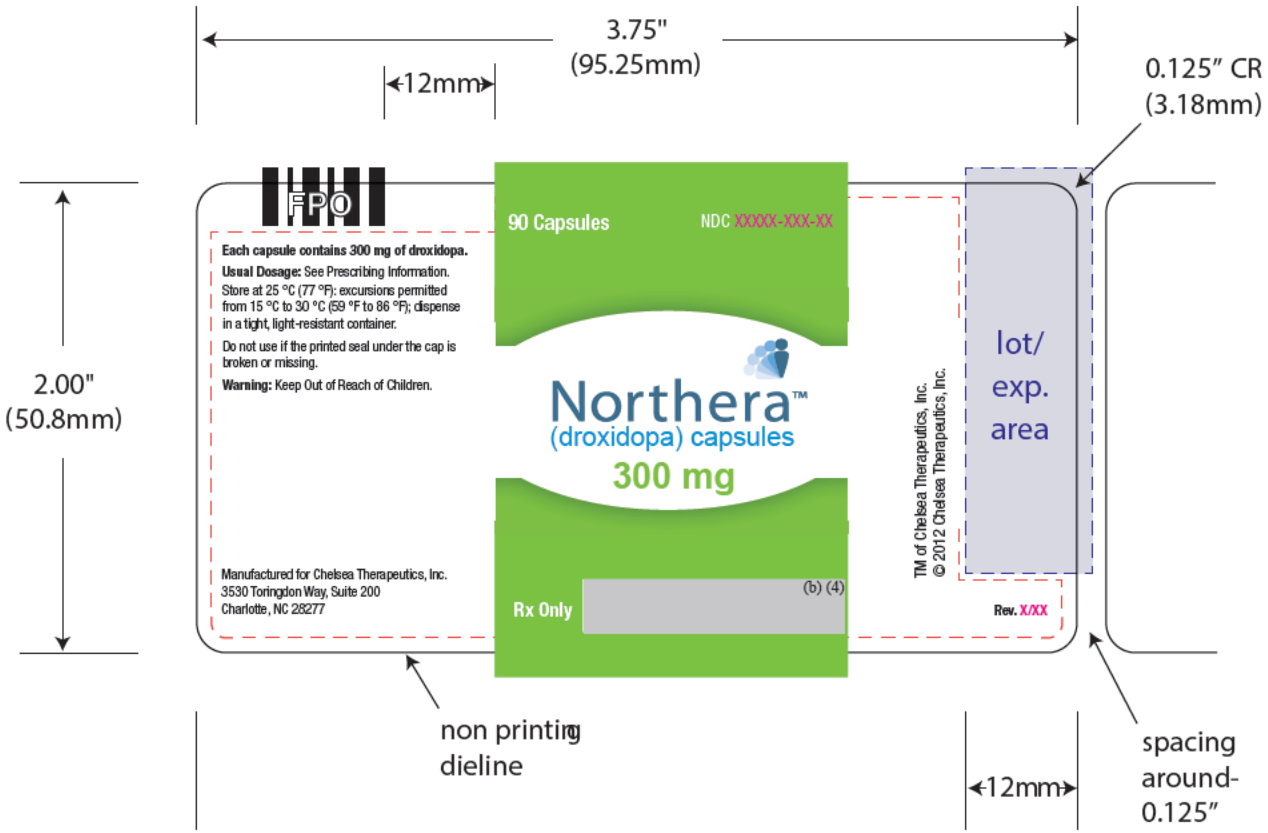
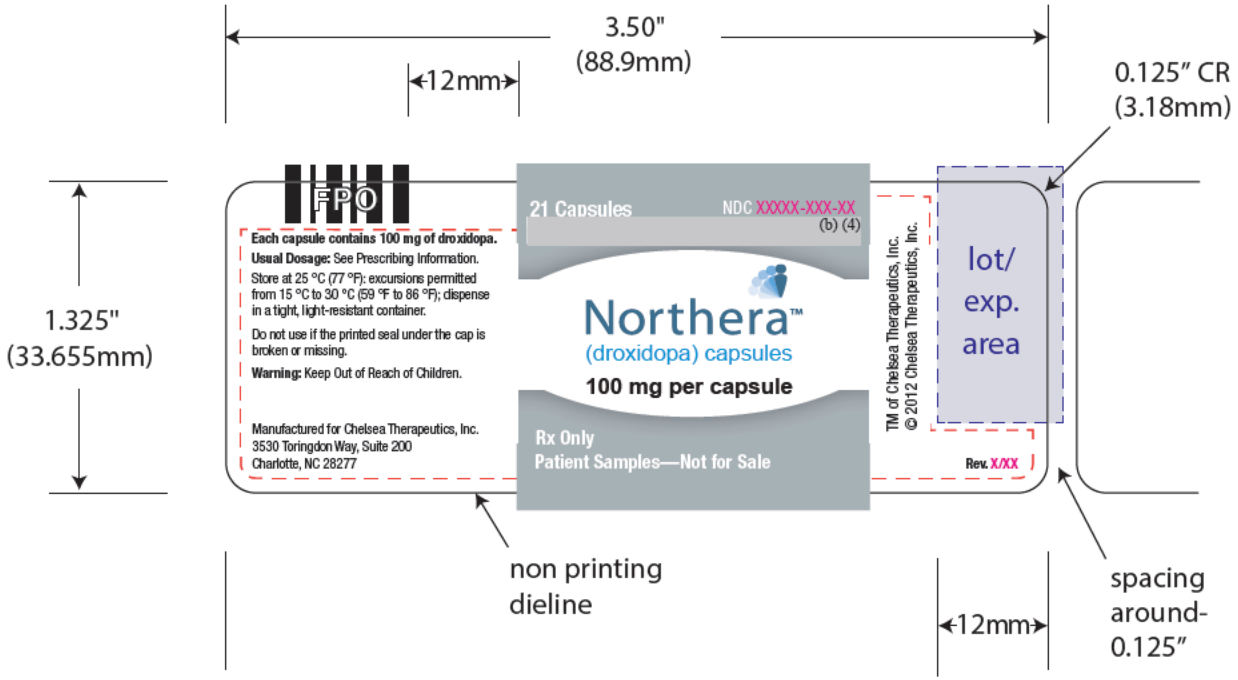
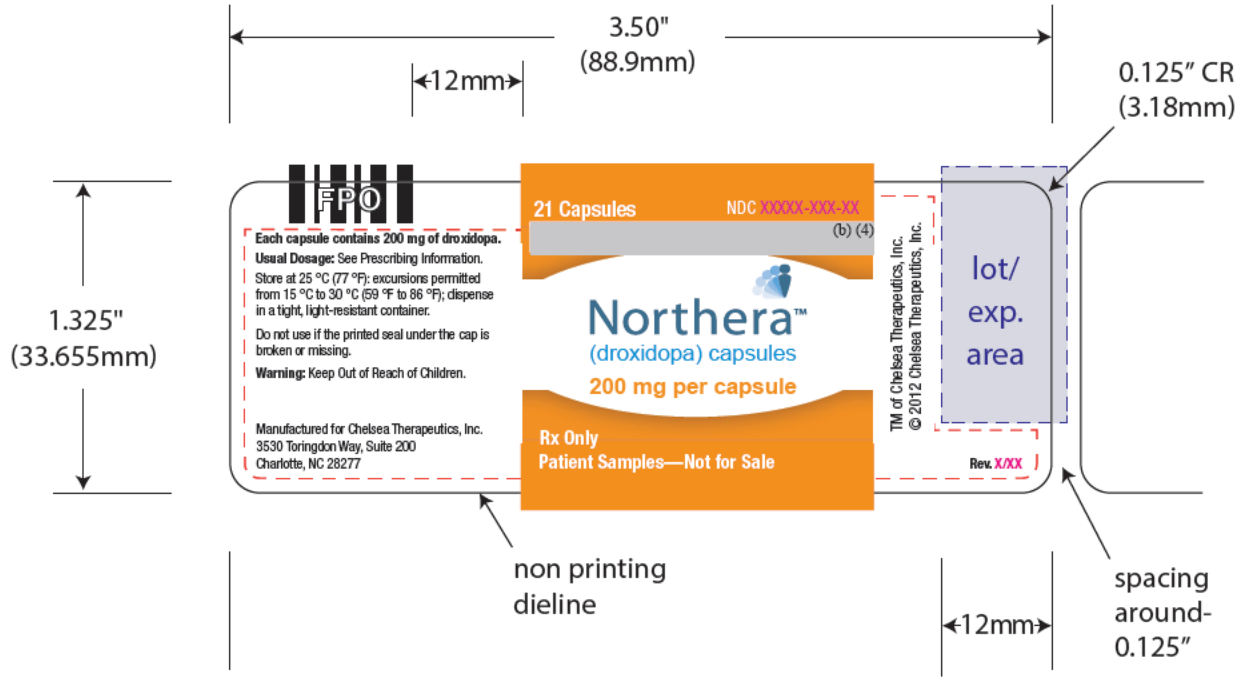

3.75"
(95.25mm)
12mm
0.125" CR
(3.18mm)
2.00"
(50.8mm)
FPO
90 Capsules
NDC XXXXX-XXX-XX
Each capsule contains 300 mg of droxidopa.
Usual Dosage: See Prescribing Information.
Store at 25 °C (77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F); dispense in a tight, light-resistant container.
Do not use if the printed seal under the cap is broken or missing.
Warning: Keep Out of Reach of Children.
Northera™
(droxidopa) capsules
300 mg
Manufactured for Chelsea Therapeutics, Inc.
3530 Toringdon Way, Suite 200
Charlotte, NC 28277
Rx Only
(b) (4)
TM of Chelsea Therapeutics, Inc.
© 2012 Chelsea Therapeutics, Inc.
lot/
exp.
area
Rev. X/XX
non printing
dieline
12mm
spacing
around-
0.125"

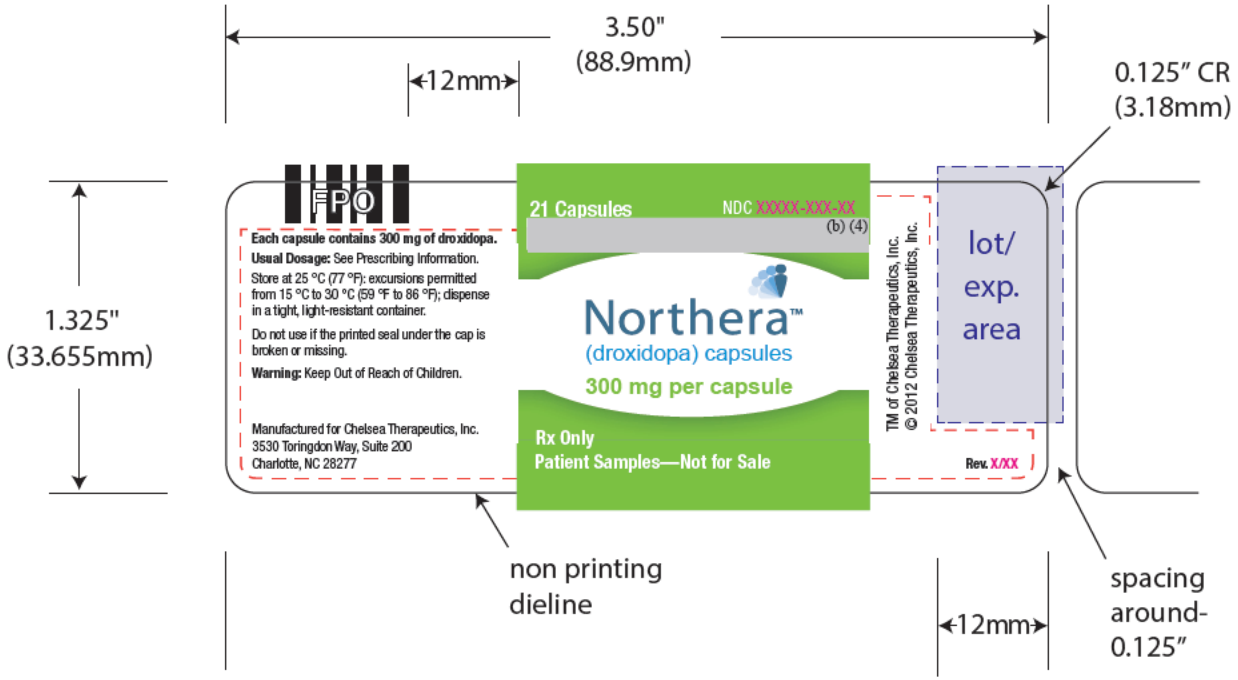
(b) (4)


3.50"
(88.9mm)
12mm
0.125″ CR
(3.18mm)
1.325"
(33.655mm)
FPO
Each capsule contains 100 mg of droxidopa.
Usual Dosage: See Prescribing Information.
Store at 25 °C (77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F); dispense in a tight, light-resistant container.
Do not use if the printed seal under the cap is broken or missing.
Warning: Keep Out of Reach of Children.
Manufactured for Chelsea Therapeutics, Inc.
3530 Toringdon Way, Suite 200
Charlotte, NC 28277
21 Capsules
NDC XXXXX-XXX-XX
(b) (4)
Northera™
(droxidopa) capsules
100 mg per capsule
Rx Only
Patient Samples—Not for Sale
TM of Chelsea Therapeutics, Inc.
© 2012 Chelsea Therapeutics, Inc.
lot/
exp.
area
Rev. X/XX
non printing
dieline
12mm
spacing
around-
0.125″

(b) (4)


3.50"
(88.9mm)
12mm
0.125" CR
(3.18mm)
1.325"
(33.655mm)
FPO
Each capsule contains 200 mg of droxidopa.
Usual Dosage: See Prescribing Information.
Store at 25 °C (77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F); dispense in a tight, light-resistant container.
Do not use if the printed seal under the cap is broken or missing.
Warning: Keep Out of Reach of Children.
Manufactured for Chelsea Therapeutics, Inc.
3530 Toringdon Way, Suite 200
Charlotte, NC 28277
21 Capsules
NDC XXXXX-XXX-XX
(b) (4)
Northera™
(droxidopa) capsules
200 mg per capsule
Rx Only
Patient Samples—Not for Sale
TM of Chelsea Therapeutics, Inc.
© 2012 Chelsea Therapeutics, Inc.
lot/
exp.
area
Rev. X/XX
non printing
dieline
12mm
spacing
around-
0.125"

(b) (4)


3.50"
(88.9mm)
12mm
0.125″ CR
(3.18mm)
1.325"
(33.655mm)
FPO
Each capsule contains 300 mg of droxidopa.
Usual Dosage: See Prescribing Information.
Store at 25 °C (77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F); dispense in a tight, light-resistant container.
Do not use if the printed seal under the cap is broken or missing.
Warning: Keep Out of Reach of Children.
Manufactured for Chelsea Therapeutics, Inc.
3530 Toringdon Way, Suite 200
Charlotte, NC 28277
21 Capsules
NDC XXXX-XXX-XX
(b) (4)
Northera™
(droxidopa) capsules
300 mg per capsule
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0.125″