



Glenmark Pharmaceuticals Inc.
RECALL RETURN RESPONSE FORM
DILTIAZEM HYDROCHLORIDE EXTENDED RELEASE CAPSULES 60 MG, 90 MG & 120 MG
(100's PACK CONTAINER)
(NDC: 68462-850-01 (60 mg), 68462-851-01 (90 mg) & 68462-562-01 (120 mg))
Retail Level
11/01/2024

Please fill out this form completely. By doing so, this will acknowledge that you have read and understand the withdrawal instructions and have taken the appropriate action.

Customer Name:		DEA#:
<i>DEA # is required, if it is not provided, the processing of your form will be delayed.</i>		
Address:		
City:	State:	Zip:
Contact Name (Please Print):		
Telephone#:	Email:	
Contact Signature:	Date:	
DEBIT MEMO# (If unsure, leave blank):		

Wholesaler Information if not directly purchased from Glenmark Pharmaceuticals Inc.:

Wholesaler Name:	DEA#:	
City:	State:	Zip:

I have checked my stock and communicated to my customers at the appropriate level:

- I confirm that all locations that received the impacted products have been notified to the Retail level _____ (Initial and date)
- I do not have any stock of the recalled items. **OR**
- I have quarantined and listed in the box below the quantity of recalled units and I will be returning to Inmar, as soon as possible. Upon receipt of this Response Form, Inmar, will issue return authorization label(s) Please indicate the # of needed box labels _____.

Item Description	NDC#	Lot#/ Pack Size	Exp. Date	Total Full/Sealed and Partial/Open Bottle Count
Diltiazem Hydrochloride Extended Release Capsules, USP 90 mg	68462-851-01	17222452/100 capsules	11/2024	
Diltiazem Hydrochloride Extended Release Capsules, USP 120 mg	68462-562-01	17222470/100 capsules	11/2024	

Recall Event ID RCL263-24 / N131231



Item Description	NDC#	Lot#/ Pack Size	Exp. Date	Total Full/Sealed and Partial/Open Bottle Count
Diltiazem Hydrochloride Extended Release Capsules, USP 60 mg	68462-850-01	17222544/100 capsules	11/2024	
Diltiazem Hydrochloride Extended Release Capsules, USP 120 mg	68462-562-01	17222547/100 capsules	11/2024	
Diltiazem Hydrochloride Extended Release Capsules, USP 120 mg	68462-562-01	17230304/100 capsules	12/2024	
Diltiazem Hydrochloride Extended Release Capsules, USP 120 mg	68462-562-01	17230598/100 capsules	02/2025	
Diltiazem Hydrochloride Extended Release Capsules, USP 90 mg	68462-851-01	17230607/100 capsules	02/2025	
Diltiazem Hydrochloride Extended Release Capsules, USP 120 mg	68462-562-01	17230680/100 capsules	11/2024	
Diltiazem Hydrochloride Extended Release Capsules, USP 60 mg	68462-850-01	17230784/100 capsules	03/2025	
Diltiazem Hydrochloride Extended Release Capsules, USP 60 mg	68462-850-01	17231080/100 capsules	04/2025	

If you have any questions regarding this form or product return please contact Inmar at 866-945-0822
Office hours 9am to 5pm EST Mon thru Fri.

**Please fax this form to: 1-817-868-5362 or E-mail rxrecalls@inmar.com
Recall Event ID RCL263-24 / N131231**



URGENT: DRUG RECALL

**Diltiazem Hydrochloride Extended Release Capsules 60 mg, 90 mg and 120 mg
(100's Bottles pack Container)**

**NDC: 68462-850-01 (60 mg), 68462-851-01 (90 mg) & 68462-562-01 (120 mg)
(Glenmark)**

November 1, 2024

Dear Pharmacy, Wholesale and Retail Customer:

This is to inform you of that Glenmark is initiating a voluntary recall to the Retail level involving the following prescription product:

Diltiazem Hydrochloride Extended Release Capsules 60 mg, 90 mg & 120 mg (100's Pack Container)

S. No.	NDC	Batch #	Pack Size	Expiry
1.	68462-851-01	17222452	100 capsules	11/2024
2.	68462-562-01	17222470	100 capsules	11/2024
3.	68462-850-01	17222544	100 capsules	11/2024
4.	68462-562-01	17222547	100 capsules	11/2024
5.	68462-562-01	17230304	100 capsules	12/2024
6.	68462-562-01	17230598	100 capsules	02/2025
7.	68462-851-01	17230607	100 capsules	02/2025
8.	68462-562-01	17230680	100 capsules	11/2024
9.	68462-850-01	17230784	100 capsules	03/2025
10.	68462-850-01	17231080	100 capsules	04/2025

The recall to the *retail level* of the above identified product batches for Diltiazem Hydrochloride Extended Release Capsules has been initiated by Glenmark out of an abundance of precaution because the results of certain finished product analysis does not comply with the Agency's current recommended limit of "N-Nitroso-Desmethyl-Diltiazem" i.e. 0.074 ppm.



Sincerely,

GLENMARK PHARMACEUTICALS INC., USA

Thomas Callaghan **Thomas Callaghan** Digitally signed by Thomas Callaghan
Date: 2024.11.01 10:48:15 -04'00'

Executive Director - Regulatory Affairs, North America

US Agent for Glenmark Pharmaceuticals Limited

Enclosure(s):

Product Labels

Recall Return Response Form



Please see details of product batches listed in above table and refer enclosed product labels for ease in identifying the product.

Please examine your inventory and if you have any inventory available for the batches specified in the above table, you should quarantine such product immediately and not dispense any further product from these lots. Glenmark Pharmaceuticals Inc., USA initiated shipment of this product on 27 Jan. 2023.

In addition, if you are a wholesaler/ distributor, who has further distributed this product, please identify those retail customers and notify them at once of this Product recall. Your notification to your retail customers may be enhanced by including a copy of this recall notification letter. Again, this recall should be carried out to the retail level only. Because this is not a consumer level recall, notice to the consumer level is not required.

We are requesting the batches specified in the above table to be returned to Inmar Rx Solutions (address below) using the Postage Paid Product Return label that was provided in your Recall Return Packet.

Inmar Rx Solutions
3845 Grand Lakes Way
Grand Prairie, TX 75050

Please complete and return the enclosed response form preferably within 72 hours of receipt of this notification. Please either fax your response to 817-868-5362 or email to Rxrecalls@Inmar.com.

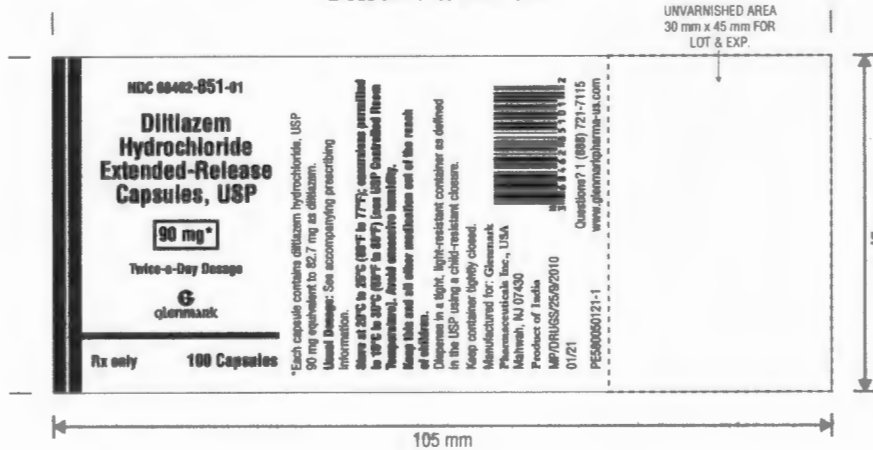
If you have any questions regarding your recall return please contact Inmar at 866-945-0822

Inmar office hours are Monday through Friday, from 9am to 5pm EST.

This recall is being made with the knowledge of the Food and Drug Administration.

Thank you for your cooperation,

SAME SIZE ARTWORK
 LABEL SIZE : 105 mm x 45 mm



MINIMUM FONT SIZE: 4.8 pt

DATE: 13-01-2021
 VERSION: 08

GLENMARK PHARMACEUTICALS LTD. PRODUCT NAME: <u>Diltiazem ER Tabs 90 mg</u> ITEM CODE: <u>PE58005</u> VERSION: <u>0121-1</u> PHARMACODE: <u>NA</u> COUNTRY: <u>USA</u> LOCATION: <u>INDORE</u> PACK : <u>LAB - 100'S</u> ACTUAL SIZE: <u>105 mm x 45 mm</u> SPECIFICATION: _____	DATE:	PANTONE SHADE NO: <input type="checkbox"/> BLACK <input type="checkbox"/> 186 C <input type="checkbox"/> 2945 C <input type="checkbox"/> NON PRINTING COLOUR	
	PKG. DEV.:	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout	
	RA	Regulatory Text	
	PRODUCTION:	Machine Suitability	
	QA:	Entire Text	
	REMARKS:		
	FCPDC001/01.00		

May Breedlove
 Digitally signed by May Breedlove
 Date: 2021.01.14 15:12:02 -05'00'

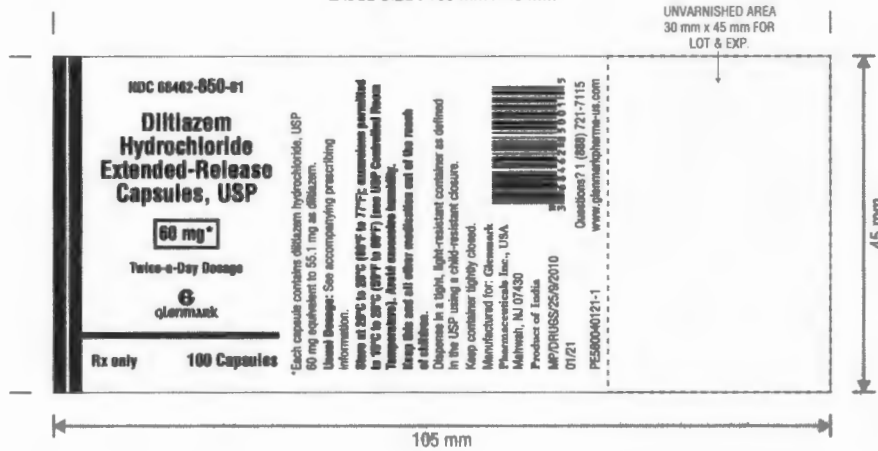
Carole Capella

Digitally signed by Carole Capella
 Date: 2021.01.15 12:54:37 -05'00'

Kristin DiStefano

Digitally signed by Kristin DiStefano
 Date: 2021.01.19 08:29:14 -05'00'

SAME SIZE ARTWORK
 LABEL SIZE : 105 mm x 45 mm



MINIMUM FONT SIZE: 4.8 pt

DATE: 13-01-2021
 VERSION: 09

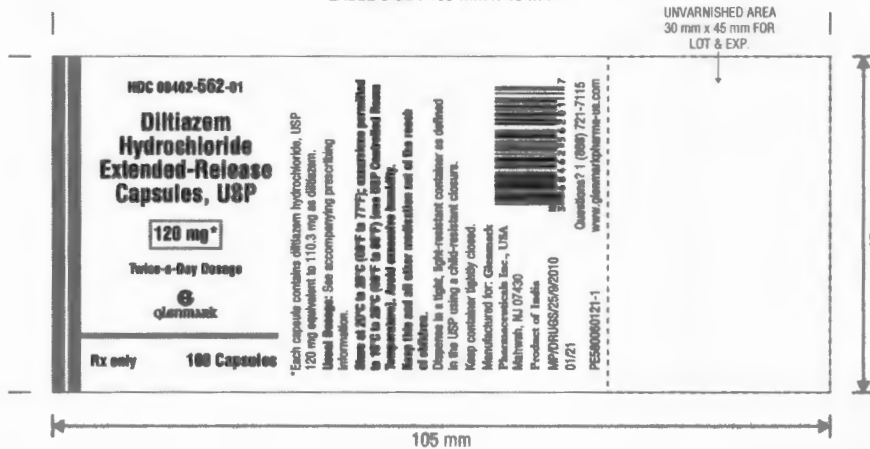
GLENMARK PHARMACEUTICALS LTD. PRODUCT NAME: <u>Diltiazem ER Tabs 60 mg</u> ITEM CODE: <u>PE58004</u> VERSION: <u>0121-1</u> PHARMACODE: <u>NA</u> COUNTRY: <u>USA</u> LOCATION: <u>INDORE</u> PACK : <u>LAB - 100'S</u> ACTUAL SIZE: <u>105 mm x 45 mm</u> SPECIFICATION: _____	DATE:	PANTONE SHADE NO: BLACK 100 C NON PRINTING COLOUR	
	PKG. DEV.:	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout	
	RA	Regulatory Text	
	PRODUCTION:	Machine Suitability	
	QA:	Entire Text	
	REMARKS:		
	FCPDC001/01.00		

May Breedlove
 Digitally signed by May Breedlove
 Date: 2021.01.14 15:10:25 -05'00'

Carole Capella
 Digitally signed by Carole Capella
 Date: 2021.01.15 12:54:20 -05'00'

Kristin DiStefano
 Digitally signed by Kristin DiStefano
 Date: 2021.01.19 08:28:42 -05'00'

SAME SIZE ARTWORK
 LABEL SIZE : 105 mm x 45 mm



MINIMUM FONT SIZE: 4.8 pt

DATE: 13-01-2021
 VERSION: 08

G GLENMARK PHARMACEUTICALS LTD. PRODUCT NAME: <u>Diltiazem ER Tabs 120 mg</u> ITEM CODE: <u>PE58006</u> VERSION: <u>0121-1</u> PHARMACODE: <u>NA</u> COUNTRY: <u>USA</u> LOCATION: <u>INDORE</u> PACK : <u>LAB - 100'S</u> ACTUAL SIZE: <u>105 mm x 45 mm</u> SPECIFICATION: _____	DATE:	PANTONE SHADE NO: <input type="checkbox"/> BLACK <input type="checkbox"/> 186 C <input type="checkbox"/> 143 C <input type="checkbox"/> NON PRINTING COLOUR	
	PKG. DEV.:	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout	
	RA	Regulatory Text	
	PRODUCTION:	Machine Suitability	
	QA:	Entire Text	
	REMARKS:		
		FCPDC001/01.00	

May Breedlove

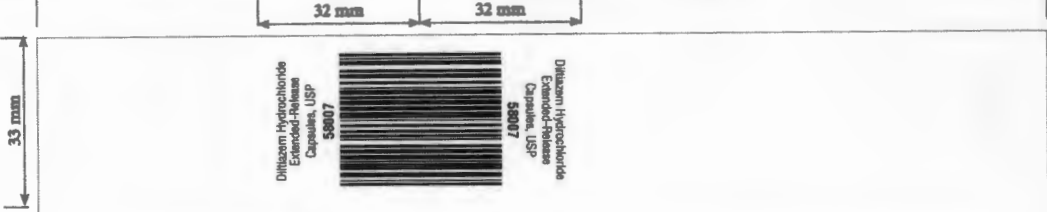
Digitally signed by
 May Breedlove
 Date: 2021.01.14
 15:26:29 -05'00'

Carole Capella

Digitally signed by
 Carole Capella
 Date: 2021.01.15
 12:55:00 -05'00'

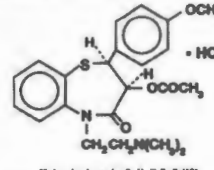
Kristin DiStefano

Digitally signed by
 Kristin DiStefano
 Date: 2021.01.19
 08:30:03 -05'00'



Diltiazem Hydrochloride Extended-Release Capsules, USP

DESCRIPTION
 Diltiazem hydrochloride is a calcium ion channel influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-dihydro-2-(4-methoxyphenyl)-4-(2H-tetrazol-5-yl)-2H-1,4-benzodiazepine 3HCl. The chemical structure is



Diltiazem hydrochloride, USP is a white crystalline powder or small crystals. It is freely soluble in chloroform, formic acid, methanol, water, sparingly soluble in dehydrated alcohol and insoluble in ether. It has a molecular weight of 452.58 g/mol. Each Diltiazem Hydrochloride Extended-Release Capsule, USP contains either 90 mg diltiazem hydrochloride (equivalent to 55.1 mg diltiazem), 90 mg diltiazem hydrochloride (equivalent to 62.7 mg diltiazem), or 120 mg diltiazem hydrochloride (equivalent to 110.3 mg diltiazem).

Also contains: Diethyl phthalate, ethyl cellulose, methacrylic acid and styryl acrylate copolymer, polyorbital, polyoxane, sodium lauryl sulfate, sugar spheres (corn starch, hydroxypropyl cellulose and sucrose) and talc. The capsules shells contain D&C Yellow No. 10 (90 mg only), FD&C Red No. 3, FD&C Red No. 40, FD&C Yellow No. 8, gelatin, sodium lauryl sulfate and titanium dioxide. The black printing ink contains black iron oxide, potassium hydroxide and shellac.

For oral administration.
 FDA approved dissolution test specifications differ from USP.

CLINICAL PHARMACOLOGY
 The therapeutic effects of diltiazem hydrochloride are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action
 Diltiazem Hydrochloride Extended-Release Capsules produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus, hypertensive individuals experience an antihypertensive effect, whereas those who are normotensive do not.

Hemodynamic and Electrophysiologic Effects
 Like other calcium channel antagonists, diltiazem decreases electrical and arteriovenular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In men, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given workload. Studies in dogs, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect, cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Increased heart failure has, however, been reported in occasional patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Diltiazem Hydrochloride Extended-Release Capsules produces antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. Diltiazem Hydrochloride Extended-Release Capsules decrease vascular resistance, increase cardiac output (by increasing stroke volume), and produce a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited, while maximum achievable systolic pressure is usually reduced. Heart rate at maximum exercise does not change or is slightly reduced. Chronic therapy with diltiazem hydrochloride produces no change or an increase in plasma catecholamines. No increase of activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem Hydrochloride Extended-Release Capsules antagonize the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of diltiazem hydrochloride in doses of up to 360 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (see **WARNINGS**).

Pharmacokinetics and Metabolism
 Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem hydrochloride undergoes extensive metabolism in which 2% to 4% of the unchanged drug appears in the urine. *In vitro* binding studies show diltiazem hydrochloride is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem hydrochloride binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple administration is approximately 3.0 to 4.5 hours. Diltiazem hydrochloride is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Minimum therapeutic plasma levels of diltiazem hydrochloride appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 60% increase in bioavailability in the hepatically impaired patients. A single study in nine patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Diltiazem Hydrochloride Extended-Release Capsules (Twice-a-Day Dosage)
 A single 120 mg dose of the capsule results in detectable plasma levels within 2 to 3 hours and peak plasma levels at 6 to 11 hours. The apparent elimination half-life after single or multiple dosing is 5 to 7 hours. A departure from linearity similar to that observed with the diltiazem hydrochloride tablet is observed. As the dose of diltiazem hydrochloride extended-release capsules is increased from a daily dose of 120 mg (60 mg b.i.d.) to 240 mg (120 mg b.i.d.) daily, there is an increase in area-under-the-curve of 2.6 times. When the dose is increased from 240 mg to 360 mg daily, there is an increase in area-under-the-curve of 1.8 times. The average plasma levels of the capsule doses twice daily at steady-state are equivalent to the tablet doses four times daily when the same total daily dose is administered.

INDICATIONS AND USAGE
 Diltiazem Hydrochloride Extended-Release Capsules (Twice-a-Day Dosage) are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive medications, such as diuretics.

CONTRAINDICATIONS
 Diltiazem hydrochloride is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

Cardiac Conduction
 Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may easily result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (9 of 2,111 patients or 0.43%). Concurrent use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem (see **ADVERSE REACTIONS**).

Congestive Heart Failure
 Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (d₁₆). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 4%) showed improvement in indices of ventricular function without significant decrease in contractile function (d₁₆). Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

Hypotension
 Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in asymptomatic hypotension.

Acute Hepatic Injury
 Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 2 weeks) and have been reversible upon discontinuation of the drug. The relationship to diltiazem hydrochloride is uncertain in some cases, but probable in some (see **PRECAUTIONS**).

PRECAUTIONS

General
 Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see **ADVERSE REACTIONS**) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions
 Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concurrently with any agents known to affect cardiac contractility and/or conduction (see **WARNINGS**). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem hydrochloride (see **WARNINGS**).

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system.

Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Benzothiazines: Studies showed that diltiazem increased the AUC of metoprolol and terfenadine by 3- to 4-fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of metoprolol and terfenadine also increased (1.5- to 2.5-fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (e.g., prolonged sedation) of both metoprolol and terfenadine.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride with beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem hydrochloride concurrently with propranolol in six normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding site by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see **WARNINGS**).

Insulin: In nine healthy subjects, diltiazem significantly increased the mean baseline AUC 0-5.5-fold and C_{max} 4.1-fold compared to placebo. The T_{max} and T_{1/2} of insulin were not significantly affected by diltiazem. Enhanced effects and increased toxicity of insulin may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during coadministration and should be based on clinical assessment.

Carbamazepine: Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (54%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacologic effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Dantrolene: Cases of bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of dantrolene concurrently with diltiazem. Monitor heart rate in patients receiving concomitant diltiazem and dantrolene.

Cyclosporine: A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine doses ranging from 15% to 45% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Digoxin: Administration of diltiazem hydrochloride with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization (see **WARNINGS**).

Verapamil: Concurrent use of diltiazem increases exposure to verapamil and may exacerbate bradycardia and conduction disturbances. Avoid concomitant use of verapamil and diltiazem.

Quinidine: Diltiazem significantly increases the AUC 0-∞ of quinidine by 51%, T_{1/2} by 36%, and decreases its C_{max} by 33%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

Ritaparil: Coadministration of ritaparil with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with ritaparil or any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered.

325 mm

May Breedlove
 Digitally signed by May Breedlove
 Date: 2021.01.21 15:52:25 -0500

Carole Capella
 Digitally signed by Carole Capella
 Date: 2021.01.21 15:52:25 -0500

Kristin DiStefano
 Digitally signed by Kristin DiStefano
 Date: 2021.01.21 15:52:25 -0500

200 mm

GLENMARK PHARMACEUTICALS LTD.		DATE: 15.01.2021	PHANTOM SHADE NO: Black
PRODUCT NAME: Diltiazem SR caps US	ITEM CODE: PE58007	VERSION: 0121-1	PKG. DEV.:
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COUNTRY: US	LOCATION: Indore	PRODUCTION:	Machine Suitability
PACK: 33 x 32 mm	QA:	REMARKS: NA	Extra Test
ACTUAL SIZE: 325 x 200 mm	SPECIFICATION: 60 Gsm Maplitho Paper	FCPCD001/01.00	

Statin: Diltiazem is an inhibitor of CYP3A4 and has been shown to increase significantly the AUC of some statins. The risk of myopathy and rhabdomyolysis with statins metabolized by CYP3A4 may be increased with concomitant use of diltiazem. When possible, use a non-CYP3A4-metabolized statin together with diltiazem; otherwise, dose adjustments for both diltiazem and the statin should be considered along with close monitoring for signs and symptoms of any statin-related adverse events.

In a healthy volunteer cross-over study (N=10), coadministration of a single 20 mg dose of simvastatin at the end of a 14 day regimen with 120 mg SR diltiazem Extended-Release resulted in a 5-fold increase in mean simvastatin AUC versus simvastatin alone. Subjects with increased average steady-state exposure of diltiazem showed a greater fold increase in simvastatin exposure. Computer-based simulations showed that at a daily dose of 480 mg of diltiazem, an 8- to 9-fold mean increase in simvastatin AUC can be expected. If coadministration of simvastatin with diltiazem is required, limit the daily dose of simvastatin to 10 mg and diltiazem to 240 mg. In a non-subject crossover, open label, 4-way cross over study, coadministration of diltiazem (120 mg SR, diltiazem SR) for 2 weeks with single 20 mg dose of losartan resulted in 3- to 4-fold increase in mean losartan AUC and C_{max} versus losartan alone. In the same study, there was no significant change in 20 mg single dose pravastatin AUC and C_{max} during diltiazem co-administration. Diltiazem plasma levels were not significantly affected by losartan or pravastatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No teratogenic effect on fertility was observed in rats.

Pharmacology:
Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities, in the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well controlled studies in pregnant women; therefore, use diltiazem hydrochloride in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:
Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem hydrochloride is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS:
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either diltiazem hydrochloride tablets or Diltiazem Hydrochloride Extended-Release Capsules, as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 500), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving diltiazem hydrochloride tablets or Diltiazem Hydrochloride Extended-Release Capsules were (i.e., greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.8%), bradycardia (1.5%), and rash (1.5%).

Double Blind Placebo Controlled Hypertension Trials		
Adverse	Diltiazem N = 218 # pts (%)	Placebo N = 211 # pts (%)
Headache	38 (12%)	17 (8%)
AV block first degree	24 (7.8%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.8%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
AKI phos increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Inoemia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) with Diltiazem Hydrochloride Extended-Release Capsules or diltiazem hydrochloride tablets or have been observed in angina or hypertension trials.

Cardiovascular: Angina, arrhythmia, second- or third-degree AV block (see Conduction Warning), bundle branch block, congestive heart failure, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tremor.

Gastrointestinal: Anorexia, diarrhea, dry mouth, dyspepsia, mild elevations of SGOT, SGPT, and LDH (see Hepatic Warnings), thirst, vomiting, weight increase.

Dermatologic: Patechiae, photosensitivity, pruritus, urticaria.

Other: Ankylosis, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarthritis pain, sexual difficulties, tinnitus.

The following post-marketing events have been reported infrequently in patients receiving diltiazem hydrochloride: acute generalized exanthematous pustulosis, allergic reactions, alopecia, angioedema (including facial or periorbital edema), anisocoria, erythema multiforme (including Stevens-Johnson Syndrome, toxic epidermal necrolysis), entropion-related symptoms, general hypotension, hemolytic anemia, increased bleeding time, leukopenia, photosensitivity (including lichenoid keratosis and hyperpigmentation at sun-exposed skin areas), pupura, retinopathy, myopathy, and thrombocytopenia. There have been observed cases of a generalized rash, some characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have

been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and diltiazem hydrochloride therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

OVERDOSEAGE:
The oral LD₅₀ in mice and rats range from 415 to 740 mg/kg and from 880 to 810 mg/kg, respectively. The intravenous LD₅₀ in these species were 80 and 38 mg/kg, respectively. The oral LD₅₀ in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over twofold. Within the usual-dose range of blood levels in overdose cases.

There have been reports of diltiazem overdose in doses ranging from 1 g to 1.8 g. Of cases with known outcome, most patients recovered and in cases with a fatal outcome, the majority involved multiple drug ingestion.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine, as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure and in cases of cardiac failure isotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium.

The effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose has been inconsistent. In a few reported cases, overdose with calcium channel blockers associated with hypotension and bradycardia that was initially refractory to atropine became more responsive to atropine after the patients received intravenous calcium. In some cases, intravenous calcium has been administered (1 g calcium chloride or 3 g calcium gluconate) over 5 minutes and repeated every 10 to 20 minutes as necessary. Calcium gluconate has also been administered as a continuous infusion at a rate of 2 g per hour for 10 hours. Infusions of calcium for 24 hours or more may be required. Patients should be monitored for signs of hypercalcemia.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences the following measures may be considered:

Bradycardia: Administer atropine (0.5 to 1 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. If high degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer isotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g., dopamine or norepinephrine bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DIOSAGE AND ADMINISTRATION:
Dosages must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. Although individual patients may respond to lower doses, the usual optimum dosage range in clinical trials was 240 to 360 mg/day.

Diltiazem Hydrochloride Extended-Release Capsules have an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of Diltiazem Hydrochloride Extended-Release Capsules or the concomitant antihypertensive may need to be adjusted when adding one to the other. See **WARNINGS** and **PRECAUTIONS** regarding use with beta-blockers.

HOW SUPPLIED:
Diltiazem Hydrochloride Extended-Release Capsules, USP (Twice-a-Day Dosage) are available as follows:

Strength	Quantity	NDC Number	Description
60 mg	Bottles of 100 with child-resistant closure	68462-850-01	The 60 mg capsules are hard shell gelatin capsules with a dark pink opaque cap and a white opaque body, imprinted with "Y" on the cap and "569" on the body with black ink, filled with white to off-white pellets.
90 mg	Bottles of 100 with child-resistant closure	68462-851-01	The 90 mg capsules are hard shell gelatin capsules with a dark pink opaque cap and a white opaque body, imprinted with "Y" on the cap and "589" on the body with black ink, filled with white to off-white pellets.
120 mg	Bottles of 100 with child-resistant closure	68462-862-01	The 120 mg capsules are hard shell gelatin capsules with a dark pink opaque cap and a dark pink opaque body, imprinted with "Y" on the cap and "582" on the body with black ink, filled with white to off-white pellets.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Avoid excessive humidity.

Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.

Manufactured by:
Glenmark Pharmaceuticals Limited
Pillayur, Madhya Pradesh 454775, India

Manufactured for:
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Glenmark Pharmaceuticals Inc., USA
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Revision No. 1
Revised: January 2021

325 mm

May Breedlove
Digitally signed by May Breedlove
Date: 2021.01.15 11:02:58 -05'00'

Carole Capella
Digitally signed by Carole Capella
Date: 2021.01.15 13:55:38 -05'00'

Kristin DiStefano
Digitally signed by Kristin DiStefano
Date: 2021.01.19 08:30:58 -05'00'

200 mm

GLENMARK PHARMACEUTICALS LTD.		DATE: 15.01.2021	PANTONE SHADE NO: Black
PRODUCT NAME: Diltiazem SR caps US		PKG. DEV.:	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout
ITEM CODE: PE58007	VERSION: 0121-1	RA	Regulatory Text
PHARMACODE: NA	BARCODE: 58007	PRODUCTION:	Machine Suitability
COUNTRY: US		QA:	Ende Test
LOCATION: Indore		REMARKS: NA	
PACK: 33 x 32 mm			
ACTUAL SIZE: 325 x 200 mm			
SPECIFICATION: 60 Gsm Maplitho Paper			
FCPCD001/01.00			