pro-drug that needs to be metabolized to another compound, fexofenadine, in order to have its antihistamine effect. At the same time that FDA withdrew terfenadine, they approved the active metabolite, fexofenadine (154). The withdrawn product was known by the tradename, Seldane®, while the active metabolite is known as Allegra-D®. Fexofenadine does not result in a statistically significant increase in risk of QT prolongation or in torsades de pointes. It has been reported that, "[a]nalysis of trial evidence from all phases of fexofenadine's clinical development in over 6,000 patients … showed no statistically significant increases in mean QTc or serious cardiac arrhythmias, including torsades de pointes" (155).

## f. Cisapride and Its Regulatory History

This concerns part of the regulatory history of cisapride. Cisapride is a gastrointestinal promotility agent used for gastroesophageal reflux disease and delayed gastric emptying time. The drug blocks both the $I_{Kr}$ channel and the $I_{Ks}$ channel (156).

Cisapride was marketed from 1993 to 1999, and was withdrawn from the market in 2000. During the marketing period, FDA received adverse event reports from 341 patients. These patients included 117 who developed QT prolongation, 107 with torsades de pointes, 18 with ventricular fibrillation, 27 with ventricular tachycardia, 25 with cardiac arrest, and 15 with sudden death (157). The deaths were directly or indirectly associated with an arrhythmic event. In Jun. 1998, FDA informed practitioners of adverse cardiac events through additions to the boxed warning in the label and by requiring "Dear Health Care Professional" letters sent by the drug's manufacturer (158). The boxed warning and the letters did not concern all uses of cisapride, but addressed increased risk in patients taking concurrent medications that interfere with cisapride metabolism, that prolong the QT interval, or that have other diseases that predispose to such arrhythmias. Eventually, the manufacturer voluntarily withdrew the drug from the market. In the words of Smalley et al. (159), "[i]n March 2000, prior to when an FDA advisory committee was scheduled to review cisapride's benefits and risks for the approved indication, the manufacturer terminated marketing of cisapride in the United States effective as of July 2000."

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