

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-745**

**SUMMARY REVIEW**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS**

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**DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION**

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**DATE:** May 30, 2007

**DRUG:** Ryzolt (tramadol HCl extended-release tablets), 100 mg, 200 mg and 300 mg

**NDA:** 21-745

**SPONSOR:** Labopharm Canada Inc.

**INDICATION:** For the management of moderate to moderately severe pain

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Labopharm Canada Inc. submitted NDA 21-745 in support of marketing approval for Ryzolt, for the management of moderate to moderately severe pain, on November 28, 2005. An approvable letter was issued on September 28, 2006. At that time, the Division determined that the sponsor had not provided substantial evidence of efficacy. (See my review and basis for the action, also dated September 28, 2006.) The sponsor's interpretation of the efficacy results from their two pivotal efficacy trials, Studies 003 and 005, was based on their statistical analyses that employed the Last Observation Carried Forward (LOCF) imputation methodology to address missing data. When more appropriate, conservative imputation strategies were employed in our analyses of the data, statistically significant evidence of efficacy was not demonstrated.

A teleconference was held with the sponsor on October 20, 2006 and the Division's re-analyses of the efficacy data were discussed. The sponsor contended that the Division's decision to not accept the results of their efficacy analyses that employed the imputation strategy that had been included in the Special Protocol Agreement (SPA) for these studies, was inappropriate. The Division clearly explicated our reasoning for not accepting those analyses in the following response that was documented in the minutes of the teleconference:

The Division agreed that study MDT3-005 was carried out under a Special

Protocol Agreement and that the primary analysis by LOCF appeared to show efficacy. However, as communicated previously, primary analysis (sic) employing LOCF as the imputation methodology for missing data would not be sufficient unless confirmed by sensitivity analyses. Although some sensitivity analyses performed by the applicant appeared to confirm the efficacy results, these analyses all shared the common flaw of attributing good scores to patients who were unable to tolerate Ryzolt and subsequently discontinued treatment. Indeed, essentially all the efficacy of the drug in these analyses was attributable to patients who dropped out. If such a drug were approved, it would present insurmountable problems in labeling as the patient population for which the drug was effective appears to be the population which could not tolerate it.

The Division emphasized that it has been consistent in its advice to sponsors regarding preferred imputation strategies for trials of analgesic products. In this case, although there was agreement on the protocol and the planned analyses, including incorporation of sensitivity analyses, the Division does not agree with Labopharm as to the interpretation of the resultant data.

A formal End-of-Review (EOR) conference was held on November 27, 2006. Alternative approaches to the handling of missing data were discussed, in particular for Study 005. One specific type of imputation strategy was presented by the sponsor that on face appeared to be potentially useful, as noted in the minutes of the EOR conference:

The Sponsor discussed two broad classes of alternatives to LOCF. One class involved imputing what might have happened to dropouts if they had continued the assigned treatment. The other class involved imputing what did happen but was not observed, taking into account that the patients did discontinue treatment. The Division was more interested in the second class. The Sponsor described an analysis in which a typical placebo score, rather than a baseline score, was imputed, as an example of the second class. The Division believed this analysis might be very useful. Care was needed, however, in defining a typical placebo score, as the placebo group was also subject to informative censoring.

The use of an average of all scores during the study (Time Weighted Average or TWA) versus a landmark score at the end of study to analyze the primary outcome measure was also discussed:

The Sponsor explained that the objective of the TWA is to get the sense of robustness of the efficacy and to see real drug effect. BOCF imputation, which assigns unfavorable values for a patient who drops out of the study, focuses on patient status as (sic) the end of the study thereby limiting the 'power' of the study. TWA accounts for the overall experience of the patient during the trial, whether or not they are on treatment. The Division agreed that the TWA might be a good way to summarize the experience of a patient over 12 weeks, but noted that the 12-week experience is itself a surrogate for outcomes over a longer term. Patients who do not tolerate the treatment for 12 weeks cannot be expected to benefit from it in the long term. The Sponsor stated that the frequency of patient dropout observed during the trial would be much less in clinical practice where dosing would be based on tolerability and effect. The Division noted that the trials did not investigate the effects in such a setting. Accordingly, for a trial of only

12 weeks, the Division believes the end-of-study analysis is more relevant than the time weighed (sic) average.

The sponsor was advised to reanalyze their data using their proposed new imputation strategies and provide these analyses in their resubmission. They were also advised that this resubmission would most likely be determined to be a Class 2 resubmission on a six-month review clock, although the Division might be able to complete the review in less than six months.

A complete response to the approvable letter was submitted on December 18, 2006 and was, indeed, determined to be a Class 2 resubmission. On December 19, 2006, a request for Formal Dispute Resolution on the action taken by the Division was received by the Office of New Drugs (OND). This request was denied, based on the fact that the sponsor had already submitted a complete response to the approvable letter. On January 24, 2007, a second request for FDR regarding the Division's action was received by OND. This request was also denied, for the same reason as the previous request. Yet another request for FDR on the same matter was submitted to the Center Director's Office on March 14, 2007. Once again, the request was denied. Requests for FDR on the Division's determination that the complete response was a Class 2 resubmission were also denied by both the Office of New Drugs II and OND. On February 8, 2007, the sponsor submitted a response to a request for information from the statistical reviewer.

In their resubmission, the sponsor employed four new sensitivity analyses. These included: 1) Placebo Mean or Median Trajectory Carried Forward; 2) Last On-Study Observation Carried Forward (LOnSCF); 3) Time Weighted Average; and 4) a Completers Analysis. The reviews by Dr. Jin Chen, the clinical reviewer, and Dr. Yongman Kim, the statistical reviewer, provide detailed discussions of the results of these analyses, as well as additional analyses performed by the reviewers themselves, and the reader is referred to their reviews for those details. I will briefly summarize the results of the sensitivity analyses below.

The results of the sponsor's Completers Analysis, which was based only on subjects who completed the 12-week treatment period, did not demonstrate a statistically significant treatment effect for Ryzolt. While a statistically significant treatment effect was demonstrated when the LOnSCF strategy was employed, this method of imputation is similar to the use of LOCF and does not address the Division's concern regarding good scores being assigned to subjects who could not tolerate the drug. The sponsor's Time Weighted Average analyses employing either LOCF or BOCF imputation strategies did demonstrate statistically significant treatment effects. However, those results can only be considered supportive data as they were highly driven by a relatively large effect at Week 2 that was not sustained through Week 12.

The sponsor's Placebo Mean Trajectory Carried Forward and Placebo Median Trajectory Carried Forward analyses demonstrated statistically significant treatment effects for Ryzolt. However, these strategies calculated changes between visits for the placebo

group which were then subtracted from the last observed pain scores in the Ryzolt subjects with missing data. Again, this methodology does not address the Division's concern, as it may result in favorable outcomes being applied to subjects who dropped out due to adverse events. Dr. Kim expressed his concern (page 14 of his review) that, "...the methods give more benefit to early dropouts and could assign even better scores than the last observation carried forward method."

Dr. Kim performed a continuous responder analysis as an additional sensitivity probe. A continuous responder analysis had been performed in the original review, but this new analysis was considered to be less conservative as only dropouts due to adverse events or lack of efficacy were counted as non-responders. Nevertheless, this less conservative analysis still failed to show a statistically significant treatment effect for Ryzolt. Other analyses performed by the review team were also unsuccessful at overcoming the primary problems associated with this dataset.

### ***Discussion***

The sponsor's complete response to the Division's approvable letter consists of a number of sensitivity analyses that further probe the efficacy assessment included in the original submission. These sensitivity analyses have failed to provide support for a determination that substantial evidence of efficacy exists for this particular formulation of tramadol in the treatment of moderate to moderately severe pain. Further attempts by the clinical and statistical review staff to reanalyze the data also failed to demonstrate evidence of efficacy.

As noted in the original approvable letter, the sponsor must submit at least one additional adequate and well-controlled study that demonstrates the efficacy of Ryzolt, employing appropriate statistical analysis methodologies. The sponsor should also consider the possibility that the specific pharmacokinetic profile of their product may be inappropriate for once a day dosing.

***Action:*** Approvable

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