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Office of Surveillance and Epidemiology

Date:	September 25, 2008
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Subject:	New Molecular Entity Review Follow-up
Drug Name(s):	Aripiprazole (Abilify®)
Submission Number:	NDA 21436
Applicant/sponsor:	Otsuka
OSE RCM #:	2007-2336

CONTENTS

EXECUTIVE SUMMARY

The FDA has initiated a review process for drugs classified as new molecular entities[1] (NME). The safety profile of aripiprazole, a new molecular entity (indicated to treat schizophrenia, bipolar disorder and as an adjunctive treatment of major depressive disorder) was discussed at a meeting on March 17, 2008. Since its approval in November 2002, there have been approximately 13.6 million aripiprazole prescriptions dispensed to approximately 2 million US patients.[2]

The review of aripiprazole's safety profile identified bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes as follow-up issues of interest. The search of the Adverse Event Reporting System (AERS)[3] resulted in post-marketing cases of hepatic failure (7), pancytopenia (6), bone marrow failure (3), hemolytic anemia (3), Torsade de pointes (2), and hepatitis fulminant (1). Death was the reported outcome in four hepatic failure cases; however, these cases were confounded by underlying disease states as well as concomitant medications labeled for an association with hepatotoxicity. Overall, the 22 post-marketing AERS cases reviewed did not provide compelling evidence to suggest an association between the use of aripiprazole and the adverse events of interest.

Recommendations:

- At this time, we do not recommend revisions to the current aripiprazole label to include language regarding the adverse events of bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes.
- We will continue to monitor the AERS database for any new post-marketing cases of bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes.

1 BACKGROUND

1.1 INTRODUCTION

The FDA piloted a review process for drugs classified as new molecular entities (NME). Aripiprazole was selected as the final drug product to undergo the NME pilot review process. The review involved a template, which was used by multidisciplinary reviewers from both OSE and OND.

On March 17, 2008, OSE and OND brought together a multidisciplinary workgroup to review the safety profile of aripiprazole since approval on November 15, 2002; including clinical trial safety data, post-marketing adverse event data, new data from completed postmarketing commitments, and labeling changes. A portion of the OSE post-marketing review utilized a data mining analysis, drug use, and an AERS analysis to provide an overview of post-marketing adverse events reported for aripiprazole. The AERS analysis included the top 50 preferred MedDRA[4] terms reported in AERS, the top 20 preferred terms with death as an outcome, and the designated

[1] A new molecular entity (NME) means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.
[2] See appendix 1 table 1 for the actual numbers.
[3] Adverse Event Reporting System - computerized information database designed to support the FDA's post-marketing safety surveillance
[4] Medical Dictionary for Regulatory Affairs

medical events (DME)[5] reported for aripiprazole. The AERS analysis of the DMEs associated with the use of aripiprazole discovered reports of bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes. As a result, the multidisciplinary review team identified that the post-marketing adverse event cases for these seven events required further review and evaluation.

In this analysis, we provide a review of post-marketing aripiprazole adverse event reports retrieved from the AERS database coded with the preferred terms (PT) bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes.

1.2 REGULATORY HISTORY

Aripiprazole (Abilify®) is an atypical antipsychotic, which received FDA approval on November 15, 2002 for the treatment of schizophrenia in adults. The following indications are also FDA approved:

- September 29, 2004 – Acute manic or mixed episodes associated with Bipolar Disorder
- March 1, 2005 – Maintenance therapy in Bipolar I Disorder
- October 29, 2007 – Schizophrenia in adolescents aged 13 to 17 years old
- November 16, 2007 – Adjunctive treatment to treat patients with Major Depressive Disorder
- February 27, 2008 – Acute manic or mixed episodes associated with Bipolar I Disorder in pediatrics aged 10 to 17 years old

The exact mechanism of action of aripiprazole is unknown; however, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors. Aripiprazole is metabolized in the liver via the CYP450 isoenzymes, CYP 2D6 and 3A4. [6]

1.3 PRODUCT LABELING

The current aripiprazole label does not specifically contain language regarding bone marrow failure, hemolytic anemia, pancytopenia, hepatic failure, hepatitis fulminant, liver transplant, or Torsade de pointes; however, leukopenia, neutropenia, thrombocytopenia, hepatitis, jaundice, hepatic enzyme increased, and electrocardiogram QT interval prolonged are all labeled in the *Adverse Reactions* section.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

2.2 AERS SELECTION OF CASES

[5] A Designated Medical Event (DME) is an event that is inherently serious and often drug-related. OSE created the DME list for working purposes; it has no regulatory significance.
[6] Abilify Product Label, August 2008, Otsuka Pharmaceutical Co., Japan; http://packageinserts.bms.com/pi/pi_abilify.pdf

On August 21, 2008, DPV searched the AERS database for those cases (as well as any new cases) that were discovered in the previous AERS analysis during the NME pilot project. The following PTs were used to perform the searches: bone marrow failure, haemolytic anaemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes. The actual case counts are provided in Table 1 below.

Table 1- AERS search results for aripiprazole from Marketing (November 15, 2002) to August 21, 2008

Preferred Term (PT)	Crude count	Duplicate cases	Unique case count
Bone marrow failure	10*	6	3
Haemolytic anaemia	3	0	3
Hepatic failure	8	1	7
Hepatitis fulminant	1	0	1
Liver transplant	1	0	1**
Pancytopenia	6	0	6
Torsade de pointes	3	1	2

* One bone marrow failure case re-classified to pancytopenia group.
**This case was retrieved in the hepatic failure search as well.

The criterion for case inclusion was simply if the adverse event occurred during therapy with aripiprazole. Of the cases retrieved from the AERS database there were no cases excluded from the case series selection and analysis. The hands-on review of all cases identified eight duplicate cases which were consolidated, and therefore, are not included in the total unique case counts.

2.3 DRUG UTILIZATION DATABASES

2.3.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ (see Methods and Materials) was used to determine the various retail and non-retail channels of distribution for Abilify® (aripiprazole).[7] The examination of wholesale sales data for year 2007 indicates that approximately 76% of Abilify® (aripiprazole) extended units (tablets, mL, etc.) were distributed to outpatient retail pharmacy settings. Outpatient retail pharmacy settings include chain, independent, food stores with pharmacies, and mail order pharmacies. Non-retail settings accounted for approximately 24% of sales, and mail order channels accounted for approximately 7% of sales. For this review, we examined utilization patterns to assess outpatient population exposure.

2.3.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

Outpatient use and patient demographics were measured from Verispan, LLC: Vector One®: National (VONA) and Total Patient Tracker (TPT) from November 2002 through October 2007, inclusive (Appendix 2). From these data sources, estimates of the number of prescriptions dispensed, and the number of patients who received a prescription for Abilify® (aripiprazole) were examined. For comparative purposes, other products in the atypical anti-psychotic market were also included in the analysis of dispensed prescriptions: USC 64190 (clozapine, ziprasidone, risperidone, olanzapine, quetiapine, paliperidone). In addition, diagnoses associated with the use of Abilify were obtained from the Verispan's Physician's Drug and Diagnosis Audit (PDDA).

[7] IMS Health, IMS National Sales Perspectives™, Years 2002 – 2007, Extracted February 2007. Original File: 0802Abil.dvr.

2.4 LITERATURE SEARCH

DPV conducted a search of PubMed on August 11, 2008 using the following terms in an 'AND' search with aripiprazole:

- Bone marrow failure
- Hemolytic anemia
- Hepatic failure
- Hepatitis fulminant
- Liver transplant
- Pancytopenia
- Torsade de pointes

In addition to the 22 AERS cases identified, the search of the literature did not identify any new case reports.

3 RESULTS

3.1 HEMATOLOGIC DISORDERS

3.1.1 Bone Marrow Failure (n=3)

The AERS database was searched for bone marrow failure reports associated with aripiprazole therapy and the searched initially identified four cases. Upon further review, one of the cases was actually pancytopenia and is discussed in section 3.1.3, therefore leaving three cases for discussion in this section. There were no reports with an outcome of death in this subgroup; however, two cases required hospitalization. Three cases were foreign and one case was from the US. The patients were aged 41 and 68 years old; and one case did not report an age. These cases included three females and one case of unknown gender. None of the three cases reported laboratory values for the affected blood elements.

- The first case described a 68-year old female diagnosed with hypoplastic anemia within the first month of aripiprazole therapy. The diagnosis was made based on laboratory tests that revealed, "decreased white blood cell count, decreased hemoglobin, hypocellular marrow, and decreased platelets." Hypocellular marrow is a characteristic of myelodysplastic syndrome.[8] The patient was also being treated with mirtazapine and esomeprazole, which are both labeled for anemia, in addition to bendrofluazide, diazepam, and loperamide. Aripiprazole and mirtazapine were discontinued approximately five weeks after her diagnosis and she had not yet recovered at the time of reporting.
- The second case described a 41-year old female who experienced severe anemia due to bone marrow depression approximately six weeks after the initiation of aripiprazole for a severe psychotic episode. The patient required corrective treatment with blood transfusions. The patient received concomitant treatment with Trizivir®[9] (~10 years) and valproic acid (~6 months). Trizivir has a boxed warning for hematologic toxicity and bone marrow suppression and valproic acid is labeled as having the potential to increase the area under the curve

[8] Besa, E. "Myelodysplastic Syndrome." Emedicine. 27 Jun. 2006. 26 Mar 2008. http://www.emedicine.com/med/topic2695.htm.
[9] Trizivir Product Label, May 2007, GlaxoSmithKline, USA; Drugs @ FDA; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm; Trizivir is a combination of abacavir, lamivudine and zidovudine.

(AUC) of zidovudine and therefore increases the risk of bone marrow suppression. All drugs were discontinued at the time of diagnosis, but Trizivir was restarted once the patient showed signs of recovery.

- The final case did not provide enough information to evaluate for a causal association.

3.1.2 Hemolytic anemia (n=3)

The AERS database was searched for hemolytic anemia reports associated with aripiprazole therapy and the search identified three unique cases. There were no reports with an outcome of death in this subgroup; however, two cases reported hospitalization. Two cases were from the US and one was foreign. This included two females and one male; and only one case reported an age for the patient, and it was 42 years old.

- The first case described a patient who was diagnosed after an unknown duration of aripiprazole therapy with immunological hemolytic anemia during a hospitalization for bronchopneumonia.[10] The patient required a blood transfusion as part of her recovery and the event of hemolytic anemia ultimately prolonged her hospitalization.

- The second case described a 37-year old patient who experienced hemolytic anemia after approximately 1&1/2 years of therapy with aripiprazole 75 mg daily[11] for schizophrenia. The case is somewhat confounded by the concomitant use of omeprazole[12], which is labeled for hemolytic anemia (post-marketing experience).

- The final case did not provide enough information to evaluate for a causal association.

3.1.3 Pancytopenia (n=6)

The AERS database was searched for pancytopenia reports associated with aripiprazole therapy and the searched identified six unique cases. There were no reports with an outcome of death in this subgroup; however three cases required hospitalization. Three cases each were from US and foreign report sources. This included three females and two males (one case did not report gender). Four cases reported age information, and they were 13, 45, 60, and 66 years old.

The best representative case in the group describes a positive dechallenge. The patient was a 60-year old female who was diagnosed with pancytopenia within one month of initiation of therapy with aripiprazole. The pancytopenia progressed over a three-month period until aripiprazole therapy was discontinued and therapy with quetiapine was initiated. Within approximately two months of discontinuing aripiprazole and continuing all other concomitant therapies, the laboratory data (white blood cells, red blood cells and platelets) showed improvement.

Four of the remaining five cases had confounding factors that may have played a role in the development of the pancytopenia.

[10] The medications and treatments that potentially were used during hospitalization to treat the bronchopneumonia were not provided.
[11] The maximum recommended dose for schizophrenia in adults is 30mg/day.
[12] Prilosec Product Label, April 2007, AstraZeneca, USA; Drugs @ FDA;
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

- The first case described a 13-year old male patient who developed pancytopenia an unknown time after the initiation of aripiprazole for temper outbursts. He also received concomitant treatment with famotidine[13], which is labeled for pancytopenia.

- The second case described a 45-year old female who experienced pancytopenia within three months of initiating therapy with aripiprazole for schizophrenia. She also received concomitant treatment with ramipril[14], which is labeled for pancytopenia, as well as anastrazole[15] (labeled for leucopenia), and trastuzumab[16] (labeled for neutropenia and leucopenia). The event persisted beyond the discontinuation of all medications with the exception of clonazepam.

- The third case described an elderly female (age unspecified) who went into acute hepato-renal failure and was diagnosed with pancytopenia some time after the initiation of aripiprazole. The patient also had the underlying hematological disorder of thalassemia minor.

- The fourth case described a 66-year old female who experienced pancytopenia within three months of aripiprazole initiation for psychosis. The patient's medical history included breast carcinoma for which she received radiation therapy one year prior. A myelogram was performed on the patient and it revealed "a myelodysplastic syndrome like stubborn cytopenia", which can be caused by radiation therapy.[17]

- The final case did not provide enough information to evaluate for a causal association.

3.2 HEPATIC DISORDERS

3.2.1 Hepatic Failure including Liver Transplant (n=7)

The AERS database was searched for hepatic failure and liver transplant reports associated with aripiprazole therapy and the searched identified seven unique cases. One of these seven cases reported both hepatic failure and liver transplantation. There were four reports with an outcome of death and the remaining three cases required hospitalization. Four cases were from the US and three cases were foreign. The patients ranged in age from 40 to 84 years old (n=6) with a median of 59.5 years, and included four males and three females.

In all four cases of death, the deaths occurred within 70 days of initiating therapy with aripiprazole. There was an underlying or confounding factor contributing to the development of hepatic failure in all of these cases.

- The first case described a 67-year old nursing home patient who developed fulminant liver failure within one to three weeks of initiating aripiprazole therapy for schizophrenia. The case

[13] Famotidine Product Label, September 2006, Mylan Pharmaceuticals, Inc, USA; National Library of Medicine; http://dailymed.nlm.nih.gov/dailymed/about.cfm
[14] Altace Product Label, August 2007, Monarch Pharmaceuticals, Inc, USA; National Library of Medicine; http://dailymed.nlm.nih.gov/dailymed/about.cfm
[15] Arimidex Product Label, September 2005, AstraZeneca, USA; Drugs @ FDA; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
[16] Herceptin Product Label, January 2008, Genentech, Inc., USA; Drugs @ FDA; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
[17] NCI: National Cancer Institute. Bethesda (MD): General information about myelodysplastic syndromes. 2008 Aug 22 [modified 2008 Aug 14]. Available from http://www.cancer.gov/cancertopics/pdq/treatment/myelodysplastic/patient

was heavily confounded by the use of concomitant valproic acid for more than one year at the time of his death in addition to scheduled and as needed use of acetaminophen at minimum daily doses of 2.6 grams. Valproic acid[18] has a boxed warning for hepatotoxicity.

- The second case described an 84-year old patient who died of hepatic failure within 40 days of initiating therapy with aripiprazole for the treatment of dementia. In addition, the patient suffered from an undescribed underlying hepatic disease, which was "considered the direct cause of her death." This underlying disease is coupled with the fact that aripiprazole has a boxed warning for increased mortality in elderly patients with dementia-related psychosis

- The third case reported a 60-year old patient who developed neuroleptic malignant syndrome (NMS) leading to hepatic failure and death within two months of initiating therapy with aripiprazole for schizophrenia.

- The final case of death described a 59-year old patient who died within 70 days of initiating therapy with aripiprazole for schizophrenia. He experienced an aggravation of the hepato-biliary system within one month of aripiprazole initiation and within nine days of risperidone initiation. Aripiprazole was discontinued at that time and the risperidone dose was increased until it ultimately was discontinued 11 days later. The patient died one month after the discontinuation of both drugs. The patient had a history of chronic hepatitis in addition to the concomitant use of risperidone[19], which is labeled for hepatic failure.

Of the three remaining cases, the time to onset of hepatic failure occurred within the first five months of initiating aripiprazole therapy.

- The first case described a 45-year old patient experiencing hepatic failure ultimately leading to a liver transplant within three months of initiating therapy with aripiprazole, valproic acid, topiramate, flurazepam, and possibly acetaminophen. The patient's transaminase levels were within normal limits for two months until the valproic acid dose was gradually increased leading to jaundice and worsening hepatic function causing a discontinuation of the drug. The concomitant use of valproic acid, topiramate and acetaminophen was somewhat confounding to the case.

- The second case described a 40-year old patient who developed NMS leading to renal and hepatic failure within five months of initiating therapy with aripiprazole for schizoaffective disorder. Aripiprazole was the newest medication added to her regimen in addition to venlafaxine XR[20], which is labeled for an association with hepatic failure.

- The final case described a patient who after taking one dose of aripiprazole developed hepatic and renal failure that "improved right away" upon self-discontinuation of the drug and an undescribed hospitalization.

[18] Depakote Product Label, October 2006, Abbott Laboratories, USA; Drugs @ FDA; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
[19] Risperdal Product Label, August 2007, Janssen, L.P., USA; Drugs @ FDA; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
[20] Effexor XR Product Label, February 2008, Wyeth Pharmaceuticals, Inc, USA; National Library of Medicine; http://dailymed.nlm.nih.gov/dailymed/about.cfm

3.2.2 Hepatitis fulminant (n=1)

The AERS database was searched for hepatitis fulminant reports associated with aripiprazole therapy. The search identified one foreign case involving a 44-year old female who experienced hepatitis fulminant 118 days after the initiation of aripiprazole for schizophrenia and required hospitalization. This case was heavily confounded by the concomitant use of valproic acid[7], which is labeled for hepatotoxicity and carbamazepine[21], which is labeled for hepatic failure. The patient's hepatic function deteriorated after several increases in the dose of carbamazepine with no change in the dose of aripiprazole. Within less than one month of the discontinuation of carbamazepine and valproic acid, the patient recovered. The aripiprazole therapy continued throughout the event.

3.3 TORSADE DE POINTES

3.3.1 Torsade de pointes (n=2)

The AERS database was searched for Torsade de pointes reports associated with aripiprazole therapy and the search identified two unique cases. Neither of the cases had an outcome of death; however, both cases required hospitalization. Both cases were from the US, involving females aged 58 and 59 years old.

- The first case described a 58-year old female patient that was hospitalized for cardiac arrest and Torsade de pointes approximately 1&1/2 years after the initiation of aripiprazole for schizophrenia. According to the report, the hospital records "revealed that most of the etiology was secondary to propafenone, which caused increased QT and a pro-arrhythmic effect." Aripiprazole therapy continued after her discharge from the hospital. She was hospitalized again "a couple of months later" for uncontrolled hypertension and a prolonged QT interval, which corrected upon the discontinuation of aripiprazole. The patient had an extensive medical history including, but is not limited to severe hypertension and atrial fibrillation, for which she received multiple concomitant medications[22].

- The second case described a 59-year old patient receiving aripiprazole for 18 days prior to experiencing prolonged QT intervals, Torsade de pointes, seizure, embolic stroke, and respiratory acidosis. After the discontinuation of aripiprazole, the Torsade de pointes had resolved, but the QT prolongation persisted intermittently. The patient's past medical history included aortic valve replacement, Marfan syndrome, hypertension, stroke, and diabetes. Concomitant therapy with risperidone[8] and fluoxetine[23] may have played a confounding role as they are both labeled for prolonging the QT interval and additionally, fluoxetine is labeled for Torsade de pointes.

[21] Tegretol Product Label, December 2007, Novartis Pharmaceuticals Corporation, USA; Drugs @ FDA; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

[22] Amlodipine, citalopram, digoxin, hydralazine, hydrochlorothiazide/triamterene, labetalol, metoprolol, valproic acid, verapamil, and warfarin

[23] Prozac Product Label, March 2008, Eli Lilly & Co., USA; Drugs @ FDA; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

3.4 DRUG UTILIZATION DATA

Among the six selected products analyzed (clozapine, ziprasidone, risperidone, olanzapine, quetiapine, and paliperidone), aripiprazole accounted for approximately 13.5% of the total prescriptions dispensed during January to October 2007 (Appendix 1: Figure 1).[24]

Abilify® is available in a variety of formulations, including oral tab, oral solution, disintegrating tab, and IM injectable solution. The oral tablet is the most widely used dosage form, with the 10 mg strength of Abilify® being dispensed with a slightly greater frequency (Appendix 1: Figure 2).[25]

For the entire period of November 2002 to October 2007, the majority of use was among the age range 41-50 years with approximately 20% of total dispensed prescriptions for Abilify®. The age range 31-40 years and pediatric patients, ages 12-16, both accounted for approximately 14.4% of total dispensed prescriptions each (Appendix 1: Figure 3).[26] A greater proportion of prescriptions were dispensed to male patients than female patients for ages 20 years and under; there was a 70:30 ratio for dispensed prescriptions between males and females in the pediatric age ranges 2-5 years and 6-11 years. The male to female distribution of prescriptions was nearly equal for the age 21 to 30 year group. For ages 31 years and above, the ratio shifted to more prescriptions dispensed to female patients than male patients (Appendix 1: Table 1).

In terms of number of patients exposed, a little over 2 million patients have received a prescription for Abilify® since it began marketing in November 2002. The proportion of age and gender distribution was similar to the dispensed prescription data (Appendix 1: Table 2, 3).[27]

Since its introduction into the market, Psychiatrists have been the number one prescribers of Abilify® throughout the entire study period. During the most recent 3-month period ending in October 2007, Psychiatrists accounted for about 66% of dispensed prescriptions. Nurse Practitioners and General Practice specialists accounted for approximately 8% and 5% of dispensed prescriptions, respectively. 11% of dispensed prescriptions were ascribed to unspecified specialty during this same time period (Appendix 1: Figure 4).[28]

The most common diagnoses encountered in the office-based practice setting for all ages from November 2002 through October 2007 was affective psychoses at 36% (ICD-9 296) followed by schizophrenic disorders at 34% (ICD-9 295) and other non-organic psychoses at 6% (ICD-9 298) (Appendix 1: Table 4).[29]

3.5 LITERATURE SEARCH

The literature search of PubMed did not identify any new case reports of bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes associated with aripiprazole use.

[24] VONA, Nov02-Oct07, Extracted Feb 2008. File: 2007-2336 Abilify NME TRx by Antipsychotic Agents.qry
[25] VONA, Nov02-Oct07, Extracted Feb 2008. File: 2007-2336 Abilify NME TRx by Strength.qry
[26] VONA, Nov02-Oct07, Extracted Feb 2008. File: VONA 2007-2336 Abilify NME TRx by Age2.qry and VONA 2007-2336 Abilify NME TRx by Peds.qry
[27] Verispan, Total Patient Tracker. Files: TPT 2007-2336 Abilify NME Gender Aggregate Patient Count.xls; TPT 2007-2336 Abilify NME Aggregate Patient Count.xls; TPT 2007-2336 Abilify Aggregrate Age Range Patient Count.xls
[28] VONA, Nov02-Oct07, Extracted Feb 2008. File: VONA 2007-2336 Abilify NME TRx by Physician Specialty.qry
[29] Verispan, Physician Drug and Diagnosis Audit, Nov02-Oct07, Extracted Feb 2008. File: PDDA 2007-2336 Abilify NME Dx3.qry

4 DISCUSSION/CONCLUSION

4.1 ADVERSE EVENTS CASES

Of 6,701[30] postmarketing reports for aripiprazole, we reviewed and discussed 22 in this document. Aripiprazole's product label describes leukopenia, neutropenia and thrombocytopenia discovered through the development program. Bone marrow failure, hemolytic anemia, and pancytopenia are not in the label, however, pancytopenia was reported in the majority of the hematological post-marketing cases, of which one pancytopenia case described a positive dechallenge response. Although the case described a positive dechallenge, neither this case, nor the other hematological event cases were compelling in suggesting a significant safety signal between aripiprazole and these events. Seven of these cases were confounded by a combination of underlying hematologic disorders, in addition to concomitant medications labeled for an association with bone marrow suppression, hematological toxicity, hemolytic anemia, and pancytopenia; and three cases did not provide enough information to evaluate a causal association.

An additional eight cases described serious hepatic disorders, including seven cases of hepatic failure and one case of hepatitis fulminant. Based on information from the development program, aripiprazole is labeled for hepatitis, jaundice, and hepatic enzyme elevation. Four post-marketing cases of hepatic failure resulted in death; however, the occurrence of the hepatic failure was not strongly associated with the use of aripiprazole, as other significant co-existing factors may have played a role in the development of the reported hepatic failures. One case is unlikely based upon the fact that the patient only received one dose and seven cases were confounded by a combination of underlying hepatic disorders, in addition to concomitant medications labeled for an association with hepatotoxicity. Three of these cases involved the concomitant use of valproic acid, a product that is associated with serious hepatotoxicity. Although valproic acid undergoes metabolism via glucuronidation, valproic acid is described in the literature as having the potential to decrease aripiprazole levels (metabolized by CYP 2D6, 3A4).[31] Although both drugs are highly protein bound (aripiprazole > 99%, valproic acid[32] ~ 90%), there is no mention in the medical literature of the concomitant use of aripiprazole influencing valproic acid levels.[33] Based on the mechanisms of aripiprazole's and valproic acid's metabolism, it is not expected that aripiprazole would influence serum valproic acid levels; and none of the cases reported serum levels of either agent.

We also reviewed two cases describing Torsade de pointes. Both of these cases were confounded by the use of concomitant medications, including one case reporting an antiarrhythmic agent known to be associated with QT prolongation and Torsade de pointes. Aripiprazole is labeled for electrocardiogram QT prolonged, without mention of Torsade de pointes.

In the 22 post-marketing cases, an association appears to be unlikely between the reported events and aripiprazole use, due to the sparse number of reports for each reported event, the presence of confounding factors, and the lack of compelling evidence in the cases.

[30] The value of 6701 was the current number of reports in the AERS database from marketing until August 21, 2008.
[31] Besag FM, Berry D. Interactions between Antiepileptic and Antipsychotic Drugs. Drug Safety. 2006;29(2):95-118.
[32] Valproic acid's protein binding is concentration dependent, and the free fraction increases from ~ 10% at 40 mcg/ml to 18.5% at 130 mcg/ml. Protein binding is reduced in the elderly, in patients with chronic hepatic diseases, renal impairment, and in the presence of other drugs (eg aspirin). Valproic acid product label. Banner Pharmacaps, Inc. Feb 2008. http://dailymed.nlm.nih.gov/dailymed
[33] Besag FM, Berry D. Interactions between Antiepileptic and Antipsychotic Drugs. Drug Safety. 2006;29(2):95-118.

4.2 DRUG UTILIZATION DATA

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that Abilify® is distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. Long-term care facilities are the second most common distribution channel, accounting about 15% of wholesale sales for 2007. Mail order accounted about 7% of wholesale sales during year 2007. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Verispan's Vector One®: National provides estimates of the number of prescriptions dispensed through outpatient retail pharmacies in the United States. Mail order and long-term care data were not included in total prescription or patient numbers for this review. Thus prescription and patient counts represent an underestimation.

Verispan's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Verispan recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

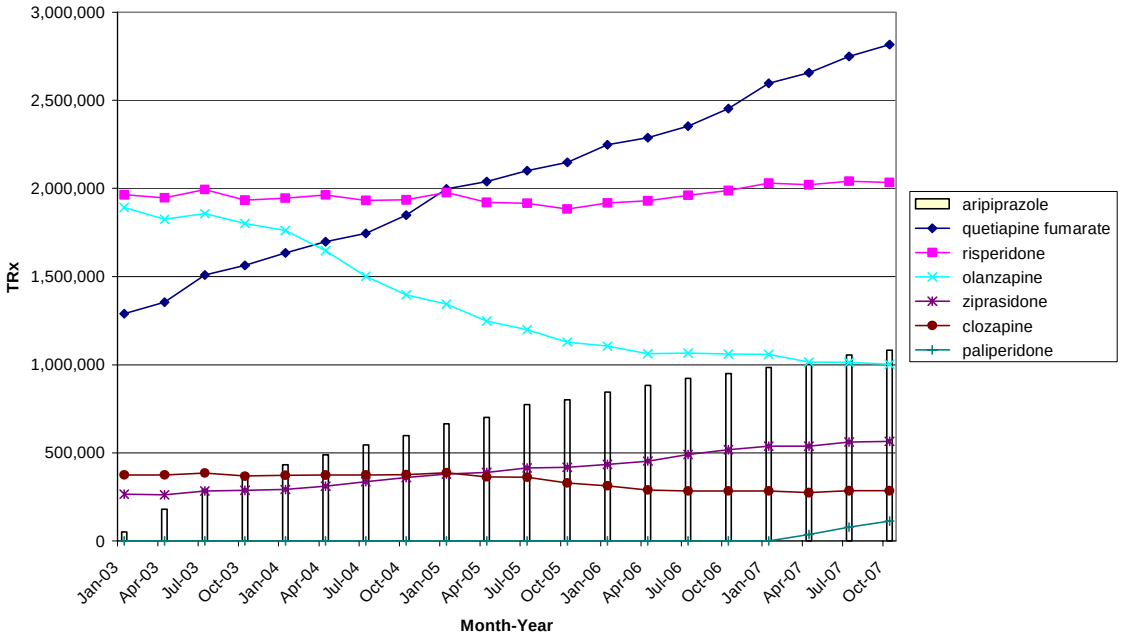
5 RECOMMENDATIONS

- At this time, we do not recommend revisions to the current aripiprazole label to include language regarding the adverse events of bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes.
- We will continue to monitor the AERS database for any new post-marketing cases of bone marrow failure, hemolytic anemia, hepatic failure, hepatitis fulminant, liver transplant, pancytopenia, and Torsade de pointes.

APPENDICES

Appendix 1 – Figures and Tables

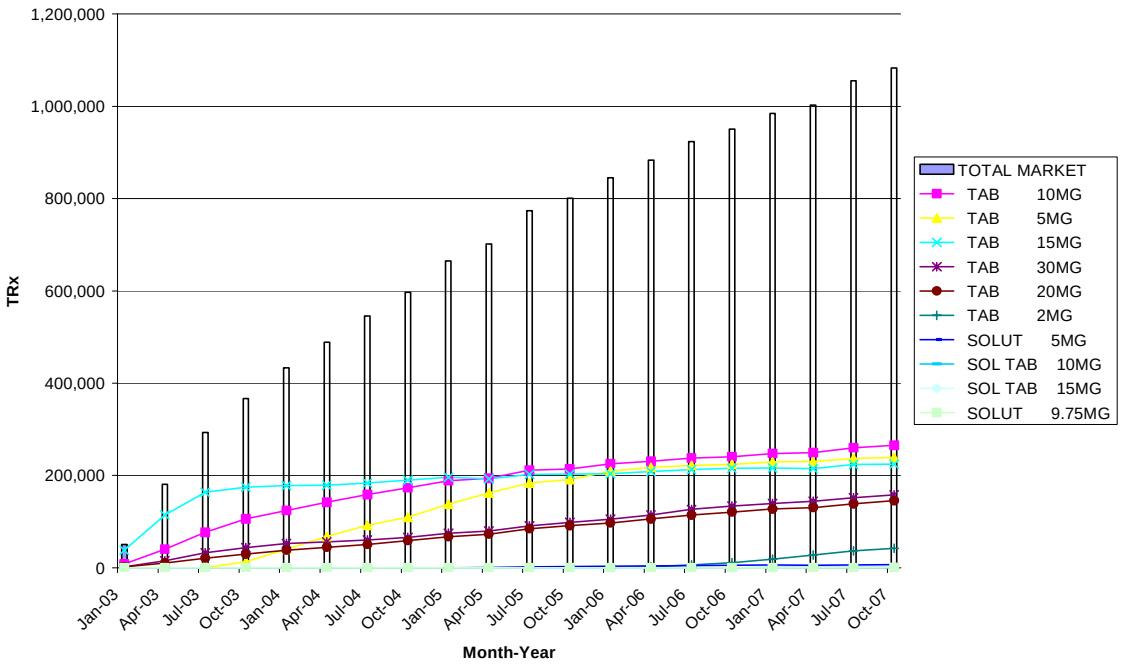
Figure 1: Total prescriptions dispensed for aripiprazole and selected anti-psychotic agents, Nov02-Oct07



Source: Verispan, LLC: Vector One®: National, Nov02-Oct07, Extracted Feb08.

File: 2007-2336 Abilify NME TRx by Antipsychotic Agents.qry

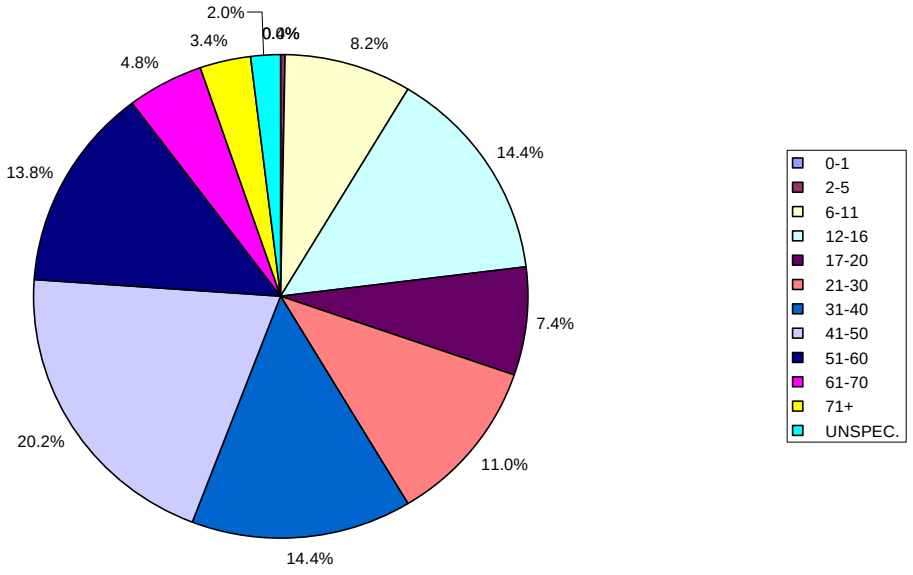
Figure 2: Total dispensed prescriptions for Ablilify by product form/strength, Nov02-Oct07



Source: Verispan, LLC: Vector One®: National, Nov02-Oct07, Extracted Feb08.

File: 2007-2336 Abilify NME TRx by Strength.qry

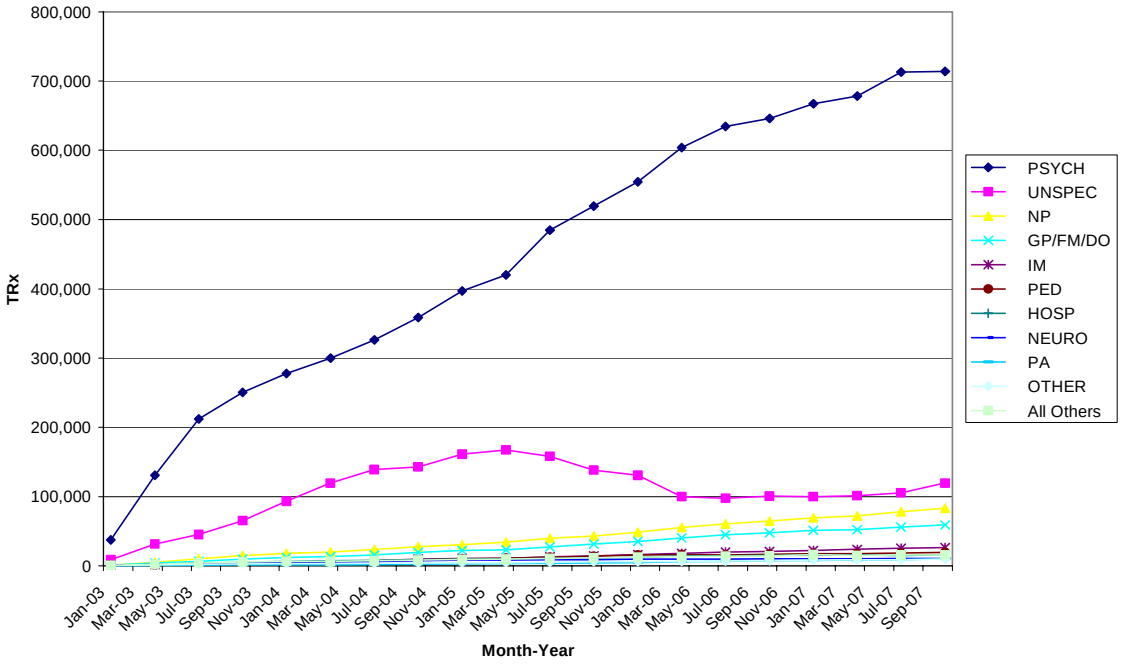
Figure 3: Proportion of toal dispensed prescriptions for Abilify by patient age, Nov02-Oct07 cumulative



Source: Verispan, LLC: Vector One®: National, Nov02-Oct07, Extracted Feb08

File: 2007-2336 Abilify NME TRx by Age2.qry and 2007-2336 Abilify NME TRx by Peds.qry

Figure 4: Total dispensed prescriptions for Abilify by prescribing specialty, Nov02-Oct07



Source: Verispan, LLC: Vector One®: National, Nov02-Oct07, Extracted Feb08.

File: 2007-2336 Abilify NME TRx by Physician Specialty.qry

Table 1. Total number of dispensed prescriptions for Abilify® in U.S. outpatient retail pharmacies by patient age and gender, Nov02-Oct07 cumulative

	Total			Male			Female			UNSPEC.		
	TRxs	*Share*		TRxs	*Share*		TRxs	*Share*		TRxs	*Share*	
	N	%V	%H	N	%V	%H	N	%V	%H	N	%V	%H
TOTAL MARKET	13,621,561	*100.0%*	*100.0%*	6,256,862	*100.0%*	*45.9%*	7,040,472	*100.0%*	*51.7%*	324,227	*100.0%*	*2.4%*
0-1	1,348	*0.0%*	*100.0%*	620	*0.0%*	*46.0%*	704	*0.0%*	*52.2%*	24	*0.0%*	*1.8%*
2-5	48,150	*0.4%*	*100.0%*	34,526	*0.6%*	*71.7%*	13,070	*0.2%*	*27.1%*	554	*0.2%*	*1.2%*
6-11	1,116,686	*8.2%*	*100.0%*	796,693	*12.7%*	*71.3%*	309,520	*4.4%*	*27.7%*	10,473	*3.2%*	*0.9%*
12-16	1,961,302	*14.4%*	*100.0%*	1,247,672	*19.9%*	*63.6%*	691,961	*9.8%*	*35.3%*	21,669	*6.7%*	*1.1%*
17-20	1,011,160	*7.4%*	*100.0%*	557,575	*8.9%*	*55.1%*	442,005	*6.3%*	*43.7%*	11,580	*3.6%*	*1.1%*
21-30	1,499,079	*11.0%*	*100.0%*	757,253	*12.1%*	*50.5%*	729,647	*10.4%*	*48.7%*	12,179	*3.8%*	*0.8%*
31-40	1,965,659	*14.4%*	*100.0%*	797,907	*12.8%*	*40.6%*	1,152,245	*16.4%*	*58.6%*	15,507	*4.8%*	*0.8%*
41-50	2,746,352	*20.2%*	*100.0%*	1,048,685	*16.8%*	*38.2%*	1,676,207	*23.8%*	*61.0%*	21,460	*6.6%*	*0.8%*
51-60	1,885,359	*13.8%*	*100.0%*	663,771	*10.6%*	*35.2%*	1,206,616	*17.1%*	*64.0%*	14,972	*4.6%*	*0.8%*
61-70	653,135	*4.8%*	*100.0%*	197,419	*3.2%*	*30.2%*	451,134	*6.4%*	*69.1%*	4,582	*1.4%*	*0.7%*
71+	465,832	*3.4%*	*100.0%*	120,561	*1.9%*	*25.9%*	336,395	*4.8%*	*72.2%*	8,876	*2.7%*	*1.9%*
UNSPEC.	267,499	*2.0%*	*100.0%*	34,180	*0.5%*	*12.8%*	30,968	*0.4%*	*11.6%*	202,351	*62.4%*	*75.6%*

Source: Verispan LLC: Vector One® : National, Nov02-Oct07, Extracted Feb 2008

Files: 2007-2336 Abilify NME TRx by AgeGender.qry and 2007-2336 Abilify NME TRx by Ped AgeGender.qry

Table 2: Total projected number of patients receiving a prescription for Abilify by patient age from Nov02-Oct07

		Projected Patient Count	
Product Brand	**Custom Age Group**	N	%
Abilify	**All Age Groups**	2156400	*100.00%*
	0 - 1	681	*0.03%*
	2 - 5	13,318	*0.62%*
	6 - 11	177,946	*8.25%*
	12 - 16	315,053	*14.61%*
	17 - 20	200,637	*9.30%*
	21 - 30	303,588	*14.08%*
	31 - 40	365,300	*16.94%*
	41 - 50	442,021	*20.50%*
	51 - 60	285,615	*13.25%*
	61 - 70	103,588	*4.80%*
	71 - 85	83,133	*3.86%*
	Unknown Age	109,983	*5.10%*

Source Verispan, LLC: Total Patient Tracker, Nov02-Oct07, Extracted Feb08.
File: TPT 2007-2336 Abilify Aggregate Age Range Patient Count.xls

Table 3: Total projected number of *patients* receiving a prescription for Abilify by patient gender from Nov02-Oct07

	Projected Patient Count	
	N	***Total Patient Share %***
TOTAL	**2156400**	***100.00%***
Male	920133	*42.67%*
Female	1186642	*55.03%*

Source: Verispan, LLC: Total Patient Tracker, Nov02-Oct07. Files: TPT 2007-2336 Abilify NME Aggegrate Patient Count.xls, TPT 2007-2336 Abilify NME Gender Aggregate Patient Count.xls

Table 4: Most common indications associated with the use of Abilify in office-based practice setting, November 2002 - October 2007

	Uses (000)	***Share %***
ABILIFY	11,664	*100.0%*
296 AFFECTIVE PSYCHOSES	4,224	*36.2%*
295 SCHIZOPHRENIC DISORDERS	3,989	*34.2%*
298 OTH NONORGANIC PSYCHOSES	750	*6.4%*
311 DEPRESSIVE DISORDER NEC	366	*3.1%*
300 NEUROTIC DISORDERS	359	*3.1%*
309 ADJUSTMENT REACTION	262	*2.3%*
314 HYPERKINETIC SYNDROME	247	*2.1%*
313 EMOTIONAL DIS CHILD/ADOL	203	*1.7%*
312 CONDUCT DISTURBANCE NEC	190	*1.6%*

299 PSYCHOSES OF CHILDHOOD	188	*1.6%*
301 PERSONALITY DISORDERS	187	*1.6%*
297 PARANOID STATES	175	*1.5%*
All Others	524	*4.5%*

Source: Verispan, LLC: Physician Drug and Diagnosis Audit, Nov02-Oct07, Extracted Feb08

File: PDDA 2007-2336 Abilify NME Dx3.qry

Description of all data sources used:

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all

patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

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