



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

4338 02 APR 30 A9:38

Phone: (215) 591 3000
FAX: (215) 591 8600

April 30, 2002

Dockets Management Branch
U.S. Food and Drug Administration (HFA-305)
Room 1061
5630 Fishers Lane
Rockville, Maryland, 20852

**CITIZEN PETITION
EXPEDITED RESPONSE REQUESTED**

**REQUEST FOR IMMEDIATE FINAL APPROVAL OF
TEVA'S ANDA No. 75-977 (TRAMADOL HYDROCHLORIDE TABLETS, 50 mg)**

On behalf of Teva Pharmaceuticals USA, Inc., (Teva), the undersigned submits this Petition under section 505(j) of the Federal Food, Drug and Cosmetic Act (FDCA), and 21 C.F.R. § 10.30, to request the Commissioner of Food and Drugs to grant immediate final approval of Teva's "approvable" ANDA No. 75-977 (tramadol hydrochloride 50 mg tablets). Because Teva's ANDA has been eligible for final approval for more than 60 days, and because FDA has failed to respond to Teva's repeated requests for final approval of its ANDA as amended, Teva requests that the Agency consider this petition on an expedited basis and provide a final ruling within 10 business days.¹

A. Action Requested

Teva's ANDA, which FDA has already deemed "approvable" on all bases except labeling related to the innovator company's exclusive titration dosing regimen for chronic pain, is eligible as amended for immediate final approval because the labeling:

- complies with the regulatory "same labeling" requirement,
- fully protects the exclusivity of the innovator company, and
- as a matter of law does not and cannot render Teva's drug less safe than the innovator product for the uses for which it is labeled.

¹ A copy of this Petition is also being submitted as a separate comment to Docket 01P-4595 involving Apotex Corp.'s Citizen Petition regarding tramadol labeling issues.

02P-0191

CAI

There is no statutory basis for FDA to withhold final approval of the ANDA, yet in several conversations with various FDA officials, Teva has been informed that perceived safety concerns regarding the omission of the exclusive 25 mg titration dose have led to a deadlock within the Agency on the approvability of Teva's ANDA. This inability to decide is of great concern to Teva, not only because of the delay it has caused in the availability of generic tramadol products, but also because it reflects that the Agency has fundamentally misunderstood, or disregarded, the legal/regulatory basis of Teva's labeling amendment and how under Teva's labeling approach, the omission of the 25 mg titration schedule cannot, as a matter of law, or as a matter of fact, pose an approval-blocking safety risk. This is because the exclusive titration schedule relates solely to the use of tramadol for treatment of chronic pain, a use for which Teva's product will not be labeled.

It is now nearly three months past the date Teva's ANDA became eligible for final approval, and Teva has exhausted every step required and available to it under the law to secure final approval of its tramadol HCl ANDA. Every additional day of delay unlawfully imposes further irreparable harm on Teva and American consumers who have a right of access to more affordable generic versions of tramadol. Although ANDA applicants are not required to submit Petitions in order to seek final approval of pending ANDAs, Teva is submitting this Petition at the request of the Office of Chief Counsel in order to give the Agency a final administrative opportunity to fulfill its statutory obligation to approve Teva's ANDA². Because the issues raised herein are not new to the Agency, and given the mounting injury to Teva and American consumers with each additional day of FDA inaction, we respectfully request that within 10 days of this Petition, the Agency provide Teva with a written decision on its tramadol ANDA, either granting immediate final approval, notifying Teva of changes that will allow immediate approval, or explaining in full the Agency's reasons for refusing to grant approval. We will treat a failure to respond as a final Agency decision not to approve Teva's ANDA.

B. Statement of Grounds

Teva's Proposed Labeling

Teva's proposed tramadol labeling approach is simple and unambiguously meets the statutory and regulatory requirements for approval: by only seeking approval of the non-exclusive, non-titration dosed use of tramadol in treating patients with acute pain, Teva's product is, by definition, equally safe as Ultram for that use, because the two products' dosing instructions for that use are identical. Thus, Teva's tramadol is safe for use ***under the conditions prescribed, recommended, or suggested in its proposed labeling***, and has met all other approval requirements, and FDA therefore has no lawful basis to further withhold final approval of Teva's ANDA.

² Notwithstanding the limited disclosure of Teva's proposed labeling in this Petition, Teva expressly reserves all rights of confidentiality to data and other trade secret information contained in its ANDA.

To illustrate this concept more specifically, the approved labeling of the innovator product (Ultram) provides for two separate and distinct therapeutic uses of tramadol, each of which requires a separate and distinct dosing regimen:

Use 1: Treatment of “moderate to moderately severe **chronic** pain not requiring rapid onset of analgesic effect.”

Approved Dosing: The exclusivity-protected 25 mg titration dosing schedule.

Use 2: Treatment of **acute** pain, i.e., pain for which “rapid onset of analgesic effect is required.”

Approved Dosing: 50 to 100 mg every four to six hours as needed, *with no titration.*

Teva’s tramadol product will only be labeled for the second of these uses, treatment of acute pain, for which neither Teva’s nor the innovator’s labeling recommends titration dosing of any kind:

Teva’s Tramadol	Ultram
<p>DOSAGE AND ADMINISTRATION Adults (17 years of age and over)</p> <p><i>[Exclusivity-protected use for treatment of chronic pain using titration dosing schedule omitted per 21 U.S.C. §§ 355(j)(5)(D)(iv), 355(j)(2)(A)(v), and 21 C.F.R. § 314.94(a)(8)(iv)].</i></p> <p>For <u>patients for whom rapid onset of analgesic effect is required</u> and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, <u>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.</u></p>	<p>DOSAGE AND ADMINISTRATION Adults (17 years of age and over)</p> <p>For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.</p> <p>For the subset of <u>patients for whom rapid onset of analgesic effect is required</u> and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, <u>ULTRAM 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.</u></p>

See ANDA 75-977, Labeling Amendment, Feb. 5, 2002, at 30 (emphasis added).

Additionally, it merits noting that the approved labeling of R. W. Johnson's Ultracet® provides for a dose of 75 mg of tramadol for the treatment of acute pain. This is yet another example of the sponsor proposing and the agency approving a non-titration dosing regimen for the treatment of acute pain.

Teva is entitled as a matter of law to omit protected indications or other labeling elements from its generic tramadol labeling, so long as the omission does not render Teva's drug unsafe for use ***under the conditions prescribed, recommended, or suggested in its proposed labeling.*** See 21 U.S.C. §§ 355(j)(5)(D)(iv), 355(j)(2)(A)(v), and 21 C.F.R. § 314.94(a)(8)(iv); *see also, Zeneca v. Shalala*, 1999 U.S. Dist. LEXIS 12327 at 31-34 (D. Md. Aug. 11, 1999), *affirmed* 216 F.3d 161 (4th Cir. 2000). Due to the exclusivity for the dosing regimen for the chronic pain use of Ultram, Teva has requested approval only for the non-exclusive use of tramadol for the treatment of acute pain requiring rapid relief. Importantly, **for this use of tramadol, the Dosage and Administration instructions for Teva's tramadol are identical to those for Ultram.** Thus, there can be no legitimate concern by FDA that Teva's proposed labeling would be less safe than the currently approved Ultram labeling for the acute pain use for which Teva seeks approval, and any further refusal to approve Teva's ANDA on the basis of such perceived concern would be contrary to law, arbitrary, and capricious.

Approval of Teva's Tramadol ANDA Would be Consistent With Relevant Case Law and Past FDA Approval Decisions

In *Zeneca v. Shalala, supra*, FDA approved a generic propofol product that contained a sulfite preservative (not present in the innovator product) that would be potentially very harmful to sulfite-sensitive patients. FDA determined that the presence of this preservative did not render the generic product unsafe because the generic product's sulfite warning eliminated the risk to sulfite-sensitive patients – specifically, ***when used as labeled*** with the sulfite warning, the generic product would not be given to such patients. The Courts agreed with and upheld FDA's approval decision. The same logic must be applied to Teva's tramadol, because ***when used as labeled, i.e., only for acute pain***, the product will not be given to chronic pain patients for whom the 25 mg titration dosing regimen is recommended. In other words, whereas the safety concern with generic propofol was cured by adding a sulfite warning, any safety concern that might exist if generic tramadol were prescribed for chronic pain without titration is cured by omitting the chronic pain use and the titration schedule that is exclusive for that use.

More generally, many innovator drugs receive approval and 3-year exclusivity for completely new indications, and FDA has no problem approving ANDAs that omit such exclusive indications, as well as any indication-specific dosing instructions. For example, FDA approved generic versions of Capoten (captopril) that omitted the exclusivity-protected use in diabetic nephropathy, even though the dosing and administration for the approved non-exclusive generic use (hypertension) was twice as high as the recommended dosing for diabetic nephropathy (50 mg t.i.d. vs. 25 mg t.i.d.). As the Agency is well aware, the courts upheld the authority to grant such generic captopril approvals under challenge by Bristol-Myers Squibb. *See Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996).

Thus, the Agency's focus on a supposed safety risk of omitting the chronic pain use and its exclusive 25 mg titration schedule from Teva's labeling is unnecessary, inappropriate, and completely ignores two crucial facts: (1) by limiting the labeled use of Teva's tramadol to the treatment of acute pain, Teva's product will not be labeled for the use (chronic pain) for which Ultram's labeling requires titration dosing; and (2) for the use in treating patients with acute pain, Teva's labeling has the same dosing instructions as Ultram. Therefore, there simply cannot be any reasonable basis to refuse to approve Teva's ANDA, as currently amended.

The Grammatically Garbled Ultram Labeling Should Not Be Used as an Excuse to Block Approval of Teva's ANDA

One might quibble with the characterization of Ultram labeling including a distinct use for "acute" pain, by noting that the Dosage and Administration section uses the grammatically inelegant phrase "for the subset of patients for whom rapid onset of analgesic effect is required...for pain relief" and does not explicitly use the word "acute." Such an objection would frivolously elevate form over substance, because this labeling statement is a clear and unequivocal reference to acute pain, and indeed, as FDA itself announced in a 1996 Talk Paper, "tramadol was approved March 3, 1995, for the management of acute and chronic pain." FDA Talk Paper T96-23 (April 3, 1996). Moreover, in medical terms, "acute" is the antonym of "chronic" and is defined in terms of speed of onset of the condition. *See, e.g.,* Stedman's Online Medical Dictionary: "*acute*: Referring to a health effect, usually of rapid onset, brief, not prolonged; sometimes loosely used to mean severe." (emphasis added); Merriam-Webster Medical Dictionary: "having a sudden onset, sharp rise, and short course." With respect to the Ultram labeling, reference to pain that requires "rapid onset of analgesic effect" is clearly a shorthand to acute pain, as distinguished from chronic pain for which titration dosing is recommended. And, even if the Ultram statement of use for "patients for whom rapid onset of analgesic effect is required" could be semantically construed to include certain types of chronic pain requiring rapid relief, the fact would remain that Teva's labeling safely excludes all patients for whom the 25 mg titration dosing regimen is recommended.

Another issue that may have arisen in FDA's consideration of Teva's approach is the fact that the distinction between chronic and acute pain is mentioned only in the Dosage and Administration section, and not in the "Indications" section, of the Ultram labeling. This fact does not detract from Teva's right to carve out this exclusivity-protected use for several reasons. First, as the statute and regulations make clear, the right to "carve out" patented or exclusivity protected labeling is not limited to "indications" (however defined or wherever placed in the labeling), but extends to any protected aspects of labeling. *See* 21 U.S.C. §§ 355(j)(5)(D)(iv), 355(j)(2)(A)(v), and 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). Second, as demonstrated by *Zeneca v. Shalala, supra*, different labeling is permissible even where the indication sections of the innovator and generic drugs are identical, but the change to the generic labeling results in it not being labeled for a certain subset of patients (in that case sulfite-sensitive patients). Third, the omission of the chronic/acute pain distinction from the Ultram "Indications" section appears to be a semantic anomaly resulting from the convoluted changes in dosing directions by the NDA sponsor. Although FDA has acknowledged that Ultram was approved for both acute and chronic pain, *see* FDA Talk Paper T96-23, *supra*, prior to the addition of the

exclusive 25 mg titration schedule, Ultram's Dosage and Administration section referred only to "the treatment of painful conditions," with dosing distinctions based solely on the *severity* of the pain – i.e., whether the patient had "moderate pain" or "more severe pain." The Dosage and Administration section was then changed to refer to two *types* of pain, chronic and acute, and to make dosing distinctions based upon the type of pain being treated – i.e., "**chronic** pain not requiring rapid onset of analgesic effect," or **acute** pain for which "rapid onset of analgesic effect is required." This new dosing distinction between types of pain perhaps should also be explicitly reflected in the indications section of Ultram's labeling, but the NDA sponsor chose not to seek such a change,³ and FDA, for its part, failed to recognize and prevent the anticompetitive effects on future generic applicants of the shifted focus of the Ultram Dosage and Administration labeling.

Finally, Teva's labeling will still have sufficient and appropriate information to assure its safe use as labeled for the treatment of pain requiring rapid relief. For example, just as in the Ultram labeling, Teva's labeling will describe the 50 mg titration trials in the Titration Trials section. See ANDA Amendment at 22. Moreover, Teva's labeling could also include the statement on individualization of dosage as it appears in the Ultram labeling without violating R. W. Johnson's exclusivity. Specifically, the Ultram labeling includes the statement: "Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose." This statement (although not proposed in Teva's February 5 supplement) would further address any lingering dosing concerns without infringing the Ultram exclusivity, because notwithstanding the fact that FDA approved this language at the same time as the exclusive 25 mg titration dosing, it would be preposterous to conclude that any clinical trials were "essential to the approval" of such a self-evident description of the state of "good pain management practices."

Conclusion

The Agency must recognize that Teva's approach to tramadol labeling is completely different than the "discontinued labeling" approach advocated by other applicants, which would require a determination by FDA that the discontinued 50 mg titration schedule was not withdrawn for safety reasons. Teva respectfully suggests that the discontinued labeling approach is unnecessary and inappropriate in this situation, because for the use for which it is labeled, Teva's tramadol has the same dosage labeling as the *currently* approved innovator labeling. Moreover, Teva's approach differs from other applicants who have focused on the definition of "safety" and comparisons between reducing adverse events and reducing drug withdrawal due to adverse events, *see e.g.*, Docket No. 01P-0495, Comments of Apotex, April 11, 2002. Teva's approach is a simple matter of applying the law to an established set of undisputed facts, and we are concerned that the Agency's focus on questions of its authority to permit discontinued labeling, and the safety issues arising under the discontinued labeling approach may be obscuring FDA's ability to properly recognize that Teva's approach fully complies with the statutory and regulatory approval requirements without raising any approval-blocking safety issues.

³ Indeed, R. W. Johnson appears to have intentionally sought to avoid the use of the word "acute" in the Ultram labeling in order to protect its marketing strategy for Ultracet, which touts Ultracet as allowing "Fast onset and long duration of pain relief," and "Flexible PRN dosing." See Ultracet web site at www.ultracet.com.

More than two months have passed since American consumers became entitled to access to more affordable generic versions of tramadol and FDA has failed to act. Every day of further delay is another day in which the Agency has failed to faithfully implement the public health mandate expressed in the Hatch-Waxman Amendments, and another day of unwarranted monopoly profits for the brand name marketer of Ultram at the expense of American consumers, health insurers, and state and federal governments who are forced to waste millions of dollars by the lack of generic competition. The agency should not allow the innovator company's devious anticompetitive labeling strategies to block legitimate, and safe, generic tramadol products.

The Agency has more than enough information and authority to lawfully grant final approval of Teva's tramadol ANDA, and we expect it to do so forthwith. We look forward to your most expeditious decision on this pending ANDA.

C. Environmental Impact

The actions requested by this Petition are subject to categorical exclusion pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

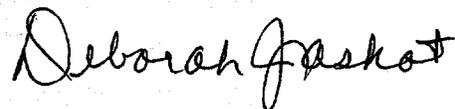
An Economic Impact Statement will be provided at the request of the Commissioner.

It is noted however, that by not expeditiously granting the Petition, FDA will continue to impose growing economic hardships upon many thousands of American patients, state governments, and public and private corporations and health insurance providers, due to the continued lack of price-lowering generic competition for tramadol drug products. Such a result is contrary to the public interest.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the Petition.

Sincerely,



Cc: Lester Crawford, D.V.M., Ph.D.
Janet Woodcock, MD
Daniel Troy, Esq.
Alex Azar, II, Esq.
Gary Buehler