

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200671Orig1s000

LABELING

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

DURLAZA (aspirin) Extended Release Capsules, for oral use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

DURLAZA is a nonsteroidal anti-inflammatory drug indicated to reduce the risk of death and myocardial infarction (MI) in patients with chronic coronary artery disease, such as patients with a history of MI or unstable angina pectoris or with chronic stable angina and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack (1)
Limitation of Use: Use immediate-release aspirin, not DURLAZA in situations where a rapid onset of action is required (such as acute treatment of myocardial infarction or before percutaneous coronary intervention). (1, 4)

DOSAGE AND ADMINISTRATION

The recommended dose is 162.5 mg per day with a full glass of water at the same time each day (2)

DOSAGE FORMS AND STRENGTHS

- Capsules, 162.5 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to nonsteroidal anti-inflammatory drug products (4)
- Asthma, rhinitis, and nasal polyps (4)

WARNINGS AND PRECAUTIONS

- Increased risk of bleeding. (5.1)

- DURLAZA can cause gastric mucosal irritation and bleeding. Patients with a history of active peptic ulcer disease are at particular risk. (5.2)
- DURLAZA can cause fetal harm when administered to a pregnant woman. (5.3, 8.1)

ADVERSE REACTIONS

- Most common adverse reactions are Gastrointestinal (6).

To report SUSPECTED ADVERSE REACTIONS, contact New Haven Pharmaceuticals at (877) 824-2483 or www.newhavenpharma.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Alcohol: do not take DURLAZA 2 hours before or 1 hour after consuming alcohol (7)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension and hyperkalemia (7)
- Anticoagulant and antiplatelets: increased risk of bleeding (7)
- Anticonvulsants: decreased phenytoin concentration and increased serum valproic acid levels (7)
- Methotrexate: increased risk of bone marrow toxicity (7)
- NSAIDs: Increased risk of bleeding. Nonselective NSAIDs may interfere with DURLAZAs antiplatelet effect (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Avoid use during the third trimester (8.1)
- Hepatic Impairment: Avoid use in patients with severe impairment (8.6)
- Renal Impairment: Avoid use in patients with GFR less than 10 mL/min (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DURLAZA is indicated to:

1. Reduce the risk of death and myocardial infarction (MI) in patients with chronic coronary artery disease, such as patients with a history of MI or unstable angina pectoris or with chronic stable angina
2. Reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack

Limitation of Use: Use immediate-release aspirin, not DURLAZA in situations where a rapid onset of action is required (such as acute treatment of myocardial infarction or before percutaneous coronary intervention).

2 DOSAGE AND ADMINISTRATION

The recommended dose of DURLAZA is one capsule (162.5 mg) once daily. Take the capsules with a full glass of water at the same time each day.

Swallow DURLAZA capsules whole. Do not cut, crush or chew capsules.

Do not take DURLAZA 2 hours before or 1 hour after consuming alcohol [*see Warnings and Precautions (5)*].

3 DOSAGE FORMS AND STRENGTHS

DURLAZA (aspirin) Extended Release Capsules are supplied as white to off-white opaque capsules each containing 162.5 mg of aspirin.

4 CONTRAINDICATIONS

DURLAZA is contraindicated:

- In patients with a hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs).
- In patients with the syndrome of asthma, rhinitis, and nasal polyps. DURLAZA may cause severe urticaria, angioedema, or bronchospasm.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

DURLAZA increases the risk of bleeding. Risk factors for bleeding include the use of other drugs that increase the risk of bleeding (e.g., anticoagulants, antiplatelet agents, and chronic use of NSAIDs) [*see Drug Interactions (7)*].

5.2 Peptic Ulcer Disease

DURLAZA may cause gastric ulceration and bleeding. Avoid DURLAZA in patients with active peptic ulcer disease.

5.3 Fetal Toxicity

DURLAZA can cause fetal harm when administered to a pregnant woman. Maternal aspirin use during later stages of pregnancy may cause low birth weight, increased incidence for intracranial hemorrhage in premature infants, stillbirths and neonatal death. Because NSAIDs may cause premature closure of the fetal ductus arteriosus, avoid DURLAZA in the third trimester of pregnancy [see *Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following is a list of adverse reactions that have been reported in the literature for products containing low dose aspirin [see *Warnings and Precautions (5)*].

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, lethargy, seizures.

Fluid and Electrolyte: Hyperkalemia, metabolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, hepatic enzyme elevation, hepatitis, Reye's Syndrome

Renal: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

7 DRUG INTERACTIONS

Alcohol: Do not take DURLAZA 2 hours before or 1 hour after consuming alcohol. Alcohol can interfere with the controlled release properties of DURLAZA.

Renin-angiotensin system (RAS) inhibitors: In patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function, coadministration of NSAIDs, including DURLAZA, with RAS inhibitors may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving RAS inhibitors and DURLAZA.

NSAIDs, including DURLAZA may attenuate the antihypertensive effects of RAS inhibitors.

Anticoagulant and antiplatelets: Increased risk of bleeding

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): The concurrent use of DURLAZA with other NSAIDs increases the risk of bleeding and may result in renal impairment.

Ibuprofen can interfere with the anti-platelet effect of low dose aspirin. Patients who use DURLAZA and take a single dose of ibuprofen 400 mg should dose the ibuprofen at least 2-4

hours or longer after ingestion of DURLAZA. Wait 8 hours after ibuprofen dosing, before giving aspirin, to avoid significant interference.

Nonselective NSAIDs may interfere with the antiplatelet effect of low-dose aspirin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Avoid use during the third trimester of pregnancy because NSAIDs such as DURLAZA may cause premature closure of the fetal ductus arteriosus. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

8.2 Labor and Delivery

Avoid DURLAZA 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

8.3 Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants from DURLAZA, choose either to discontinue DURLAZA or discontinue nursing.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In a large collaborative overview of aspirin for vascular event prevention, including over 14000 patients over 65 years of age, 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.

8.6 Hepatic Impairment

Avoid DURLAZA in patients with severe hepatic insufficiency.

8.7 Renal Impairment

Avoid DURLAZA in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

10 OVERDOSAGE

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma

concentrations approaching 200 mcg/mL. Plasma concentrations of aspirin above 300 mcg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 mcg/mL [see *Clinical Pharmacology* (12.3)]. A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, contact a Poison Control Center immediately.

Signs and Symptoms: In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.

Treatment: Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage or emesis, administer activated charcoal, as a slurry, if less than 3 hours have passed since ingestion.

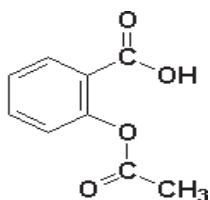
Severity of aspirin intoxication is determined by measuring the blood salicylate level. Monitor acid-base status with serial blood gas and serum pH measurements. Maintain fluid and electrolyte balance.

In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Replace fluid intravenously and correct acidosis. Monitor plasma electrolytes and pH to promote alkaline diuresis of salicylate if renal function is normal. Glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can reduce the body aspirin content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

11 DESCRIPTION

DURLAZA Capsules contain aspirin, which is a platelet aggregation inhibitor, for oral administration. Chemically, aspirin is acetylsalicylic acid. It has the following structural formula:



Aspirin is white or almost white crystalline powder or colorless crystals consisting of cubical and squared crystals. It is slightly soluble in water, and soluble in ethanol. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary odor. It has a molecular weight of 180.16 g/mole and a molecular formula $C_9H_8O_4$.

Durlaza capsules also include the following inactive ingredients: ethylcellulose, povidone, castor oil, tartaric acid, magnesium stearate, colloidal anhydrous silica, and talc.

The capsule shell contains gelatin and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aspirin [acetylsalicylic acid (ASA)] inhibits prostaglandin synthesis resulting in inhibition of platelet aggregation for their lifespan of about 7-10 days. The acetyl group of aspirin binds with a serine residue of cyclooxygenase-1 (COX-1), resulting in irreversible inactivation of the enzyme. Inhibition of COX-1 prevents conversion of arachidonic acid to thromboxane A₂ (TXA₂), which is a potent agonist of platelet aggregation.

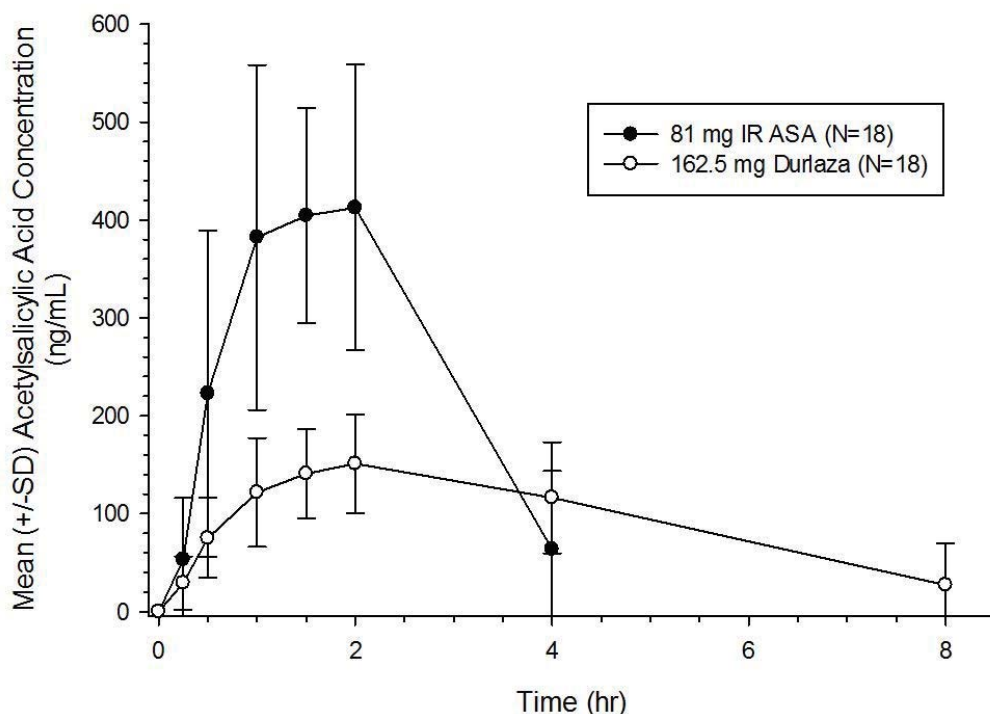
12.2 Pharmacodynamics

The dose-response relationship for DURLAZA and immediate release (IR) aspirin towards COX-1 inhibition was characterized by examining the inhibition of serum TXB₂ and urine 11-dehydro-TXB₂ at 24 h following a single dose. Doses over the range of 20 mg to 325 mg for DURLAZA and 5 mg to 81 mg for IR aspirin respectively were studied. Half-maximal inhibition of serum TXB₂ and urine 11-dehydro-TXB₂ occurred with doses of DURLAZA (ID₅₀) about 2-fold the dose of immediate release (IR) aspirin. Based on this relationship, the pharmacodynamic effect of DURLAZA 162.5 mg is similar to that attained with IR aspirin 81 mg. The mean inhibition of serum TXB₂ following DURLAZA (82%) is lower when compared to IR aspirin 81 mg (93%) following the first dose. However, upon repeat administration, near maximal inhibition of serum TXB₂ is achieved, similar to what is achieved following repeated daily doses of IR aspirin.

12.3 Pharmacokinetics

Following oral administration, DURLAZA exhibits extended release of aspirin from the encapsulated microparticles, thereby prolonging the absorption of aspirin across the GI tract compared to IR aspirin (Figure 1). Once absorbed, aspirin is metabolized, distributed, and excreted in a manner similar to that of aspirin absorbed from IR dosage forms.

Figure 1: Mean acetylsalicylic acid concentration-time profile following single dose administration of 162.5 mg DURLAZA or 81 mg immediate release ASA



Absorption: Following administration of DURLAZA, the time to reach peak plasma concentration of aspirin is slightly longer compared to following IR aspirin dosage form. Median T_{max} for DURLAZA is about 2 h when compared to 1 h following IR aspirin (see Figure 1). The mean C_{max} for DURLAZA is approximately 35% of that following IR aspirin 81 mg. The area under the plasma concentration-time curve for aspirin following administration of DURLAZA is approximately 70% of that following IR aspirin. The rate of DURLAZA absorption is dependent on food, alcohol, and gastric pH.

Distribution: The volume of distribution of usual doses of aspirin in normal subjects averages approximately 170 mL/kg of body weight.

Metabolism: Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin following DURLAZA administration are essentially undetectable 4-8 hours after dosing. In contrast to immediate release aspirin, measurable levels of salicylic acid at 24 hours following a single dose of DURLAZA were observed. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites.

Elimination: The mean plasma half-life of aspirin may range from 20 to 60 min. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicylic acid, and 10% phenolic and 5% acyl glucuronides of salicylic acid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenesis, mutagenesis or impairment of fertility studies were conducted with DURLAZA. Aspirin is not considered to be genotoxic or carcinogenic. Studies with oral aspirin in pregnant rats demonstrated the occurrence of fetal malformations at oral doses at or above 250 mg/kg [Human equivalent dose (HED) 40 mg/kg].

13.2 Animal Toxicology and/or Pharmacology

A single oral dose of 2500 mg/kg (HED 405 mg/kg) DURLAZA was well-tolerated in the gastrointestinal tract of the rat whereas a single oral dose of IR aspirin ≥ 740 mg/kg (HED 120 mg/kg) caused lethality and gastric mucosal damage.

14 CLINICAL STUDIES

14.1 Chronic Coronary Artery Disease

This indication is supported by the results of six large, randomized, multi-center, placebo controlled trials of predominantly male post-MI subjects and one randomized placebo-controlled study of men with unstable angina pectoris. Aspirin therapy in MI subjects gave about 20% reduction in the relative risk of the combined endpoint of death or nonfatal reinfarction. In the study of male unstable angina patients, aspirin reduced the event rate from 10% in the placebo patients to 5% in the patients treated with aspirin.

It is also supported by a randomized, multi-center, double-blind trial designed to assess the effect of aspirin in reducing the risk of MI in patients with chronic stable angina pectoris. Aspirin reduced the relative risk of the primary combined endpoint of nonfatal MI, fatal MI, and sudden death by 34%. The secondary endpoint for vascular events (the first occurrence of MI, stroke, or vascular death) was also significantly reduced.

14.2 Ischemic Stroke and Transient Ischemic Attack (TIA)

In clinical trials of subjects with ischemic stroke or TIAs, aspirin has been shown to reduce the relative risk of the combined endpoint of stroke or death and the combined endpoint of TIA, stroke, or death by about 13 - 18%.

16 HOW SUPPLIED/STORAGE AND HANDLING

DURLAZA Capsules, 162.5 mg, are supplied as follows:

Size 2 white to off-white opaque capsules imprinted with the name Durlaza

Bottles of 30 capsules NDC 58487-001-01

Bottles of 90 capsules NDC 58487-001-02

Special Precautions for Storage: Store at 25 °C (77 °F); excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature].

17 **PATIENT COUNSELING INFORMATION**

Discuss the following with patients prior to initiating treatment with DURLAZA and periodically during the course of ongoing treatment:

Bleeding

- Inform patients that they may bruise or bleed more easily or that it may take longer to stop bleeding and to report to their physician any prolonged, unusual or excessive bleeding. Inform patients to notify their physician about blood in their stool or urine and the signs and symptoms of occult bleeding [see *Warnings and Precautions (5)*].
- Inform patients about the signs and symptoms of GI side effects and seek medical advice when experiencing any of these signs and symptoms [see *Warnings and Precautions (5)*].

Hypersensitivity

- Advise the patient to discontinue DURLAZA and seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur [see *Contraindications (4)*].

Alcohol Consumption

- Inform patients they should not take DURLAZA 2 hours before or 1 hour after consuming alcohol. Counsel patients who drink three or more alcoholic drinks every day about the risk of bleeding involved in chronic, heavy alcohol use while taking DURLAZA [see *Warnings and Precautions (5)*].

Administration Instructions

- Advise patients to swallow DURLAZA capsules whole and not to chew or crush them.
- Remind patients not to discontinue DURLAZA without first notifying and discussing with their physician. Advise patients not to use extra medicine to make up a missed dose.
- Advise patients not to take ibuprofen around the same time as DURLAZA [see *Drug Interactions (7)*].

Pregnancy and Lactation

- Advise patients that ASA containing products such as DURLAZA cause harm to fetuses especially during the third trimester of pregnancy. Inform patients to notify their physician if they are pregnant, plan to become pregnant, breastfeed or are considering breastfeeding prior or during receiving treatment with DURLAZA [see *Use in Special Populations (8.2,8.3)*].

Manufactured for New Haven Pharmaceuticals, Inc.

North Haven, CT 06473

DURLAZA Capsules manufactured in USA

Distributed by Cardinal Health 105, Inc.



(b) (4)	
File name: Durlaza 30 count Professional Sample Carton	(b) (4)
Date: 9/11/13, 9/24/13, 2/4/15, 3/18/15 (2)	
Control Number: 18321, 18350, 19596, 19676, 19680	
Size: 1.625 x 1.625 x 2.593	
(b) (4)	
Proof: (b) (4)	

1.625 X 1.625 X 2.593

Manufactured for:



New Haven Pharmaceuticals, Inc.
North Haven, CT 06473

Made in USA www.durlaza.com

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XXXXXX 19682

NDC 58487-001-01

DURLAZA™
(ASPIRIN)
Extended Release
Capsules

162.5 mg

PROFESSIONAL
SAMPLE
(b) (4)

Rx only

30 Capsules

DOSAGE: See package insert for full
Prescribing Information (b) (4)

Swallow capsules whole.
Do not crush or chew.

Each capsule contains 162.5 mg
of aspirin.

Store at 25°C (77°F); excursions
permitted to 15-30°C (59-86°F) (see
USP Controlled Room Temperature).
Keep out of reach of children.

LOT:

EXP:



(b) (4)

File name: Durlaza 30 count Professional Sample Label

Date: 10/18/13, 2/4/15, 3/18/15 (2)

Control Number: 18446, 19593, 19678, 19682

Size: 4.25" x 1"

(b) (4)

Proof: (b) (4)

(b) (4)

(b) (4)

90 Capsules

DURLAZA™
(ASPIRIN)
Extended Release
Capsules
162.5 mg

NDC 58487-001-02

DURLAZA™
(ASPIRIN)
Extended Release
Capsules

162.5 mg

(b) (4)

90 Capsules

Rx only



DURLAZA™
(ASPIRIN)
Extended Release
Capsules

Manufactured for:
New Haven Pharmaceuticals, Inc.
North Haven, CT 06473

Made in USA

©2015 New Haven Pharmaceuticals, Inc.
XXXXXXX 19681



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5848700102 8

NDC 58487-001-02

DURLAZA™
(ASPIRIN)
Extended Release
Capsules

162.5 mg

(b) (4)

90 Capsules

Rx only



DURLAZA™
(ASPIRIN)
Extended Release
Capsules

DOSAGE: See package insert for
full Prescribing Information (b) (4)

Swallow capsules whole.
Do not crush or chew.

Each capsule contains 162.5 mg
of aspirin.

Store at 25°C (77°F); excursions
permitted to 15-30°C (59-86°F)
[see USP Controlled Room
Temperature].

Keep out of reach of children.

www.durlaza.com

DURLAZA™
(ASPIRIN)
Extended Release
Capsules

162.5 mg

90 Capsules

LOT:
EXP:



LOT
EXP

File name: Durlaza 90 count Trade Carton

Date: 9/11/13, 9/24/13, 2/4/15, 3/18/15 (2)

Control Number: 18273, 18351, 19595, 19677, 19681

Size: 2.0 x 2.0 x 4.25

(b) (4)

Proof: (b) (4) (b) (4)

Reference ID: 3815987

2.0 X 2.0 X 4.25

Manufactured for:

NDC 58487-001-02



New Haven
Pharmaceuticals, Inc.
North Haven, CT 06473

Made in USA

DURLAZA™
(ASPIRIN)
**Extended Release
Capsules**

162.5 mg

(b) (4)

©2015 New Haven
Pharmaceuticals, Inc.
XXXXXX

19683

Rx only

90 Capsules

DOSAGE: See package insert
for full Prescribing Information
(b) (4)

Swallow capsules whole.
Do not crush or chew.

Each capsule contains
162.5 mg of aspirin.

Store at 25°C (77°F);
excursions permitted to
15-30°C (59-86°F) [see USP
Controlled Room Temperature].

Keep out of reach of children.

www.durlaza.com

LOT:

EXP:



(b) (4)

File name: Durlaza 90 count Trade Bottle Label

Date: 10/18/13, 2/4/15, 3/18/15 (2)

Control Number: 18447, 19594, 19679, 19683

Size: 4.875" x 1.75"

(b) (4)

Proof: (b) (4) (b) (4)

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
09/04/2015