

DRAFT TALK PAPER

After discussion with FDA, Roche Laboratories has voluntarily withdrawn POSICOR® (mibefradil) from the market.

5 Mibefradil is a calcium-channel blocker, chemically unlike the 10 other approved products in this class. POSICOR was approved in June of last year, to be used in the treatment of hypertension and chronic stable angina.

Mibefradil reduces the activity of the liver enzymes called
10 CYP2D6 and CYP3A4. These enzymes are important in the elimination of many other drugs, and inhibiting the enzymes can cause these other drugs to accumulate in the body to dangerous levels. A few other drugs have enzyme-inhibiting effects similar to those of mibefradil, but each of
15 these other known inhibitors meets one or another otherwise-unmet medical need.

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

Notwithstanding these general and specific warnings, during the next few months FDA and Roche learned of
25 several cases in which patients had suffered serious adverse reactions when POSICOR had been given concomitantly with drugs whose processing is dependent on CYP3A4. In December, the labeling of POSICOR was changed to strengthen the warnings, and two more drugs

30 (lovastatin and simvastatin) were added to the label's list of
those that should never be coadministered with mibefradil.

From spontaneous reports and ongoing trials, FDA and Roche have continued to learn of adverse reactions related to coadministration of POSICOR with one or another drug dependent for its processing on CYP2D6 or CYP3A4.
35 Because there are so many such drugs, the risk of inadvertent concomitant use can probably not be eliminated by labeling. This risk might be offset if mibefradil were known to be effective in patients who do not
40 respond to other antihypertensive and anti-anginal drugs, but no such data are available.

Patients now taking POSICOR should not simply discontinue treatment; instead, they should consult promptly with their physicians about appropriate
45 alternative therapy. In addition, patients now taking POSICOR should not add any new medication to their current treatment without consulting their physicians.

Questions about POSICOR can be addressed to Roche's 24-hour hotline at 1-800-526-6367.

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