FDA
TALK PAPER

Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T98-33
June 8, 1998

Print Media: 301-827-6242
Broadcast Media: 301-827-3414
Consumer Inquiries: 800-532-4440

ROCHE LABORATORIES ANNOUNCES WITHDRAWAL OF POSICOR FROM THE MARKET

Roche Laboratories of Nutley, NJ has announced that it is voluntarily withdrawing the heart drug, Posicor (mibefradil), from the market as a result of new information about potentially harmful interactions with other drugs.

In many cases, drug interactions can be addressed by appropriate labeling changes and public education, but due to the complexity of the prescribing information needed in this case, and seriousness of side effects, FDA and Roche agreed that it would be difficult to administer Posicor safely. The following may be used to respond to inquiries.

Posicor is a calcium-channel blocker, chemically unlike the other approved products in this class. Posicor was approved in June of last year, to be used in the treatment of patients with hypertension and chronic stable angina.

Posicor reduces the activity of certain liver enzymes that are important in helping the body eliminate many other drugs. Inhibiting these enzymes can cause some of these other drugs to accumulate in the body to dangerous levels.

When Posicor entered the market in August of 1997, its enzyme-inhibiting properties were described in the labeling. The labeling specifically listed three drugs (astemizole, cisapride, and terfenadine) that could be expected to accumulate to dangerous levels if Posicor was coadministered.

In December, after learning of several cases in which patients suffered serious adverse reactions after taking Posicor with one or more of the other drugs, FDA strengthened the labeling of Posicor, and two more drugs (lovastatin and simvastatin) were added to the label's list of those that should never be coadministered with Posicor. FDA also issued a public warning about this problem and the company issued a Dear Doctor letter to physicians.

From spontaneous reports and ongoing trials, FDA and Roche have continued to learn of adverse reactions related to coadministration of Posicor with several other drugs. At present, more than 25 drugs are known to be potentially dangerous if used with Posicor -- a number and diversity of drugs that cannot be practically addressed by standard label warnings.

Since Posicor has not been shown to offer special benefits (such as treating patients who do not respond to other antihypertensive and anti-anginal drugs), the drug's problems are viewed as an unreasonable risk to consumers.

Patients now taking Posicor should not simply discontinue treatment because stopping medications can be risky. Instead, patients should promptly consult with their physicians about appropriate alternative therapy. In addition, patients now taking Posicor should not add any new medication to their current treatment without consulting their physicians.

Roche Laboratories is providing information in a "Dear Doctor" letter to physicians, pharmacists, nurse practitioners, and other health care professionals. Questions about the withdrawal of Posicor can be addressed to Roche's 24-hour hotline at 1-800-205-4611.

The following is a list of drugs that depend on the same liver enzyme as Posicor (mibefradil). Use of them in combination with Posicor could be dangerous.

Generic name	**Trade Name**
amiodarone	Cordarone
astemizole	Hismanal
bepridil	Vesture
cisapride	Propulsid
cyclosporine	Neoral, Sandimmune
cyclophosphamide	Cytoxan
desipramine	Norpramin
erythromycin	Erythrocin, Ilosone, others
etoposide	VePesid
flecainide	Tambocor
flutamide	Eulexin
halofantrine	Halfan
ifosfamide	Ifex
imipramine	Tofranil
lovastatin	Mevacor
mexiletine	Mexitil
pimozide	Orap
propafenone	Rythmol
quinidine	Cardioquin, Quinaglute, Quinidex, others
simvastatin	Zocor
tacrolimus	Prograf
tamoxifen	tamoxifen
terfenadine	Seldane
thioridazine	Mellaril
vinblastine	Velban
vincristine	Oncovin

For more information about this withdrawal of Posicor, see:

"Dear Doctor" letter (Roche)

News Release (Roche)

FDA HOME PAGE

This is the retyped text of a news release from Roche.

NEWS RELEASE

Contact: Valerie Suga
(973) 562-2174

For Immediate Release

ROCHE ANNOUNCES VOLUNTARY WITHDRAWAL OF POSICOR

1-800-205-4611 Established to Answer MD/Consumer Questions

NUTLEY, NJ, June 8, 1998 -- Roche today announced the voluntary market withdrawal of the anti-hypertensive and anti-anginal medication POSICOR (mibefradil) and is advising physicians to propose alternative therapies to their patients.

The company is taking this action based on evolving information concerning the potential for drug interactions, some of them serious, which may occur when POSICOR is taken together with some other medications. The decision follows the analysis of the preliminary results of a three-year long-term study of POSICOR in congestive heart failure. The study demonstrated no overall difference between POSICOR or placebo when added to standard therapy in this patient population, but it provided further information on drug interactions.

In both hypertension and chronic angina pectoris, POSICOR has consistently proved to be effective and well tolerated, when used appropriately. However, the combination of POSICOR and some other commonly used drugs, among them cardiovascular agents, may increase the frequency of the side-effects of these other medications.

In principle, drug interactions can be addressed by appropriate labeling; however, with respect to POSICOR, Roche believes that the complexity of such prescribing information would make it difficult to implement. As patient well-being is of highest priority to Roche, the company has decided to voluntarily withdraw the compound from the market.

Roche is working closely with the Food & Drug Administration to inform physicians and other health care professionals of its decision. Patients should not simply discontinue treatment with POSICOR; instead they should consult their physicians promptly about appropriate alternative therapy. In addition, patients should not add any new medication to their present treatment without consulting their physician. Information about the withdrawal for both healthcare professionals and consumers will be communicated via:

* A special hotline, 1-800-205-4611

* A nationally distributed letter to physicians, pharmacists, nurse practitioners, physician assistants and other health care professionals

* Communication of patient information through physicians, pharmacies, local/national constituency groups and community groups

# # #

Hoffmann-La Roche Inc.
Public Affairs Department
340 Kingsland Street
Nutley, New Jersey 07110-1199

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MEDWATCH

FDA HOME PAGE

U.S. Food and Drug Administration

This is the retyped text of a letter from Roche Laboratories. Contact the company for a copy of any referenced enclosures.

Voluntary Market Withdrawal
All Lots: Posicor 50 mg and 100 mg Tablets
NDC #s: 0004-0080-01, 0004-0080-27, 0004-0080-49, 0004-0081-01, 0004-0081-49

June 8, 1998

Dear Doctor:

Roche Laboratories announced today the voluntary market withdrawal of the antihypertensive and anti-anginal medication POSICOR (mibefradil dihydrochloride).

The company is taking this action based on evolving information concerning the potential for drug interactions, some of them serious, that may occur when Posicor is taken together with some other medications. The decision follows the analysis of the preliminary results of a three-year long-term study of Posicor in congestive heart failure. The study demonstrated no overall difference between Posicor or placebo when added to standard therapy in this patient population, but it provided further information on drug interactions.

In both hypertension and chronic angina pectoris, Posicor has consistently proved to be effective and well tolerated, when used appropriately; however, the combination of Posicor and some other commonly used drugs, among them cardiovascular agents, may increase the frequency of the side-effects of these other medications. In principle, drug interactions can be addressed by appropriate labeling; however, with respect to Posicor, Roche Laboratories believes that the complexity of such prescribing information would make it too difficult to implement. As patient well-being is of highest priority to Roche, the company has decided to voluntarily withdraw the compound from the market.

The company is working closely with the Food and Drug Administration to inform physicians and other health care professionals of its decision.

Please immediately discontinue prescribing and dispensing Posicor, and immediately contact your patients who are currently prescribed Posicor so that they can discontinue treatment and receive appropriate alternative therapy. To receive a refund, patients should be instructed to immediately return any unused Posicor tablets via regular US mail to the following address:

Capital Returns, Inc.
ATTN: CVRET
4066 N. Port Washington Road
Milwaukee, WI 53212

Patients must include the following information when returning any unused Posicor tablets:

Name
Address
Unused product in original pharmacy packaging
Pharmacy receipt

Patients will receive a refund based on the value of the number of tablets returned, not to exceed the price paid on the receipt, plus the cost of shipping via regular U.S. mail.

Effective immediately, the Posicor compliance program, PosiCare, will be discontinued.

In order to ensure a smooth return process, it is very important that you fill out and return the enclosed Business Reply Card (BRC). In addition, if you have any Posicor samples (50mg or 100mg tablets) in your office, please use the enclosed UPS shipping label(s) to return the samples to Capital Returns, Inc. at the same address listed above and on the shipping label. Please include your return address on each label.

If you have any questions, please call Roche Laboratories at 1-800-205-4611.

Sincerely,

Russell H. Ellison, MD
Vice President
Medical Affaris

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

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MEDWATCH

FDA HOME PAGE

Heart Drug Withdrawn; Interaction Risks Cited

By JOHN SCHWARTZ
Washington Post Staff Writer

A drug company is withdrawing a popular medicine for chronic chest pain and high blood pressure from the market because it could cause death if taken with certain other drugs, officials announced yesterday.

Hoffmann-LaRoche and the Food and Drug Administration, however, warned that patients should not stop taking the drug, Posicor, without first consulting a physician about switching to another medication.

Posicor, which is taken by nearly 200,000 Americans and 400,000 people worldwide, has side effects that make it unacceptably risky, said Murray M. Lumpkin of the FDA's Center for Drug Evaluation and Research.

"You could theoretically argue it would be perfectly safe to use," Lumpkin said, "but the reality is . . . in the population for whom this is intended—primarily the elderly—there are not going to be people taking only Posicor." The FDA asked the company to withdraw the drug, and the manufacturer complied voluntarily.

"Patient well-being is really our highest priority," said Hoffmann-La Roche spokeswoman Valerie Suga.

The FDA has received 400 reports of health problems in Posicor patients, including 24 deaths. Lumpkin noted that those reports do not conclusively link the problems to the drug but indicate a problem may exist.

Posicor, which goes by the generic name mibefradil, blocks the normal function of the liver. It keeps that crucial organ from breaking down some medications, and those medications can then build up to hazardous levels. Other substances, including grapefruit juice, can have a similar effect—but Posicor's was especially pronounced, Lumpkin said.

When the FDA approved the drug last June, it required Hoffmann-La Roche to warn patients not to take it with certain drugs, including the antihistamine Hismanal. Over time, the list of dangerous drug interactions lengthened to 25, and in December the FDA warned against taking Posicor with cholesterol-lowering "statin" drugs such as Pravachol and Zocor. That, along with another troubling tendency of the drug to slow heart rates to potentially dangerous levels, made Posicor an unacceptable risk—especially in light of the fact that testing had proved the drug no more effective than other medications for the same conditions, Lumpkin said.

A patient advocacy group denounced the FDA yesterday, saying that the agency's recent attempts to speed drug approvals because of harsh criticism from industry and lawmakers had compromised public health.

Posicor "is an example of the risks that the American public will face in the future because of the flood of new drugs that the FDA has rushed to approve in the last several years," said Larry D. Sasich and Sidney M. Wolfe of Public Citizen's Health Research Group. "Rather than putting the safety of the American public first, the FDA now 'cooperates' with the drug industry, whose only interest is selling drugs, to approve more drugs faster, whether they are needed or not."

FDA spokeswoman Lorrie McHugh said that the Public Citizen allegations had no merit. "Posicor met all federal standards for approval" and included all pertinent warnings from the start, McHugh said. "If anything, FDA acted responsibly by getting ahead of the game and recommending to the company that it voluntarily withdraw the drug once we knew the complexity and scope of the interactions," she said. Posicor was a high-priority drug for Hoffmann-La Roche, which promoted it aggressively to doctors. Such promotional activities, which are increasingly popular in the pharmaceutical field, have drawn complaints from physicians that they might violate ethics rules intended to prevent the industry from improperly influencing doctors. "Speaker programs like this are standard in the industry," said Suga, "and very valuable to educate health care professionals."

The company announced a hot line for patients and doctors to receive more information: 1-800-205-4611.

News Release

Contact: Valerie Suga
(973) 562-2174

Roche

For Immediate Release

ROCHE ANNOUNCES VOLUNTARY WITHDRAWAL OF POSICOR®

1-800-205-4611 Established to Answer MD/Consumer Questions

NUTLEY, NJ, June 8, 1998-- Roche today announced the voluntary market withdrawal of the anti-hypertensive and anti-anginal medication POSICOR (mibefradil) and is advising physicians to propose alternative therapies to their patients.

The company is taking this action based on evolving information concerning the potential for drug interactions, some of them serious, which may occur when POSICOR is taken together with some other medications. The decision follows the analysis of the preliminary results of a three-year long-term study of POSICOR in congestive heart failure. The study demonstrated no overall difference between POSICOR or placebo when added to standard therapy in this patient population, but it provided further information on drug interactions.

In both hypertension and chronic angina pectoris, POSICOR has consistently proved to be effective and well tolerated, when used appropriately. However, the combination of POSICOR and some other commonly used drugs, among them cardiovascular agents, may increase the frequency of the side-effects of these other medications.

In principle, drug interactions can be addressed by appropriate labeling; however, with respect to POSICOR, Roche believes that the complexity of such prescribing information would make it difficult to implement. As patient well-being is of highest priority to Roche, the company has decided to voluntarily withdraw the compound from the market.

Roche is working closely with the Food & Drug Administration to inform physicians and other health care professionals of its decision. Patients should not simply discontinue treatment with POSICOR; instead they should consult their physicians promptly about appropriate alternative therapy. In addition, patients should not add any new medication to their present treatment without consulting their physician. Information about the withdrawal for both healthcare professionals and consumers will be communicated via:

- A special hotline, 1-800-205-4611
- A nationally distributed letter to physicians, pharmacists, nurse practitioners, physician assistants and other health care professionals
- Communication of patient information through physicians, pharmacies, local/national constituency groups and community groups

# # #

June 12, 1998

Dear Doctor:

Re: IMPORTANT INFORMATION ON DRUG INTERACTION AND THERAPY SUBSTITUTION FOR POSICOR

We wish to thank you for your support during the first few days following the withdrawal of POSICOR, as well as your questions and comments which have reached us. This recent feedback indicated that a few patients have experienced drug interactions upon substituting certain alternate therapy for Posicor. We wish to immediately share the following information with you and suggest it be taken into consideration if you choose to prescribe either calcium channel blockers or beta blockers as alternate therapy:

1. **If you choose to substitute amlodipine or atenolol, they should preferably be started two to three days after Posicor discontinuation.**
2. **If you choose to substitute other calcium channel blockers (except felodipine) or other beta blockers (except timolol), they should preferably be started seven days after Posicor discontinuation.**
3. **If you choose to substitute felodipine or timolol, they should preferably be started fourteen days after Posicor discontinuation.**
4. **No special precaution regarding the timing for switching is necessary for other antihypertensive or anti-anginal medications (e.g., ACE inhibitors, angiotensin II antagonists, diuretics, nitrates).**

Any drugs metabolized by the cytochrome P450 3A4 or 2D6 isoenzymes may interact with Posicor. Therefore, as a reminder, the co-administration of mibefradil with drugs metabolized by the 3A4 or 2D6 isoenzymes of the cytochrome P450 system may result in increased plasma levels of those drugs, so dose adjustments may be necessary as mibefradil is withdrawn.

The consequences of clinically relevant interactions depend on the side effect profile of the individual drug to be used. Posicor's inhibition of the CYP 450 3A4 and 2D6 isoenzymes may increase the side effects of the drugs metabolized by these enzymes or prevent the formation of active metabolites. It takes an average of 7 days, but can take up to 14 days, for sufficient elimination of the metabolites of Posicor to minimize the inhibition of CYP 450 system. You should consider this pharmacokinetic information along with the patient's medical history and current status when initiating drugs metabolized by the CYP 450 system, including those identified on the attached table.

Roche

Pharmaceuticals

Dear Doctor:

December 1997

We would like to inform you of important new warning information concerning the use of POSICOR® (mibefradil dihydrochloride), a treatment for hypertension and chronic stable angina pectoris. This concerns:

1. a warning related to suppression of sinoatrial activity and severe bradycardia occurring with POSICOR, and
2. a warning and contraindication concerning drug interactions and statin-induced rhabdomyolysis with POSICOR and certain HMG-CoA reductase inhibitors.

This letter emphasizes the importance of patient selection, patient monitoring, and attention to concomitant drug therapy to ensure that POSICOR is used appropriately. Please see enclosed complete product information.

I. Decreased Sinus Node Activity and Severe Bradycardia

The use of POSICOR has been associated with the appearance of symptomatic slow junctional rhythm. Ventricular rates have been as low as 30 to 40 bpm and many patients have been symptomatic. To date there have been about three dozen such reports arising from an exposure of 75,000 patients. This adverse effect has occurred mainly in elderly patients who were on concomitant beta-blocker therapy. Similar findings of symptomatic slow junctional rhythm have also been reported with other heart rate lowering compounds such as beta-blockers, digoxin, diltiazem and verapamil, especially when more than one of these agents are used at the same time.

In order to assist you in the appropriate use of POSICOR, please review the following package insert revision:

> **WARNINGS: *Suppression of Sinoatrial Node Activity:* Use of mibefradil has been associated with slowing or complete suppression of sinoatrial node activity. The supervening junctional rhythms have often been slow (as slow as 30 to 40 bpm). Many of the reports have incorrectly identified the adverse event as complete AV block. The reports have been most common in the elderly, mainly in association with the concomitant use of beta-blockers. Care should be taken when combining POSICOR with beta-blockers, particularly when pretreatment sinus rate is below 55 bpm, and this combination should be avoided in the elderly when pretreatment sinus rate is below 55 bpm (see PRECAUTIONS). In patients with low heart rates, use of any combination of agents that can slow the sinus node or affect the AV node (eg, beta-blockers, digitalis, and the calcium channel blockers mibefradil, diltiazem, and verapamil) should in general be undertaken only after careful consideration, as such combinations can unmask underlying sick sinus syndrome. Use of POSICOR in patients with sick sinus syndrome without a pacemaker is contraindicated (see CONTRAINDICATIONS).**

POSICOR is associated with a dose related decrease in heart rate. This effect is achieved whether POSICOR is given as monotherapy or in combination with beta-blockers. In susceptible patients, as described in the revised warnings section, the decrease in sinus node activity may result in severe sinus bradycardia or sinus arrest. In reported cases, cardiac pacing has been taken over by the AV node, but sometimes at low rates that were poorly tolerated.

Roche Laboratories Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

II. Interaction of POSICOR (mibefradil dihydrochloride) with certain HMG-CoA Reductase Inhibitors

Roche has received 7 domestic reports of statin-induced rhabdomyolysis in patients receiving simvastatin and POSICOR (4 of the cases were also receiving cyclosporine), presumably due to inhibition by POSICOR of the metabolism of simvastatin, markedly increasing simvastatin's plasma concentration. POSICOR is a strong inhibitor of cytochrome P450 3A4, the enzyme responsible for metabolizing several of the HMG-CoA reductase inhibitors. POSICOR also inhibits metabolism of cyclosporine, increasing its blood levels; cyclosporine itself decreases excretion of all HMG-CoA reductase inhibitors and substantially increases their blood levels.

POSICOR would be expected to have effects on blood levels of certain other HMG-CoA reductase inhibitors. Based on the similarity of lovastatin and simvastatin metabolism, coadministration of POSICOR and lovastatin would also be expected to result in markedly increased plasma concentrations of lovastatin. Atorvastatin and cerivastatin are also metabolized by CYP450 3A4, but the metabolites are active, so the overall effect of POSICOR on their HMG-CoA reductase activity may not be large. Studies of atorvastatin and cerivastatin with erythromycin, a moderate inhibitor of CYP450 3A4, have not shown marked increases in the blood levels of these HMG-CoA reductase inhibitors, but at present there are no studies with stronger inhibitors, such as mibefradil, ketoconazole, or itraconazole.

Since fluvastatin and pravastatin are not significantly metabolized by CYP450 3A4, POSICOR would not be expected to have a significant effect on their blood levels. Please see enclosed complete product information.

In order to assist you in the appropriate use of POSICOR, please review the following package insert revisions:

> CONTRAINDICATIONS: POSICOR is contraindicated in patients who:
>
> Are concurrently receiving terfenadine, astemizole, cisapride, lovastatin or simvastatin (see WARNINGS and PRECAUTIONS).
>
> WARNINGS: ***Interaction Resulting in HMG-CoA Reductase Inhibitor-Induced Rhabdomyolysis:*** **Mibefradil inhibits the action of CYP450 3A4. When this enzyme is inhibited, plasma concentrations of those drugs that are metabolized by CYP450 3A4 may become elevated, sometimes by more than an order of magnitude (see PRECAUTIONS).**
>
> **Rhabdomyolysis is a known rare adverse effect of all of the HMG-CoA reductase inhibitors (the "statin" cholesterol-lowering agents).**
>
> **The statins are not identically metabolized:**
>
> - **Lovastatin and simvastatin are dependent on CYP450 3A4 for their metabolic clearance. Among patients receiving simvastatin and mibefradil there have been reported cases of rhabdomyolysis. These events appear to reflect an incidence of rhabdomyolysis higher than that seen during treatment with simvastatin alone. Because of the metabolic similarities of lovastatin and simvastatin, coadministration of POSICOR with either of these two drugs is contraindicated.**
>
> - Atorvastatin and cerivastatin are biotransformed by CYP450 3A4 to active and inactive metabolites. Also, only small changes in HMG-CoA reductase inhibitor activity have been seen in studies where atorvastatin and cerivastatin were combined with erythromycin (a less potent CYP450 3A4 inhibitor than mibefradil). Nevertheless, until there is more information on the coadministration of CYP450 3A4 inhibitors (including mibefradil) with atorvastatin and cerivastatin, coadministration of either of these two drugs with POSICOR should generally be avoided.

- Fluvastatin and pravastatin are not significantly metabolized by CYP450 3A4; no clinically important interaction with mibefradil is anticipated. Therefore, no specific dose adjustment of fluvastatin or pravastatin is recommended with coadministration of POSICOR (mibefradil dihydrochloride).

Drug Interactions - Cyclosporine/Tacrolimus and HMG-CoA Reductase Inhibitors:
The calcineurin immunosuppressants tacrolimus (FK-506) and cyclosporine are metabolized by CYP450 3A4, so their blood levels rise (in the case of cyclosporine, about twofold) when POSICOR is coadministered; dose adjustment may be necessary. Because the immunosuppressants themselves inhibit a drug-transport system that participates in the excretion of HMG-CoA reductase inhibitors, elevated levels of the immunosuppressants can cause additional elevations in the blood levels of any of the HMG-CoA reductase inhibitors. **Use of POSICOR should be avoided in patients also receiving both a calcineurin immunosuppressant and an HMG-CoA reductase inhibitor.**

We trust this information will assist you in using POSICOR to manage your hypertensive and angina patients appropriately. Please see enclosed complete product information.

If you have any questions about POSICOR, we encourage you to call the toll-free number for Roche Medical Services at 1-800-526-6367. Also, if you are aware of any serious adverse events potentially associated with the use of POSICOR, please report such information to Roche at the above number or the Food and Drug Administration MedWatch program at 1-800-FDA-1088.

Sincerely,

Russell H. Ellison, MD
Vice President
Medical Affairs

FDA
TALK PAPER

Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

Correction: The 12/18/97 version of this statement could be read to say that **Posicor≥** should not be taken with any statin or with any immunosuppressant. That is inaccurate. Two of the statins, fluvastatin and pravastatin, are not significantly metabolized in the same way as the other statins. Mibefradil therefore would NOT be expected to have significant effects on fluvastatin and pravastatin blood levels or increase the risk of muscle injury. On the other hand, neither of the immunosuppressants tacrolimus and cyclosporine should be used together with **≤Posicor≥** and any statin. The statement concerning the 3-way combination should therefore read: The new label warns against the simultaneous use of **≤Posicor≥**, any statin and either of the immunosuppressants tacrolimus or cyclosporine. Also, the list of statins on page 3 should have included fluvastatin.

T97-65
Dec. 19, 1997

Susan M. Cruzan: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Inquiries: 800-532-4440

WARNING LABELING CHANGES FOR NEW HEART DRUG ≤POSICOR≥

FDA is advising doctors about new warnings in the labeling of the drug **≤Posicor≥** (mibefradil), a treatment for hypertension and chronic angina. The new warnings provide additional information about two risks associated with the drug: extremely low heart rates, and, when **≤Posicor≥** is taken with certain cholesterol lowering drugs, a risk of muscle injury that can be life-threatening. The following may be used to respond to questions.

The new warning regarding low heart rates advises physicians against prescribing **≤Posicor≥** to patients at high risk of developing dangerously low heart rates. Such patients, especially older people, include those whose heart rates are already relatively low and those taking another drug that slows heart rate.

≤Posicor≥'s risk of inducing excessively slow heart rates is similar to that of several other commonly used drugs, and was described in the labeling when the drug was first approved in June 1997. The new, strengthened warning was developed after FDA and the manufacturer, Roche Laboratories, of Nutley, NJ, received reports of dangerously lowered heart rates in about 20 patients who had taken **≤Posicor≥**. Many of the patients described in the reports had relatively low heart rates before starting **≤Posicor≥**, or had certain types of pre-existing heart disease that put them at high risk of such low rates. More than half of them were also taking another heart-rate-lowering drug, usually a beta-blocker. No deaths have been reported, but many patients became weak and lightheaded.

The second new warning states that **≤Posicor≥** should not be given to patients who are also receiving lovastatin or simvastatin. These drugs used to lower cholesterol are known as statins. In addition, pending availability of further information, coadministration of **≤Posicor≥** with atorvastin or cerivastatin is strongly discouraged. Two of the "statins", fluvastatin and pravastatin, are not significantly metabolized in the same way as the other drugs. Mibefradil therefore would NOT be expected to have significant effects on

fluvastatin or pravastatin blood levels or to increase the risk of muscle injury.

The new label also warns against the simultaneous use of ≤**Posicor**≥, any statin, and either of the immunosuppressants tacrolimus or cyclosporine.

This new warning was added after the agency received 7 reports of drug-associated muscle injury among patients who had taken ≤**Posicor**≥ and simvastatin.

Drug-induced muscle injury is a known rare side effect of all of the statin cholesterol-lowering drugs including atorvastatin, cervistatin, fluvastatin, lovastatin, pravastatin, and simvastatin, and it seems to increase in frequency with increasing dose. Patients with drug-induced muscle injury usually experience nonspecific muscular symptoms (weakness, tenderness, and pain), but the most important consequences of injury are not muscular. The breakdown products of muscle can cause temporary or permanent damage to kidneys; and in severe cases, the heart can also be affected. Either of these complications can lead to death.

Although ≤**Posicor**≥ does not itself cause muscle injury, administration of ≤**Posicor**≥ interferes with the body's metabolism of lovastatin and simvastatin and may interfere with the metabolism of atorvastatin and cerivastatin. The observed incidence of muscle injury with coadministration of ≤**Posicor**≥ and simvastatin appears to be much higher than the incidence seen during treatment with simvastatin alone. The immunosuppressants tacrolimus and cyclosporine interfere with the elimination of all of the statins, and ≤**Posicor**≥ increases blood levels of cyclosporine and tacrolimus, so the three-way combination of ≤**Posicor**≥, a statin, tacrolimus, or cyclosporine should also be avoided. Health care providers should report any adverse events related to ≤**Posicor**≥ to Roche Laboratories (800-526-6367) or to FDA. Reports may be submitted to FDA by telephone 800-332-1088), by fax (800-332-0178), or by mail using a postage paid MedWatch form from the back of the Physicians Desk Reference. The Medwatch report should be mailed to:

- MedWatch (HF-2)
- Food and Drug Administration
- 5600 Fishers Lane
- Rockville, MD 20857

BACKGROUND: **POSICOR** LABELING CHANGES<

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21ST STORY of Level 1 printed in FULL format.

The Lancet

June 13, 1998

SECTION: VOL. 351; No. 9118; Pg. 1791

LENGTH: 148 words

HEADLINE: Posicor withdrawn voluntarily from market by Roche

BYLINE: Bradbury, Jane

BODY:

Roche announced on June 8 that it was voluntarily withdrawing Posicor (mibefradil) from sale in response to new information about potentially harmful interactions with other drugs.Mibefradil, a calcium-channel blocker, was approved in the USA in June, 1997, for treatment of hypertension and chronic stable angina. The drug is currently available in 38 countries.

Mibefradil reduces the activity of some liver detoxifying enzymes, a fact noted in its original labelling where astemizole, cisapride, and terfenadine were named as drugs that should not be co-administered with mibefradil. The US FDA now lists more than 25 drugs that may be potentially dangerous if given with mibefradil (http://www.fda.gov/opacom/hpnews.html). Because of the number and diversity of drugs involved, it is not practicable to address the problem in standard label warnings, say the FDA and Roche.

LANGUAGE: ENGLISH

LOAD-DATE: July 1, 1998

This is the retyped text of a letter from Roche Laboratories.

June 12, 1998

Dear Doctor:

Re: IMPORTANT INFORMATION ON DRUG INTERACTION AND THERAPY SUBSTITUTION FOR POSICOR

We wish to thank you for your support during the first few days following the withdrawal of POSICOR, as well as your questions and comments which have reached us. This recent feedback indicated that a few patients have experienced drug interactions upon substituting certain alternate therapy for Posicor. We wish to immediately share the following information with you and suggest it be taken into consideration if you choose to prescribe either calcium channel blockers or beta blockers as alternate therapy:

1. **If you choose to substitute amlodipine or atenolol, they should preferably be started two to three days after Posicor discontinuation.**
2. **If you choose to substitute other calcium channel blockers (except felodipine) or other beta blockers (except timolol), they should preferably be started seven days after Posicor discontinuation.**
3. **If you choose to substitute felodipine or timolol, they should preferably be started fourteen days after Posicor discontinuation.**
4. **No special precaution regarding the timing for switching is necessary for other antihypertensive or anti-anginal medications (e.g., ACE inhibitors, angiotensin II antagonists, diuretics, nitrates).**

Any drugs metabolized by the cytochrome P450 3A4 or 2D6 isoenzymes may interact with Posicor. Therefore, as a reminder, the co-administration of mibefradil with drugs metabolized by the 3A4 or 2D6 isoenzymes of the cytochrome P450 system may result in increased plasma levels of those drugs, so dose adjustments may be necessary as mibefradil is withdrawn.

The consequences of clinically relevant interactions depend on the side effect profile of the individual drug to be used. Posicor's inhibition of the CYP 450 3A4 and 2D6 isoenzymes may increase the side effects of the drugs metabolized by these enzymes or prevent the formation of active metabolites. It takes an average of 7 days, but can take up to 14 days, for sufficient elimination of the metabolites of Posicor to minimize the inhibition of CYP 450 system. You should consider this pharmacokinetic information along with the patient's medical history and current status when initiating drugs metabolized by the CYP 450 system, including those identified on the attached table.

If you have any questions, please call Roche Laboratories at 1-800-205-4611.

Sincerely,

Russell H. Ellison, MD
Vice President
Medical Affairs
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Nutley, New Jersey 07110-1199

DRUGS THAT MAY INTERACT WITH MIBEFRADIL

GENERIC NAME: TRADE NAME

amiodarone: Cordarone
astemizole: Hismanal
bepridil: Vascor
cisapride: Propulsid
cyclosporine: Neoral, Sandimmune
cyclophosphamide: Cytoxan
desipramine: Norpramin
erythromycin: Erythrocin, Ilosone, others
etoposide: VePesid
flecainide: Tambocor
flutamide: Eulexin
halofantrine: Halfan
ifosfamide: Ifex
imipramine: Tofranil
lovastatin: Mevacor
mexiletine: Mexitil
pimozide: Orap
propafenone: Rythmol
quinidine: Cardioquin, Quinaglute, Quinidex, others
simvastatin: Zocor
tacrolimus: Prograf
tamoxifen: Nolvadex
terfenadine: Seldane
thioridazine: Mellaril
vinblastine: Velban
vincristine: Oncovin

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