CARACO
PHARMACEUTICAL LABORATORIES, LTD.

SUN
PHARMA

URGENT DRUG RECALL
VENLAFAXINE HCl ER 150 MG TABLETS

March 21, 2014

Dear Trading Partner,

This notice is to inform you of a drug product recall involving:

Drug Product Name: Venlafaxine HCl ER 150 mg tablets

Manufacturer: Sun Pharmaceutical Industries, Ltd

Firm Drug Product Code: 758

Dosage Form: Extended Release Tablets

Route of Administration: Oral

Intended Use/ Indications: Indicated for the treatment of major depressive disorder.

Package Type and Size: 30 and 90 tablets in a bottle

NDC Numbers: 41616-758-83 (30 CRC) and 41616-758-81 (90 CRC).

Affected Lots:

Product name	Pack Size	Lot Number	Expiry Date
Venlafaxine Hydrochloride Extended-Release Tablets, 150 mg	30	JKL3354A	04/2014
	90	JKL3354B	04/2014
	30	JKL5457B	09/2014
	90	JKL5457C	09/2014
	30	JKL5445A	09/2014
	90	JKL5445B	09/2014
	30	JKL5444A	08/2014
	90	JKL5444B	08/2014
	30	JKL5840A	10/2014
	90	JKL5840B	10/2014
	30	JKL6588A	11/2014

1150 Elijah McCoy Drive Detroit, Michigan 48202 Tel: 313-871-8400 Fax: 313-871-8314

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Reason for the Recall:
This recall is voluntarily initiated based upon stability results. The product may not meet the drug release specification throughout it expiry period. As a precaution, Caraco is voluntarily recalling these lots.

The affected lots were shipped between August 13, 2012 and August 9, 2013. Please find enclosed copies of the drug label.

Immediately examine your inventory and quarantine lot subject to this recall. Please stop distributing these lots immediately. **This recall has been classified as a retail level recall (Class II).** In addition, if you have further distributed this product, please notify them at once of this product recall. Your notification to you customers may be enhanced by including a copy of this recall letter.

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

For return of affected product, please email **recallnotice@inmar.com** or call 800-967-5952. Please complete and return the enclosed response form as soon as possible.

Affected product should be sent to:

Inmar
4332 Empire Road
South Dock
Fort Worth, TX 76155

If there are any further questions, please feel free to contact me at 800-818-4555 x 4105.

Sincerely,

Robert Kurkiewicz
Sr. Vice President, Regulatory

1150 Elijah McCoy Drive Detroit, Michigan 48202 Tel: 313-871-8400 Fax: 313-871-8314

CARACO PHARMACEUTICAL LABORATORIES, LTD.

SUN PHARMA

URGENT: DRUG RECALL – RESPONSE FORM

Please Complete Form and Fax to: 817-868-5362

or Email to: recallnotice@inmar.com

We do not have any stock ☐

Or,

Please enter the quantity you shall be returning to Inmar

Product name	Pack Size	Lot Number	Expiry Date	Quantity Being Returned to Inmar
Venlafaxine Hydrochloride Extended-Release Tablets, 150 mg	30	JKL3354A	04/2014	
	90	JKL3354B	04/2014	
	30	JKL5457B	09/2014	
	90	JKL5457C	09/2014	
	30	JKL5445A	09/2014	
	90	JKL5445B	09/2014	
	30	JKL5444A	08/2014	
	90	JKL5444B	08/2014	
	30	JKL5840A	10/2014	
	90	JKL5840B	10/2014	
	30	JKL6588A	11/2014	

Name_____ Title_____

Company_____

Address_____

City _____State _____ Zip Code_____

Phone Number_____ Email_____

For return of affected product, please email recallnotice@inmar.com or call 800-967-5952

1150 Elijah McCoy Drive Detroit, Michigan 48202 Tel: 313-871-8400 Fax: 313-871-8314

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

Protect from moisture and humidity.

CARACO

Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured at:
Sun Pharmaceutical Ind. Ltd.
Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

NDC 41616-758-83

Venlafaxine Hydrochloride Extended-Release Tablets

150 mg*

Rx only

30 TABLETS

SUN PHARMACEUTICAL INDUSTRIES LTD.

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

*Each extended-release tablet contains venlafaxine hydrochloride equivalent to 150 mg of venlafaxine.

Usual Dosage: Once daily. See accompanying information.

PJLB1258 PJLB1258
ISS. 07/2009

GUJ/DRUGS/25/789

Batch No.:

Exp.:

N 41616758832

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

Protect from moisture and humidity.

CARACO PHARMACEUTICAL LABORATORIES, LTD.

Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured at:
Sun Pharmaceutical Ind. Ltd.
Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

NDC 41616-758-81

Venlafaxine Hydrochloride Extended-Release Tablets

150 mg*

Rx only
90 TABLETS

SUN PHARMACEUTICAL INDUSTRIES LTD.

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

*Each extended-release tablet contains venlafaxine hydrochloride equivalent to 150 mg of venlafaxine.

Usual Dosage: Once daily.
See accompanying information.

PJLB1259 PJLB1259
ISS. 07/2009

GUJ/DRUGS/25/789

Batch No.:

Exp.:

3 41616 75881 8

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use venlafaxine hydrochloride extended-release tablets safely and effectively. See full prescribing information for venlafaxine hydrochloride extended-release tablets.

Venlafaxine Hydrochloride Extended-Release Tablets, for oral use
Initial U.S. Approval: 1993

WARNING: Suicidality and Antidepressants
See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Venlafaxine hydrochloride extended-release tablets are not approved for use in pediatric patients. (5.1)

INDICATIONS AND USAGE

[illegible]
- Major Depressive Disorder (MDD) (1.1)

DOSAGE AND ADMINISTRATION

- Initial Treatment (2.1)

Indication	Starting Dose	Dose Increase	Maximum Dose
Major Depressive Disorder	[illegible]	[illegible]	[illegible]

- Venlafaxine hydrochloride extended-release tablets should be taken as a single daily dose with food in either the morning or evening at the same time each day. (2)

[illegible]

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

[illegible]

Serum Triglycerides

Venlafaxine hydrochloride extended-release capsules treatment for up to 12 weeks in pooled premarketing trials was associated with a mean final on-therapy increase in fasting serum triglyceride concentration of approximately 8.2 mg/dL compared with a mean final increase of 0.4 mg/dL for placebo.

ECG Changes

In a flexible-dose MDD study with doses of venlafaxine hydrochloride immediate-release tablets in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo [See *Warnings and Precautions (5.17)*].

Other Adverse Reactions Observed During the Premarketing Evaluation of Venlafaxine Hydrochloride Immediate-Release Tablets and Venlafaxine Hydrochloride Extended-Release Capsules

[illegible]

...exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism of venlafaxine, reducing the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of the active metabolite. CYP2D6 inhibitors such as quinidine would be expected to do this, but the effect would be similar to what is seen in patients who are genetically CYP2D6 poor metabolizers [see *Clinical Pharmacology (12.3)*]. Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

Ketoconazole: [illegible]

[illegible]

Concomitant use of CYP3A4 inhibitors and venlafaxine may increase levels of venlafaxine and ODV. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

7.4 Drugs Metabolized by Cytochrome P450 Isoenzymes

CYP2D6

[illegible]

Imipramine - Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} ... [illegible]

[illegible]

10.2 Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

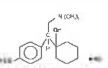
Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference*® (PDR).

11 DESCRIPTION

Venlafaxine hydrochloride extended-release tablets are extended-release tablets for oral administration that contain venlafaxine hydrochloride, a structurally novel antidepressant. Venlafaxine hydrochloride is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the molecular formula of $C_{17}H_{27}NO_2 \cdot HCl$. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient is 0.43.

[illegible]

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

[illegible]

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

In one longer-term study, adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8-week open trial on venlafaxine hydrochloride extended-release capsules (75, 150, or 225 mg, qAM) were randomized to continuation of their same venlafaxine hydrochloride extended-release capsules dose or to placebo, for up to 26 weeks of observation for relapse. [illegible] (3) a final CGI Severity of Illness item score of ≥ 4 for any patient who withdrew from the study for any reason. Patients receiving continued venlafaxine hydrochloride extended-release capsules treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

In a second longer-term trial, adult outpatients meeting DSM-III-R criteria for major depressive disorder, recurrent type, who had responded (HAM-D-21 total score ≤ 12 at the day 56 evaluation) and continued to be improved [defined as the following criteria being met for days 56 through 180: (1) no HAM-D-21 total score ≥ 20; (2) no more than 2 HAM-D-21 total scores > 10, and (3) no single CGI Severity of Illness item score ≥ 4 (moderately ill)] during an initial 26 weeks of treatment on venlafaxine hydrochloride immediate-release tablets (100 to 200 mg/day, on a b.i.d. schedule) were randomized to continuation of their same dose of venlafaxine hydrochloride immediate-release tablets or to placebo. The follow-up period to observe patients for relapse, defined as a CGI Severity of Illness item score ≥ 4, was for up to 52 weeks. Patients receiving continued treatment with venlafaxine hydrochloride immediate-release tablets experienced significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Venlafaxine hydrochloride extended-release tablets are available as follows:

37.5 mg, round, pink and white colored biconvex bilayer coated tablet imprinted with "758" with black ink on one side and plain on other side.

[illegible]

75 mg, round, pink and white colored biconvex bilayer coated tablet imprinted with "759" with black ink on one side and plain on other side.

Bottles of 30's with Child Resistant Cap	NDC 41616-759-83
Bottles of 90's with Child Resistant Cap	NDC 41616-759-81
Bottles of 100's with Child Resistant Cap	NDC 41616-759-88
Bottles of 100's with Non Child Resistant Cap	NDC 41616-759-06
Bottles of 1000's with Non Child Resistant Cap	NDC 41616-759-16

150 mg, oval, pink and white colored biconvex bilayer coated tablet imprinted with "760" with black ink on one side and plain on other side.

Bottles of 30's with Child Resistant Cap	NDC 41616-760-83
Bottles of 90's with Child Resistant Cap	NDC 41616-760-81
Bottles of 100's with Child Resistant Cap	NDC 41616-760-88
Bottles of 100's with Non Child Resistant Cap	NDC 41616-760-06
Bottles of 1000's with Non Child Resistant Cap	NDC 41616-760-16

17 PATIENT COUNSELING INFORMATION

[illegible]

- Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.
- Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
- How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
  - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
  - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
  - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

[illegible]

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** [illegible]

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

* Effexor XR is a registered trademark of Wyeth Pharmaceuticals Inc.

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Medication Guide

PJPI0206

Venlafaxine Hydrochloride Extended-Release Tablets

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide

- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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