CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-745

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	October 30, 2008
From	Ellen Fields, M.D., M.P.H.
NDA/BLA # Supp #	NDA 21-745 Resubmission
Proprietary / Established name	Ryzolt (tramadol hydrochloride extended-release tablets)
Dosage forms / strength	Extended-release tablets/100mg, 200mg, 300mg
Proposed Indication	Management of moderate to moderately severe pain
Recommended:	Approval

1. Introduction to Review

Labopharm Canada Inc. originally submitted NDA 21-745 on November 28, 2005, in support of marketing approval for Ryzolt, for the management of moderate to moderately severe pain. The product is an extended-release tablet formulation of tramadol HCl that was studied in dosage strengths of 100, 200 and 300 mg. The Ryzolt tablet is comprised of a dual-matrix delivery system with an outer layer that is designed to release tramadol in an extended manner, but at a faster rate than the core layer. This application was a 505(b)(2) submission relying upon the Agency's prior finding of safety and effectiveness of Ultram for some portions of the submission.

The Division took an Approvable action on September 28, 2007 based on the lack of support for the efficacy of Ryzolt and the use of inappropriate imputation strategies for missing data in the Sponsor's statistical analyses. A second Approvable action (resubmission dated December 2007) was taken on May 30, 2008 for the same reason. In order to resolve deficiencies in the application, the Sponsor was told to provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial. The Sponsor subsequently submitted three requests for Formal Dispute Resolution which were denied, however a path forward consisting of a new statistical analysis approach to one of the efficacy studies was provided by Dr. John Jenkins.

The result of the statistical reanalysis is the subject of this memo.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

The following is a summary of the efficacy and safety findings as described in the original NDA review completed by Dr. Jin Chen, Dr. Mwango Kashoki's Team Leader memo, and the Division Director's Memo by Dr. Bob Rappaport. Please refer to these reviews for additional details.

The sponsor submitted the results of three adequate and well-controlled trials in their original application. Two of these trials, Study MDT3-003 (003) and Study MDT3-005 (005) were submitted in support of their claim that the product is effective. Study MDT3-002 (002) was identical in design to Study 003 and was included in the application, although the Sponsor acknowledged that it failed to demonstrate efficacy.

Study 003 was a parallel-group, randomized, double-blind, placebo-controlled, multicenter trial that compared Ryzolt 100 mg, 200 mg and 300 mg to placebo, in adults with osteoarthritis of the knee and a minimal pain intensity score of greater than 150 mm on the WOMAC Pain Subscale. The primary outcome measure was the percent change in the WOMAC Pain Subscale score from baseline to the end of the study at Week 12. Forty-six percent of subjects in the tramadol treatment group and 41% in the placebo group dropped out of the study prior to Week 12.

The Sponsor's analysis of the primary outcome employed a last observation carried forward (LOCF) imputation methodology and found that only the 300-mg dose demonstrated a statistically significant treatment effect compared to placebo. The Sponsor also analyzed the data employing a baseline observation carried forward (BOCF) imputation methodology which demonstrated no statistically significant treatment effect for any dose of Ryzolt compared to placebo.

Additionally, the Sponsor performed a responder analysis and looked at 10%, 30%, and 50% improvement. They found that the 200mg dose demonstrated a statistically significant effect at 10% and 30%, and the 300mg dose demonstrated a statistically significant effect at 30% and 50%. The Sponsor's analysis inappropriately utilized the LOCF imputation. Since patients who drop out (either due to lack of efficacy or adverse events) are treatment failures, they should be counted as non-responders. The statistical reviewer reanalyzed the data using a continuous responder analysis without the LOCF imputation, and no statistically significant separation in the curves was demonstrated. Analysis of secondary outcomes using BOCF imputation methodology showed no statistically significant treatment effects for any dose of Ryzolt compared to placebo.

Study 005 was a parallel-group, randomized, double-blind, placebo-controlled, multicenter trial that compared Ryzolt to placebo, in adults with osteoarthritis of the knee and a minimal pain intensity score of greater than or equal to 4 on an 11-point Pain Intensity Numerical Rating Scale. The trial employed an initial open-label phase during which subjects were titrated to individual Ryzolt doses based on optimal efficacy and tolerability. Thirty-five percent of the subjects dropped out during the open-label phase, 22% due to adverse events (AEs) and 3% due to lack of efficacy. The remaining subjects underwent washout followed by randomization to either their previously demonstrated optimal dose or placebo. The subjects were titrated to these doses over two weeks and then maintained on the doses for 12 weeks. The primary outcome measure was the percent change in the group mean Pain Intensity score from baseline (defined as the end of the washout period) to the end of the study at Week 12. Twenty-four percent of cases in the active treatment group and 22 percent of cases in the placebo group dropped out of the study prior to Week 12.

Employing the LOCF imputation methodology, the Sponsor found that there was a statistically significant treatment effect for the Ryzolt group compared to the placebo group. However, a reanalysis employing the BOCF imputation methodology by Dr. Youngman Kim found no statistically significant treatment effect.

The sponsor also conducted a responder analysis which they interpreted as supportive of efficacy. However, when the statistical reviewer performed a continuous responder analysis, he found that, employing a van der Waerden test, there was no statistically significant separation between the Ryzolt and placebo curves. The secondary outcome measures were also not supportive of efficacy for Ryzolt.

There were no new safety findings revealed during review other than those already known to be associated with the use of tramadol.

The Biopharmaceutics review showed that there is a 9-hour period of relatively lower plasma level with once-daily dosed Ryzolt compared to Ultram dosed according to the label every six hours.

On September 28, 2007 an Approvable action was taken for this application based on the following deficiencies as stated in the action letter:

1. "You have not provided substantial evidence that Ryzolt is effective for your proposed indication of the management of moderate to moderately severe pain. Your conclusion that efficacy has been demonstrated in studies MDT3-003 and MDT3-005 depends on the use of a last observation carried forward (LOCF) imputation methodology for patients who dropped out of the studies. We consider this method of imputing missing data inappropriate, and efficacy was not confirmed when other methods, such as baseline observation carried forward (BOCF) or continuous responder analysis (of the patient's status at the end of the study) were employed. Provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial. Ryzolt produced at your commercial manufacturing site should be used in future clinical trials."

2. "The pharmacokinetic profile of Ryzolt demonstrated low plasma levels of tramadol, compared to Ultram, for a significant portion of time during the proposed 24-hour dosing interval. This finding may be, at best, partially responsible for your inability to demonstrate efficacy in the clinical trials. Provide a discussion, and data as appropriate, to address this concern."

On December 18, 2006 a Complete Response to the Approvable action was submitted to the Agency. In the time between the Approvable action on the original submission and the Complete Response, the Sponsor had met with the Division to discuss deficiencies related primarily related to Study 005. The resubmission contained reanalyses of the primary efficacy data from Study 005.

The Sponsor employed four new sensitivity analysis methods to assess the treatment effect of Ryzolt using LOCF imputation methodology. Details regarding these analyses and the Sponsor's response to deficiency #2 may be found in Dr. Jin Chen's clinical review.

An Approvable action was taken on May 30, 2007 based on the following deficiency as stated in the action letter:

"You have failed to demonstrate the efficacy of Ryzolt for your proposed indication of the management of moderate to moderately severe pain. Your conclusion of efficacy is dependent on the use of imputation strategies for missing data that do not adequately address the problem of good scores being assigned to subjects who dropped out because they were unable to tolerate the product. Provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial."

The Sponsor proceeded to file a request for formal dispute resolution (FDRR) on October 15, 2007 concerning the approvable action taken by the Division. It requested that the Agency rule that the data already submitted demonstrate substantial evidence of effectiveness for approval of NDA 21-745. Dr. Curtis Rosebraugh, ODE II Director, upheld the Division's findings in a letter dated November 20, 2007. The Sponsor appealed the FDRR at the Office level, which was answered by Dr. John Jenkins on January 18, 2008. Dr. Jenkins also concluded that the Sponsor had not met the statutory standard for demonstration of efficacy of Ryzolt; however, he provided a path forward for further review of the application that could obviate the need for an additional clinical trial.

In consultation with staff from the Office of Biostatistics, Dr. Jenkins recommended that the Sponsor reanalyze the primary endpoint for Study 005 using the following method of imputation (taken from Dr. Jenkins' letter of January 18, 2008):

> "Missing data at the end of the study will be imputed by scores drawn randomly from the placebo observations at end of study rather than by baseline scores. Specifically:
>
> 1. Stratify the placebo completers in tertiles with respect to outcome: upper third, middle third, lower third.
> 2. Stratify the combined active and placebo groups by tertile with respect to baseline score.
> 3. For each missing observation at week 12, substitute a random score from the placebo completers, drawn from the same tertile that the baseline score for that individual fell into.
> 4. Conduct the protocol-specified primary analysis on the now complete data set."

On March 31, 2008, the Sponsor appealed the FDRR to CDER. Dr. Douglas Throckmorton responded on June 27, 2008 and recommended "prompt submission of the statistical analysis suggested by Dr. Jenkins in the form of a Complete Response. A positive finding on this analysis will provide the needed assurance to support the efficacy of Ryzolt for the proposed indication."

A Complete Response was submitted on July 2, 2008, and is the subject of this memo.

3. CMC/Microbiology/Device
This submission did not contain any new CMC information.

4. Nonclinical Pharmacology/Toxicology
This submission did not contain any new Pharmacology/Toxicology information

5. Clinical Pharmacology/Biopharmaceutics
This submission did not contain any new Clinical Pharmacology information

6. Clinical Microbiology
N/A

7. Clinical/Statistical

7.1. Efficacy
This submission consists of a reanalysis of study MDT3-005. The primary analysis of this study was described in the statistical review of the 2006 resubmission by Yongman Kim, Ph.D., and is summarized in the statistical review of this resubmission by Thomas Permutt, Ph.D., Director of the Division of Biometrics II. A complete review of the study design and results may be found in Dr. Jin Chen's clinical review of September, 2006.

As stated above in Section 2, Study 005 was a parallel-group, randomized, double-blind, placebo-controlled, multicenter trial that compared Ryzolt to placebo, in adults with osteoarthritis of the knee and a minimal pain intensity score of greater than or equal to 4 on an 11-point Pain Intensity Numerical Rating Scale. The primary endpoint was the percent change in the group mean Pain Intensity score from baseline (defined as the end of the washout period) to the end of the study at Week 12.

In the original NDA submission and the Complete Response of December, 2006, the Sponsor employed the LOCF imputation methodology to account for missing data, and found that there was a statistically significant treatment effect for the Ryzolt group compared to the placebo group. In the case of dropouts due to lack of efficacy, a bad pain measurement would likely be captured and carried forward, however for dropouts due to adverse events, the pain score carried forward could be a good score. This would result in the imputation of a good outcome for a patient who could not continue taking the drug. The reanalysis of the data by Dr. Kim employing the BOCF imputation methodology found no statistically significant treatment effect.

Dr Kim also performed a continuous responder analysis and found that, employing a van der Waerden test, there was no statistically significant separation between the Ryzolt and placebo curves. The secondary outcome measures were also not supportive of efficacy for Ryzolt.

In the current submission, the Sponsor performed a reanalysis of the data using a modified version of the method put forth by Dr. Jenkins and described in Section 2. The definition of

tertile was modified so that there would not be any overlap between tertiles, and the imputation procedure was performed multiple times and averaged in order to account for variations between repetitions in estimating standard errors. These modifications are described in detail in Dr. Permutt's review. He found them acceptable.

The results of the Sponsor's analysis are summarized in the table below.

Multiple imputation results: No overlapping tertiles					
			t-statistic		
Imputations	Mean	SE	Value	df	p-value
10	0.359	0.189	1.90	165	0.059
20	0.372	0.189	1.97	124	0.051
30	0.374	0.190	1.97	94	0.052
40	0.373	0.190	1.97	107	0.052
50	0.371	0.190	1.96	115	0.053
75	0.374	0.189	1.97	138	0.050
100	0.372	0.189	1.96	162	0.051
125	0.373	0.189	1.97	187	0.050
150	0.373	0.189	1.97	208	0.050
200	0.372	0.190	1.96	253	0.051
250	0.373	0.189	1.97	306	0.050
300	0.374	0.190	1.97	355	0.049
350	0.375	0.189	1.98	406	0.049
The seed used to select the imputed values for the i^{th} dataset was defined as: $36 + 10 \times i$.					

Source: Resubmission, p.7

In Dr. Permutt's review, he states that

> "There is a minor problem of multiplicity, as in trials with interim analyses. The figures, including the p-value, based on more data are more reliable than those based on fewer, so that more weight should be given to the last line of the table than the first...."

Dr. Permutt concluded that the result of the Sponsor's analysis is statistically significant, albeit at the weakest possible level usually accepted.

7.2. Safety

The Sponsor submitted a safety update for Ryzolt as of June 10, 2008 which includes the IND Annual Report for 2007 and two Periodic Safety Update Reports for the dates August 2006 to February 2007, and February 2007 to February 2008. There have been no significant changes to the safety profile since the submission of the safety updates of March, 2006, June, 2006, and December, 2006, which were reviewed by Dr. Chen.

There have been three clinical studies conducted on Ryzolt since the completion of the review of the original NDA submission. A summary of the safety findings are shown in the table below.

Study	Completed	Design	N	Deaths	SAEs	Common AEs	Withdrawals due to AEs
MDT1-014	2006	R, 2-way XO, PK to compare 4X50mg IR tramadol vs. 1 X 200mg Ryzolt, fasting	26	0	0	dizziness headache nausea	1 subject with moderate vomiting
MDT1-017	2007	OL, single-dose, R, XO, fasting, dose proportionality 150mg and 250mg vs. 200mg Ryzolt	26	0	0	dizziness nausea	1 subject with moderate vomiting
MDT1-020	2008	DB, R, XO, PK and efficacy in healthy young and elderly vol, fasting; 200mg Ryzolt vs. placebo	35	0	0	nausea dizziness vomiting somnolence	0

The above information does not suggest any change in the safety profile of Ryzolt.

Summary of World Wide Experience

Tramadol Contramid OAD (European Proprietary name) has been approved in 29 countries. The Sponsor estimates the number of daily doses sold since launch to be ———. From August 3, 2006 to February 2, 2008, 72 adverse drug reactions were reported to the Sponsor. Of these, 40 were nonserious expected, 24 serious expected, 3 nonserious unexpected, and 5 serious unexpected. Expectedness was based on European labeling. None of the reports resulted in changes in the European labeling.

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The nonserious unexpected reactions included speech disorder, movement disorder and dry mouth in a 62 year old female receiving 300mg; drug ineffective in a female receiving 300mg; and dysuria and increased PSA in a 65 year old male receiving 300mg.

The serious unexpected adverse reactions included a CVA in an 80 year old female receiving unknown strength or formulation of tramadol; bile duct stenosis and cholangitis in a 76 year old female receiving unknown strength and formulation of tramadol; mild gastrointestinal hemorrhage in a male receiving unspecified dosage of Tramadol Contramid OAD; sudden death in a 37 year old receiving unknown strength or formulation of tramadol; and confusional state, hepatic encephalopathy and esophageal hemorrhage in a 35 year old male receiving 100mg of unknown formulation of tramadol. This patient had at least 11 concomitant medications.

8. Advisory Committee Meeting

No Advisory Committee was convened to discuss this application.

9. Other Relevant Regulatory Issues

N/A

10. Financial Disclosure

N/A

11. Labeling

Other aspects of the review will address labeling in more detail. Only highlights of labeling discussions and areas of concern are to be addressed in this memo.

11.1. Proprietary name
The proprietary name, Ryzolt, was found acceptable by the Division of Medication Error Prevention and Analysis, as stated in the review dated September 12, 2008.

11.2. Physician labeling
The label is being modified to include pertinent aspects of the statistical reanalysis of study 005.

11.3 Carton and immediate container labels
These were previously found acceptable.

DSI Audits

There were no DSI inspections associated with this submission.

12. Conclusions and Recommendations

12.1. Recommended regulatory action
I recommend approval of Ryzolt for the management of moderate to moderately severe pain. The reanalysis provided by the Sponsor meets the criteria for approval as specified by Drs. John Jenkins and Douglas Throckmorton in their responses to the FDRR, and reviewed by Dr. Thomas Permutt.

12.2. Safety concerns to be followed postmarketing
No new safety concerns were described in this submission.

12.3. Risk Minimization Action Plan, if any
At this point in time, there does not appear to be a need for a Risk Evaluation and Mitigation Strategy. Should new safety concerns be identified in the future, this issue may be revisited.

12.4. Postmarketing studies, voluntary or required (e.g., under PREA, Subpart H)
N/A

12.5. Comments to be conveyed to the applicant in the regulatory action letter (e.g., deficiencies and information needed to resolve each deficiency)
N/A

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/s/

Ellen Fields
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