

Johnson & Johnson

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June 20, 2002

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Woodcock:

Johnson & Johnson Pharmaceutical Research and Development, L.L.C. ("JJPRD") and Ortho-McNeil Pharmaceutical, Inc. ("OMP") (hereafter referred to jointly as "Ortho-McNeil") are writing to seek a reconsideration of some of the decisions reached in your letter dated June 11, 2002, regarding the labeling that FDA will accept in abbreviated new drug applications ("ANDAs") for generic tramadol products. JJPRD is the sponsor of the new drug application for Ultram® (tramadol hydrochloride tablets) and OMP markets the product. FDA's letter authorized generic companies to market tramadol products with a label that omits the current 25 mg titration regimen, but includes the 50 mg titration regimen that is known to result, based on a clinical trial, in a significantly higher rate of treatment failure. The letter also finds the two regimens to be therapeutically equivalent.

One of FDA's great strengths has been that it operates as an evidence-based scientific agency, reaching conclusions only after a careful review of the most current scientific data available. Unfortunately, in this case it appears that FDA first reached a decision, and then attempted to find a rationale to justify it. Although FDA's letter attempts to set forth the agency's rationale at some length, it is clear, as discussed herein, that no evidence exists to support the agency's conclusions on safety or therapeutic equivalence.

Good medicine is a value that is simply more important than the approval of generic drugs at any cost. Yet here, FDA has chosen to reverse its own December 1999 decision to approve the 25 mg titration schedule and ignore the extensive data regarding the benefits of that regimen. FDA simply asserts that the 50 mg regimen is the same. It is unimaginable that an NDA applicant could have persuaded FDA to reach a similar conclusion on the strength of such slim evidence.

As a result of the agency's decision in this case, doctors, and therefore patients, will – with FDA's blessing – be denied access to the best prescribing information for generic tramadol products. FDA has admitted that there is a better way to treat at least a portion of the patients using tramadol, but has decided that this better method will not be disclosed in the labeling for

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the generic versions of tramadol. In addition, it has said it will approve a label that contains no starting dose. Doctors can "infer" the starting dose. This latter conclusion is particularly striking, given that the Review Division required Ortho-McNeil – as it does all NDA applicants – to establish all aspects of dosing, including the starting and minimum doses, by multiple adequate and well controlled trials. Notwithstanding these facts, the agency has found the two regimens to be therapeutically equivalent, in turn granting an "AB" rating, which will thus lead to mandatory substitution in many states, even though the generic will not be available in the same dosage as Ultram. Exactly how a pharmacist who receives a prescription that contains instructions for the 25 mg titration regimen for tramadol will fill that prescription with "therapeutically equivalent" 50 mg pills with different labeling is entirely unclear.

Much of the discussion around the balancing of interests facilitated by the Hatch-Waxman law has focused on the balance of economic interests. But the Act contains a careful medical balance as well. There are medical reasons why the Act requires that generics be "the same" as innovator products and meet the same standards. The further the agency shifts that balance by declaring different products "the same," the further FDA, doctors, and patients will get from good medicine. These actions directly contradict provisions of the law which require that acceptable adjustments in the generics labeling versus the innovator labeling must not render the generic product less safe and/or efficacious than the innovator product. Based on the fact that FDA itself had previously endorsed and approved the 25 mg titration schedule as the preferred dosing regimen, this is clearly not the outcome of its most recent guidance to the generic manufacturers of tramadol.

Although Ortho-McNeil believes that there are substantial scientific and legal grounds on which to challenge FDA's decision, the company has decided to take no steps to obstruct or attempt to block the entry of generics to the market. Nonetheless, the FDA's decision is a disservice to patients and physicians, and Ortho-McNeil respectfully requests that the FDA reconsider its conclusions set forth in the June 11 letter and determine that the 16-day titration regimen that starts with 25 mg per day is, in fact, superior to the 10-day titration regimen that starts with 50 mg per day.

I. Background on Tramadol Labeling

Ultram is indicated for the management of moderate to moderately severe pain. The drug has side effects that may cause patients to terminate therapy. The events most commonly associated with discontinuation of treatment are nausea, vomiting, and dizziness/vertigo.

Ultram was originally approved with a recommended dosing of 50 to 100 mg every 4 to 6 hours, not to exceed 400 mg/day. Ortho-McNeil undertook post-approval clinical studies to investigate whether other dosing regimens would reduce the adverse events associated with use of Ultram that led to a high rate of treatment discontinuations. FDA approved a revised label in August 1998, which incorporated results of a study that showed that a slow titration of the drug beginning with 50 mg/day and increasing over ten days to 200 mg/day could reduce discontinuation due to adverse events, particularly dizziness and vertigo, in comparison to no

titration or a four day titration. The study did not demonstrate a statistically significant reduction in nausea and vomiting, which were the primary causes of treatment discontinuation. Thus, while this study resulted in a minor change to the labeling at the time, it did not lead to any adjustment in specific dosing instructions.

A second study was undertaken to determine whether an even slower titration schedule would further reduce discontinuations due to nausea and vomiting. The study was a multi-center, randomized, double-blind study of patients with chronic pain. The study demonstrated that starting with an initial dose of 25 mg/day with gradual dosing increases to 200 mg/day through a 16-day titration schedule reduced the incidence of discontinuations due to nausea and vomiting in subjects who previously had difficulty tolerating tramadol. The percentage of subjects who discontinued treatment was significantly lower in the 16-day titration group (about 22%) than in the 10-day titration group (46.3%).

Based on this study, FDA on December 23, 1999, approved a change in the Dosage and Administration section of the Ultram labeling. For patients "not requiring rapid onset of analgesic effect," the 16-day titration regimen beginning at 25 mg is recommended. For "the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risks of discontinuation due to adverse events associated with initial higher doses," a nontitrated regimen of up to 400 mg/day is recommended. FDA awarded three years of exclusivity to the change and, as extended by the pediatric exclusivity provisions, that exclusivity extends through June 23, 2003.

II. FDA's Decision

FDA's decision was issued in response to citizen petitions submitted by three manufacturers seeking approval of generic tramadol products. The issue raised by the petitions was the appropriate labeling for the products in light of the fact that elements of Ultram's labeling are protected by exclusivity.

Under Hatch-Waxman legislation and FDA's implementing regulations, the labeling of a generic drug must generally be identical to the labeling of the reference listed drug. Aspects of labeling that are protected by exclusivity may be omitted, however, provided that the labeling differences "do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."¹ The three citizen petitions advanced various proposals for generic tramadol labeling that would omit the titration regimen in the Ultram labeling while purporting to comply with this requirement.

The FDA's decision rejected all of the labeling proposals suggested by the petitioners and instead identified new labeling that the FDA would accept. Under the FDA's decision, the

¹ 21 C.F.R. § 314.127(a)(7).

portion of Ultram's current dosing regimen recommending titration beginning at 25 mg per day and increasing by 25 mg every 3 days to reach 100 mg per day would be deleted. The portion of the regimen that recommends a subsequent increase by 50 mg every 3 days to reach 200 mg per day would be retained. The FDA concluded that this version of Ultram's current dosing information is equivalent to the 10-day dosing regimen beginning at 50 mg that was included in the Ultram labeling prior to the current 16-day regimen.

The principal basis for the FDA's decision was its conclusion that there is no proven advantage in safety or effectiveness in the general population of the 16-day titration regimen over the 10-day titration regimen. Although Ortho-McNeil's study showed a clear advantage of the 16-day regimen in reduced adverse effects and discontinuations, the FDA found that study unpersuasive in comparing the safety of the two regimens because it was conducted in patients who had experienced adverse effects from tramadol. Since the FDA found no evidence existed that the 16-day regimen was superior to the 10-day regimen in the general population, it determined that the 10-day regimen was as safe and effective as the 16-day regimen. As indicated previously, this is a complete reversal of the December 1999 endorsement by FDA that this regimen was indeed superior and should be the starting regimen for patients.

III. Comparison of the Two Titration Regimens

The FDA rejected the position of certain ANDA applicants that a tramadol product would be safe even if its labeling did not include a titration regimen. The FDA stated that information on titration provides "essential safety information that . . . should remain in the labeling."² The FDA concluded, however, that the labeling of generic products could include a different titration regimen than that of the branded product.

The crux of the FDA's decision is its conclusion that a 10-day titration regimen that begins with 50 mg of tramadol per day is as safe and effective as the 16-day titration regimen that begins with 25 mg per day. Since there are existing clinical data which supported FDA's initial approval of the 25 mg titration schedule as safer for patients, and since there were no additional clinical trials conducted which support the conclusion reached in its most recent guidance to potential generic suppliers of tramadol, we believe FDA should reconsider this view.

The attached graph, taken from the FDA-approved Ultram labeling, illustrates that the two regimens are not equivalent – it shows markedly different rates of treatment discontinuance depending on which titration regimen is used. Also attached is a single-line graph that would appear in the generic product labeling pursuant to the June 11 decision. By omitting data on the 25 mg titration regimen, this latter graph completely fails to inform the reader of the generic label about the superior titration regimen.

² FDA Decision at 8.

FDA's analysis appears to be based on the assumption that the proportion of patients who react adversely to tramadol is a trivial portion of the "general population." Of course, physicians cannot identify tramadol-intolerant patients in advance. Thus, administering tramadol according to the 10-day titration regimen will clearly result in more adverse events and therapy discontinuations than the 16-day regimen in *any* given patient population. The tramadol-intolerant patients will have better results with the 16-day regimen than with the 10-day regimen, as the Ortho-McNeil clinical study demonstrated. Thus, the FDA's conclusion that there might be no significant difference in therapy discontinuations between groups of patients on the two different regimens would be true only if the tramadol-intolerant segment of each group is miniscule.

In fact, all the available evidence shows that the tramadol-intolerant segment of the population is large. As information submitted to FDA in the Ultram new drug application shows, patients initiating treatment with tramadol at non-titrated doses of 200-400 mg/day discontinue therapy at a rate of 35% from all causes – hardly a trivial number. In other studies, about 20% of patients discontinue therapy due to nausea and vomiting, and that discontinuation rate could be the same in the 10-day titration regimen as in the non-titrated regimen. These data demonstrate that a large segment of the general population experiences adverse effects from tramadol and, thus, many patients will benefit from the 16-day titration regimen, even under the FDA's assumption that the benefit of that regimen has only been shown with respect to tramadol-intolerant patients.

In addition, Ortho-McNeil has pointed out that the 16-day titration regimen improves the effectiveness of tramadol therapy by reducing the discontinuation rate. The FDA disputed that conclusion on the ground that "[i]t is not obvious" that the slower titration "increases tolerability for patients who have not been shown to be intolerant of tramadol previously." In addition, the FDA asserted that the 16-day titration schedule may result in "decreased efficacy by delivering a subtherapeutic dose for up to 16 days."

We do not understand the basis for the assertion that the 16-day titration regimen, which clearly reduces discontinuations, won't improve effectiveness and may be at subtherapeutic doses. Although the doses on the first three days of the regimen are at 25 mg, which is less than the starting dose in the 10-day regimen approved by the FDA for generic tramadol products, doses on the rest of the 16 days are within the range of doses for the 10-day regimen. The suggestion that dosing on all 16 days of the regimen may be subtherapeutic is inexplicable.

IV. Other Confusing Aspects of the Labeling

In addition to omitting the best titration regimen, the labeling that FDA has approved for generic tramadol products has other confusing aspects as well. The dosing instructions announced in the June 11 letter include no clear starting amount but state only that the daily dose "may be increased by 50 mg as tolerated every 3 days. . . ." The FDA letter suggests that physicians will

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“infer” that 50 mg is the starting dose,³ but it is certainly confusing for physicians to read dosing instructions that rely on a presumed inference.

Also, we question how pharmacists will implement the AB rating in the absence of dosing instructions on the 25 mg titration regimen. Half of the new prescriptions for Ultram are written to begin at the 25 mg dose. Without dosing instructions on the 25 mg titration regimen in the generic product labeling, it is unclear what pharmacists would do with new prescriptions calling for that regimen.

V. Conclusion

The FDA's determination that the 10-day and 16-day titration regimens are equally safe and effective is inconsistent with the clinical evidence. Because adverse reactions to tramadol are frequent, it is clear that using the 16-day regimen in the general patient population will result in fewer adverse reactions and discontinuations than the 10-day regimen. FDA should reconsider its decision. If, as a result of such reconsideration, FDA requires generic tramadol products to include the 16-day titration regimen in their labeling, Ortho-McNeil will not enforce its Orange Book-listed patent (U.S. Patent 6,339,105) against products that are so labeled. Ortho-McNeil will similarly waive any regulatory exclusivity rights that might otherwise obtain, such that no legal impediment will exist to the approval of labeling including this 16-day titration regimen. Consequently, Ortho-McNeil will no longer have any economic interest in that regimen. We believe that this result is in the best interest of patients, and we urge FDA to require the 16-day titration regimen in generic tramadol labeling.

Very truly yours,



Helen Torelli

Attachments

cc: Lester M. Crawford, Jr., D.V.M., Ph.D.
Lee Simon, M.D.
Gary Buehler
Daniel Troy
Robert Wood

³ FDA Decision at 11.