CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-192

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-192
Submission Code	N
Letter Date	September 27, 2007
Stamp Date	September 27, 2007
PDUFA Goal Date	July 27, 2008
Reviewer(s) Name(s)	Michelle M. Chuen, M.D.
Review Completion Date	June 13, 2008
Established Name	Iloperidone
Trade Name	None
Therapeutic Class	Antipsychotic
Applicant	Vanda Pharmaceuticals Inc.
Priority Designation	S
Formulation	1, 2, 4, 6, 8, 10, and 12 mg Tablets
Dosing Regimen	12-24 mg/day administered BID
Indication	Schizophrenia
Intended Population	Adults with Schizophrenia

Table of Contents

1 EXECUTIVE SUMMARY 5

1.1 RECOMMENDATION ON REGULATORY ACTION 5
1.1.1 Risk Management Activity 5
1.1.2 Required Phase 4 Commitments 5
1.1.3 Other Phase 4 Requests 5
1.2 SUMMARY OF CLINICAL FINDINGS 5
1.2.1 Brief Overview of Clinical Program 5
1.2.2 Efficacy 6
1.2.3 Safety 6
1.2.4 Dosing Regimen and Administration 7
1.2.5 Drug-Drug Interactions 7
1.2.6 Special Populations 7

2 INTRODUCTION AND BACKGROUND 7

2.1 PRODUCT INFORMATION 7
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 8
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 8
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 8
2.5 PRESUBMISSION REGULATORY ACTIVITY 8
2.6 OTHER RELEVANT BACKGROUND INFORMATION 12

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 12

3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) 12
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 12
3.3 STATISTICAL REVIEW AND EVALUATION 12
3.4 DSI CLINICAL SITE INSPECTIONS 12

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 15

4.1 SOURCES OF CLINICAL DATA 15
4.2 TABLES OF CLINICAL STUDIES 15
4.3 REVIEW STRATEGY 19
4.4 DATA QUALITY AND INTEGRITY 20
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 21
4.6 FINANCIAL DISCLOSURES 21

5 CLINICAL PHARMACOLOGY 23

5.1 PHARMACOKINETICS 23
5.2 PHARMACODYNAMICS 24
5.3 EXPOSURE-RESPONSE RELATIONSHIPS 26

6 INTEGRATED REVIEW OF EFFICACY 26

6.1 INDICATION 26
6.1.1 Methods 26
6.1.2 General Discussion of Endpoints 26
6.1.3 Study Design 26
6.1.4 Efficacy Findings 27
6.1.5 Clinical Microbiology 31
6.1.6 Efficacy Conclusions 31

7 INTEGRATED REVIEW OF SAFETY 31

7.1 METHODS AND FINDINGS 31
7.1.1 Deaths 32
7.1.2 Other Serious Adverse Events 43
7.1.3 Dropouts and Other Significant Adverse Events 53
7.1.4 Other Search Strategies 60
7.1.5 Common Adverse Events 61
7.1.6 Less Common Adverse Events 65
7.1.7 Laboratory Findings 65
7.1.8 Vital Signs 70
7.1.9 Electrocardiograms (ECGs) 73
7.1.10 Immunogenicity 75
7.1.11 Human Carcinogenicity 75
7.1.12 Special Safety Studies 75
7.1.13 Withdrawal Phenomena and/or Abuse Potential 76
7.1.14 Human Reproduction and Pregnancy Data 76
7.1.15 Assessment of Effect on Growth 76
7.1.16 Overdose Experience 76
7.1.17 Postmarketing Experience 77
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 77
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 77
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 81
7.2.3 Adequacy of Overall Clinical Experience 81
7.2.4 Adequacy of Routine Clinical Testing 81
7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup 82
7.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study 82
7.2.7 Assessment of Quality and Completeness of Data 82
7.2.8 Additional Submissions, Including Safety Update 83
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS 83
7.4 GENERAL METHODOLOGY 85
7.4.1 Pooling Data across Studies to Estimate and Compare Incidence 85
7.4.2 Explorations for Predictive Factors 85
7.4.3 Causality Determination 85

8 ADDITIONAL CLINICAL ISSUES 86

8.1 DOSING REGIMEN AND ADMINISTRATION 86
8.2 DRUG-DRUG INTERACTIONS 86
8.3 SPECIAL POPULATIONS 86
8.4 PEDIATRICS 86
8.5 ADVISORY COMMITTEE MEETING 87
8.6 LITERATURE REVIEW 87
8.7 POSTMARKETING RISK MANAGEMENT PLAN 87
8.8 OTHER RELEVANT MATERIALS 87

9 OVERALL ASSESSMENT 87

9.1 CONCLUSIONS 87
9.2 RECOMMENDATION ON REGULATORY ACTION 88
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 88
9.3.1 Risk Management Activity 88
9.3.2 Required Phase 4 Commitments 88

9.3.3 Other Phase 4 Requests....89
9.4 LABELING REVIEW....89
9.5 COMMENTS TO APPLICANT....89

10 APPENDICES....93

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS....93
10.2 LINE-BY-LINE LABELING REVIEW....130
10.3 APPENDIX TO INDIVIDUAL STUDY REPORTS....131
10.4 APPENDIX TO DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY (SECTION 4)....177
10.5 APPENDIX TO INTEGRATED REVIEW OF SAFETY (SECTION 7)....180

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.