

CORRESPONDENCE



Ketek — The FDA Perspective

TO THE EDITOR: In response to the article by Ross in this issue of the *Journal*,¹ we wish to clarify how the Food and Drug Administration (FDA) reviewed Ketek (telithromycin). Although there are other statements or suggestions in the article that also need clarification, we address a few key points in the limited space available here.

First, safety concerns were identified by the FDA early in the review process and taken very seriously throughout four years and three review cycles. The FDA's approval decision followed a careful review of the safety data submitted, including foreign postmarketing adverse-event reports that accumulated during the FDA's review of the application. Although the FDA did not rely on study 3014 to support approval, we reviewed the study for safety findings that would have counted "against the drug," as is consistent with good review practice.

Second, there was no intention to deceive the advisory committee or the public regarding our review of study 3014. Before the second advisory committee meeting, the FDA had only preliminary information regarding inspections of a few of over 1800 clinical study sites. Although the findings at one site had raised serious data-integrity concerns and had led to a referral for criminal investigation, we did not know at that time that we would conclude months later, after additional inspections and further review, that the entire study should not be relied upon. The FDA did not discuss data-integrity issues at the second advisory committee meeting to avoid compromising the ongoing investigations, recognizing that the FDA retained the ultimate decision authority.

Finally, noninferiority studies were considered acceptable as the basis for approval for treatment

of certain respiratory infections when the Ketek New Drug Application was submitted. Concurrent with the Ketek review, our thinking on noninferiority studies was evolving. Today, noninferiority studies are no longer considered acceptable for two of the three indications for which Ketek was originally approved. We are applying this new regulatory position to more recently submitted and planned applications.

The FDA monitored the safety of Ketek after approval and conducted a 1-year postapproval safety review in the spring of 2005. After three reports of serious hepatotoxicity were published in January 2006, we conducted an analysis of the available safety data that led to the addition of a bolded warning regarding hepatotoxicity in June 2006. After an advisory committee review of Ketek in December 2006, in February 2007 we added a boxed warning and Medication Guide to the label and removed two indications. Although we believe

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that the potential benefits of Ketek outweigh its risks when it is used according to the current approved label, we continue our safety surveillance and will take further actions if warranted.

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1. Ross DB. The FDA and the case of Ketek. *N Engl J Med* 2007;356:1601-4.

Dopamine Agonists and Valvular Heart Disease

TO THE EDITOR: Schade et al. (Jan. 4 issue)¹ report an adjusted incidence-rate ratio of 4.9 for valvular regurgitation among patients taking the dopamine agonist cabergoline, especially at a daily dose above 3 mg and a duration of use of 6 months or more. The authors also report an incidence-rate ratio of 2.6 for cabergoline at a dose of 3 mg or less, adjusted for the cumulative duration of use. In the same issue, Zanettini et al.² report a relative risk of moderate or severe valvular regurgitation of 4.6 to 7.3 among patients taking cabergoline. They also describe a dose effect on the severity of valvular dysfunction. Of note, Zanettini et al. do not report the prevalence of left ventricular dilatation and remodeling, which weakens their assertion that the tenting area of the mitral valve is solely an index of “stiffening of the leaflets.”

Cabergoline is a first-line therapy in prolactin-secreting pituitary tumors. The usual dose is 0.25 to 2.0 mg weekly (maximum, 4.5 mg). Young patients with hyperprolactinemia often receive therapy for life. Have the authors examined the prevalence of valvular dysfunction at lower doses of cabergoline in their studies? Further work with rigorous quantitative echocardiography is required to study the effect of lower doses of cabergoline administered over a long period in patients with hyperprolactinemia.

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- Schade R, Anderson F, Suissa S, Haverkamp W, Garde E. Dopamine agonists and the risk of cardiac regurgitation. *N Engl J Med* 2007;356:29-38.
- Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007;356:39-46.

TO THE EDITOR: Schade et al. and Zanettini et al. report a high incidence of significant valvular regurgitation in patients taking the ergot-derived dopamine agonist pergolide for the treatment of Parkinson's disease. Zanettini et al. report that severe regurgitation was associated with a high mean cumulative dose of pergolide (i.e., 6498 mg). In another study,¹ patients who took a high daily dose of pergolide (more than 5 mg) had a slightly higher prevalence of restrictive valvular disease than did patients who took lower doses.

We studied 90 patients with Parkinson's disease (mean age, 61 years, of whom 24% were women) who were taking pergolide and 42 healthy matched controls. The average daily dose of pergolide was 2.93 mg, the average cumulative dose was 4541 mg, and the median duration of treatment was 51 months. None of the patients had restrictive valvular morphology or severe valvular regurgitation. The prevalence of moderate valvular regurgitation was 4.4% in the pergolide group and 2.4% in the control group, a difference that was not significant. Discrete leaflet thickening of left-sided valves without restricted motion was found in 11.1% of patients in the pergolide group, as compared with none in the control group. These findings corroborate previous reports¹ that low daily and cumulative doses of pergolide do not appear to be associated with clinical valvular disease.

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- Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet* 2004;363:1179-83.