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**Docket No. 02P-0191**  
**Response by Teva Pharmaceuticals USA**  
**To Comments of R.W. Johnson PRI and Ortho-McNeil Pharmaceutical Inc.**

Teva Pharmaceuticals USA Inc. (Teva) submits this response to the May 17, 2002 comments submitted by R. W. Johnson Pharmaceutical Research Institute and Ortho-McNeil Pharmaceuticals (collectively "McNeil"), the sponsor and marketer of Ultram® brand tramadol hydrochloride tablets (tramadol). In an attempt to preserve and extend its monopoly position, McNeil had advanced a variety of arguments intended to prevent the approval of Teva's Abbreviated New Drug Application (ANDA) for a generic tramadol drug product; none of them survives scrutiny. Teva demonstrates below that McNeil's arguments are individually incorrect and collectively insufficient to justify continuing to keep Teva's product off the market.

**I. Teva is Entitled to Carve Out The Chronic Pain/Titration Dosing Condition of Use From its Generic Tramadol Labeling**

McNeil challenges Teva's right to carve out the exclusivity-protected condition of use of Ultram, using a titration dosing schedule for chronic pain, because: allegedly "Ultram's labeling does not set forth chronic pain and acute pain as distinct therapeutic uses," McNeil Comm. at 2 (header); "nothing in the original labeling could possibly be construed as referring to treatment of acute pain, treatment of chronic pain, or both as distinct uses;" and "nothing in the 1998 language can be read as recognizing treatment of chronic pain and treatment of acute pain as distinct uses." McNeil Comm. at 3, 4. McNeil's position is frivolous, misleading, and turns the entire Hatch-Waxman exclusivity scheme on its head by allowing unlimited sequential opportunities to "evergreen" the monopoly on drugs whose legitimate patent and exclusivity rights have long since expired.

Teva directly addressed McNeil's observation that the "Indications" section of the Ultram labeling does not expressly include the words "chronic" and "acute," and refuted McNeil's argument that this poses a barrier to approval of Teva's ANDA. Pet. at 5-6. In many important

respects, McNeil has chosen to ignore the substance of these arguments. McNeil's silence with respect to Teva's arguments is revealing:

- McNeil does not contest that a generic applicant may “carve out” non-indication elements of innovator labeling. 21 C.F.R. § 314.94(a)(8)(iv) (permitting generic omission of an “indication or other aspect of labeling protected by patent or... exclusivity.”) (emphasis added). Thus, whether or not the chronic pain/titration condition of use is an “indication” or merely another “aspect of labeling” protected by exclusivity is irrelevant to Teva’s right to omit that part of the labeling.
- McNeil does not contest that in medical terms “acute” refers to rapid or sudden onset, and that the reference in Ultram’s labeling to pain requiring “rapid onset of analgesic effect” can only be a reference to acute pain. *See* Pet. at 5.
- McNeil does not contest that FDA believed from the beginning that Ultram was initially approved for management of “acute and chronic pain,” and that FDA announced that fact to the world in a 1996 FDA Talk Paper. Pet. at 5. And, in the event one would argue that an FDA Talk Paper is not an authoritative statement of the Agency’s understanding of a drug’s conditions of use, FDA’s official *List Of Approved Drugs For Which Additional Pediatric Information May Produce Health Benefits In The Pediatric Population* (the “Pediatric List”) also denotes that Ultram’s approved uses were “Management of acute and chronic pain.” *See* <http://www.fda.gov/cder/pediatric/peddrugsfinal.htm>.<sup>1</sup>

Moreover, McNeil’s own statements and actions belie its current position that “nothing in the original labeling could possibly be construed as referring to treatment of acute pain, treatment of chronic pain, or both as distinct uses,” and that “nothing in the 1998 language can be read as recognizing treatment of chronic pain and treatment of acute pain as distinct uses,” McNeil Comm. at 3, 4. Specifically,

- The approved Ultram labeling discloses that the original pivotal approval trials were conducted separately in patients with *acute pain*, i.e., “pain following surgical procedures and pain following oral surgery (extraction of impacted molars)” and in “patients with a variety of *chronic* painful conditions.” Ultram labeling, Clinical Studies section. Clearly McNeil and FDA differentiated between these types of pain, McNeil studied Ultram for use in both types of pain, and FDA approved Ultram for use in both types of pain.
- Contrary to its current position, in practice McNeil clearly considers the acute and chronic uses of Ultram to be separate and distinct, and explicitly measures the use of Ultram for each type of pain. Dr. Thomas Gibson, one of the physicians at Ortho-McNeil with responsibility for tramadol, testified at an FDA Advisory Committee meeting *on*

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<sup>1</sup> Under the statutory Pediatric Exclusivity scheme, inclusion on this list constituted a necessary prerequisite for Ultram to obtain the 6 month pediatric exclusivity it was ultimately awarded, so there can be no question that this document is an authoritative expression of FDA’s position that Ultram is and was approved for both types of pain.

April 28, 1998 that McNeil's internal data showed that approximately 40% of Ultram use was for "acute" pain and 60% for "chronic" pain.<sup>2</sup>

McNeil's comments focus heavily on the old Ultram labeling to argue against the clear and distinct uses of tramadol for acute and chronic pain. McNeil's revisionist history is severely flawed in this respect, as shown above. Moreover, McNeil's focus is misdirected. The only Ultram labeling at issue here is the *currently* approved labeling, and there can be no doubt that this labeling provides two approved separate and distinct conditions of use: (1) chronic pain with titration dosing, and (2) acute pain without titration dosing. To blur the distinction between uses with and without titration dosing, McNeil argues that "nothing links the new titration regimen to chronic pain patients," and suggests that

Teva's entire argument depends on an assertion that, when the improved 25 mg titration regimen was introduced...FDA concurrently intended, for the first time, to establish the separate and distinct uses of the product for treatment of chronic pain and treatment of acute pain. But all that was intended by this labeling change was the introduction of a superior titration regimen.

McNeil Comm. at 4. McNeil mischaracterizes the bases of Teva's position, and more importantly, McNeil's assertions misrepresent reality, because:

- The FDA Medical Team Leader, Dr. John Hyde, noted in his Review Memorandum of the Ultram labeling supplement on December 20, 1999, that "The applicant [i.e., McNeil] also proposed making changes [to] the Dosage and Administration section to describe the dose titration for chronic pain before, rather than after, the description of dosing for acute pain." See <http://www.fda.gov/ohrms/dockets/dailys/01/Oct01/102501/cp00001.pdf>, at 77.
- The reason for specifically separating the chronic and acute conditions of use is explained by Dr. Hyde's conclusion that "[e]vidence was not provided that the 25 mg dose will provide adequate pain relief and [it] is reasonable to presume it would not. The labeling should clearly reflect that the titration dosing regimen is for chronic usage, where immediate analgesic effect may not be required." *Id.* at 75.
- FDA's limitation of the titration dosing regimen to chronic pain patients makes perfect sense because McNeil's study in support of the 25 mg titration dosing schedule was intentionally limited to chronic pain patients who had exhibited intolerance to Ultram in a previous trial. *Id.* at 63.

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<sup>2</sup> Available at <http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3411t2.rtf>. The relevant passage is as follows:  
DR. ANDORN: Well, two questions, if I may. One is I notice you're keeping data on the number of new prescriptions and repeat prescriptions. Can you share with us the proportion?  
DR. BURTON: I think Dr. Gibson may have some information on that. Dr. Gibson is one of the physicians in Ortho-McNeil with responsibility for tramadol.  
DR. GIBSON: Our data suggests that about 60 percent of the use is for chronic use and 40 percent for acute.  
DR. ANDORN: Thank you.

- The words of the approved Ultram labeling’s exclusive titration regimen themselves include the express limitation to “chronic pain” patients, thus directly refuting McNeil’s claim that “nothing links the new titration regimen to chronic pain patients.”

Thus, there is simply no merit to McNeil’s assertions that the Ultram labeling does not set forth two distinct conditions of use for Ultram, one for chronic pain using the exclusive titration regimen, and one for acute pain using a non-titrated dosing regimen.

## II. Teva’s Labeling is Safe and Lawful

McNeil raises two objections to Teva’s labeling: (1) that physicians allegedly will prescribe Teva’s tramadol in a manner contrary to its approved labeling resulting in adverse events; and (2) that the risk/benefit language in the non-titrated acute pain regimen allegedly requires inclusion of the exclusive titration schedule. McNeil’s objections are misleading, unfounded, and incorrect as a matter of law and fact.

A. First, McNeil argues that “physicians will almost certainly not read [Teva’s acute pain dosing instructions] as limiting the indication of Teva’s product to patients with acute pain,” and as a result patients will suffer nausea, vomiting and other side effects “that could have been avoided.” McNeil Comm. at 4-5. McNeil’s argument is specious. McNeil itself admits that titration dosing of Ultram is inappropriate for patients requiring rapid onset of pain relief. McNeil Comm. at 4 (“all patients should be titrated unless rapid onset of analgesic effect is required.”). Thus, for such acute pain patients, doctors either (1) will prescribe Ultram or Teva’s product without titration, or (2) select another drug if the risks outweigh the benefits of rapid dosing. For such acute pain patients doctors cannot choose to titrate Ultram because the titration schedule is limited to patients *not* requiring rapid pain relief, and, for the same reason, doctors would not be able to titrate Teva’s tramadol even if it included titration dosing. This is illustrated by the following table.

	<b>Non-Titrated Dosing</b>	<b>Titration Dosing</b>
	For patients for whom <b><u>rapid onset of analgesic effect is required</u></b> and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses. . . .	For patients with moderate to moderately severe chronic pain <b><u>not requiring rapid onset of analgesic effect.</u></b> . . .
Acute Pain Patient	<ul style="list-style-type: none"> <li>• <b>Ultram</b> <i>or</i></li> <li>• <b>Teva Tramadol</b> <i>or</i></li> <li>• <b>Other Therapy (if risks outweigh the benefits)</b></li> </ul>	<b><i>Contraindicated</i></b>
Chronic Pain Patient	<b><i>Contraindicated</i></b>	<b>Ultram</b>

Thus, the fact that Teva's omission of the chronic pain titration schedule independently prevents titration that is not permissible under Ultram's labeling, in no way renders Teva's tramadol labeling unsatisfactory or less safe than Ultram for the non-titrated acute pain use.

McNeil's position that patients will suffer avoidable side effects and failed therapy, McNeil Comm. p. 5, can only be true based on the *assumption* and *speculation* that doctors will willfully disregard Ultram's or Teva's labeling by prescribing either product for an unlabeled use, i.e., treating patients with chronic pain without titration dosing. McNeil is not the first branded drug company to raise a false spectre of safety based on the presumption that doctors will ignore or disregard a generic drug's labeling, and FDA should not succumb now to such scare tactics. Rather, as it did in the case of generic propofol, FDA should presume that doctors *will* follow the generic drug's labeling and only prescribe Teva's tramadol for the conditions of use for which it is labeled.

In the propofol case, *Zeneca v. Shalala*, FDA and the courts rejected the argument that a generic drug's labeling (which differed from the branded drug in permissible ways) would be insufficient to assure safe use of the generic "because physicians will ignore" the generic labeling. FDA opposed Zeneca's invitation to evaluate generic drug safety based on the *assumption* that the generic labeling will be ignored or disregarded. The district court likewise rejected this approach because the "regulations related to the labeling and packaging of drugs are a fundamental part of FDA's regulatory scheme. To assume that health care providers would either fail to read or ignore clear warnings would call into question that entire scheme." *Zeneca v. Shalala*, 1999 U.S. Dist. LEXIS 12327 at \*30 (D. Md. Aug. 11, 1999), *affirmed* 216 F.3d 161 (4th Cir. 2000).

Moreover, in *Zeneca*, as here, the brand and generic drug had the identical statement in the "Indication" section of the labeling, but because the generic drug contained a sulfite preservative, it was labeled to explicitly exclude the subset of patients who might be sulfite-sensitive, without any change to the general Indications statement. Here, McNeil's unfounded assumption that doctors will prescribe Teva's tramadol off-label for chronic pain patients without titration dosing is unsupported by fact, unsupportable by law, contrary to the intent of the law, and should be rejected.

If in this case FDA were to make a "safety" determination based on assumptions about doctors ignoring certain labeling elements and prescribing drugs for unlabeled uses, FDA would quickly find itself in a regulatory quagmire, as many prescription drugs are commonly prescribed, and often overtly marketed, for unapproved uses for which there is no safety information at all in the approved labeling. In such event the Agency could expect to receive petitions from companies and patient advocacy groups seeking withdrawal of approval of drugs based on the approved labeling's lack of relevant safety information for unlabeled uses. And, given the requirement of administrative consistency under the Administrative Procedure Act, FDA could have little basis to refuse to grant such petitions.

**B.** Second, McNeil argues that Teva's labeling is "less safe and less effective" for the remaining nontitrated dosing regimen" based on the fact that both Ultram's and Teva's

tramadol require non-titrated dosing “*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.*” McNeil Comm. at 3, 5-6. (emphasis added). Thus, McNeil alleges, “[u]nless the comparative benefits of the titration regimen are explained in the labeling, a physician would have no basis for assessing whether the benefits of the nontitrated regimen outweigh its risk of discontinuance due to adverse events.” *Id.* at 5-6. McNeil’s argument is based on the false premise that the titration dosing schedule is a permissible substitute for patients requiring rapid pain relief, and that the risk/benefit considerations mentioned in the non-titration regimen call for a comparison of using titrated versus non-titrated dosing for acute pain patients. As shown above, neither the Ultram nor Teva labeling permits titrated dosing for acute pain patients. Hence, McNeil’s argument simply collapses.

Moreover, the argument that physicians will have inadequate information from Teva’s labeling to assess the risks of tramadol use in acute pain patients is untrue because:

- McNeil’s titration regimen itself provides no information whatsoever about “the risk of discontinuance due to adverse events,” but merely claims improved “tolerability” using the titration schedule for chronic pain patients.
- Other non-exclusive elements of Teva’s labeling do provide sufficient information about the well-known risks and adverse events of tramadol, including
  - discussion of a 50 mg titration trial which instructs physicians on how to “reduce discontinuations due to dizziness or vertigo.” (In contrast to this non-exclusive risk information on dizziness and vertigo, the Ultram labeling discussion of the 25 mg titration trial relates only to discontinuance due to the inconvenience of nausea and vomiting).
  - An extensive tabular listing of adverse events from Ultram’s original pivotal trials, disclosing incidences of dizziness/vertigo (26-33%), nausea (24-40%), and vomiting (9-17%).

Thus McNeil will continue to enjoy its exclusivity for titration dosing for chronic pain, because Teva’s product labeling will safely exclude such use, and physicians will be able to prescribe Ultram for any such patients.

McNeil’s argument could be interpreted as claiming that the statement “*for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses*” in the non-titrated dosing regimen is actually part of its exclusivity-protected titration dosing regimen for chronic pain. Certainly that would be the practical effect of accepting McNeil’s arguments, but doing so would unlawfully expand McNeil’s limited supplemental exclusivity from covering a narrow and marginally useful change in chronic dosing, to covering the entire product and all uses and dosing regimens, including the non-titrated dosing schedule. However, McNeil has already benefited from a 5-year new drug exclusivity for Ultram when used with no titration dosing, and a 3-year exclusivity for the 50 mg titration dosing regimen. To

allow McNeil to now leverage its 25 mg titration exclusivity into another full product exclusivity would not only violate the statutory exclusivity provisions which require new clinical studies that are essential to approval of the exclusive use, 21 U.S.C. § 355(j)(5)(D)(iv), it would grossly pervert the intent of the Hatch-Waxman amendments by further delaying all generic competition for tramadol products.

Finally, if FDA were to refuse to approve Teva's tramadol ANDA based on the conclusion that the titration dosing schedule and related labeling statements are essential for the safe use of Teva's product, FDA would be violating its own longstanding policy that NDA sponsors are not eligible to receive a three-year exclusivity period for studies that establish new risks of approved drugs. *See* 54 Fed. Reg. 28872, 28899 (Proposed Rule, July 10, 1989) (noting that "Studies that establish new risks **will not be eligible** for exclusivity because protection of the public health **demand**s that all products' labeling contain **all** relevant warnings." (emphasis added)). This policy was adhered to by the Agency in the preamble to the final ANDA regulations, where FDA again explained that labeling "changes that would not warrant exclusivity are, as discussed in the preamble to the proposed rule, changes in labeling that involve warnings or other similar risk information that must be included in the labeling of generic competitors. Applicants obtaining approval for such changes in labeling would, in any event, have no valid interest in precluding such information from the labeling of other products." 59 Fed. Reg. 50338, 50356-57 (Final Rule, October 3, 1994) (emphasis added). Failure to follow this stated policy in this case would be arbitrary and capricious.

### **III. LABELING FOR ACUTE PAIN DOES NOT ALTER THE THERAPEUTIC EQUIVALENCY OF TEVA'S ANDA AND ULTRAM.**

McNeil argues that Teva's tramadol cannot be given an "AB" rating in the Orange Book if it is approved only for non-titrated use in acute pain patients. McNeil's argument is based on the unfounded premise that "the safety profile of [Teva's product] . . . would be far different than the safety profile of the current Ultram product." McNeil Comm. at 7. Not only is this contention wholly unsupported as a scientific matter, it is based on a fundamental misunderstanding of the criteria for therapeutic equivalence ratings. Specifically, a product may be rated as "therapeutically equivalent" if "there is no difference in their potential for adverse effects when used under the conditions of their labeling." This means that generic drugs which omit an exclusivity-protected condition of use may still be given an AB rating based on the conditions of use in the generic labeling. This is well established FDA policy, and FDA has specifically rejected McNeil's argument, noting that

[I]t would be inconsistent with the established standards for making therapeutic equivalence determinations to rate two products as not therapeutically equivalent simply because one is labeled with fewer than all the approved indications...the fact that a pioneer drug is labeled with a protected indication does not mean that generic copies of the same drug are not therapeutically equivalent to the pioneer.

59 Fed. Reg. 50338, 50357 (Oct. 3, 1994). *Cf. Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. 1996) (court rejected claim that generic drug was not therapeutically equivalent because the generic drug did not include all of the indications approved for the innovator's drug).

Moreover, the Orange Book specifically permits AB ratings for generic drugs that omit protected conditions of use, noting that

there may be variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use. When such variations may, in the Agency's opinion, affect prescribing or substitution decisions by health professionals, a note will be added to the Description of Special Situations [section of the Orange Book].

Orange Book at p. 11 (emphasis added). Here, although Teva omits the chronic pain/titration dosing condition of use, Teva's ANDA has the *same* dosing instructions as Ultram for patients with acute pain. Thus, even if FDA determines that the omission of the exclusive titration dosage affects practitioners' prescribing or substitution decisions, the proper response would be for FDA to add a note to the Description of Special Situations contained in the Orange Book, not to withhold an AB rating. In any event, Teva does not believe that any such special situation note is necessary.

Consequently, there is no merit to McNeil's argument that Teva's tramadol may not receive an AB rating.

#### **IV. TEVA WILL ACCEPT APPROVAL, AND INITIATE MARKETING, OF A NON-SCORED TRAMADOL TABLET**

McNeil claims that the scoring of Ultram tablets is part and parcel of its titration dosing exclusivity because it allows patients to easily obtain a 25 mg tablet, and that Teva should not be permitted to market its tramadol product using scored tablets. Teva disagrees that the score is eligible for exclusivity because no new clinical trials were necessary to establish that a scored 50 mg tablet can be broken into two 25 mg tablets. Moreover, because the non-exclusive use of tramadol for acute pain calls for dosing of 50-100 mg, such scoring has a legitimate non-exclusive use, specifically, allowing a patient to take a 75 mg dose of tramadol.

Nevertheless, if it will expedite FDA's final approval of Teva's ANDA, Teva is willing to leave this issue aside for future determination, and to initiate marketing its tramadol product in the form of a non-scored 50 mg tablet.

#### **V. CONCLUSION**

McNeil is attempting to protect an entire product from generic competition through highly strategic use of clinically insignificant labeling language that would have the effect of "evergreening" its monopoly for the foreseeable future. McNeil's tactics and arguments are a

blatant abuse of the original intent of the Hatch-Waxman amendments and are a disservice to the American public. FDA should, and indeed must, promptly approve Teva's tramadol ANDA.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Deborah J. Skot". The signature is written in a cursive, flowing style.

DAJ