Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 20, 2008
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From:	Amarilys Vega, MD, MPH, Medical Reviewer Division of Epidemiology (DEPI)
Subject:	Aripiprazole-Related Extrapyramidal Symptoms: A Review of Scherk 2007 Meta-analysis Findings
Drug Name(s):	Aripiprazole (Abilify®)
NDA #:	21436
Applicant/sponsor:	Otsuka Pharmaceutical Co., Ltd.
OSE RCM #:	2336

CONTENTS

EXECUTIVE SUMMARY

Aripiprazole was selected to undergo a complete safety review as part of the New Molecular Entity (NME) Evaluation Pilot Project. A medical literature review was conducted by OSE and presented to the evaluation group on March 17, 2008. A meta-analysis published by Scherk et al in 2007 was of special interest to the group. This study's objective was to assess the efficacy and safety of Second Generation Antipsychotics (SGAs) in the treatment of acute mania through a meta-analysis of randomized clinical trials. Scherk's study suggested that, based on adverse event incidence rates, some SGAs (including aripiprazole) were more likely to generate extrapyramidal symptoms (EPS) than placebo. EPS rating scales for dyskinesias and parkinsonian reactions failed by a very small margin to reach statistical significance for an increase in EPS-related events in the aripiprazole group when compared to placebo. Akathisia was the most frequently reported EPS-related event. These findings are consistent with information provided in the label. An adverse event dose-effect analysis was not done in this meta-analysis.

In the aripiprazole's NME Evaluation document the reviewer noted in reference to Scherk's study that "*when comparing second generation antipsychotics (SGAs) to placebo, the incidence of extrapyramidal symptoms was significantly higher in the aripiprazole and risperidone trials and in the pooled analysis of all second generation antipsychotics*". In a summary in the same document the reviewer also noted that, "*In a meta-analysis, aripiprazole presented a significantly higher extrapyramidal symptoms incidence rate than most second generation antipsychotics (SGAs) and placebo*". A more detailed review of the meta-analysis showed that a significantly higher extrapyramidal symptoms incidence rate for aripiprazole was observed only when it was compared to placebo. There were no significant differences in EPS incidence among SGAs when compared to placebo.

EPS was not defined in any of the studies included in the Scherk meta-analyses nor in most of aripiprazole trials reviewed for the NME Evaluation Pilot Project. EPS manifestations may be described by terms other than akathisia and extrapyramidal syndrome and, unless included as part of a comprehensive definition of EPS, could easily be excluded from the analysis potentially leading to an underestimation of the true EPS incidence rate. Medical Dictionary for Regulatory Activities (MedDRA) terms included in Standardized MedDRA Query (SMQ) *'Extrapyramidal Syndrome'* should be considered when assessing the occurrence of EPS.

Conclusions

- In a meta-analysis by Scherk, aripiprazole's EPS overall incidence rate was higher than placebo, but similar to the incidence rates of other SGAs. These findings were consistent with the label.
- EPS-related adverse events were not clearly defined in studies included in this meta-analysis making the interpretation of EPS findings difficult. Consistent use of an EPS definition could potentially improve the assessment of EPS incidence rate. MedDRA SMQ 'Extrapyramidal Syndrome' is a good source of EPS-related terms.
- Adverse event dose-effect analysis was not done in this meta-analysis.

Recommendations

- In the aripiprazole NME Evaluation background document, change the summary statement bullet in Section F.2-2b. to read: "*In a meta-analysis, aripiprazole presented significantly higher extrapyramidal symptoms incidence rate than placebo*."
- For future aripiprazole submissions, request from the sponsor a complete list of terms included in their definition of EPS

1 BACKGROUND

Aripiprazole was selected to undergo a complete safety review as part of the New Molecular Entity (NME) Evaluation Pilot Project, a joint effort between Office of New Drugs (OND) and Office of Surveillance and Epidemiology (OSE). Aripiprazole is an atypical antipsychotic with D_2 and 5-HT_{1A} receptors partial agonist activity.

A medical literature review was conducted by OSE and presented to the evaluation group on March 17, 2008. A systematic review and meta-analysis published by Scherk[1] et al in 2007 was of special interest to the group due to his findings on the incidence rate of extrapyramidal symptoms (EPS). In aripiprazole's NME Evaluation background document, Section F.2 AEs Unlabeled - Rebound/withdrawal reactions/Safety findings summary/2.b. Extrapyramidal symptoms the reviewer noted that, *"In a meta-analysis, aripiprazole presented significantly higher extrapyramidal symptoms incidence rate than most second generation antipsychotics (SGAs) and placebo."* In addition, the reviewer also noted in this same document section, under sub-heading III. Extrapyramidal symptoms/Meta-analysis/Scherk 2007, "*When comparing second generation antipsychotics (SGAs) to placebo, the incidence of extrapyramidal symptoms was significantly higher in the aripiprazole and risperidone trials and in the pooled analysis of all second generation antipsychotics. Akathisia was significantly more pronounced in patients treated with aripiprazole and ziprasidone."* The goal of this review is to more closely review the meta-analysis and clarify the statements noted above by providing more details about Scherk's systematic review and meta-analysis regarding EPS occurrence in patients treated with aripiprazole. Thus, only EPS-related study findings are addressed in this review.

Extrapyramidal disorders

Extrapyramidal disorders result from dysfunctions in basal ganglia. A wide variety of symptoms may emerge from this dysfunction including acute dystonic reactions, parkinsonian syndrome, akathisia, akinesia, rabbit syndrome, tardive dyskinesia, and neuroleptic malignant syndrome[2].

Aripiprazole Label Excerpt: Extrapyramidal disorders

Aripiprazole label contains several paragraphs dedicated to extrapyramidal symptoms in clinical trials under *Label Section 6. Adverse Reactions* (see Appendix 1). Based on evidence from the clinical trials, the label divides extrapyramidal symptoms in two categories only: akathisia-related events and EPS-related events (excluding events related to akathisia). However, the label does not describe which conditions are included in the EPS-related events category. All pivotal trials described in the label detected a higher incidence of akathisia when comparing aripiprazole-treated subjects with subjects receiving placebo (see Appendix 2 Table 1). The frequency of occurrence of EPS-related events (excluding akathisia) in short-term, placebo-controlled trials in adults patients with schizophrenia and in long-term, placebo-controlled trials of patients with agitation associated with schizophrenia or bipolar mania was similar in both the placebo and the aripiprazole-treated groups. Among all aripiprazole treated subjects described in the label, pediatric patients with schizophrenia had the highest frequency of EPS-related events (excluding akathisia) (see Appendix 2 Table 1).

[1] Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. Arch Gen Psychiatry. 2007 Apr;64(4):442-55

[2] Strauss, Gordon D.American Psychiatric Press Textbook of Psychiatry, 2nd Edition Edited by Robert E. Hales, Stuart C. Yudofsky, John A. Talbott Washington, DC, American Psychiatric Press, Inc., 1994

2 METHODS

The methodology and findings of Scherk's study and of the 3 studies included in Scherk's meta-analysis involving the use of aripiprazole were reviewed and all EPS-related findings were abstracted. Scherk's meta-analysis included the following randomized, double-blind, placebo-controlled trials:

(1) Keck 2003[3] - Aripiprazole Study Group. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania.

(2) McQuade[4] 2003 - Aripiprazole vs placebo in acute mania: safety and tolerability pooled analysis.

(3) Sachs[5] 2006 - Aripiprazole Study Group. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study.

3 RESULTS

3.1 SCHERK'S STUDY DESCRIPTION

Study Title
The title of the meta-analysis paper was '*Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trial*s'.

Study Objectives
Study the efficacy and safety of SGAs in the treatment of acute mania through a meta-analysis.

Methods
Second generation antipsychotics (SGAs) are used in the treatment of acute mania but there is considerable variation in treatment guidelines across committees or working groups. Scherk's study design included comparisons of several acute mania treatment options: (1) SGAs vs Placebo, (2) SGAs vs Haloperidol, (3) SGAs vs Mood Stabilizers, and (4) SGAs plus Mood Stabilizer combination vs Mood Stabilizer alone. An adverse event dose-effect analysis was not done in this meta-analysis.

Medical Literature Search Strategy
The clinical trials included in the meta-analysis were identified using the following search strategy:

1. Searched Databases – PsiTri database and MEDLINE

2. Publications selection criteria

- All published and unpublished randomized controlled trials assessing the efficacy of aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and zotepine in the treatment of mania.

[3] Keck PE Jr, Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, Ingenito G; Aripiprazole Study Group. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry. 2003 Sep;160(9):1651-8

[4] McQuade RD, Marcus R, Sanchez R. Aripiprazole vs placebo in acute mania: safety and tolerability pooled analysis. Paper presented at: 5th International Conference on Bipolar Disorder; June 12-14, 2003; Pittsburgh, Pa

[5] Sachs G, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, Abou-Gharbia N,Impellizzeri C, Kaplita S, Rollin L, Iwamoto T; Aripiprazole Study Group. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. J Psychopharmacol. 2006 Jul;20(4):536-46.

- Disease terms: mania, manic, bipolar

3. Investigators searched for further trials and missing data necessary for the meta-analysis by directly inquiring of selected publications' first and last authors and manufacturers (Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Janssen-Cilag, and Pfizer).

4. Only trials considered as having low risk for bias were included (based on The Cochrane Collaboration Handbook trial quality categories).

Outcome Parameters
The following were identified as outcomes in the analysis

(1) Primary outcome - Young Mania Rating Scale (YMRS) or similar scales scores (mean change from baseline to end point - generally a reduction of at least 50% on YMRS).

(2) Other outcomes - Rate of response and effectiveness criteria: dropouts for any reason, dropouts due to adverse events, drop outs due to inefficacy, mean weight gain, rate of somnolence, and EPS.

(3) EPS objective measures included:

- Simpson Angus Scale (SAS) – for parkinsonian and related adverse events
- Extrapyramidal Symptoms Rating Scale (ESRS) – for dyskinesias
- Barnes Akathisia Scale (BAS) – for akathisia

Analysis
Outcome data were combined for meta-analysis to obtain four main group comparisons: (1) SGAs vs Placebo, (2) SGAs vs Haloperidol, (3) SGAs vs Mood Stabilizers, and (4) SGAs plus Mood Stabilizer combination vs Mood Stabilizer alone. In addition, exploratory SGAs pooled analyses were conducted and reported only when heterogeneity was not detected. Continuous data were analyzed employing standardized mean differences and 95% CIs while dichotomous data were analyzed using relative risk and 95% CIs. Random-effects model of DerSimonia and Laird was used in all cases. Study heterogeneity was assessed by visual inspection of the forest plots and by χ^2 test. Based on the assumption of heterogeneity, the significance level was set at p-value < 0.1. Whenever heterogeneity was detected, NNT and NNH were calculated. All calculations were performed using MetaView, with significance level set at p-value <0.05. Scherk did not assess adverse event dose-response effects.

3.2 SUMMARY OF PUBLICATIONS INCLUDED IN SCHERK'S META-ANALYSIS

Following is a summary of the three studies used to assess the safety and tolerability of aripiprazole that were included in Scherk's meta-analysis.

3.2.1 Keck et al 2003

Keck's study titled '*A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania*' was a 3-week, multicenter, randomized, double-blind, placebo-controlled study conducted in subjects with bipolar disorder suffering from acute manic or mixed episodes. Two hundred sixty two subjects were randomized to aripiprazole (130) and placebo arms (132). Aripiprazole starting dose was 30 mg/day (lowered to 15 mg/day if needed for tolerability). The primary efficacy measure was the mean change from baseline in total score on the Young Mania Rating Scale. Safety and tolerability assessments included reports of adverse events and three objective EPS measures from the following scales: (1) Simpson-Angus Rating Scale, (2) Barnes Rating Scale for Drug- Induced Akathisia, and the (3) Abnormal Involuntary Movement Scale (AIMS).

Akathisia and tremor were the most common EPS-related adverse events reported in the aripiprazole group. In addition, small but statistically significant changes from baseline were detected in the aripiprazole group for Simpson-Angus Rating Scale and Barnes Rating Scale.

3.2.2 McQuade et al 2003

This source provides data from a meeting abstract that described McQuade's study. This study, titled '*Aripiprazole vs. Placebo in Acute Mania: Safety and Tolerability Pooled Analysis*', described data from two three-week, randomized, double-blind, placebo-controlled studies conducted in 653 subjects (aripiprazole n = 393, placebo n = 260) with acute mania. Dosage was not described in the abstract. McQuade did not report dose-dependent extrapyramidal adverse event incidence rates.

3.2.3 Sach et al 2006

Sach's study titled 'Aripiprazole *Study Group. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study'* was a three-week, multicenter, randomized, double-blind, placebo-controlled conducted in 272 subjects (aripiprazole n= 137, placebo n=135) with bipolar I disorder presenting with acute manic or mixed episodes. Aripiprazole's starting dose was 30 mg/day (lowered to 15 mg/day if needed for tolerability and subsequently increased to 30 mg/day for clinical response). Subjects unable to tolerate a dose of 15 mg/day were discontinued from the study. The main efficacy measure was the mean change from baseline to endpoint in the Young Mania Rating Scale. Safety and tolerability assessments included reports of adverse events and three objective EPS measures: (1) Simpson-Angus Rating Scale, (2) Barnes Rating Scale for Drug- Induced Akathisia, and (3) the Abnormal Involuntary Movement Scale.

Akathisia was the most frequently reported EPS-related event in both the aripiprazole (17.6%) and placebo groups (4.5%). There was a small but significant mean change in the Barnes Rating Scale scores.

3.3 Extrapyramidal Symptoms-Related Findings in Scherk's Meta-Analysis

When comparing SGAs vs placebo Scherk observed that the incidence of EPS was significantly higher in the aripiprazole (NNH, 13; 95% CI, 9-20), risperidone, and SGAs pooled groups. In addition, the author noted that objective extrapyramidal symptoms severity measurements (SAS and ESRS) did not show overall differences in the aripiprazole (RR 0.17, CI 0.0-0.35, p-value 0.05, marginally close to significance), olanzapine (RR -0.18, CI -0.43-0.07, p-value 0.15), risperidone (RR 0.24, CI -0.01-0.49, p-value 0.06), and ziprasidone (RR 0.10, CI -0.03-0.23, p-value 0.13) trials. Aripiprazole's EPS relative risk confidence interval overlapped with the confidence intervals of quatiapine (pooled), risperidone (pooled), ziprasidone, and with the confidence interval of All-SGAs-pooled. See

FIGURE 1containing Scherk's funnel plot presenting this comparison.

FIGURE 1 Scherk's SGAs vs Placebo Comparison for EPS

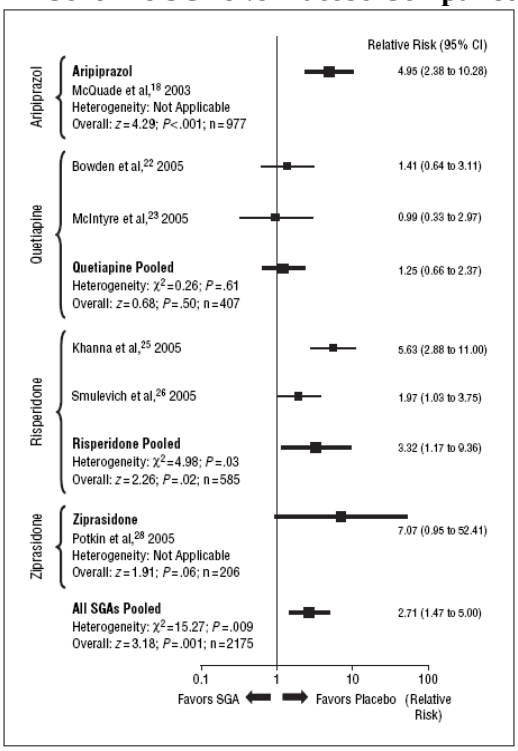

Figure 3. Mean rates of extrapyramidal adverse effects: second-generation antipsychotics (SGAs) vs placebo. CI indicates confidence interval.

A comparison between SGAs and haloperidol showed a significantly higher incidence rate of EPS when compared to aripiprazole (p-value <0.001). In none of the three aripiprazole-related studies included in this meta-analysis were subjects treated with mood stabilizers and compared to subjects treated with aripiprazole.

4 DISCUSSION

Extrapyramidal Symptoms – Incidence Rate

Scherk's analysis suggested that, based on adverse event incidence rates, some SGAs (including aripiprazole) were more likely to generate EPS than placebo. EPS rating scales for dyskinesias and parkinsonian reactions (SAS and ESRS) failed by a very small margin to reach statistical significance for an increase in EPS-related events (excluding akathisia) in the aripiprazole group. Nevertheless, Scherk considered the increase in EPS incidence rate as more clinically relevant than the results obtained from objective EPS measures. Aripiprazole's EPS relative risk confidence interval overlapped with those of all other SGAs' thus suggesting that there is no difference in EPS incidence rates among aripiprazole and all other SGAs when compared with placebo (see **FIGURE 1**). Scherk's study findings are consistent with the information described in aripiprazole's label.

In the aripiprazole NME Evaluation Pilot Project document Section F. Medical Literature Review – Extrapyramidal Symptoms the reviewer noted that "*when comparing second generation antipsychotics (SGAs) to placebo, the incidence of extrapyramidal symptoms was significantly higher in the aripiprazole and risperidone trials and in the pooled analysis of all second generation antipsychotics"*. In the same document Section F.2 AEs Unlabeled – Rebound/Withdrawal Reactions summary bullet 2.b regarding extrapyramidal symptoms and in reference to the Scherk's study, the reviewer also noted that "*In a meta-analysis, aripiprazole presented significantly a higher extrapyramidal symptoms incidence rate than most second generation antipsychotics (SGA) and placebo*". The first but not the second statement was supported by Scherk's analysis since EPS rating

scales failed to reach significance and all EPS relative risk confidence intervals overlap. Thus, the summary statement in the NME Pilot Evaluation bullet 2.b.should read instead, "*In a meta-analysis, aripiprazole presented significantly higher extrapyramidal symptoms incidence rate than placebo.*"

Extrapyramidal Symptoms – Definition's Impact on Data Capture and Analysis

The EPS definition was not provided for any of the studies included in Scherk's meta-analysis nor in most of aripiprazole trials reviewed for the NME Evaluation Pilot Project, making the interpretation of EPS findings difficult. In Scherk's meta-analysis, Keck's and Sach's studies reported only the incidence of adverse events that occurred in 10% or more of subjects in either the placebo or the aripiprazole group. In Keck's study the most common extrapyramidal symptoms reported in the aripiprazole-treated group were akathisia (11%) and tremor (6%). Akathisia (17.6%) was also the most frequently EPS-related event reported in Sachs' study. However, EPS manifestations may be also captured by other less frequently considered adverse event terms such as tics, motor dysfunction, movement disorder, and restlessness which, unless included as part of a comprehensive definition of EPS, could be excluded from the EPS adverse event analysis. Exclusion of these adverse events from the analysis may result in an underestimation of the true incidence of EPS. Medical Dictionary for Regulatory Activities (MedDRA) terminology Standardized MedDRA Query (SMQ) *'Extrapyramidal Syndrome'* includes 90 PT terms that should be considered in the process of adverse event data capture and analysis (see Appendix 3 Table 2). The consistent use of an EPS definition would result in a more homogenous data capture and more reliable estimates of EPS incidence rate.

Dose-Response Analyses

Individual studies included in Scherk's meta-analysis did not have information on dose. Consequently, this meta-analysis did not provide any dose-effect assessment. Only two of the clinical trials reviewed as part of aripiprazole's NME Evaluation Pilot Project described dose-related adverse events: somnolence (Marder[6] et al 2003) and nausea, upper abdominal pain, constipation, and back pain (Cutler et al 2006[7]).

5 CONCLUSIONS

- In a meta-analysis by Scherk, aripiprazole's EPS overall incidence rate was higher than placebo, but similar to the incidence rates of other SGAs. These findings were consistent with the label.
- EPS-related adverse events were not clearly defined in studies included in this meta-analysis making the interpretation of EPS findings difficult. Consistent use of an EPS definition could potentially improve the assessment of EPS incidence rate. MedDRA SMQ 'Extrapyramidal Syndrome' is a good source of EPS-related terms
- Adverse event dose-effect analysis was not done in this meta-analysis.

[6] Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, Saha A, Ali M, Iwamoto T. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res. 2003 Jun 1;61(2-3):123-36.

[7] Cutler AJ, Marcus RN, Hardy SA, O'Donnell A, Carson WH, McQuade RD. The efficacy and safety of lower doses of aripiprazole for the treatment of patients with acute exacerbation of schizophrenia. CNS Spectr. 2006 Sep;11(9):691-702

6 RECOMMENDATIONS

- In the aripiprazole NME Evaluation background document, change summary statement bullet in Section F.2 to read: "*In a meta-analysis, aripiprazole presented significantly higher extrapyramidal symptoms incidence rate than placebo*."
- For future aripiprazole submissions, request from the sponsor a complete list of terms included in their definition of EPS

cc:

OMP: Temple,Robert
DPP: Zornberg, Gwen/ Dubitsky, Gregory/ Laughren, Thomas
OSE: Tonning, Joseph/ Diak, Ida-Lina/ Pitts, Marilyn/ Avigan, Mark

APPENDICES

APPENDIX 1 ARIPIPRAZOLE LABEL EXCERPT: EXTRAPYRAMIDAL SYMPTOMS SECTION

Extrapyramidal Symptoms[8]

In short-term, placebo-controlled trials in Schizophrenia in adults, the incidence of reported EPS related events, excluding events related to akathisia, for aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo. In the short-term, placebo-controlled trial of Schizophrenia in pediatric (13-17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 9% vs. 6% for placebo. In the short-term, placebo-controlled trials in Bipolar Mania in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 15% vs. 8% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. In the short-term, placebo-controlled trials in Major Depressive Disorder, the incidence of reported EPS-related events, excluding events related to akathisia, for adjunctive aripiprazole-treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 25% vs. 4% for adjunctive placebo-treated patients.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the adult Schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the pediatric (13 to 17 yrs) Schizophrenia trial, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Simpson Angus Rating Scale (aripiprazole, 0.24; placebo, -0.29). In the Bipolar Mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. In the Major Depressive Disorder trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.31; placebo, 0.03 and aripiprazole, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive aripiprazole and adjunctive placebo groups.

Similarly, in a long-term (26-week), placebo-controlled trial of Schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

In the placebo-controlled trials in patients with agitation associated with Schizophrenia or Bipolar Mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 2% vs. 2% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 2% vs. 0% for placebo. Objectively collected data on the Simpson Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) for all treatment groups did not show a difference between aripiprazole and placebo.

[8] Aripiprazole product label.

APPENDIX 2 TABLE 1 ARIPIPRAZOLE LABEL: EPS-RELATED ADVERSE EVENTS IN CLINICAL TRIALS

ARIPIPRAZOLE LABEL:

EPS-RELATED ADVERSE EVENTS FREQUENCY IN CLINICAL TRIALS

BY STUDY INDICATION

	Placebo	Aripiprazole	Risk Ratio
Short-term, placebo-controlled trials			
Schizophrenia in adults			
EPS - Akathisia	4%	8%	2.0
EPS - Other	12%	13%	1.1
Schizophrenia in pediatric			
EPS - Akathisia	6%	9%	1.5
EPS - Other	7%	25%	3.6
Bipolar Mania in adults			
EPS - Akathisia	4%	15%	3.8
EPS - Other	8%	15%	1.9
Major Depressive Disorder adjunctive therapy			
EPS - Akathisia	4%	25%	6.3
EPS - Other	5%	8%	1.6
Other Long-term Placebo-controlled trials			
Patients with agitation associated with Schizophrenia or Bipolar Mania			
EPS - Akathisia	2%	0%	**
EPS - Other	2%	2%	1.0

APPENDIX 3 TABLE 2 EXTRAPYRAMIDAL SYNDROME (SMQ)

EXTRAPYRAMIDAL SYNDROME (SMQ): SUBORDINATE SMQS AND CORRESPONDING PT TERMS *(MedDRA v.11)*[9]		
Akathisia (SMQ) PT Name	**Dystonia (SMQ)** PT Name	**Parkinson-like events** (SMQ) PT Name
Akathisia	Blepharospasm	Akinesia
Extrapyramidal disorder	Drooling	Bradykinesia
Hyperkinesia	Dystonia	Cogwheel rigidity
Hyperkinesia neonatal	Emprosthotonus	Drooling
Movement disorder	Extrapyramidal disorder	Dysphonia
Psychomotor hyperactivity	Laryngospasm	Extrapyramidal disorder
Restlessness	Meige's syndrome	Gait disturbance
Motor dysfunction	Movement disorder	Hypertonia
Dyskinesia (SMQ) PT Name	Muscle contractions involuntary	Hypokinesia
Athetosis	Muscle spasms	Hypokinesia neonatal
Buccoglossal syndrome	Muscle spasticity	Masked facies
Chorea	Muscle twitching	Movement disorder
Choreoathetosis	Oculogyric crisis	Muscle rigidity
Drooling	Oesophageal spasm	On and off phenomenon
Dyskinesia	Opisthotonus	Parkinsonism
Dyskinesia neonatal	Oropharyngeal spasm	Tremor
Dyskinesia oesophageal	Pleurothotonus	Tremor neonatal
Extrapyramidal disorder	Posture abnormal	Mobility decreased
Movement disorder	Posturing	Hypertonia neonatal
Muscle twitching	Risus sardonicus	Parkinsonian crisis
Oculogyric crisis	Tic	Bradyphrenia
Tardive dyskinesia	Tongue spasm	Musculoskeletal stiffness
Tic	Torticollis	Walking disability
Respiratory dyskinesia	Torticollis psychogenic	Parkinsonian gait
Ballismus	Trismus	Parkinsonian rest tremor
Motor dysfunction	Abasia	Micrographia
Grimacing	Muscle tightness	Freezing phenomenon
Dopamine dysregulation syndrome	Uvular spasm	Motor dysfunction
	Musculoskeletal stiffness	Parkinson's disease
	Motor dysfunction	Postural reflex impairment
	Facial spasm	
	Spasmodic dysphonia	
	Oromandibular dystonia	

[9] Medical Dictionary for Regulatory Activities, *version* 11.0

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