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SCHOOL OF
MEDICINE

Department of Anesthesiology

June 6, 2002

Tim Gilbert

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Dear Tim:

**Re: Docket No. 02P-0191 (Petition by TEVA Pharmaceuticals USA
regarding approval of its ANDA for Tramadol Hydrochloric tablets)**

These comments are in response to the May 17, 2002 letter from Johnson & Johnson. In that document, Johnson & Johnson makes a number of statements that I do not believe are supported by the evidence I have reviewed that was filed with FDA. These are repeated in several places and I address them as follows:

Teva's proposed label

At page 4-5, Johnson & Johnson suggests that physicians will not read the proposed Teva label as limiting the indication of Teva's product to acute pain.

With respect, I disagree. Tramadol has been on the market for many years and physicians who use it routinely and have a good understanding of its efficacy and side-effect profile are less likely to change their practice. If a physician does not see the need to read the Teva label, he or she is unlikely to read the J&J label also. Furthermore, there are many physicians that never treat chronic pain patients but manage acute pain routinely. If such a doctor decides to use Tramadol in this setting and he does not have experience with the drug, there is a very high probability that he will read the label or consult with a knowledgeable colleague. If J&J's label happens to be the reference they choose to determine a dosing regimen, the titration schedule for chronic use of the medication appropriately should be ignored. J&J's own product labeling targets both the category of patients suffering from acute pain and the category of patients suffering from chronic pain. There is no reason why a physician cannot use J&J's product or another company's product for acute pain. The titration method recommended for chronic pain patients would be inappropriate for acute pain management.

At page 5, Johnson & Johnson argues that the absence of titration instructions and the reference to "higher doses" makes the label "unintelligible."



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Once again I disagree. I have reviewed the proposed Teva label as set out in Teva's citizen petition and am of the opinion that physicians would be able to understand the instructions for use. In the case of Tramadol, physicians would understand the "risk of discontinuance due to adverse events associated with higher doses" to mean that tolerability of the medication is limited at higher doses. Further, physicians using the drug for acute pain management will not need to evaluate the dosing instructions for chronic pain patients.

Safety of product without inclusion of 25 mg/16 day titration labeling information

Johnson & Johnson several times overstates the results of their clinical trials. For example, they make the following statements:

- "the titration regimen was proven to result in lower incidents of dizziness/vertigo, nausea and vomiting". (page 5)
- "...the truncated labeling Teva suggests will likely result in the prescription of the non-titrated, up-to-400 mg/day regimen for patients who should be prescribed a titration regimen, and these patients will suffer a higher incidence of adverse effects and a higher discontinuance rate." (page 6)
- "...the titration regimen included in the current Ultram labeling was proven by a clinical study to reduce adverse effects compared to the original Ultram dosing regimen" (page 7)

I reviewed the reports of clinical trials submitted to FDA and to my knowledge, there is no evidence that the claim of reduced side effects is correct. In fact, these studies demonstrated only that fewer patients would discontinue tramadol. There is no data presented to show that the actual incidents of such side effects were reduced.

In addition, these trials were conducted in a subpopulation of patients, those who had previously discontinued taking tramadol and were attempting a second course of therapy. These patients do not represent the entire population of those for whom tramadol would be prescribed. In my opinion, I do not feel that results of this trial can be extrapolated to the entire patient population. For example, one might assume that the subset of patients who discontinued the medication because of side effects tolerated the second trial of the medication because they had no side effects or the symptoms were greatly attenuated. On the other hand, it could be that the patients were motivated for other reasons to stick it out the second time.

Accordingly, I cannot support the claim that the titration dosing reduces discontinuance in the general patient population, nor can I conclude that adverse effects are reduced in either the subpopulation assessed in the trial or the patient population as a whole.

Titration regimen is not “safer”

Johnson & Johnson claims that “Ortho-McNeil’s clinical studies have demonstrated that the 16-day titration regimen, which starts patients at 25 mg/day is safer than the non-titrated regimen which starts patients at up to 400 mg/day”.

In my view, Johnson & Johnson has not presented any evidence to support increased safety by using the 25 mg/16 day titration dosing schedule. The intensity of the side effects described by Johnson & Johnson (dizziness, vertigo, nausea and vomiting) should be categorized as nuisance side effects and do not rise to the level of safety concerns. I have reviewed U.S. patent 6,339,105, and note that the patentee agrees with this characterization. Column 2 at lines 4-6 states “...nuisance side effects such as drowsiness, vomiting and dizziness can occur during the initiation of treatment...”

There are other drugs that have nuisance side effects, yet are safe and effective for human use. Benadryl, for example, is a good OTC drug for treating pruritis. A negative side effect of the drug is that it causes sedation. At the level of sedation caused by Benadryl is not a safety concern for patients and doctors in general. Occasionally, a patient will have severe sedation and cannot function while taking Benadryl. Either another drug will be substituted or some sort of titration regimen will be used in order to obtain the benefits while reducing the side effects.

Prescription of tramadol and other analgesics can be appreciated in the same light. For patients that do not tolerate the standard dosing regimen, titration to effectiveness is the standard approach. If Johnson & Johnson has information to suggest that the symptoms in the non-titrated group are more severe than the titrated group and analgesia is more intense, this is valuable information and the clinician should have access to it. If such information truly represents a safety issue, it should be reported to FDA as an adverse event. If there is no difference within or between the groups, then Johnson & Johnson is at least overstating the data.

Accordingly, I disagree with Johnson & Johnson’s conclusions that:

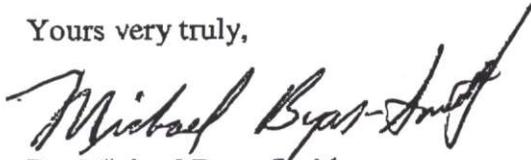
- “if the titration regimen is deleted from the labeling of a generic tramadol product, the resulting product would be less safe and less effective for the remaining nontitrated dosing regimen” (page 5).
- “the nontitrated regimen would be less safe and less effective than it is when presented in the context of the full and approved labeling” (page 6).

Finally, having reviewed carefully Johnson & Johnson’s letter of May 17, 2002, I see no reason to change the opinion contained in my letter that

1. No safety issues are presented by the proposed generic labeling.

2. There is no evidence to suggest that the 25 mg/16 day titration dosing schedule results in a lower incidence of side effects.
3. There is no evidence that the titration dosing improves efficacy of the drug.

Yours very truly,

A handwritten signature in black ink, appearing to read "Michael Byas-Smith". The signature is written in a cursive, flowing style with some loops and flourishes.

Dr. Michael Byas-Smith