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Dockets Management Branch  
Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20857

**Re: Docket No. 02P-0191 (Petition of Teva Pharmaceuticals USA Regarding Approval of Its ANDA for Tramadol Hydrochloride Tablets)**

These comments are a further submission by Johnson & Johnson Pharmaceutical Research & Development L.L.C. and Ortho-McNeil Pharmaceutical, Inc. (hereafter jointly referred to as "Ortho-McNeil"). On May 17, 2002, Ortho-McNeil submitted comments to this docket, and on May 23, 2002, Teva Pharmaceuticals USA ("Teva") filed a response to our comments. This is a reply to Teva's response. Ortho-McNeil manufactures and markets Ultram® (tramadol hydrochloride).

Teva's response is replete with rhetoric that we trust the Food and Drug Administration will ignore. The FDA accepted our clinical studies in support of the titration regimen, revised our label and granted the company three years of exclusivity as required by law. It is inappropriate for Teva to suggest that the changes were "frivolous" or simply an attempt to "evergreen". We improved an important analgesic agent in response to an unacceptable 30% discontinuation rate seen with the non-titrated dosing, and we did so in precisely the manner that the FDA intended, by carefully justifying our changes with clinical trials designed to improve the safety and tolerability of tramadol.

Teva seems to be suggesting, on page two of its latest submission, that we have conceded FDA's authority to edit the current Ultram label in the manner Teva proposes. That assertion is untrue. Ortho-McNeil concedes that case law allows the FDA to carve out protected indications as well as the clinical trial information and dosing information that support them. That is not this case. As discussed more fully below, Teva proposes to provide incomplete dosing information (which, in any event, encroaches on our legally protected exclusivity) that does not provide guidance to the physician for the two-thirds of the *indicated* patient population (those who take Ultram for chronic pain) and, incredibly, suggests that doctors will somehow intuit that such patients should

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simply be prescribed some other analgesic. The case law that Teva relies on is inapplicable to this situation.

**I. Teva Has Failed To Demonstrate that Treatment of Acute Pain Is a Distinct Therapeutic Use in the Ultram Labeling.**

Ultram is currently indicated for patients with moderate to moderately severe pain, whether that pain is acute or chronic. Were Teva to receive the labeling it has requested, its Dosing and Administration section would provide dosing instructions for only a subset of the population for whom the drug is indicated – acute and chronic pain patients for whom rapid onset of analgesic effect is necessary and for whom the benefits outweigh the risks. The labeling would necessarily omit all of the information regarding Ortho-McNeil's studies that provide the necessary context to evaluate what risk would be incurred and, therefore, make it impossible to determine who would qualify as a member of the "subset."

Teva apparently recognizes that this situation is untenable. Through a tortured reading of the Ultram label, Teva argues that the approved labeling for Ultram includes treatment of acute pain and treatment of chronic pain as distinct indications and that Teva is free to omit information to avoid Ortho-McNeil's exclusivity rights. As we pointed out in our initial comments, however, the approved labeling for Ultram does not contain separate indications for chronic and acute pain as distinct therapeutic uses. Teva makes two attempts to avoid this problem, but both attempts are unpersuasive.

First, Teva quotes FDA and Ortho-McNeil releases to the effect that Ultram is approved for management of acute and chronic pain. That statement is indisputable but irrelevant – Ultram is indicated for treatment of moderate to moderately severe pain. These terms refer to the severity of pain, whereas an acute pain indication merely refers to the duration of pain, not the intensity. Thus, the two dosing schemes set forth in the current Ultram label are to be used depending on intensity of pain, not duration. Teva, however, argues that acute and chronic pain are set forth as distinct therapeutic uses, such that the labeling related to treatment of chronic pain can be easily deleted, and that is not true. Even if the titration regimen were deleted from the labeling as Teva proposes, the indication would still include treatment of patients with chronic pain, and the remaining dosing regimen would still include patients with chronic pain, who may need the rapid onset of analgesic effect that Teva's proposed dosing would address.

Second, Teva points to various ways in which FDA or Ortho-McNeil has referred to the use of Ultram for acute pain or for chronic pain. (Teva Resp. at 2-3) These arguments are all red herrings. Acute pain is a recognized condition, but the Ultram labeling does not adopt treatment of acute pain as a distinct therapeutic use of the product. There is nothing inconsistent between those two facts.

Indeed, Ortho-McNeil's research consistently shows that acute painful conditions have never made up a large proportion of Ultram prescriptions. Ortho-McNeil did single and multiple dose pain trials in acute pain models, as then-current FDA guidance required, but after Ultram was approved, FDA questioned the use of Ultram for "sprains and strains" and other acute indications. Since that time, Ortho-McNeil has promoted Ultram for treatment of chronic pain. By contrast, if FDA approves Teva's proposed label, Teva argues it would have an indication *limited* to acute pain, despite the fact that there is no acute pain indication, and despite that fact that its labeling would include dosing instructions for only a portion of the indicated population.

**II. Teva Has Failed to Show that Its Proposed Product Labeling Would Result in a Product That Is As Safe As Ultram for Its Indicated Uses.**

**A. Teva's Proposed Label Omits Important Information.**

As Ortho-McNeil has pointed out, Teva's proposed labeling would render its product less safe than Ultram for its indicated use and thus is unapprovable under the FDA's regulations. None of Teva's counter-arguments have merit.

Teva argues that physicians will not be confused and misled by its proposed labeling because the nontitration dosing will be "contraindicated" for chronic pain patients in Teva's labeling. (Teva Resp. at 4) We cannot fathom how Teva reaches this conclusion. There is no such contraindication in Teva's proposed labeling: it is simply silent as to the appropriate dosing regimen for the majority of patients for whom the product is indicated. Teva offers no evidence that physicians would in fact adopt this highly unlikely interpretation of the proposed labeling.

Teva also argues that doctors using its product for chronic pain patients would be using it off-label, and that off-label use should not be considered by FDA in deciding whether its product is safe. But the indication would sweep in all treatment of moderate to moderately severe pain – without limitation to acute pain. There would be no instructions in the labeling about how to use the product for most patients coming within the approved indication, but the product would be approved for use in that patient population by virtue of the language of the indication. As a result, Teva's proposed labeling would clearly be less safe than Ultram's.

Finally, Teva hasn't answered the obvious problem that its proposed dosing instruction simply cannot be understood in the absence of the preceding paragraph of the Ultram label. It argues that the phrase "for whom the benefits outweigh the risk of discontinuance due to adverse events associated with higher initial doses" can be understood because its labeling would include a

sentence about the titration regimen that was approved in 1998<sup>1</sup> and because there would a table of adverse reactions. But the 50 mg titration regimen is entirely irrelevant: it refers only to the reduction of dizziness and vertigo through titration. Thus, the sentence would seriously mislead practitioners, who cannot know that the adverse events of nausea and vomiting can also be reduced through titration. We cannot see how the general adverse event table – which, incidentally, includes information on chronic trials and would not relevant to Teva’s proposed label – would further enlighten prescribers to the risks of nontitration.

**B. Ultram’s Exclusivity Extends to Portions of the Label Teva Proposes to Adopt.**

The dosing language sought by Teva is as follows:

“For patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, tramadol hydrochloride tablets 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.” (emphasis added)

The underlined portion of the language, concerning the weighing of risks and benefits, was added to the label as part of Ortho-McNeil’s labeling supplement approved in June, 2000, and refers directly to the results of research conducted by Ortho-McNeil in support of its approval. As such, the underlined language is entitled to the same three-year exclusivity as the preceding paragraph, and is indeed part and parcel of the information necessary to properly use that regimen.<sup>2</sup> FDA has no authority to encroach upon Ortho-McNeil’s exclusivity by allowing Teva to use protected language.

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<sup>1</sup> The sentence reads: “In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer discontinuances due to dizziness or vertigo than titration over only 4 days or no titration.”

<sup>2</sup> Teva contends that this language is not entitled to exclusivity, citing the preamble to FDA’s rules implementing the Hatch-Waxman exclusivity clauses. 59 Fed. Reg. 50338, 50356-57 (Final Rules, October 3, 1994). It is true that the rule precludes exclusivity for Warnings and similar risk information, but the contested language is dosing information. Warnings appear in the warnings section. Similar risk information appears in the precautions, adverse reactions, and contraindications sections.

Absent the protected language, the Teva label would simply provide for a nontitrated dosing regimen that closely resembles Ultram's original label, but without the discussion in the original label regarding a lower initial dose for moderate pain. Such a label is clearly less safe than Ultram's current label, and is in fact less helpful than Ultram's original label. There is no justification for a Teva label that is confusing, covers only a subset of the approved indications, fails to provide necessary information for that subset, and results in a label that is less safe than the reference drug.

### **III. Teva's Product Cannot Be AB-Rated.**

As we pointed out already, Teva's product could not be AB-rated to Ultram because it would have a different safety profile and its labeling would have significant differences in the Dosage and Administration section. Either one of these circumstances makes an AB rating unavailable under the criteria in the Orange Book. Teva's product would simply not be substitutable for Ultram under its labeled conditions of use.

Teva's response that FDA awards an AB rating to generic products that do not include all of the reference drug's indications is beside the point. Teva's product would have the same indication as Ultram but would provide dosing instructions for only a portion of the indicated patient population. This would clearly result in a different safety profile, since patients within Teva's indicated population would all lose the benefit of the titrated dosing regimen.

Moreover, the differences in the labeling are by themselves sufficient to negate an AB rating under the Orange Book criteria. It is doubtful that FDA would want to set a precedent whereby two drugs with the very same indication but different dosing instructions would be rated as therapeutically equivalent.

### **IV. Ultracet Is Not Ultram.**

Ortho-McNeil also markets Ultracet™ (37.5 mg tramadol hydrochloride/32.5 mg acetaminophen tablets), which is a combination product consisting of tramadol, the active ingredient in Ultram, plus acetaminophen. Ultracet is indicated for:

“the short term (five days or less) management of acute pain.”

What the Ultracet label shows is that when the FDA wants to carve out an acute use, it does so by quite directly limiting the duration of therapy in the Indications section of the label. Thus, the Ultracet label contains all of the necessary information to permit a physician to make an informed decision; the Teva label would be devoid of such information. Obviously, there is no way to provide a 16-day titration regimen for a drug that can only be used for five days. It is

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simply impossible to extrapolate the indications and dosing recommendations of Ultracet to Ultram.

It is also worth noting that most of the studies on Ultracet were well underway before Ortho-McNeil recognized the benefits of titration for tramadol and settled on an optimal regimen. Although Ortho-McNeil requested in its original application that FDA permit the addition of information concerning titration to the Ultracet label, the agency declined, since studies to support titration have not been completed for this drug.

**V. Conclusion.**

It would be a grave error of law and policy for the FDA to allow generic tramadol products to be approved with prescribing information that is essentially unintelligible, provides inadequate dosing instructions for fully two-thirds of the likely patient population, and cannot be read as a coherent whole. The result of Teva's omissions is a nonsensical package insert that no FDA reviewer would ever allow to see the light of day, and that fails to provide accurate information to patients. Such a label would be a sham. No party to this debate, we submit, seriously believes that use of Teva's label would be limited in the ways Teva suggests. The benefits of titration would simply be lost for all tramadol users. Such a result does not serve the public health and should not be facilitated by FDA.

Very truly yours,



Helen Torelli