URGENT: DRUG RECALL

CARVEDILOL TABLETS USP 3.125mg, 6.25mg, 12.5mg, and 25mg
100s and 500s Container pack (Tablets)
(NDC 68462-162-01, 68462-162-05, 68462-163-01, 68462-163-05, 68462-164-05, 68462-165-05)

February 28, 2025

Dear Pharmacy, Wholesale and Retail Customer:

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

Carvedilol Tablets USP 3.125mg (100's Tablets)

Sr. No.	NDC Code	Batch Number	Pack Size	Expiry Date
1	68462-162-01	19231450	100's Tablets in Container	Mar-25
2	68462-162-01	19233345	100's Tablets in Container	Jul-25
3	68462-162-01	19234275	100's Tablets in Container	Sep-25
4	68462-162-01	19240280	100's Tablets in Container	Dec-25

Carvedilol Tablets USP 3.125mg (500's Tablets)

Sr. No.	NDC Code	Batch Number	Pack Size	Expiry Date
1	68462-162-05	19231450	500's Tablets in Container	Mar-25
2	68462-162-05	19231464	500's Tablets in Container	Mar-25
3	68462-162-05	19231471	500's Tablets in Container	Mar-25
4	68462-162-05	19231493	500's Tablets in Container	Mar-25
5	68462-162-05	19232083	500's Tablets in Container	Apr-25
6	68462-162-05	19232103	500's Tablets in Container	Apr-25
7	68462-162-05	19232658	500's Tablets in Container	Jun-25
8	68462-162-05	19233328	500's Tablets in Container	Jul-25
9	68462-162-05	19233343	500's Tablets in Container	Jul-25
10	68462-162-05	19233344	500's Tablets in Container	Jul-25
11	68462-162-05	19233345	500's Tablets in Container	Jul-25

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

Sr. No.	NDC Code	Batch Number	Pack Size	Expiry Date
12	68462-162-05	19234275	500's Tablets in Container	Sep-25
13	68462-162-05	19240280	500's Tablets in Container	Dec-25
14	68462-162-05	19234843	500's Tablets in Container	Nov-25
15	68462-162-05	19235039	500's Tablets in Container	Nov-25
16	68462-162-05	19240296	500's Tablets in Container	Dec-25

Carvedilol Tablets USP 6.25mg (100's Tablets)

Sr. No.	NDC Code	Batch Number	Pack Size	Expiry Date
1	68462-163-01	19231618	100's Tablets in Container	Mar-25
2	68462-163-01	19232064	100's Tablets in Container	Apr-25
3	68462-163-01	19232324	100's Tablets in Container	May-25
4	68462-163-01	19233369	100's Tablets in Container	Jul-25
5	68462-163-01	19234162	100's Tablets in Container	Sep-25
6	68462-163-01	19240543	100's Tablets in Container	Jan-26

Carvedilol Tablets USP 6.25mg (500's Tablets)

Sr. No.	NDC Code	Batch Number	Pack Size	Expiry Date
1	68462-163-05	19231174	500's Tablets in Container	Feb-25
2	68462-163-05	19231199	500's Tablets in Container	Feb-25
3	68462-163-05	19231517	500's Tablets in Container	Mar-25
4	68462-163-05	19231527	500's Tablets in Container	Mar-25
5	68462-163-05	19231566	500's Tablets in Container	Mar-25
6	68462-163-05	19231568	500's Tablets in Container	Mar-25
7	68462-163-05	19231595	500's Tablets in Container	Mar-25
8	68462-163-05	19231618	500's Tablets in Container	Mar-25
9	68462-163-05	19231634	500's Tablets in Container	Mar-25
10	68462-163-05	19231638	500's Tablets in Container	Mar-25
11	68462-163-05	19232043	500's Tablets in Container	Apr-25
12	68462-163-05	19232051	500's Tablets in Container	Apr-25
13	68462-163-05	19232064	500's Tablets in Container	Apr-25
14	68462-163-05	19232322	500's Tablets in Container	May-25
15	68462-163-05	19232324	500's Tablets in Container	May-25
16	68462-163-05	19232365	500's Tablets in Container	May-25
17	68462-163-05	19232380	500's Tablets in Container	May-25

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Sr. No.	NDC Code	Batch Number	Pack Size	Expiry Date
18	68462-163-05	19232389	500's Tablets in Container	May-25
19	68462-163-05	19232736	500's Tablets in Container	Jun-25
20	68462-163-05	19232743	500's Tablets in Container	Jun-25
21	68462-163-05	19232746	500's Tablets in Container	Jun-25
22	68462-163-05	19232756	500's Tablets in Container	Jun-25
23	68462-163-05	19232757	500's Tablets in Container	Jun-25
24	68462-163-05	19233369	500's Tablets in Container	Jul-25
25	68462-163-05	19233371	500's Tablets in Container	Jul-25
26	68462-163-05	19233405	500's Tablets in Container	Jul-25
27	68462-163-05	19233416	500's Tablets in Container	Jul-25
28	68462-163-05	19234162	500's Tablets in Container	Sep-25
29	68462-163-05	19234183	500's Tablets in Container	Sep-25
30	68462-163-05	19234192	500's Tablets in Container	Sep-25
31	68462-163-05	19234204	500's Tablets in Container	Sep-25
32	68462-163-05	19234223	500's Tablets in Container	Sep-25
33	68462-163-05	19234243	500's Tablets in Container	Sep-25
34	68462-163-05	19234263	500's Tablets in Container	Sep-25
35	68462-163-05	19240223	500's Tablets in Container	Dec-25
36	68462-163-05	19240543	500's Tablets in Container	Jan-26
37	68462-163-05	19231448	500's Tablets in Container	Mar-25
38	68462-163-05	19231164	500's Tablets in Container	Feb-25
39	68462-163-05	19234165	500's Tablets in Container	Sep-25
40	68462-163-05	19234242	500's Tablets in Container	Sep-25
41	68462-163-05	19234743	500's Tablets in Container	Nov-25
42	68462-163-05	19234774	500's Tablets in Container	Nov-25
43	68462-163-05	19234993	500's Tablets in Container	Nov-25
44	68462-163-05	19240203	500's Tablets in Container	Dec-25
45	68462-163-05	19240211	500's Tablets in Container	Dec-25
46	68462-163-05	19240214	500's Tablets in Container	Dec-25
47	68462-163-05	19240247	500's Tablets in Container	Dec-25
48	68462-163-05	19240249	500's Tablets in Container	Dec-25
49	68462-163-05	19240272	500's Tablets in Container	Dec-25
50	68462-163-05	19240319	500's Tablets in Container	Dec-25

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
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Carvedilol Tablets USP 12.5mg (500's Tablets)

S. No.	NDC	Batch No.	Pack Style	Expiry Date
1	68462-164-05	19231899	500's Tablets in Container	Apr-25
2	68462-164-05	19231922	500's Tablets in Container	Apr-25
3	68462-164-05	19231927	500's Tablets in Container	Apr-25
4	68462-164-05	19231967	500's Tablets in Container	Apr-25
5	68462-164-05	19231979	500's Tablets in Container	Apr-25
6	68462-164-05	19232226	500's Tablets in Container	May-25
7	68462-164-05	19232234	500's Tablets in Container	May-25
8	68462-164-05	19232265	500's Tablets in Container	May-25
9	68462-164-05	19232271	500's Tablets in Container	May-25
10	68462-164-05	19232758	500's Tablets in Container	Jun-25
11	68462-164-05	19232759	500's Tablets in Container	Jun-25
12	68462-164-05	19232762	500's Tablets in Container	Jun-25
13	68462-164-05	19232788	500's Tablets in Container	Jun-25

Carvedilol Tablets USP 25mg (500's Tablets)

Sr. No.	NDC Code	Batch Number	Pack Size	Expiry Date
1	68462-165-05	19231107	500's Tablets in Container	Feb-25
2	68462-165-05	19231114	500's Tablets in Container	Feb-25
3	68462-165-05	19231152	500's Tablets in Container	Feb-25
4	68462-165-05	19234866	500's Tablets in Container	Jan-26

The recall to the retail level of the above-identified Carvedilol Tablets USP 3.125mg, 6.25mg, 12.5mg, and 25mg batches have been initiated out of an abundance of caution due to the presence of a nitrosamine, 'N-Nitroso Carvedilol I' Impurity above the current Acceptable Intake Level in certain batches. To date, Glenmark has not received any reports of adverse events related to this recall.

Nitrosamines are common in water and foods, including cured and grilled meats, dairy products, and vegetables. These impurities may increase the risk of cancer if people are exposed to them above acceptable levels over long periods of time. There is no immediate risk to patients taking the medication.

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

Please see the details of product batches listed in the above table and refer to the 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 05/11/2023.

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.

Glenmark is 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 **877-535-3243**

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

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

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

Thank you for your cooperation,

Sincerely,

GLENMARK PHARMACEUTICALS INC., USA

thomas.callaghan@glenmarkpharma.com
Digitally signed by thomas.callaghan@glenmarkpharma.com
Date: 2025.02.28 09:19:29 -05'00'

Thomas Callaghan

Executive Director - Regulatory Affairs, North America

US Agent for Glenmark Pharmaceuticals Limited

Enclosure(s):

Product Labels

Recall Return Response Form

Product labels:

Carvedilol Tablets USP 3.125mg (100 Tablets in Container)

JAR SIZE : 40 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 30 mm

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

Carvedilol Tablets USP 3.125mg (500 Tablets in Container)

JAR SIZE : 40 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 30 mm

Carvedilol Tablets USP 6.25mg (100 Tablets in Container)

JAR SIZE : 40 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 30 mm

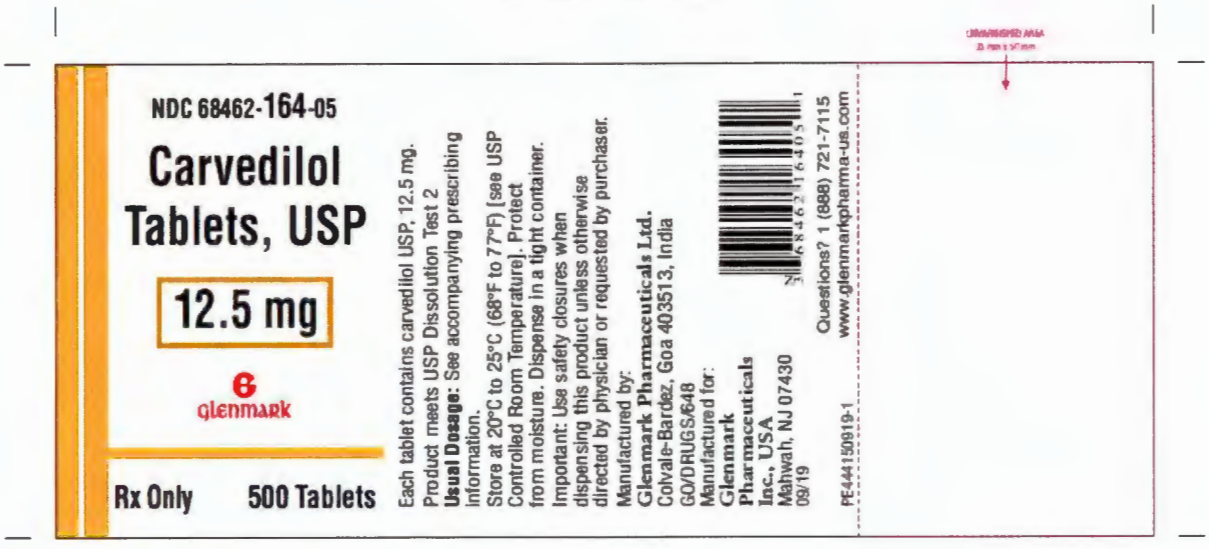
Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

Carvedilol Tablets USP 6.25mg (500 Tablets in Container)

JAR SIZE : 60 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 45 mm

Carvedilol Tablets USP 12.5mg (500 Tablets in Container)

JAR SIZE : 150 CC
SAME SIZE ARTWORK
LABEL SIZE : 130 mm x 50 mm



Carvedilol Tablets USP 25mg (500 Tablets in Container)

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

JAR SIZE : 250 CC
SAME SIZE ARTWORK
LABEL SIZE : 130 mm x 55 mm

UNVARNISHED AREA
32 mm x 55 mm

Glenmark Pharmaceuticals Inc. USA 750 Corporate Drive, Mahwah, NJ 07430
T: 1 201 684 8000 F: 1 201 831 0080 www.glenmarkpharma.com/usa

JAR SIZE : 40 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 30 mm

May Breedlove
Digitally signed by May Breedlove
Date: 2019.11.06 10:08:17 -05'00'

Donna-Marie Walters
Digitally signed by Donna-Marie Walters
Date: 2019.11.06 10:40:55 -05'00'

Carole Capella
Digitally signed by Carole Capella
Date: 2019.11.06 12:54:53 -05'00'

MINIMUM FONT SIZE: 3.9 PT

GLENMARK PHARMACEUTICALS LTD.		**DATE:**	**PANTONE SHADE NO:** BLACK 186 C
PRODUCT NAME: Carvedilol Tablets USP 3.125 mg		**PKG. DEV.:**	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout
ITEM CODE: PE44476 **VERSION:** 0919-1		**RA**	Regulatory Text
PHARMACODE:		**QA:**	Entire Text
COUNTRY: USA		**PRODUCTION:**	Machine Suitability
LOCATION: GOA		**REMARKS:**	
PACK : LABEL - 100 TABLETS			
ACTUAL SIZE: 105 mm x 30 mm			
SPECIFICATION: A UV VARNISH COATED FASPRINT NG/PERMANENT (HITAC)/ PET 23 STICKER LABEL FROM AVERY DENISON PRINTED AS PER APPROVED ARTWORK. BATCH PRINTING AREA REMAINS UNVARNISHED			

JAR SIZE : 40 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 30 mm

May Breedlove
Digitally signed by May Breedlove
Date: 2019.11.06 10:17:39 -05'00'

Donna-Marie Walters
Digitally signed by Donna-Marie Walters
Date: 2019.11.06 10:41:32 -05'00'

Carole Capella
Digitally signed by Carole Capella
Date: 2019.11.06 12:55:08 -05'00'

MINIMUM FONT SIZE: 3.9 PT

GLENMARK PHARMACEUTICALS LTD.		**DATE:**	**PANTONE SHADE NO:** BLACK 186 C
PRODUCT NAME: Carvedilol Tablets USP 3.125 mg		**PKG. DEV.:**	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout
ITEM CODE: PE44477	**VERSION:** 0919-1	**RA**	Regulatory Text
PHARMACODE:		**QA:**	Entire Text
COUNTRY: USA		**PRODUCTION:**	Machine Suitability
LOCATION: GOA		**REMARKS:**	
PACK : LABEL - 500 TABLETS			
ACTUAL SIZE: 105 mm x 30 mm			
SPECIFICATION: A UV VARNISH COATED FASPRINT NG/PERMANENT (HITAC)/ PET 23 STICKER LABEL FROM AVERY DENISON PRINTED AS PER APPROVED ARTWORK. BATCH PRINTING AREA REMAINS UNVARNISHED			

JAR SIZE : 40 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 30 mm

May Breedlove — Digitally signed by May Breedlove Date: 2019.11.06 10:16:51 -05'00'

Donna-Marie Walters — Digitally signed by Donna-Marie Walters Date: 2019.11.06 10:42:04 -05'00'

Carole Capella — Digitally signed by Carole Capella Date: 2019.11.06 12:55:24 -05'00'

MINIMUM FONT SIZE: 3.9 PT

GLENMARK PHARMACEUTICALS LTD.		**DATE:**	**PANTONE SHADE ID:** BLACK 2 / 2945 C / 186 C
PRODUCT NAME: Carvedilol Tablets USP 6.25 mg		**PKG. DEV.:**	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout
ITEM CODE: PE44478 **VERSION:** 0919-1		**RA**	Regulatory Text
PHARMACODE:		**QA:**	Entire Text
COUNTRY: USA		**PRODUCTION:**	Machine Suitability
LOCATION: GOA		**REMARKS:**	
PACK : LABEL - 100 TABLETS			
ACTUAL SIZE: 105 mm x 30 mm			
SPECIFICATION: A UV VARNISH COATED FASPRINT NG/PERMANENT (HITAC)/ PET 23 STICKER LABEL FROM AVERY DENISON PRINTED AS PER APPROVED ARTWORK. BATCH PRINTING AREA REMAINS UNVARNISHED			

JAR SIZE : 60 CC
SAME SIZE ARTWORK
LABEL SIZE : 105 mm x 45 mm

May Breedlove — Digitally signed by May Breedlove Date: 2019.11.06 10:16:26 -05'00'

Donna-Marie Walters — Digitally signed by Donna-Marie Walters Date: 2019.11.06 10:42:45 -05'00'

Carole Capella — Digitally signed by Carole Capella Date: 2019.11.06 12:55:40 -05'00'

MINIMUM FONT SIZE: 4.5 PT

GLENMARK PHARMACEUTICALS LTD.		**DATE:**	**PANTONE SHADE NO:** BLACK 186 C / 2945 C
PRODUCT NAME: Carvedilol Tablets USP 6.25 mg		**PKG. DEV.:**	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout
ITEM CODE: PE44479 **VERSION:** 0919-1		**RA**	Regulatory Text
PHARMACODE:		**QA:**	Entire Text
COUNTRY: USA		**PRODUCTION:**	Machine Suitability
LOCATION: GOA		**REMARKS:**	
PACK : LABEL - 500 TABLETS			
ACTUAL SIZE: 105 mm x 45 mm			
SPECIFICATION: A UV VARNISH COATED FASPRINT NG/PERMANENT (HITAC)/ PET 23 STICKER LABEL FROM AVERY DENISON PRINTED AS PER APPROVED ARTWORK. BATCH PRINTING AREA REMAINS UNVARNISHED			

JAR SIZE : 150 CC
SAME SIZE ARTWORK
LABEL SIZE : 130 mm x 50 mm

UNVARNISHED AREA
35 mm x 50 mm

NDC 68462-164-05

Carvedilol Tablets, USP

12.5 mg

glenmark

Rx Only **500 Tablets**

Each tablet contains carvedilol USP, 12.5 mg.
Product meets USP Dissolution Test 2.
Usual Dosage: See accompanying prescribing information.
Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in a tight container.
Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.
Manufactured by:
Glenmark Pharmaceuticals Ltd.
Colvale-Bardez, Goa 403513, India
GO/DRUGS/648
Manufactured for:
Glenmark Pharmaceuticals Inc., USA
Mahwah, NJ 07430
09/19

Questions? 1 (888) 721-7115
www.glenmarkpharma-us.com

PE44150919-1

May Breedlove
Digitally signed by May Breedlove
Date: 2019.11.06 10:06:50 -05'00'

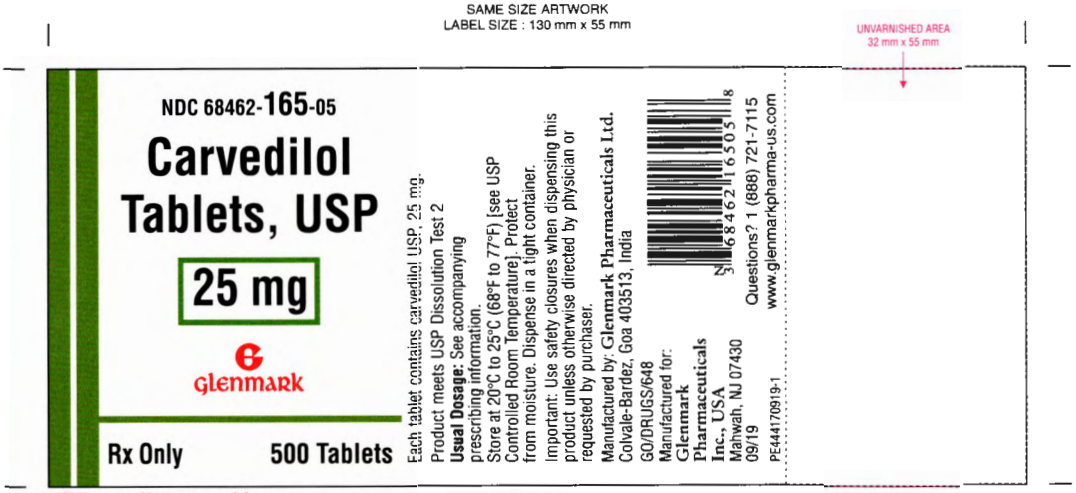
Donna-Marie Walters
Digitally signed by Donna-Marie Walters
Date: 2019.11.06 10:38:21 -05'00'

Carole Capella
Digitally signed by Carole Capella
Date: 2019.11.06 12:54:01 -05'00'

MINIMUM FONT SIZE: 5.1 PT

GLENMARK PHARMACEUTICALS LTD.		**DATE:**	**PANTONE SHADE NO:** BLACK 143 C 186 C
PRODUCT NAME: Carvedilol Tablets USP 12.5 mg		**PKG. DEV.:**	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout
ITEM CODE: PE44415 **VERSION:** 0919-1		**RA**	Regulatory Text
PHARMACODE:		**QA:**	Entire Text
COUNTRY: USA		**PRODUCTION:**	Machine Suitability
LOCATION: GOA		**REMARKS:**	
PACK : LABEL - 500 TABLETS			
ACTUAL SIZE: 130 mm x 50 mm			
SPECIFICATION: A UV VARNISH COATED FASPRINT NG/PERMANENT (HITAC)/ PET 23 STICKER LABEL FROM AVERY DENISON PRINTED AS PER APPROVED ARTWORK. BATCH PRINTING AREA REMAINS UNVARNISHED			

JAR SIZE : 250 CC
SAME SIZE ARTWORK
LABEL SIZE : 130 mm x 55 mm



May Breedlove
Digitally signed by May Breedlove
Date: 2019.11.06 10:07:34 -05'00'

Donna-Marie Walters
Digitally signed by Donna-Marie Walters
Date: 2019.11.06 10:40:24 -05'00'

Carole Capella
Digitally signed by Carole Capella
Date: 2019.11.06 12:54:32 -05'00'

MINIMUM FONT SIZE: 6 PT

GLENMARK PHARMACEUTICALS LTD.			
PRODUCT NAME: Carvedilol Tablets USP 25 mg	**DATE:**	**PANTONE SHAOE NO:** BLACK 364 C, 186 C	
ITEM CODE: PE44417 **VERSION:** 0919-1	**PKG. DEV.:**	Item code, Version, Consistency of Design, overprint area, Pack size, Dimensions & Layout	
PHARMACODE:	**RA**	Regulatory Text	
COUNTRY: USA	**QA:**	Entire Text	
LOCATION: GOA	**PRODUCTION:**	Machine Suitability	
PACK : LABEL - 500 TABLETS	**REMARKS:**		
ACTUAL SIZE: 130 mm x 55 mm			

SPECIFICATION: A UV VARNISH COATED FASPRINT NG/PERMANENT (HITAC)/ PET 23 STICKER LABEL FROM AVERY DENISON PRINTED AS PER APPROVED ARTWORK. BATCH PRINTING AREA REMAINS UNVARNISHED

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

stability resumes *[see Dosage and Administration (2)]*. Occasionally it is necessary to lower the carvedilol dose or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of, or a favorable response to, carvedilol. In a placebo-controlled trial of subjects with severe heart failure, worsening heart failure during the first 3 months was reported to a similar degree with carvedilol and with placebo. When treatment was maintained beyond 3 months, worsening heart failure was reported less frequently in subjects treated with carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patients' underlying disease than to treatment with carvedilol.

5.5 Non-allergic Bronchospasm

Patients with bronchospastic disease (e.g., chronic bronchitis, emphysema) should, in general, not receive β-blockers. Carvedilol may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if carvedilol is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous β-agonists is minimized.

In clinical trials of subjects with heart failure, subjects with bronchospastic disease were enrolled if they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is recommended that carvedilol be used with caution. The dosing recommendations should be followed closely and the dose should be lowered if any evidence of bronchospasm is observed during up-titration.

5.6 Effects on Blood Sugar

Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at any time during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.

In patients with heart failure and diabetes, carvedilol therapy may lead to worsening hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose be monitored when carvedilol dosing is initiated, adjusted, or discontinued. Trials designed to examine the effects of carvedilol on glycemic control in patients with diabetes and heart failure have not been conducted.

In a trial designed to examine the effects of carvedilol on glycemic control in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus, carvedilol had no adverse effect on glycemic control, based on HbA1c measurements *[see Clinical Studies (14.4)]*.

5.7 Peripheral Vascular Disease

β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

5.8 Deterioration of Renal Function

Rarely, use of carvedilol in patients with heart failure has resulted in deterioration of renal function. Patients at risk appear to be those with low blood pressure (systolic blood pressure less than 100 mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients with these risk factors, it is recommended that renal function be monitored during up-titration of carvedilol and the drug discontinued or dosage reduced if worsening of renal function occurs.

5.9 Major Surgery

Chronically administered β-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

5.10 Thyrotoxicosis

β-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

5.11 Pheochromocytoma

In patients with pheochromocytoma, an α-blocking agent should be initiated prior to the use of any β-blocking agent. Although carvedilol has both α- and β-blocking pharmacologic activities, there has been no experience with its use in this condition. Therefore, caution should be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

5.12 Prinzmetal's Variant Angina

Agents with non-selective β-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these patients although the α-blocking activity may prevent such symptoms. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

5.13 Risk of Anaphylactic Reaction

While taking β-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

5.14 Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha-1 blockers (carvedilol is an alpha/beta blocker). This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to the surgical technique, such as utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping alpha-1 blocker therapy prior to cataract surgery.

6 ADVERSE REACTIONS

6.1 Clinical Studies 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Carvedilol has been evaluated for safety in subjects with heart failure (mild, moderate, and severe), in subjects with left ventricular dysfunction following myocardial infarction and in hypertensive subjects The observed adverse event profile was consistent with the pharmacology of the drug and the health only be distinguished for dizziness, which increased in frequency from 2% to 5% as total daily dose increased from 6.25 mg to 50 mg.

Table 2 shows adverse events in U.S. placebo-controlled clinical trials for hypertension that occurred with an incidence of greater than or equal to 1% regardless of causality and that were more frequent in drug-treated subjects than placebo-treated subjects.

Table 2. Adverse Events (%) Occurring in U.S. Placebo-Controlled Hypertension Trials (Incidence ≥ 1%, Regardless of Causality)[a]

Body System/ Adverse Event	Carvedilol (n=1,142)	Placebo (n=462)
Cardiovascular		
Bradycardia	2	—
Postural hypotension	2	—
Peripheral edema	1	—
Central Nervous System		
Dizziness	6	5
Insomnia	2	1
Gastrointestinal		
Diarrhea	2	1
Hematologic		
Thrombocytopenia	1	—
Metabolic		
Hypertriglyceridemia	1	—

[a] Shown are events with rate > 1% rounded to nearest integer.

Dyspnea and fatigue were also reported in these trials, but the rates were equal or greater in subjects who received placebo.

The following adverse events not described above were reported as possibly or probably related to carvedilol in worldwide open or controlled trials with carvedilol in subjects with hypertension or heart failure.

Incidence greater than 0.1% to less than or equal to 1%

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

Gastrointestinal: Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients and 0.4% of heart failure patients were discontinued from therapy because of increases in hepatic enzymes) *[see Adverse Reactions (6.2)]*.

Psychiatric: Nervousness, sleep disorder, aggravated depression, impaired concentration, abnormal thinking, paroniria, emotional lability.

Respiratory System: Asthma *[see Contraindications (4)]*.

Reproductive, male: Decreased libido.

Skin and Appendages: Pruritus, rash erythematous, rash maculopapular, rash psoriaform, photosensitivity reaction.

Special Senses: Tinnitus.

Urinary System: Micturition frequency increased.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypokalemia, hypertriglyceridemia.

Hematologic: Anemia, leukopenia.

The following events were reported in less than or equal to 0.1% of subjects and are potentially important: complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder, convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing, respiratory alkalosis, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

Laboratory Abnormalities

Reversible elevations in serum transaminases (ALT or AST) have been observed during treatment with carvedilol. Rates of transaminase elevations (2 to 3 times the upper limit of normal) observed during controlled clinical trials have generally been similar between subjects treated with carvedilol and those treated with placebo. However, transaminase elevations, confirmed by rechallenge, have been observed with carvedilol. In a long-term, placebo-controlled trial in severe heart failure, subjects treated with carvedilol had lower values for hepatic transaminases than subjects treated with placebo, possibly because improvements in cardiac function induced by carvedilol led to less hepatic congestion and/or improved hepatic blood flow.

Carvedilol has not been associated with clinically significant changes in serum potassium, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. No clinically relevant changes were noted in fasting serum glucose in hypertensive patients; fasting serum glucose was not evaluated in the heart failure clinical trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of carvedilol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders
Aplastic anemia.

Immune System Disorders
Hypersensitivity (e.g., anaphylactic reactions, angioedema, urticaria).

Renal and Urinary Disorders
Urinary incontinence.

Respiratory, Thoracic, and Mediastinal Disorders
Interstitial pneumonitis.

Skin and Subcutaneous Tissue Disorders
Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.

7 DRUG INTERACTIONS

7.1 CYP2D6 Inhibitors and Poor Metabolizers

Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol *[see Clinical Pharmacology (12.3)]*. Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer.

7.2 Hypotensive Agents

Patients taking a β-blocker and a drug that can deplete catecholamines (e.g., reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Concomitant administration of clonidine with a β-blocker may cause hypotension and bradycardia. When concomitant treatment with a β-blocker and clonidine is to be terminated, the β-blocker should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

7.3 Cyclosporine

Modest increases in mean trough cyclosporine concentrations were observed following initiation of carvedilol treatment in 21 renal transplant subjects suffering from chronic vascular rejection. In about 30% of subjects, the dose of cyclosporine had to be reduced in order to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporine was reduced about 20% in these subjects. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

7.4 Digitalis Glycosides

Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore, increased monitoring

PHARMACIST—DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

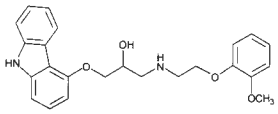
should be given. In the event of seizures, slow IV injection of diazepam is recommended.

NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time consistent with the 7 to 10 hour half-life of carvedilol.

Cases of overdosage with carvedilol alone or in combination with other drugs have been reported. Quantities ingested in some cases exceeded 1,000 milligrams. Symptoms experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

11 DESCRIPTION

Carvedilol, USP is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. Carvedilol, USP is a racemic mixture with the following structure:



Carvedilol tablets, USP are film-coated tablets containing 3.125 mg, 6.25 mg, 12.5 mg or 25 mg of carvedilol. The 3.125 mg, 6.25 mg and 25 mg tablets are white film-coated circular shaped tablets. The 12.5 mg tablets are white film-coated capsule shaped tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, povidone and titanium dioxide.

Carvedilol, USP is a white to off-white powder with a molecular weight of 406.5 g/mol and a molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

The product meets USP Dissolution test 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity.

12.2 Pharmacodynamics

Heart Failure

The basis for the beneficial effects of carvedilol in heart failure is not established.

Two placebo-controlled trials compared the acute hemodynamic effects of carvedilol with baseline measurements in 59 and 49 subjects with NYHA class II-IV heart failure receiving diuretics, ACE inhibitors, and digitalis. There were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial effects on cardiac output, stroke volume index, and systemic vascular resistance were small and variable.

These trials measured hemodynamic effects again at 12 to 14 weeks. Carvedilol significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance, and heart rate, while stroke volume index was increased.

Among 839 subjects with NYHA class II-III heart failure treated for 26 to 52 weeks in 4 U.S. placebo-controlled trials, average left ventricular ejection fraction (EF) measured by radionuclide ventriculography increased by 9 EF units (%) in subjects receiving carvedilol and by 2 EF units in placebo subjects at a target dose of 25 to 50 mg twice daily. The effects of carvedilol on ejection fraction were related to dose. Doses of 6.25 mg twice daily, 12.5 mg twice daily, and 25 mg twice daily were associated with placebo-corrected increases in EF of 5 EF units, 6 EF units, and 8 EF units, respectively; each of these effects were nominally statistically significant.

Left Ventricular Dysfunction following Myocardial Infarction

The basis for the beneficial effects of carvedilol in patients with left ventricular dysfunction following an acute myocardial infarction is not established.

Hypertension

The mechanism by which β-blockade produces an antihypertensive effect has not been established.

β-adrenoreceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac output in normal subjects, (2) reduces exercise and/or isoproterenol-induced tachycardia, and (3) reduces reflex orthostatic tachycardia. Significant β-adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.

α1-adrenoreceptor blocking activity has been demonstrated in human and animal studies, showing that carvedilol (1) attenuates the pressor effects of phenylephrine, (2) causes vasodilation, and (3) reduces peripheral vascular resistance. These effects contribute to the reduction of blood pressure and usually are seen within 30 minutes of drug administration.

Due to the α1-receptor blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (1.8%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when carvedilol is administered with food at the recommended starting dose and titration increments are closely followed *[see Dosage and Administration (2)]*.

In hypertensive patients with normal renal function, therapeutic doses of carvedilol decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma flow. Changes in excretion of sodium, potassium, uric acid, and phosphorus in hypertensive patients with normal renal function were similar after carvedilol and placebo.

Carvedilol has little effect on plasma catecholamines, plasma aldosterone, or electrolyte levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

12.3 Pharmacokinetics

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking carvedilol with food should minimize the risk of orthostatic hypotension.

Carvedilol is extensively metabolized. Following oral administration of radiolabeled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade.

Compared with carvedilol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared with extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to

these 4 U.S. trials, mortality was reduced, nominally significantly so in 2 trials.

The COMET Trial

In this double-blind trial, 3,029 subjects with NYHA class II-IV heart failure (left ventricular ejection fraction less than or equal to 35%) were randomized to receive either carvedilol (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg twice daily). The mean age of the subjects was approximately 62 years, 80% were males, and the mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the subjects had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was 42 mg per day.

The trial had 2 primary end points: all-cause mortality and the composite of death plus hospitalization for any reason. The results of COMET are presented in Table 3 below. All-cause mortality carried most of the statistical weight and was the primary determinant of the trial size. All-cause mortality was 34% in the subjects treated with carvedilol and was 40% in the immediate-release metoprolol group (P = 0.0017; hazard ratio = 0.83, 95% CI 0.74 to 0.93). The effect on mortality was primarily due to a reduction in cardiovascular death. The difference between the 2 groups with respect to the composite end point was not significant (P = 0.122). The estimated mean survival was 8 years with carvedilol and 6.6 years with immediate-release metoprolol.

Table 3. Results of COMET

End Point	Carvedilol N=1,511	Metoprolol N=1,518	Hazard Ratio	(95% CI)
All-cause mortality	34%	40%	0.83	0.74-0.93
Mortality + all hospitalization	74%	76%	0.94	0.86-1.02
Cardiovascular death	30%	35%	0.80	0.70-0.90
Sudden death	14%	17%	0.81	0.68-0.97
Death due to circulatory failure	11%	13%	0.83	0.67-1.02
Death due to stroke	0.9%	2.5%	0.33	0.18-0.62

It is not known whether this formulation of metoprolol at any dose or this low dose of metoprolol in any formulation has any effect on survival or hospitalization in patients with heart failure. Thus, this trial extends the time over which carvedilol manifests benefits on survival in heart failure, but it is not evidence that carvedilol improves outcome over the formulation of metoprolol (TOPROL-XL) with benefits in heart failure.

Severe Heart Failure (COPERNICUS):

In a double-blind trial (COPERNICUS), 2,289 subjects with heart failure at rest or with minimal exertion and left ventricular ejection fraction less than 25% (mean 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%), were randomized to placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg twice daily to the maximum tolerated dose or up to 25 mg twice daily over a minimum of 6 weeks. Most subjects achieved the target dose of 25 mg. The trial was conducted in Eastern and Western Europe, the United States, Israel, and Canada. Similar numbers of subjects per group (about 100) withdrew during the titration period.

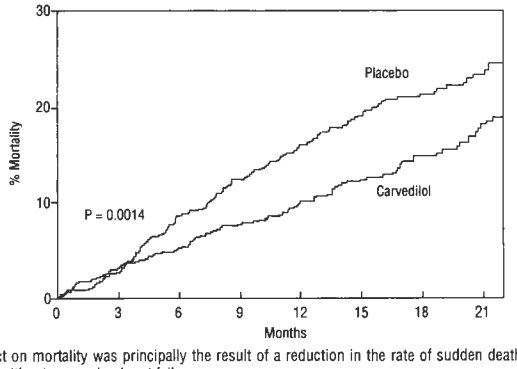
The primary end point of the trial was all-cause mortality, but cause-specific mortality and the risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were also examined. The developing trial data were followed by a data monitoring committee, and mortality analyses were adjusted for these multiple looks. The trial was stopped after a median follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per patient year on placebo to 12.8% on carvedilol; hazard ratio 0.65, 95% CI 0.52 to 0.81, $P = 0.0014$, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 4.

Table 4. Results of COPERNICUS Trial in Subjects with Severe Heart Failure

End Point	Placebo (n=1,133)	Carvedilol (n=1,156)	Hazard Ratio (95% CI)	% Reduction	Nominal *P* value
Mortality	190	130	0.65 (0.52-0.81)	35	0.00013
Mortality + all hospitalization	507	425	0.76 (0.67-0.87)	24	0.00004
Mortality + CV hospitalization	395	314	0.73 (0.63-0.84)	27	0.00002
Mortality + HF hospitalization	357	271	0.69 (0.59-0.81)	31	0.000004

Cardiovascular = CV; Heart failure = HF.

Figure 1. Survival Analysis for COPERNICUS (Intent-to-Treat)



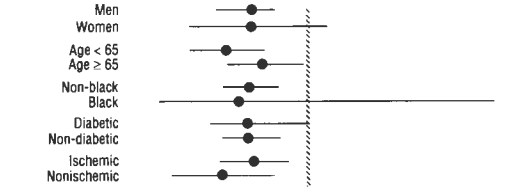
The effect on mortality was principally the result of a reduction in the rate of sudden death among subjects without worsening heart failure.

Patients' global assessments, in which carvedilol-treated subjects were compared with placebo, were based on pre-specified, periodic patient self-assessments regarding whether clinical status post-treatment showed improvement, worsening, or no change compared with baseline. Subjects treated with carvedilol showed significant improvements in global assessments compared with those treated with placebo in COPERNICUS.

The protocol also specified that hospitalizations would be assessed. Fewer subjects on carvedilol than on placebo were hospitalized for any reason (372 versus 432, $P = 0.0029$), for cardiovascular reasons (246 versus 314, $P = 0.0003$), or for worsening heart failure (198 versus 268, $P = 0.0001$).

Carvedilol had a consistent and beneficial effect on all-cause mortality as well as the combined end points of all-cause mortality plus hospitalization (total, CV, or for heart failure) in the overall trial population and in all subgroups examined, including men and women, elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see Figure 2).

Figure 2. Effects on Mortality for Subgroups in COPERNICUS



100's: NDC 68462-16
180's: NDC 68462-165
500's: NDC 68462-165
1000's: NDC 68462-16

Store at 20°C to 25°C (68°F t
Dispense in a tight container

17 PATIENT COUNSELIN

Advise the patient to read th

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- If experiencing dizzine
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- Inform patients or care who are fasting or whc hypoglycemia *[see Wa*
- Contact lens wearers n

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Glenmark Pharmaceut
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Questions? 1 (888) 721-711
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August 2023

Read the Patient Information you get a refill. There may be your doctor about your medic tablets, ask your doctor or pl

What are Carvedilol Tablets

Carvedilol tablets are a pres blockers". Carvedilol tablets

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Do not take carvedilol tablets

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What should I tell my docto

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- have thyroid problems
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What should I avoid while t

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- **Slow heartbeat.**
- **Changes in your blood in your blood sugar le**
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PHARMACIST—DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

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

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stability resumes *[see Dosage and Administration (2)]*. Occasionally it is necessary to lower the carvedilol dose or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of, or a favorable response to, carvedilol. In a placebo-controlled trial of subjects with severe heart failure, worsening heart failure during the first 3 months was reported to a similar degree with carvedilol and with placebo. When treatment was maintained beyond 3 months, worsening heart failure was reported less frequently in subjects treated with carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patients' underlying disease than to treatment with carvedilol.

5.5 Non-allergic Bronchospasm

Patients with bronchospastic disease (e.g., chronic bronchitis, emphysema) should, in general, not receive β-blockers. Carvedilol may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if carvedilol is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous β-agonists is minimized.

In clinical trials of subjects with heart failure, subjects with bronchospastic disease were enrolled if they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is recommended that carvedilol be used with caution. The dosing recommendations should be followed closely and the dose should be lowered if any evidence of bronchospasm is observed during up-titration.

5.6 Effects on Blood Sugar

Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at any time during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.

In patients with heart failure and diabetes, carvedilol therapy may lead to worsening hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose be monitored when carvedilol dosing is initiated, adjusted, or discontinued. Trials designed to examine the effects of carvedilol on glycemic control in patients with diabetes and heart failure have not been conducted.

In a trial designed to examine the effects of carvedilol on glycemic control in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus, carvedilol had no adverse effect on glycemic control, based on HbA1c measurements *[see Clinical Studies (14.4)]*.

5.7 Peripheral Vascular Disease

β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

5.8 Deterioration of Renal Function

Rarely, use of carvedilol in patients with heart failure has resulted in deterioration of renal function. Patients at risk appear to be those with low blood pressure (systolic blood pressure less than 100 mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients with these risk factors, it is recommended that renal function be monitored during up-titration of carvedilol and the drug discontinued or dosage reduced if worsening of renal function occurs.

5.9 Major Surgery

Chronically administered β-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

5.10 Thyrotoxicosis

β-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

5.11 Pheochromocytoma

In patients with pheochromocytoma, an α-blocking agent should be initiated prior to the use of any β-blocking agent. Although carvedilol has both α- and β-blocking pharmacologic activities, there has been no experience with its use in this condition. Therefore, caution should be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

5.12 Prinzmetal's Variant Angina

Agents with non-selective β-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these patients although the α-blocking activity may prevent such symptoms. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

5.13 Risk of Anaphylactic Reaction

While taking β-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

5.14 Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha-1 blockers (carvedilol is an alpha/beta blocker). This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to the surgical technique, such as utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping alpha-1 blocker therapy prior to cataract surgery.

6 ADVERSE REACTIONS

6.1 Clinical Studies 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Carvedilol has been evaluated for safety in subjects with heart failure (mild, moderate, and severe), in subjects with left ventricular dysfunction following myocardial infarction and in hypertensive subjects The observed adverse event profile was consistent with the pharmacology of the drug and the health only be distinguished for dizziness, which increased in frequency from 2% to 5% as total daily dose increased from 6.25 mg to 50 mg.

Table 2 shows adverse events in U.S. placebo-controlled clinical trials for hypertension that occurred with an incidence of greater than or equal to 1% regardless of causality and that were more frequent in drug-treated subjects than placebo-treated subjects.

Table 2. Adverse Events (%) Occurring in U.S. Placebo-Controlled Hypertension Trials (Incidence ≥ 1%, Regardless of Causality)[a]

Body System/ Adverse Event	Carvedilol (n=1,142)	Placebo (n=462)
Cardiovascular		
Bradycardia	2	—
Postural hypotension	2	—
Peripheral edema	1	—
Central Nervous System		
Dizziness	6	5
Insomnia	2	1
Gastrointestinal		
Diarrhea	2	1
Hematologic		
Thrombocytopenia	1	—
Metabolic		
Hypertriglyceridemia	1	—

[a] Shown are events with rate > 1% rounded to nearest integer.

Dyspnea and fatigue were also reported in these trials, but the rates were equal or greater in subjects who received placebo.

The following adverse events not described above were reported as possibly or probably related to carvedilol in worldwide open or controlled trials with carvedilol in subjects with hypertension or heart failure.

Incidence greater than 0.1% to less than or equal to 1%

Cardiovascular: Peripheral ischemia, tachycardia.

Central and Peripheral Nervous System: Hypokinesia.

Gastrointestinal: Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients and 0.4% of heart failure patients were discontinued from therapy because of increases in hepatic enzymes) *[see Adverse Reactions (6.2)]*.

Psychiatric: Nervousness, sleep disorder, aggravated depression, impaired concentration, abnormal thinking, paroniria, emotional lability.

Respiratory System: Asthma *[see Contraindications (4)]*.

Reproductive, male: Decreased libido.

Skin and Appendages: Pruritus, rash erythematous, rash maculopapular, rash psoriaform, photosensitivity reaction.

Special Senses: Tinnitus.

Urinary System: Micturition frequency increased.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypokalemia, hypertriglyceridemia.

Hematologic: Anemia, leukopenia.

The following events were reported in less than or equal to 0.1% of subjects and are potentially important: complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder, convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing, respiratory alkalosis, increased BUN, decreased HDL, pancytopenia, and atypical lymphocytes.

Laboratory Abnormalities

Reversible elevations in serum transaminases (ALT or AST) have been observed during treatment with carvedilol. Rates of transaminase elevations (2 to 3 times the upper limit of normal) observed during controlled clinical trials have generally been similar between subjects treated with carvedilol and those treated with placebo. However, transaminase elevations, confirmed by rechallenge, have been observed with carvedilol. In a long-term, placebo-controlled trial in severe heart failure, subjects treated with carvedilol had lower values for hepatic transaminases than subjects treated with placebo, possibly because improvements in cardiac function induced by carvedilol led to less hepatic congestion and/or improved hepatic blood flow.

Carvedilol has not been associated with clinically significant changes in serum potassium, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. No clinically relevant changes were noted in fasting serum glucose in hypertensive patients; fasting serum glucose was not evaluated in the heart failure clinical trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of carvedilol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders
Aplastic anemia.

Immune System Disorders
Hypersensitivity (e.g., anaphylactic reactions, angioedema, urticaria).

Renal and Urinary Disorders
Urinary incontinence.

Respiratory, Thoracic, and Mediastinal Disorders
Interstitial pneumonitis.

Skin and Subcutaneous Tissue Disorders
Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.

7 DRUG INTERACTIONS

7.1 CYP2D6 Inhibitors and Poor Metabolizers

Interactions of carvedilol with potent inhibitors of CYP2D6 isoenzyme (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol *[see Clinical Pharmacology (12.3)]*. Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer.

7.2 Hypotensive Agents

Patients taking a β-blocker and a drug that can deplete catecholamines (e.g., reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Concomitant administration of clonidine with a β-blocker may cause hypotension and bradycardia. When concomitant treatment with a β-blocker and clonidine is to be terminated, the β-blocker should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

7.3 Cyclosporine

Modest increases in mean trough cyclosporine concentrations were observed following initiation of carvedilol treatment in 21 renal transplant subjects suffering from chronic vascular rejection. In about 30% of subjects, the dose of cyclosporine had to be reduced in order to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporine was reduced about 20% in these subjects. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

7.4 Digitalis Glycosides

Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore, increased monitoring

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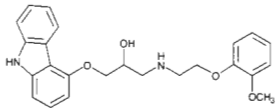
should be given. In the event of seizures, slow IV injection of diazepam or clonazepam is recommended.

NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time consistent with the 7 to 10 hour half-life of carvedilol.

Cases of overdosage with carvedilol alone or in combination with other drugs have been reported. Quantities ingested in some cases exceeded 1,000 milligrams. Symptoms experienced included low blood pressure and heart rate. Standard supportive treatment was provided and individuals recovered.

11 DESCRIPTION

Carvedilol, USP is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. Carvedilol, USP is a racemic mixture with the following structure:



Carvedilol tablets, USP are film-coated tablets containing 3.125 mg, 6.25 mg, 12.5 mg or 25 mg of carvedilol. The 3.125 mg, 6.25 mg and 25 mg tablets are white film-coated circular shaped tablets. The 12.5 mg tablets are white film-coated capsule shaped tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, povidone and titanium dioxide.

Carvedilol, USP is a white to off-white powder with a molecular weight of 406.5 g/mol and a molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

The product meets USP Dissolution test 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity.

12.2 Pharmacodynamics

Heart Failure

The basis for the beneficial effects of carvedilol in heart failure is not established.

Two placebo-controlled trials compared the acute hemodynamic effects of carvedilol with baseline measurements in 59 and 49 subjects with NYHA class II-IV heart failure receiving diuretics, ACE inhibitors, and digitalis. There were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial effects on cardiac output, stroke volume index, and systemic vascular resistance were small and variable.

These trials measured hemodynamic effects again at 12 to 14 weeks. Carvedilol significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance, and heart rate, while stroke volume index was increased.

Among 839 subjects with NYHA class II-III heart failure treated for 26 to 52 weeks in 4 U.S. placebo-controlled trials, average left ventricular ejection fraction (EF) measured by radionuclide ventriculography increased by 9 EF units (%) in subjects receiving carvedilol and by 2 EF units in placebo subjects at a target dose of 25 to 50 mg twice daily. The effects of carvedilol on ejection fraction were related to dose. Doses of 6.25 mg twice daily, 12.5 mg twice daily, and 25 mg twice daily were associated with placebo-corrected increases in EF of 5 EF units, 6 EF units, and 8 EF units, respectively; each of these effects were nominally statistically significant.

Left Ventricular Dysfunction following Myocardial Infarction

The basis for the beneficial effects of carvedilol in patients with left ventricular dysfunction following an acute myocardial infarction is not established.

Hypertension

The mechanism by which β-blockade produces an antihypertensive effect has not been established.

β-adrenoreceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac output in normal subjects, (2) reduces exercise and/or isoproterenol-induced tachycardia, and (3) reduces reflex orthostatic tachycardia. Significant β-adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.

α1-adrenoreceptor blocking activity has been demonstrated in human and animal studies, showing that carvedilol (1) attenuates the pressor effects of phenylephrine, (2) causes vasodilation, and (3) reduces peripheral vascular resistance. These effects contribute to the reduction of blood pressure and usually are seen within 30 minutes of drug administration.

Due to the α1-receptor blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (1.8%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when carvedilol is administered with food at the recommended starting dose and titration increments are closely followed *[see Dosage and Administration (2)]*.

In hypertensive patients with normal renal function, therapeutic doses of carvedilol decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma flow. Changes in excretion of sodium, potassium, uric acid, and phosphorus in hypertensive patients with normal renal function were similar after carvedilol and placebo.

Carvedilol has little effect on plasma catecholamines, plasma aldosterone, or electrolyte levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

12.3 Pharmacokinetics

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking carvedilol with food should minimize the risk of orthostatic hypotension.

Carvedilol is extensively metabolized. Following oral administration of radiolabeled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade.

Compared with carvedilol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared with extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to

these 4 U.S. trials, mortality was reduced, nominally significantly so in 2 trials.

The COMET Trial

In this double-blind trial, 3,029 subjects with NYHA class II-IV heart failure (left ventricular ejection fraction less than or equal to 35%) were randomized to receive either carvedilol (target dose: 25 mg twice daily) or immediate-release metoprolol tartrate (target dose: 50 mg twice daily). The mean age of the subjects was approximately 62 years, 80% were males, and the mean left ventricular ejection fraction at baseline was 26%. Approximately 96% of the subjects had NYHA class II or III heart failure. Concomitant treatment included diuretics (99%), ACE inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering agents (21%). The mean duration of follow-up was 4.8 years. The mean dose of carvedilol was 42 mg per day.

The trial had 2 primary end points: all-cause mortality and the composite of death plus hospitalization for any reason. The results of COMET are presented in Table 3 below. All-cause mortality carried most of the statistical weight and was the primary determinant of the trial size. All-cause mortality was 34% in the subjects treated with carvedilol and was 40% in the immediate-release metoprolol group (P = 0.0017; hazard ratio = 0.83, 95% CI 0.74 to 0.93). The effect on mortality was primarily due to a reduction in cardiovascular death. The difference between the 2 groups with respect to the composite end point was not significant (P = 0.122). The estimated mean survival was 8 years with carvedilol and 6.6 years with immediate-release metoprolol.

Table 3. Results of COMET

End Point	Carvedilol N=1,511	Metoprolol N=1,518	Hazard Ratio	(95% CI)
All-cause mortality	34%	40%	0.83	0.74-0.93
Mortality + all hospitalization	74%	76%	0.94	0.86-1.02
Cardiovascular death	30%	35%	0.80	0.70-0.90
Sudden death	14%	17%	0.81	0.68-0.97
Death due to circulatory failure	11%	13%	0.83	0.67-1.02
Death due to stroke	0.9%	2.5%	0.33	0.18-0.62

It is not known whether this formulation of metoprolol at any dose or this low dose of metoprolol in any formulation has any effect on survival or hospitalization in patients with heart failure. Thus, this trial extends the time over which carvedilol manifests benefits on survival in heart failure, but it is not evidence that carvedilol improves outcome over the formulation of metoprolol (TOPROL-XL) with benefits in heart failure.

Severe Heart Failure (COPERNICUS):

In a double-blind trial (COPERNICUS), 2,289 subjects with heart failure at rest or with minimal exertion and left ventricular ejection fraction less than 25% (mean 20%), despite digitalis (66%), diuretics (99%), and ACE inhibitors (89%), were randomized to placebo or carvedilol. Carvedilol was titrated from a starting dose of 3.125 mg twice daily to the maximum tolerated dose or up to 25 mg twice daily over a minimum of 6 weeks. Most subjects achieved the target dose of 25 mg. The trial was conducted in Eastern and Western Europe, the United States, Israel, and Canada. Similar numbers of subjects per group (about 100) withdrew during the titration period.

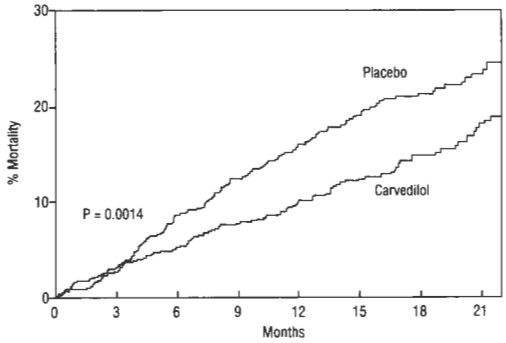
The primary end point of the trial was all-cause mortality, but cause-specific mortality and the risk of death or hospitalization (total, cardiovascular [CV], or heart failure [HF]) were also examined. The developing trial data were followed by a data monitoring committee, and mortality analyses were adjusted for these multiple looks. The trial was stopped after a median follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per patient year on placebo to 12.8% on carvedilol; hazard ratio 0.65, 95% CI 0.52 to 0.81, $P = 0.0014$, adjusted) (see Figure 1). The results of COPERNICUS are shown in Table 4.

Table 4. Results of COPERNICUS Trial in Subjects with Severe Heart Failure

End Point	Placebo (n=1,133)	Carvedilol (n=1,156)	Hazard Ratio (95% CI)	% Reduction	Nominal *P* value
Mortality	190	130	0.65 (0.52-0.81)	35	0.00013
Mortality + all hospitalization	507	425	0.76 (0.67-0.87)	24	0.00004
Mortality + CV hospitalization	395	314	0.73 (0.63-0.84)	27	0.00002
Mortality + HF hospitalization	357	271	0.69 (0.59-0.81)	31	0.000004

Cardiovascular = CV; Heart failure = HF.

Figure 1. Survival Analysis for COPERNICUS (Intent-to-Treat)



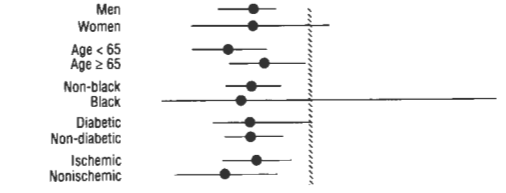
The effect on mortality was principally the result of a reduction in the rate of sudden death among subjects without worsening heart failure.

Patients' global assessments, in which carvedilol-treated subjects were compared with placebo, were based on pre-specified, periodic patient self-assessments regarding whether clinical status post-treatment showed improvement, worsening, or no change compared with baseline. Subjects treated with carvedilol showed significant improvements in global assessments compared with those treated with placebo in COPERNICUS.

The protocol also specified that hospitalizations would be assessed. Fewer subjects on carvedilol than on placebo were hospitalized for any reason (372 versus 432, $P = 0.0029$), for cardiovascular reasons (246 versus 314, $P = 0.0003$), or for worsening heart failure (198 versus 268, $P = 0.0001$).

Carvedilol had a consistent and beneficial effect on all-cause mortality as well as the combined end points of all-cause mortality plus hospitalization (total, CV, or for heart failure) in the overall trial population and in all subgroups examined, including men and women, elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics (see Figure 2).

Figure 2. Effects on Mortality for Subgroups in COPERNICUS



180's: NDC 68462-165-
500's: NDC 68462-165-
1000's: NDC 68462-165

Store at 20°C to 25°C (68°F to
Dispense in a tight container.

17 PATIENT COUNSELING

Advise the patient to read the

Patients taking carvedilol shou

- Patients should take car
- Patients should not inte
- Patients with heart failu of worsening heart failu
- Patients may experience fainting. Patients should
- If experiencing dizziness
- Patients should consult should be adjusted.
- Inform patients or careg who are fasting or who a hypoglycemia *[see War*
- Contact lens wearers ma

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August 2023

Read the Patient Information tl
you get a refill. There may be n
your doctor about your medica
tablets, ask your doctor or ph

What are Carvedilol Tablets?

Carvedilol tablets are a presc
blockers". Carvedilol tablets a

- to treat patients with cer
- to treat patients who ha
- to treat patients with hig

Carvedilol tablets are not appr

Who should not take Carvedi

Do not take carvedilol tablets i

- have severe heart failu intravenous medication
- are prone to asthma or
- have a slow heartbeat o
- have liver problems.
- are allergic to any of the the end of this leaflet fo

What should I tell my doctor

Tell your doctor about all of yo

- have asthma or other lu
- have problems with blo tablets can make some
- have diabetes.
- have thyroid problems.
- have a condition called
- have had severe allergic
- are pregnant or trying to baby. You and your doc during pregnancy.
- are breastfeeding. It is n about the best way to fe
- are scheduled for surge
- are scheduled for catara
- are taking prescription Carvedilol and certain c Carvedilol may affect the carvedilol works.

Keep a list of all the medicine start a new medicine.

How should I take Carvedilol

It is important for you to take carvedilol tablets suddenly, y that you should stop taking ca of time before stopping it cor

- Take carvedilol tablets e and how often. In order dose and then slowly in
- **Do not stop taking carv take without talking to**
- Tell your doctor if you g
- Take carvedilol tablets w
- If you miss a dose of ca time to take your next d same time.
- If you take too many ca

What should I avoid while tal

- Carvedilol tablets can ca or do anything that neec

What are possible side effect

- **Low blood pressure (w** happen, sit or lie down
- **Tiredness.** If you feel ti needs you to be alert.
- **Slow heartbeat.**
- **Changes in your blood in your blood sugar lev**
- Carvedilol tablets may hi
- Carvedilol tablets may n

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Glenmark Pharmaceuticals Inc.

RECALL RETURN RESPONSE FORM

CARVEDILOL TABLETS USP 3.125mg, 6.25mg, 12.5mg, and 25mg
100s and 500s Container pack (Tablets)
NDC 68462-162-01, 68462-162-05, 68462-163-01, 68462-163-05, 68462-164-05, 68462-165-05 Retail Level
02/28/2025

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

Customer Name:	DEA#:

DEA # is required, if it is not provided, the processing of your form will be delayed.

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_____

Carvedilol Tablets USP 3.125mg (100's Tablets)

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
1	Carvedilol Tablets USP 3.125mg	68462-162-01	19231450	100's Tablets in Container	Mar-25	

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
2	Carvedilol Tablets USP 3.125mg	68462-162-01	19233345	100's Tablets in Container	Jul-25	
3	Carvedilol Tablets USP 3.125mg	68462-162-01	19234275	100's Tablets in Container	Sep-25	
4	Carvedilol Tablets USP 3.125mg	68462-162-01	19240280	100's Tablets in Container	Dec-25	

Carvedilol Tablets USP 3.125mg (500's Tablets)

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
1	Carvedilol Tablets USP 3.125mg	68462-162-05	19231450	500's Tablets in Container	Mar-25	
2	Carvedilol Tablets USP 3.125mg	68462-162-05	19231464	500's Tablets in Container	Mar-25	
3	Carvedilol Tablets USP 3.125mg	68462-162-05	19231471	500's Tablets in Container	Mar-25	
4	Carvedilol Tablets USP 3.125mg	68462-162-05	19231493	500's Tablets in Container	Mar-25	
5	Carvedilol Tablets USP 3.125mg	68462-162-05	19232083	500's Tablets in Container	Apr-25	
6	Carvedilol Tablets USP 3.125mg	68462-162-05	19232103	500's Tablets in Container	Apr-25	
7	Carvedilol Tablets USP 3.125mg	68462-162-05	19232658	500's Tablets in Container	Jun-25	
8	Carvedilol Tablets USP 3.125mg	68462-162-05	19233328	500's Tablets in Container	Jul-25	
9	Carvedilol Tablets USP 3.125mg	68462-162-05	19233343	500's Tablets in Container	Jul-25	
10	Carvedilol Tablets USP 3.125mg	68462-162-05	19233344	500's Tablets in Container	Jul-25	
11	Carvedilol Tablets USP 3.125mg	68462-162-05	19233345	500's Tablets in Container	Jul-25	
12	Carvedilol Tablets USP 3.125mg	68462-162-05	19234275	500's Tablets in Container	Sep-25	
13	Carvedilol Tablets USP 3.125mg	68462-162-05	19240280	500's Tablets in Container	Dec-25	
14	Carvedilol Tablets USP 3.125mg	68462-162-05	19234843	500's Tablets in Container	Nov-25	
15	Carvedilol Tablets USP 3.125mg	68462-162-05	19235039	500's Tablets in Container	Nov-25	

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
16	Carvedilol Tablets USP 3.125mg	68462-162-05	19240296	500's Tablets in Container	Dec-25	

Carvedilol Tablets USP 6.25mg (100's Tablets)

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
1	Carvedilol Tablets USP 6.25mg	68462-163-01	19231618	100's Tablets in Container	Mar-25	
2	Carvedilol Tablets USP 6.25mg	68462-163-01	19232064	100's Tablets in Container	Apr-25	
3	Carvedilol Tablets USP 6.25mg	68462-163-01	19232324	100's Tablets in Container	May-25	
4	Carvedilol Tablets USP 6.25mg	68462-163-01	19233369	100's Tablets in Container	Jul-25	
5	Carvedilol Tablets USP 6.25mg	68462-163-01	19234162	100's Tablets in Container	Sep-25	
6	Carvedilol Tablets USP 6.25mg	68462-163-01	19240543	100's Tablets in Container	Jan-26	

Carvedilol Tablets USP 6.25mg (500's Tablets)

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
1	Carvedilol Tablets USP 6.25mg	68462-163-05	19231174	500's Tablets in Container	Feb-25	
2	Carvedilol Tablets USP 6.25mg	68462-163-05	19231199	500's Tablets in Container	Feb-25	
3	Carvedilol Tablets USP 6.25mg	68462-163-05	19231517	500's Tablets in Container	Mar-25	
4	Carvedilol Tablets USP 6.25mg	68462-163-05	19231527	500's Tablets in Container	Mar-25	
5	Carvedilol Tablets USP 6.25mg	68462-163-05	19231566	500's Tablets in Container	Mar-25	
6	Carvedilol Tablets USP 6.25mg	68462-163-05	19231568	500's Tablets in Container	Mar-25	
7	Carvedilol Tablets USP 6.25mg	68462-163-05	19231595	500's Tablets in Container	Mar-25	
8	Carvedilol Tablets USP 6.25mg	68462-163-05	19231618	500's Tablets in Container	Mar-25	
9	Carvedilol Tablets USP 6.25mg	68462-163-05	19231634	500's Tablets in Container	Mar-25	

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
10	Carvedilol Tablets USP 6.25mg	68462-163-05	19231638	500's Tablets in Container	Mar-25	
11	Carvedilol Tablets USP 6.25mg	68462-163-05	19232043	500's Tablets in Container	Apr-25	
12	Carvedilol Tablets USP 6.25mg	68462-163-05	19232051	500's Tablets in Container	Apr-25	
13	Carvedilol Tablets USP 6.25mg	68462-163-05	19232064	500's Tablets in Container	Apr-25	
14	Carvedilol Tablets USP 6.25mg	68462-163-05	19232322	500's Tablets in Container	May-25	
15	Carvedilol Tablets USP 6.25mg	68462-163-05	19232324	500's Tablets in Container	May-25	
16	Carvedilol Tablets USP 6.25mg	68462-163-05	19232365	500's Tablets in Container	May-25	
17	Carvedilol Tablets USP 6.25mg	68462-163-05	19232380	500's Tablets in Container	May-25	
18	Carvedilol Tablets USP 6.25mg	68462-163-05	19232389	500's Tablets in Container	May-25	
19	Carvedilol Tablets USP 6.25mg	68462-163-05	19232736	500's Tablets in Container	Jun-25	
20	Carvedilol Tablets USP 6.25mg	68462-163-05	19232743	500's Tablets in Container	Jun-25	
21	Carvedilol Tablets USP 6.25mg	68462-163-05	19232746	500's Tablets in Container	Jun-25	
22	Carvedilol Tablets USP 6.25mg	68462-163-05	19232756	500's Tablets in Container	Jun-25	
23	Carvedilol Tablets USP 6.25mg	68462-163-05	19232757	500's Tablets in Container	Jun-25	
24	Carvedilol Tablets USP 6.25mg	68462-163-05	19233369	500's Tablets in Container	Jul-25	
25	Carvedilol Tablets USP 6.25mg	68462-163-05	19233371	500's Tablets in Container	Jul-25	
26	Carvedilol Tablets USP 6.25mg	68462-163-05	19233405	500's Tablets in Container	Jul-25	
27	Carvedilol Tablets USP 6.25mg	68462-163-05	19233416	500's Tablets in Container	Jul-25	
28	Carvedilol Tablets USP 6.25mg	68462-163-05	19234162	500's Tablets in Container	Sep-25	
29	Carvedilol Tablets USP 6.25mg	68462-163-05	19234183	500's Tablets in Container	Sep-25	
30	Carvedilol Tablets USP 6.25mg	68462-163-05	19234192	500's Tablets in Container	Sep-25	

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
31	Carvedilol Tablets USP 6.25mg	68462-163-05	19234204	500's Tablets in Container	Sep-25	
32	Carvedilol Tablets USP 6.25mg	68462-163-05	19234223	500's Tablets in Container	Sep-25	
33	Carvedilol Tablets USP 6.25mg	68462-163-05	19234243	500's Tablets in Container	Sep-25	
34	Carvedilol Tablets USP 6.25mg	68462-163-05	19234263	500's Tablets in Container	Sep-25	
35	Carvedilol Tablets USP 6.25mg	68462-163-05	19240223	500's Tablets in Container	Dec-25	
36	Carvedilol Tablets USP 6.25mg	68462-163-05	19240543	500's Tablets in Container	Jan-26	
37	Carvedilol Tablets USP 6.25mg	68462-163-05	19231448	500's Tablets in Container	Mar-25	
38	Carvedilol Tablets USP 6.25mg	68462-163-05	19231164	500's Tablets in Container	Feb-25	
39	Carvedilol Tablets USP 6.25mg	68462-163-05	19234165	500's Tablets in Container	Sep-25	
40	Carvedilol Tablets USP 6.25mg	68462-163-05	19234242	500's Tablets in Container	Sep-25	
41	Carvedilol Tablets USP 6.25mg	68462-163-05	19234743	500's Tablets in Container	Nov-25	
42	Carvedilol Tablets USP 6.25mg	68462-163-05	19234774	500's Tablets in Container	Nov-25	
43	Carvedilol Tablets USP 6.25mg	68462-163-05	19234993	500's Tablets in Container	Nov-25	
44	Carvedilol Tablets USP 6.25mg	68462-163-05	19240203	500's Tablets in Container	Dec-25	
45	Carvedilol Tablets USP 6.25mg	68462-163-05	19240211	500's Tablets in Container	Dec-25	
46	Carvedilol Tablets USP 6.25mg	68462-163-05	19240214	500's Tablets in Container	Dec-25	
47	Carvedilol Tablets USP 6.25mg	68462-163-05	19240247	500's Tablets in Container	Dec-25	
48	Carvedilol Tablets USP 6.25mg	68462-163-05	19240249	500's Tablets in Container	Dec-25	
49	Carvedilol Tablets USP 6.25mg	68462-163-05	19240272	500's Tablets in Container	Dec-25	
50	Carvedilol Tablets USP 6.25mg	68462-163-05	19240319	500's Tablets in Container	Dec-25	

Carvedilol Tablets USP 12.5mg (500's Tablets

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
1	Carvedilol Tablets USP 12.5mg	68462-164-05	19231899	500's Tablets in Container	Apr-25	
2	Carvedilol Tablets USP 12.5mg	68462-164-05	19231922	500's Tablets in Container	Apr-25	
3	Carvedilol Tablets USP 12.5mg	68462-164-05	19231927	500's Tablets in Container	Apr-25	
4	Carvedilol Tablets USP 12.5mg	68462-164-05	19231967	500's Tablets in Container	Apr-25	
5	Carvedilol Tablets USP 12.5mg	68462-164-05	19231979	500's Tablets in Container	Apr-25	
6	Carvedilol Tablets USP 12.5mg	68462-164-05	19232226	500's Tablets in Container	May-25	
7	Carvedilol Tablets USP 12.5mg	68462-164-05	19232234	500's Tablets in Container	May-25	
8	Carvedilol Tablets USP 12.5mg	68462-164-05	19232265	500's Tablets in Container	May-25	
9	Carvedilol Tablets USP 12.5mg	68462-164-05	19232271	500's Tablets in Container	May-25	
10	Carvedilol Tablets USP 12.5mg	68462-164-05	19232758	500's Tablets in Container	Jun-25	
11	Carvedilol Tablets USP 12.5mg	68462-164-05	19232759	500's Tablets in Container	Jun-25	
12	Carvedilol Tablets USP 12.5mg	68462-164-05	19232762	500's Tablets in Container	Jun-25	
13	Carvedilol Tablets USP 12.5mg	68462-164-05	19232788	500's Tablets in Container	Jun-25	

Carvedilol Tablets USP 25mg (500's Tablets)

Sr. No.	Product Name	NDC Code	Batch Number	Pack Size	Expiry Date	Total Full/ Sealed and Partial/ Open Bottle Count
1	Carvedilol Tablets USP 25mg	68462-165-05	19231107	500's Tablets in Container	Feb-25	
2	Carvedilol Tablets USP 25mg	68462-165-05	19231114	500's Tablets in Container	Feb-25	
3	Carvedilol Tablets USP 25mg	68462-165-05	19231152	500's Tablets in Container	Feb-25	
4	Carvedilol Tablets USP 25mg	68462-165-05	19234866	500's Tablets in Container	Jan-26	

If you have any questions regarding this form or product return please contact Inmar at **877-535-3243** Office hours 9am to 5pm EST Mon thru Fri.

Please fax this form to: 1-817-868-5362 or E-mail rxrecalls@inmar.com

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