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Subject: 1-year Pediatric Exclusivity Postmarketing Adverse Event Review-
FINAL

Drug Name(s): Olanzapine (Zyprexa®)

Pediatric Exclusivity
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EXECUTIVE SUMMARY

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of olanzapine in pediatric patients. Up to the "data lock" date of February 10, 2008, AERS contained 21,435 reports for olanzapine (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 4.4 % of the total (949/21435).

DPV I was asked to focus on the 1-year period following the approval of pediatric exclusivity, January 10, 2007. We used an AERS data lock date of February 10, 2008, to allow time for reports received up to January 10, 2008, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received 3277 total reports (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review. Pediatric reports represent approximately 2.5% of the total number of cases (81/3277). The projected number of olanzapine prescriptions dispensed from U.S. retail pharmacies in 2007 for the pediatric population (0-17 years) was 4.5 % and the total patient share was 5.5%.¹ In addition, as requested, we provide crude numbers² (see appendix) of reports submitted to the AERS database (from marketing approval) of metabolic syndrome, weight gain, hyperglycemia, hyperlipidemia, and hyperprolactinemia in both the adult and pediatric populations.

A review of the pediatric post-marketing cases submitted during the period of pediatric exclusivity, and a review of the 44 pediatric cases with an outcome of death submitted since the beginning of marketing did not reveal any new safety concerns. The review revealed adverse events that are qualitatively similar to those currently found in the product label and described in the adult population. Among the associated adverse events in these pediatric cases, expected (labeled) metabolic effects (hyperglycemia, weight gain, etc) were described in the majority of the pediatric cases.

Based on the potential long-term consequences of weight gain, hyperglycemia and metabolic effects DPV I recommends:

- Revise the current olanzapine label to include language regarding the potential risk of the metabolic effects that are also experienced among the pediatric population.
- Continue routine monitoring of the AERS database for adverse events with the use of olanzapine in pediatric patients.

1 BACKGROUND

Olanzapine, an atypical antipsychotic agent (marketed as Zyprexa by Eli Lilly) received FDA approval on September 30, 1996. Pediatric exclusivity was granted on January 10, 2007 based on two short-term, multicenter, double-blind, placebo-controlled, flexible dose, randomized, efficacy and safety studies in adolescents aged 13 to 17 years old. The first study³ was a 3 week study in patients with acute mania in bipolar I disorder (abbreviated HGIU in the medical officer's

¹ Borders-Hemphill V. Zyprexa (olanzapine) tablets BPCA Drug Use Review. FDA Postmarketing Review. June 26, 2008.

² Duplicated reports have not been reconciled and causality has not been assessed for crude number reports.

³ Study HGIU (Acute Mania in Bipolar I Disorder): 23 sites in the US and 2 sites in Puerto Rico; 161 randomized patients, with 2:1 randomization for olanzapine versus placebo.

review), and the second study⁴ was a 6 week study in adolescents with schizophrenia (abbreviated HGIN in same review).⁵ There was unanimous agreement among the members of the DPP review team that efficacy was demonstrated in study HGIU, and after further information and discussion agreement that efficacy was also demonstrated in study HGIN.

In reference to safety, the safety data was derived from the two pivotal controlled studies (HGIU and HGIN) and from studies LOAY and HGMF (referenced in the medical officer's review, but not described in detail). There were 454 patients combined from these four studies, including 89 placebo patients from the two controlled trials previously described. Therefore, there were 365 olanzapine treated patients in this safety database, of which 136 of the patients were treated for at least 23 weeks. Overall, the adverse event profile and other safety parameters (with some differences in magnitude) are similar to those seen in adult patients treated with olanzapine. The DPP medical officer recommended highlighting these differences in the product label. Based on this information, DPP determined that the sponsor needed to respond to various requests made by the Agency, and that consensus needed to be reached on labeling prior to taking an approval action. Thus an approvable letter was issued along with DPP's proposal for labeling.

Previous OSE Post-Marketing Reviews:

- September 2, 1997. A review of reports of *hematologic events: aplastic anemia, pancytopenia, bone marrow depression, agranulocytosis, thrombocytopenia, and leukopenia* associated with olanzapine use. The review recommended continued monitoring of the safety of olanzapine.⁶
- February 9, 1999. A two-year postmarketing safety review of olanzapine. The findings of the review included a possible association between olanzapine and bradycardia, first and second-degree heart block, pancreatitis, leukopenia, neutropenia, and priapism.⁷
- December 17, 1999. A review (all ages) of the atypical antipsychotics clozapine, olanzapine, risperidone, and quetiapine and the event of *new-onset diabetes mellitus*. Although not specifically focusing on children, the review mentioned cases of diabetes mellitus with hyperosmolality associated with olanzapine. Based on the review, recommendation to increase prominence of diabetes mellitus in the labeling for clozapine, risperidone, olanzapine, and quetiapine was made.⁸
- June 25, 2003. A literature review concerning the issue of *diabetes mellitus/hyperglycemia* associated with the atypical antipsychotic drugs. The findings of the review suggested that a risk management program be put in place for these drugs.⁹
- August 15, 2003. A review of *acute liver injury* associated with olanzapine use. No actions were recommended because of the review except for continued close monitoring for well-documented cases of serious hepatic injury associated with olanzapine.¹⁰
- October 4, 2005. A class review of *galactorrhea* with atypical antipsychotic drugs in pediatric patients. The review supported further analysis of hyperprolactinemia and

⁴ Study HGIN (Acute Schizophrenia); 20 sites in US (comprising 53% of sample) and 5 sites in Russia (comprising 47% of sample); 107 patients randomized, with 2:1 randomization for olanzapine versus placebo.

⁵ Laughren T. Recommendation for approvable actions for Zyprexa Pediatric Supplements for bipolar disorder (acute mania) and schizophrenia. April 29, 2007.

⁶ Friedman B. A review of reports of hematologic events: aplastic anemia, pancytopenia, bone marrow depression, agranulocytosis, thrombocytopenia, and leukopenia with Zyprexa. FDA Postmarketing Safety Review. September 2, 1997.

⁷ Bennett K. A two-year postmarketing safety review of olanzapine. FDA Postmarketing Safety Review. February 9, 1999.

⁸ Wysowski D. New onset Diabetes Mellitus. FDA Postmarketing Safety Review. December 17, 1999.

⁹ Mosholder A. Literature review concerning the issue of diabetes mellitus/hyperglycemia associated with the atypical antipsychotic drugs. FDA Postmarketing Safety Review. June 25, 2003.

¹⁰ Kortepeter C. A review of acute liver injury associated with olanzapine use. FDA Postmarketing Safety Review. August 15, 2003.

galactorrhea with atypical antipsychotics in order to update risperidone labeling to reflect the increased numbers of reports of hyperprolactinemia and galactorrhea associated with risperidone relative to other atypical antipsychotic drugs.¹¹

- October 4, 2005. A class review of *pituitary tumors* with atypical antipsychotic drugs. The review recommended further investigation, perhaps including reanalysis of the risperidone NDA, in order to update the risperidone label to include increased hyperprolactinemia compared to other atypical antipsychotic agents.¹²
- May 25, 2006. A review of cases of *myocarditis and cardiomyopathy* associated with the use of olanzapine and quetiapine. The review recommended that both cardiomyopathy and myocarditis be added to the Adverse Events section of both olanzapine and quetiapine labels as well as continued monitoring of cardiac adverse events associated with the two drug products. In particular, pediatric cases and fatal cases with hypertrophic cardiomyopathy associated with these two drug products should undergo heightened monitoring.¹³
- January 25, 2008. A class review of selected antipsychotics and the occurrence of *agranulocytosis*. The review recommended the addition of agranulocytosis to the Precautions section of the olanzapine and risperidone label as well as elevating agranulocytosis to the Precautions section for chlorpromazine and haloperidol.¹⁴
- April 29, 2008. A class review of post-marketing cases coded with *death in children 16 years old and younger*. In general, for the cases reviewed, the causes of death were all cause death with the most cases reporting cardiac disorders/sudden death. The review recommended continued surveillance of the AERS database for deaths associated with pediatric patients treated with atypical antipsychotics with a particular focus on cardiac and diabetes related cases.¹⁵

1.1 INTRODUCTION (PRODUCT FORMULATIONS AND INDICATIONS)

Olanzapine is available in three formulations.

- Oral tablet- FDA approved September 30, 1996 and is available in 2.5, 5, 7.5, 10, 15, and 20 mg tablets
- Orally disintegrating tablets- FDA approved April 6, 2000 and is available as 5, 10, 15, and 20 mg tablets
- Intramuscular injection- FDA approved March 29, 2004 and is available in a 10mg vial

Olanzapine is indicated for:

- The treatment of Schizophrenia
- The treatment of Bipolar Disorder as monotherapy or in combination with lithium or valproate
- The treatment of agitation associated with Schizophrenia and Bipolar I Mania

¹¹ Phelan K. A class review of galactorrhea with atypical antipsychotic drugs in pediatric patients. FDA Postmarketing Safety Review. October 4, 2005.

¹² Phelan K. A class review of pituitary tumors with atypical antipsychotic drugs. FDA Postmarketing Safety Review. October 4, 2005.

¹³ LaGrenade L. A review of cases of Myocarditis and Cardiomyopathy associated with the use of olanzapine and quetiapine. FDA Postmarketing Safety Review. May 25, 2006.

¹⁴ Diak I. A mixed class review of antipsychotics and the occurrence of agranulocytosis. FDA Postmarketing Safety Review. January 25, 2008.

¹⁵ Diak I. A class review of postmarketing cases coded with death in children 16 years old and younger. FDA Postmarketing Safety Review. April 29, 2008.

1.2 PEDIATRIC LABELING¹⁶

The safety and efficacy of olanzapine have not been established in patients under the age of 18 years; however, the current labeling contains clinical trial data regarding adolescents.

WARNINGS:

- Olanzapine monotherapy in adolescents was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo.
- Olanzapine monotherapy in adolescents during long-term continuation therapy found that 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.
- Olanzapine monotherapy in adolescents was associated with no statistically significant difference in fasting HDL cholesterol levels between olanzapine-treated patients and placebo-treated patients.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

This section describes the AERS searches performed as well as the case series selection.

2.2 AERS SELECTION OF CASES

We searched the AERS database on May 1, 2008 for all reports in the database of pediatrics (age 0-16 years) and adults (17 years and greater) associated with olanzapine use from market approval until February 10, 2008 and from the pediatric exclusivity date of January 10, 2007 to February 10, 2008. We conducted separate searches as follows:

1. From Marketing to February 10, 2008 – Adults, 17 years old and older, (Section 3.1, Results, Table 1)
 - All adult cases
 - All adult cases coded serious
 - All adult cases coded ‘death’
2. From Marketing to February 10, 2008 – Pediatrics aged 0 to 16 years old, (Section 3.1, Results, Table 1)
 - All pediatric cases
 - All pediatric cases coded serious
 - All pediatric cases coded ‘death’
3. Pediatric Exclusivity Period – January 10, 2007 to February 10, 2008 – Adults, (Section 3.2, Results, Table 2)
 - All adult cases
 - All adult cases coded serious
 - All adult cases coded ‘death’

¹⁶ Zyprexa Product Label, March 2008, Eli Lilly & Co. USA; <http://www.zyprexa.com/index.jsp>.

4. Pediatric Exclusivity Period – January 10, 2007 to February 10, 2008 – Pediatrics, (Section 3.2, Results, Table 2)
 - All pediatric cases
 - All pediatric cases coded serious
 - All pediatric cases coded ‘death’

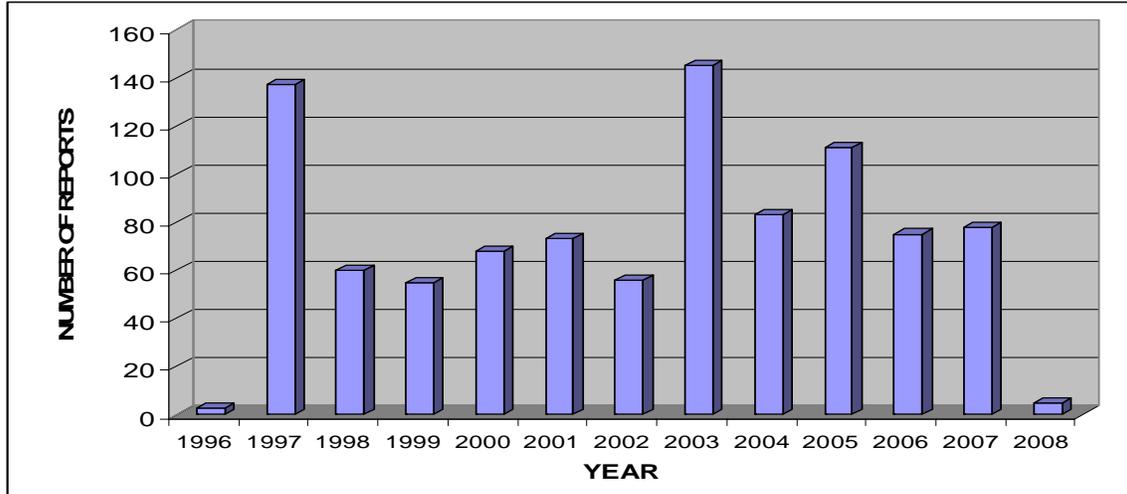
The crude counts that resulted from the searches are included in section 3. However, for cases that will receive a hands-on review, the search retrieved 69 serious outcome reports and of these 69 reports, 59 cases met the inclusion criteria for our case series. Of the 10 cases not included in our case series, three cases were duplicates and the remaining seven did not meet our inclusion criteria. The search of all pediatric reports with an outcome of death from marketing approval to February 10, 2008 retrieved 60 reports. Of these 60 reports, 14 were duplicates and two were excluded for miscoding as a pediatric patient, therefore, 44 cases are included in our case series.

3 AERS RESULTS FOR *OLANZAPINE*

3.1 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM MARKETING APPROVAL TO FEBRUARY 10, 2008 (TABLE 1)

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval Date			
(US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	16819 (11047)	13594 (8578)	2792 (1577)
Pediatrics (0-16 yrs.)	949 (732)	631 (444)	60 (41)
Age unknown (Null values)	3667	2616	603
Total	21435	16841	3455
¹ May include duplicates ² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, other serious.			

Figure 1: Reporting trend for pediatric reports from approval date (September 30, 1996) to February 10, 2008:



3.2 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM PEDIATRIC EXCLUSIVITY (TABLE 2)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	2425(1651)	2256 (1544)	258 (127)
Pediatrics (0-16 yrs)	81 (52)	69 (42)	7 (3)
Age unknown (Null Values)	771	707	85
Total	3277	3032	350

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, other serious.

3.3 CASE CHARACTERISTICS FROM ONE-YEAR REVIEW (TABLE 3)

Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

Table 3: Characteristics of serious and non-serious pediatric cases reported during the pediatric exclusivity period (January 10, 2007 through February 10, 2008) n=81	
Gender [n=74]	Male: 30 Female: 44
Age [n=78]	0- <1 month (5) 1 month - <2 yrs (10) 2-5 yrs (4) 6-11 yrs (16) 12-16 yrs (43) Mean 11 years, Median 13 years, Range 1 day to 16 years

Table 3: Characteristics of serious and non-serious pediatric cases reported during the pediatric exclusivity period (January 10, 2007 through February 10, 2008) n=81	
Origin [n=79]	US 52, Foreign 27
Event date (n=63)	1999 (2) 2000 (2) 2001 (1) 2002 (7) 2003 (8) 2004 (5) 2005 (12) 2006 (13) 2007 (13)
Daily dose [n=50] Overdose [n=1]	Mean 11 mg, Median 10 mg , Range 2.5 to 25 mg Dose ingested: 250 mg
Duration of therapy [n=24]	Mean 261 days, Median 88 days, Range 1 to 2095 days
Indications [n=37] ¹⁷	ADHD (1), Agitation (1), Anger (1), Anorexia (1), Autism (2), Behavior (1), Bipolar Disorder (9), Brief psychotic disorder (1), Delusional disorder (1), Depression (4), Emotional disorder (1), Mania (1), Muscle twitching (1), OCD (3), PTSD (1), Psychotic disorder (3), Schizophrenia (4), and Sleep disorder (1)
Outcomes, non-overlapping [n=68] ¹⁸	Death (7*), Life-Threatening (2), Hospitalization (40), Disability (1), Congenital Anomaly (2), and Other Serious (16)

* 7 Crude death cases representing six unique unduplicated cases

4 DISCUSSION/SUMMARY OF CASES

Summary of Cases received during the 1-year post-pediatric exclusivity period

4.1 TOTAL REPORTS WITH AN OUTCOME OF DEATH (N = 44)

In light of the fact that six unique pediatric cases coded with death were reported during the pediatric exclusivity period, all pediatric reports with a coded outcome of death from marketing approval until February 10, 2008 were reviewed. The AERS database contained 44 pediatric cases with an outcome of death in association with olanzapine use *since market approval*. Overall, for the 44 cases, 28 are US cases and 16 are foreign cases, including 24 males and 13 females (seven cases did not provide a gender). The patients involved ranged in age from 1 day to 16 years with a median of 13 years (two cases described fetal demise and therefore, their ages were not included).

4.1.1 Drug Exposure during Pregnancy (n = 12)

Twelve cases reported drug exposure to olanzapine in utero with two cases describing fetal demise at 22 weeks and 31-32 weeks. Of the 12 cases, five cases were of US origin and seven were foreign with four cases each of male and female and four cases of unknown gender. Five of the twelve cases provided information regarding time to death and reported the deaths occurring from as early as 30 minutes after birth to as late as 2&1/2 months after birth. Four cases reported concomitant prescription drug therapies with FDA pregnancy categories ranging from A to D¹⁹.

¹⁷ ADHD= Attention-Deficit Hyperactivity Disorder, OCD = Obsessive Compulsive Disorder, PTSD = Post-Traumatic Stress Disorder

¹⁸ Cases are assigned to one outcome according to the following hierarchy: death, hospitalization, life-threatening

¹⁹ **FDA Pregnancy Category A:** Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Of these four cases, two described benzodiazepine use, which do not currently hold an FDA pregnancy category status; however, the label suggests an increased risk of congenital malformations associated with benzodiazepine use. An additional two cases reported illicit drug use by the mother. The time of drug exposure in utero among the 12 cases ranged from 19 days to “throughout the entire pregnancy.” Three of the twelve cases reported some mechanism thought to be related to the cause of death. The first case reported that the baby had a mild heart murmur at birth and ultimately died from SIDS. The second case reported the patient died because of “heart and kidney complications”, and the final case reported sepsis as the cause of death. In the other nine cases, a cause of death could not be determined. Olanzapine currently holds an FDA pregnancy category C status.

4.1.2 Other Deaths (n = 32)

For the remaining 32 deaths, 23 were of US origin and 9 were foreign with 20 males, 9 females and 3 unknown gender cases. The ages of the patients ranged from 1 to 16 years with a median of 13.5 years. A contributing factor or definite cause of death determined on autopsy could be identified in 24 of the 32 cases.

Suicide (6)

Suicide accounted for six cases with one of those cases describing a patient that purchased the olanzapine, as he did not have a current prescription for the medication. Of note, the ages of the patients that committed suicide ranged from 12 to 16 years with a median of 13.5 years. Olanzapine has labeling describing an association with increased risk of suicidal thinking as well as stating, “the possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder and close supervision of high-risk patients should accompany drug therapy.”¹¹ This caution may lend to the thought that psychiatric illness is a confounding factor in many suicides. Thus, from AERS cases alone, it is not possible to distinguish events linked to the underlying condition from paradoxically heightened suicidality due to drug effect.

Metabolic effects (5)

In five cases, patients experienced metabolic effects described as diabetes mellitus, diabetic coma, diabetic ketoacidosis, and weight gain as contributing factors to their deaths. In two cases, one each described Diabetes Mellitus Type I and II and the remaining three did not specify. The current olanzapine label states, “Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine.”¹¹

FDA Pregnancy Category B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

FDA Pregnancy Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

FDA Pregnancy Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Cardiac events (4)

An additional four cases described the deaths resulting from cardiac events; including cardiac arrhythmia, myocarditis, “presumably myocardial infarction”, and cardiac arrest leading to sudden death. Olanzapine has a boxed warning in the label describing an association with sudden death in the elderly as well as labeling suggesting an association with cardiac arrest and arrhythmias.

Unusual use of olanzapine (5)

Five cases described patients whose cause of death was indirectly related to prescribed olanzapine use; these include three intentional deaths at the hand of their parents, one case described the manner of death as accidental and the remaining case described a drowning. In all three cases, the olanzapine was prescribed for the parents.

The remaining four cases that reported a cause of death each describe a different adverse event relating to the death, and they include acute asthma attack, necrotizing pancreatitis, hepatic steatosis, and endocranial hemorrhage along with multiple blood dyscrasias (thrombocytopenia and sickle cell beta thalassemia). Thrombocytopenia is the only adverse event labeled of these five cases.

Eight cases did not provide enough information to determine a cause of death or olanzapine’s contributing role in the outcome.

**A narrative summary for each death case is located in Appendix 1.

4.2 TOTAL NON-FATAL SERIOUS ADVERSE EVENT REPORTS (N = 59)

The AERS database contained 59 cases of non-fatal serious adverse event reports in the pediatric population (0-16 years) from January 10, 2007 to February 10, 2008. This included 37 US, 18 foreign, and 4 unknown origin cases with 34 females, 20 males, and 5 unknown gender cases ranging in age from 1 day to 16 years with a median of 13 years. Various lawyers in connection with legal cases reported twenty-three cases.

4.2.1 Metabolic Effects (n = 27)

Twenty-seven cases ranging in age from 4 to 16 years with a median of 13.5 years reported various metabolic effects associated with olanzapine therapy; including diabetes mellitus, diabetic coma, diabetic ketoacidosis, and weight gain. A possible explanation for this comes from the current olanzapine label, which states, “the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.”¹¹ We will provide a summary of the 27 cases. Fifteen cases reported a time to onset of adverse event that ranged from 11 days after initiation of olanzapine up to approximately five years after the discontinuation of olanzapine therapy. Eleven cases reported a positive family history of diabetes mellitus with two of those also reporting a family history for hypertension. Five cases reported a past medical history of obesity and three reported a history of diabetes mellitus with one of those cases reporting a history of both obesity and diabetes mellitus. Approximately 50% of the cases were confounded by the use of concomitant medications. Of note, one of the cases of weight gain was the result of a medication error. The patient received Zyprexa[®] rather than Zyrtec[®] for 29 days and

experienced a weight gain of 15 pounds.²⁰ Weight gain appears in the current olanzapine label in the Warnings section and hyperglycemia, diabetic ketoacidosis and coma appear in the Precautions section. See Appendix 4, Table 1 for a summary of the metabolic effects case counts.

4.2.2 Drug exposure during pregnancy (n = 11)

Eleven cases reported in utero exposure of olanzapine. In the nine cases reporting the duration of fetal drug exposure, the time ranged from approximately 60 days to as long as the entire length of the pregnancy (exact durations unspecified). Four cases reported congenital anomalies/birth defects, which included breast malformation, congenital hand malformation, atrial septal defect, and patent ductus arteriosus. Of the remaining seven cases, four cases described neonatal tonic problems (i.e. hypertonia, hypotonia, dystonia) of which all four infants recovered completely, one case each described neonatal drug withdrawal syndrome, necrotizing enterocolitis and septicemia, and the final case reported the baby as being small for the dates. Nine of the 11 cases reported maternal use of concomitant medications with the FDA pregnancy categories ranging from A to D. Of these nine cases, three described benzodiazepine use, which do not currently hold an FDA pregnancy category status; however, the label suggests an increased risk of congenital malformations associated with benzodiazepine use.

4.2.3 Nervous System (n = 4)

Four cases reported nervous system involvement. Three of the cases described the occurrence of seizures. The first case describes a 4-year old male who experienced a grand mal seizure after one year of concomitant therapy with olanzapine and lamotrigine. Lamotrigine is labeled for an association with grand mal seizures. At the time of reporting, olanzapine therapy was discontinued (the status of lamotrigine was unknown) and the patient no longer experienced seizures. The second case described the occurrence of a seizure 65 days after the initiation of concomitant therapy with olanzapine and sertraline. Both olanzapine and sertraline are labeled for an association with seizures. The third case described a patient that experienced recurrent seizures starting at an unknown time after the initiation of therapy with olanzapine. The case was confounded by the use of the concomitant medications escitalopram and risperidone, which are labeled for an association with seizures. The final case described a 16-year old male that attempted suicide by overdosing on 250mg of olanzapine leading to neuroleptic malignant syndrome. Seizures appear in the current olanzapine label in the Precautions section and neuroleptic malignant syndrome appears in the Warnings section.

4.2.4 Blood Dyscrasias (n = 3)

Three cases reported the occurrence of blood dyscrasias. Two of these cases described leukopenia each in a 14-year old female patient. In the first case, the leukopenia occurred within seven days of olanzapine initiation and the patient recovered two days later without discontinuation of olanzapine therapy. This case was possibly confounded by the use of the concomitant medications valproic acid, clonazepam, lorazepam, and esomeprazole, which are all labeled for an association with leukopenia. In the second case, the patient experienced leukopenia at an unknown time after olanzapine initiation, however treatment with olanzapine continued and at the time of reporting the event of leukopenia was ongoing. The final case described a case of hemolytic anemia in a 16-year old female occurring at an unknown time during concomitant therapy with clozapine and olanzapine. The hemolytic anemia resolved within a few days of

²⁰ The medication error between Zyprexa and Zyrtec was reviewed by the Division of Medical Errors and Prevention Analysis in 2006. Dallas S. DMETS Post-Marketing Medication Errors Safety Review between Zyrtec, Zyprexa, and Zantac. April 14, 2006.

clozapine discontinuation and olanzapine therapy continued throughout the event. Leukopenia appears in the current olanzapine label under the adverse events section and hemolytic anemia is not labeled.

4.2.5 Miscellaneous/Other (n = 14)

Fourteen cases reported adverse events that did not fall into any of the previously described categories. The 14 cases included three pancreatitis cases and one each of the following: accidental overdose, blepharospasm/dry eye, dystonia/dyskinesia, hyperprolactinemia and gynecomastia, intentional overdose of medications other than olanzapine, lithium toxicity, maculo-papular rash, multiple sclerosis, priapism, sinus disease, and systemic lupus erythematosus. Of the three cases of pancreatitis, one case was confounded by the concomitant use of risperidone and quetiapine, which are labeled for an association with pancreatitis. Overall, for all 14 cases, the role of olanzapine in the occurrence of the adverse event was not highly likely in six cases, but olanzapine's role could not be ruled out completely. Specifically, in the case of intentional overdose, the medications ingested were promethazine and cyproheptadine and the adverse events reported (i.e. hypertonia, mydriasis, myoclonus, dry mouth, etc.) are consistent with overdosage situations for those two agents. In the case of hyperprolactinemia with gynecomastia, the adverse event was more temporally associated with the use of risperidone. In addition, causality could not be assessed in the cases of multiple sclerosis, systemic lupus erythematosus, sinus disease, and lithium toxicity in which olanzapine was discontinued five months prior to the reported adverse events. As far as the labeling status of these adverse events in the current olanzapine label, blepharitis and dry eye, dystonia and dyskinesia, hyperprolactinemia and gynecomastia, maculo-papular rash, and priapism are all labeled.

4.2.6 Neural tube defect (n = 1)

****This case was not captured in the AERS database during the pediatric exclusivity period and is not included in the 59 non-fatal serious cases****

We were also asked to identify any cases of neural tube defects reported in the AERS database in association with olanzapine therapy. The search retrieved one case of an infant exposed to olanzapine for two months during the first trimester of pregnancy and born with a neural tube defect. It is important to note that incomplete information was provided in this case, including the absence of information regarding the mother's prenatal care and/or nutritional status, therefore making an accurate assessment of the risk to the fetus from olanzapine exposure difficult.

5 CONCLUSION

Among the 44 reviewed post-marketing cases with an outcome of death and the 59 post-marketing cases identified during the period of pediatric exclusivity, the safety profile of the pediatric population is very similar compared to the adults, and the adverse events occurred in much the same manner as well. In 2007, the pediatric population (0-17 years) accounted for approximately 4.5% [1.9% (0-12 years) and 2.6% (13-17 years)] of all olanzapine prescriptions dispensed in US retail pharmacies as well as making up approximately 5.5% [~2.4% (0-12 years) and ~3.3% (13-17 years)] of the total patient share.²¹ In addition, the adverse events reported amongst children and adolescents appear to occur in a similar frequency. Across all cases of death and non-fatal serious outcomes, metabolic effects were reported as a majority of the adverse

²¹ Borders-Hemphill V. Zyprexa (olanzapine) tablets BPCA Drug Use Review. FDA Postmarketing Review. June 26, 2008.

events. Although metabolic effects such as weight gain, hyperglycemia, and dyslipidemia are well-known effects in the adult population, special attention should be focused on the impact they have among the pediatric population. No new safety signals emerged as part of this review; however, it has made us aware that the pediatric population is not spared from the adverse events caused by olanzapine therapy. The potential risks of olanzapine therapy should be weighed against the potential benefit when choosing to initiate therapy.

6 RECOMMENDATIONS

- Revise the current olanzapine label to include language regarding the potential risk of the metabolic effects that are also experienced among the pediatric population.
- Continue routine monitoring of the AERS database for adverse events with the use of olanzapine in pediatric patients.

APPENDICES

Appendix 1- A narrative summary of all cases with an outcome of ‘death’ associated with olanzapine use from market approval to February 10, 2008.

Drug exposure during pregnancy (12):

- **ISR# 5123410; Foreign, 2006.** This fetus died at 22 weeks of gestation after exposure to olanzapine 20 mg daily throughout the pregnancy. The mother’s concomitant medications included fluoxetine, diazepam, acetaminophen, loratadine, and desloratadine.
- **ISR# 4999149; US, 2006.** This infant died 30 minutes after birth because of Trisomy 13 after exposure to olanzapine 5-10mg daily for 19 days.
- **ISR# 5130133; US, 2006.** This infant died at an unknown time after exposure to olanzapine 5 mg daily throughout the pregnancy. The mother’s concomitant medications included citalopram, trazodone, bupropion, and aripiprazole.
- **ISR# 4665076; Foreign, 2005.** This infant was born at 38 weeks of gestation “presented with severe neonatal cardiomegaly, macrosomia and died” after exposure to olanzapine 20mg daily for three months during the pregnancy. The mother developed gestational diabetes at some point in the pregnancy.
- **ISR# 3464646; Foreign, 2000.** This fetus was born still at 32 weeks of gestation after exposure to olanzapine 10-20 mg daily throughout the pregnancy. The mother smoked tobacco as well as cannabis. Autopsy results revealed, “extensive placental infarction and chronic underperfusion.”
- **ISR# 4895608; US, 2006.** This infant died after exposure to olanzapine throughout the pregnancy. The mother also used heroin and cocaine during the pregnancy.
- **ISR# 3747959; Foreign, 2001.** This infant died after exposure to olanzapine 5 mg daily throughout the pregnancy. The infant had birth defects that included enlarged kidneys, extra digits, and a cleft palate as well as, Trisomy 18 and a low heart rate.
- **ISR# 4300562; US, 2004.** This fetus died at 31-32 weeks of gestation after exposure to olanzapine 20 mg daily during the 2nd and 3rd trimesters of the pregnancy. The mother’s concomitant medications included lorazepam, prenatal vitamin, nicotine resin, and docusate sodium. The autopsy found “apparent hypertelorism, eccentric umbilical cord placement at the periphery of the placenta, and placental insufficiency” with low placental weight and a short umbilical cord.
- **ISR# 3025914; US, 1998.** This infant died within the first two months of life from sudden infant death syndrome (SIDS) after exposure to olanzapine during the 2nd and 3rd trimesters of pregnancy. The autopsy reported, “nothing structurally wrong with the baby.”
- **ISR# 5306046; US, 2007.** This infant died after exposure to olanzapine (dose unknown) throughout the pregnancy. The mother’s concomitant medications included sertraline and oxazepam. SIDS was the possible cause of death although the autopsy results could not confirm the cause.

- **ISR# 4246991; US, 2003.** This infant died within the first two months of life because of “heart and kidney complications” after exposure to olanzapine 7.5-10mg daily throughout the pregnancy. The patient underwent an autopsy with no results reported.
- **ISR #4765562; US, 2005.** This infant died within the first 2&1/2 months of life because of a sepsis infection. Exposure to olanzapine (dose unknown) occurred throughout the pregnancy

Suicide (6):

- **ISR# 4244394; US, 2003.** This 12-year old patient experienced a “pre-hospital cardiac and /or respiratory arrest and died” after the intentional ingestion of an unknown amount of olanzapine. The report did not state if the patient had a current prescription for the medication.
- **ISR# 4854277; US, 2005.** This 14-year old patient ingested unknown amounts of olanzapine, risperidone, and fluoxetine along with other unspecified substances. The post mortem blood concentrations for all of the drugs were elevated. The report did not state if the patient had a current prescription for the medication.
- **ISR# 4526000; US, 2004.** This 15-year old male died after ingesting an unknown amount olanzapine that he received from someone else. He did not currently have a prescription for this medication. The autopsy results reported an elevated olanzapine level and a cause of death as olanzapine intoxication.
- **ISR# 5388427; Foreign, 2007.** This 13-year old male hanged himself one month after an increase in dose of olanzapine to 20 mg daily, sertraline to 200mg daily, and clonazepam to 4mg daily for the treatment of depression. Sertraline and clonazepam both have labeling describing an association with suicidal ideation. The report stated that the patient had thoughts of suicide that began within two months of initiating therapy with olanzapine.
- **ISR# 5545401; Foreign, 2007.** This 14-year old hanged herself within two months of initiating therapy with olanzapine 2.5 mg daily for the treatment of agitation/anxiety and her level of arousal. Her concomitant medication included venlafaxine, which has labeling describing an association with suicidal ideation. The patient had previously attempted to commit suicide. The autopsy confirmed the cause of death to be the hanging and it revealed skin scarring from her self-inflicted cutting. The report also revealed undetectable levels of olanzapine, fluoxetine, venlafaxine, zolpidem, and amitriptyline in her blood.
- **ISR# 4588081; Foreign, 2005.** This 16-year old male committed suicide within two months of initiating therapy with olanzapine for the treatment of generalized anxiety disorder. His concomitant medication included isotretinoin, which has labeling for an association with suicide.

Metabolic Effect (5):

- **ISR# 4164689; US, 2003.** This 13-year old female experienced diabetic ketoacidosis and died after an unknown duration of therapy with olanzapine 5 mg daily (indication unknown). She also took ziprasidone. Autopsy results confirmed the cause of death.
- **ISR# 4957302; US, 2006.** This 15-year old female experienced diabetes, diabetic ketoacidosis and diabetic coma and died after over one year of therapy with olanzapine (dose unknown) for the treatment of unspecified psychiatric illnesses. Her concomitant medications included ziprasidone, methylphenidate, and sertraline.

- **ISR# 4367813; US, 2004.** This 12-year old child “lapsed into a diabetic coma and died” after an unknown duration of therapy with olanzapine 15 mg daily (indication unknown).
- **ISR# 3814020; Foreign, 2001.** This 16-year old male experienced diabetic coma and died three months after initiating therapy with olanzapine 10mg daily for the treatment of manic depressive illness and mania. His concomitant medications included valproate and topiramate.
- **ISR# 4697426; US, 2005.** This 6-year old male died from an unknown cause after an unspecified duration of therapy with risperidone for the treatment of “bipolarism” and autism. Prior to commencing therapy with risperidone (dose unknown), he received olanzapine 15mg daily and this resulted in excessive weight gain and the diagnosis of hyperglycemia, which ultimately led to its discontinuation. His concomitant medications included amphetamine/dextroamphetamine, valproate, risperidone, dexmethylphenidate, and gabapentin. The initial report from a lawyer stated, “on an unknown date, the patient experienced diabetes mellitus, diabetic coma, ketoacidosis, and pancreatitis.”

Cardiac disorders (4):

- **ISR# 5016888; Foreign, 2006.** This 16-year old male died because of cardiac arrest eight days after an increase in his olanzapine dose to 30 mg daily. Olanzapine therapy began 6&1/2 months prior to his death for the treatment of psychosis. The patient also took alprazolam (dose and duration unknown). Autopsy results were pending at the time of the report.
- **ISR# 1966741; US, 1997.** This 7-year old male experienced a cardiac arrhythmia and suddenly died four days after an increase in his olanzapine to 10 mg daily for the treatment of autism. The duration of olanzapine therapy lasted seven days. He also received diphenhydramine 25mg and droperidol 2.5mg the day of his death. Both diphenhydramine and droperidol are labeled for an association with cardiac arrhythmia. The autopsy performed reported “no gross findings.”
- **ISR# 3937929; US, 2002.** This 8-year old male died of myocarditis after experiencing ventricular fibrillation and asystole. The patient received therapy with olanzapine (dose and duration unknown) for the treatment of bipolar disorder. His concomitant medication included carbamazepine. The autopsy reported, “extensive areas of the myocardium infiltrated by a mixed lymphohistiocytic infiltrate with scattered polys and other monocytic cells.”
- **ISR# 5121343; US, 2006.** This 11-year old male died from “presumably myocardial infarction” 2&1/2 years after initiating therapy with olanzapine 2.5 mg daily for the treatment of insomnia and depression. Concomitant medications included doxepin, prednisone, and fluticasone and many other medications were mentioned, but it was unknown if they were concomitant medications. The patient experienced a thrombus prior to death (unknown date).

Unusual death (5):

- **ISR#4207658; US, 2003.** The medical examiner ruled this 2-year old female’s death accidental. The patient initiated therapy with olanzapine 5 mg daily and atomoxetine 20 mg daily for the treatment of hyperactivity and possible bipolar disorder. Within 2&1/2 months of initiating therapy, there was an increase in the atomoxetine dose with no change in the

olanzapine dose. Eight days later, she died. “The medical examiner suggested a possible drug interaction which decreased the metabolism of olanzapine” as the cause of death. The autopsy confirmed no “significant findings.”

- **ISR# 3800810; Foreign, 2001.** This 15-year old male died after drowning in a lake. His medications included olanzapine 10mg daily for three to four weeks and dextroamphetamine for years (dose unknown) for the treatment of Asberger syndrome and ADHD. Two weeks prior to the accident, there was an increase in dose of olanzapine from 5mg to 10mg daily and the patient experienced an episode of epistaxis. The autopsy results revealed no pathological abnormality.
- **ISR# 5274611; US, 2007.** This 1-year old male died from an opiate toxicity because of his father “feeding his son morphine and hydromorphone.” The urinalysis also found olanzapine in his system. The autopsy reported diagnoses of “respiratory arrest secondary to opiate toxicity, pulmonary congestion and edema, rare petechial hemorrhages of thoracic organs, congestion of the viscera, and fresh, superficial 1.5” contusion of nape of neck.”
- **ISR# 4833425; Foreign, 2005.** This 4-year old female died from asphyxiation by her mother. The patient’s mother gave her 5mg of olanzapine to sleep at which time she asphyxiated the patient.
- **ISR# 5564489; Foreign, 2007.** This 12-year old female patient’s father killed her and cut her into pieces. The patient also had traces of olanzapine found in her lungs, stomach, and kidneys.

Miscellaneous (4):

- **ISR# 3872860; US, 2002.** This 14-year old male experienced an acute asthma attack and died while taking olanzapine 20mg daily (duration and indication unknown). The patient had a medical history of asthma.
- **ISR# 3763759; US, 2001.** This 16-year old “experienced a possible drug interaction, hepatic steatosis, and was found dead” after initiating therapy with olanzapine 5 mg daily 1-2 years prior for ADHD and personality disorder. His concomitant medication included amphetamine/dextroamphetamine. The autopsy confirmed the diagnosis of hepatic steatosis, but not the cause of death.
- **ISR# 3957742; US, 2002.** This 15-year old male died from necrotizing pancreatitis within three months of initiating therapy with olanzapine (dose unknown) for the treatment of bipolar disorder and depression. His death came one month after his diagnosis of diabetes mellitus. His concomitant medications included carbamazepine, paroxetine, and valproate and they all have labeling describing an association with pancreatitis.
- **ISR# 4790560; US, 2005.** This 12- year old female died from an unknown cause within one month of initiating therapy with quetiapine and discontinuing olanzapine therapy (doses unknown). In the months just prior to her death, she had a diagnosis of diabetes mellitus and experienced diabetic ketoacidosis. Over almost two years of therapy with olanzapine, she experienced a weight gain of 29 pounds. Her concomitant medications included clonidine, escitalopram, methylphenidate, and diphenhydramine. On discharge, she was diagnosed with sickle cell beta thalassemia, thrombocytopenia, endocranial hemorrhage, encephalopathy, hypertension, and anemia.

Indeterminate cause (8):

- **ISR# 5466763; US, 2007.** This 3-year old female died from “hepatic issues” at an unspecified time after initiating therapy with olanzapine (dose and indication unknown). This was a hearsay case and details are incomplete and unconfirmed.
- **ISR# 4254663; US, 2003.** This 10-year old male died sometime after initiating therapy with olanzapine (dose and indication unknown). The patient’s medical history included a severe cardiac pathology.
- **ISR# 4234811; US, 2003.** This 12-year old female initiated olanzapine 5mg daily and died “within a few days of olanzapine introduction”.
- **ISR# 3011672; US, 1997.** This 14-year old male “became agitated on the school bus” and needed restraining and he died. He received therapy with olanzapine 12.5mg daily at the time of his death (duration and indication unknown). His concomitant medication included haloperidol.
- **ISR# 4692944; US, 2005.** This 15-year old male died approximately one month after initiating therapy with olanzapine (dose unknown) for the treatment of bipolar disorder.
- **ISR# 4747126; US, 2005.** This 15-year old male died on an unspecified date after a hospitalization for “severe right side pain” with no diagnosis determined. He currently received therapy with olanzapine 5 mg daily for the treatment of bipolarism, depression, and ADHD for the previous five years along with methylphenidate, mirtazapine, paroxetine and valproate. He had a prior history of pancreatitis.
- **ISR# 4538924; US, 2004.** This 16-year old male experienced diabetes and died after two years of therapy with olanzapine (dose unknown) for the treatment of schizophrenia and bipolar disorder.
- **ISR# 4249552; Foreign, 2003.** This 16-year old male died one day after initiating therapy with olanzapine 5 mg (indication unknown). Three days prior to his death, he received metoclopramide and biperiden resulting in an “extrapyramidal type adverse event” and the psychiatrist made the diagnosis of “catatonic type psychomotor agitation in an apparently detached person”. The autopsy revealed a pulmonary infarction, but stated the cause of death was unknown.

APPENDIX 2

Count of Metabolic Syndrome, Weight Increased, Hyperglycemia, and Hyperlipidemia Reports: All Sources Combined- US and Foreign from marketing approval until February 10, 2008

AERS search criteria:

Time period: Marketing approval to February 10, 2008

Coded outcomes: all reports, all serious reports, all death reports

Ages: 17 years and older AND 16 years and younger

MedDRA Preferred Terms: Metabolic Syndrome, Weight Increased, Hyperglycaemia, and Hyperlipidaemia

Table 1 - Crude counts¹ of AERS Reports from all sources from Marketing Approval until 2/10/08						
MedDRA Preferred Term	All reports		Serious²		Death	
	> 17 yrs	0-16 yrs	> 17 yrs	0-16 yrs	>17 yrs	0-16 yrs
Metabolic Syndrome	49	1	45	1	4	0
Weight Increased	1546	115	1234	67	124	3*
Hyperglycaemia	780	22	718	19	78	1**
Hyperlipidaemia	144	2	132	2	8	0

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, other serious.
 *Two deaths occurred in 2005 and the remaining death occurred in 2007.
 ** The one death occurred in 2005

** Table 2 is derived from the 0-16 yrs all reports column in Table 1 above

Table 2** –Pediatric age stratification of crude count AERS reports from all sources from Marketing Approval until 2/10/08 for Metabolic Syndrome, Weight Increased, Hyperglycaemia, & Hyperlipidaemia				
MedDRA Preferred Term	All reports Total	0-6 years	7-11 years	12-16 years
Metabolic Syndrome	1	0	0	1
Weight Increased	115	13	30	72
Hyperglycaemia	22	4	5	13
Hyperlipidaemia	2	0	0	2

APPENDIX 3

Count of Hyperprolactinemia Reports: All Sources Combined- US and Foreign from marketing approval until February 10, 2008

AERS search criteria:

Time period: Marketing approval to February 10, 2008

Coded outcomes: all reports, all serious reports, all death reports

Ages: 17 years and older AND 16 years and younger

MedDRA Preferred Term: Hyperprolactinemia

Table 3 - Crude counts¹ of AERS Reports from all sources from Marketing Approval until 2/10/08			
	All reports	Serious ²	Death
Adults (> 17 yrs)	21	16	1*
Pediatrics (0-16 yrs)	1	1	0
Age unknown (Null values)	1	1	0
Total	23	18	1

¹ May include duplicates

² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, and other serious.

* The one case of death occurred in 2001

APPENDIX 4

Table 1- Summary of the 27 non-fatal serious metabolic effect cases reported from January 10, 2007 to February 10, 2008

DC= Diabetic Coma, DM= Diabetes mellitus, DKA= Diabetic Ketoacidosis, MD= Metabolic Disorder²², MS= Metabolic Syndrome²³, and WI= Weight Increased

Adverse Event	Number of Cases
Weight Increased	6
Diabetes Mellitus ²⁴	5
DM + DKA	3
DM + MD	3
DM + DC + DKA + WI	2
DM + WI	2
DM + DC	1
DM + DC + DKA + MD	1
DM + DKA + DC	1
DM + MD + WI	1
Hyperglycemia + Elevated triglycerides	1
MS + WI	1

²² Metabolic disorder is coded as abnormal glucose metabolism (hypoglycemia, hyperglycemia, polydipsia, polyphagia, polyuria)

²³ The components of metabolic syndrome include abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance \pm glucose intolerance, proinflammatory state, prothrombotic state.

²⁴ Not all cases specified Type I or II.

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Mark, this is the final after meeting with OPT
and PMHS. The appendix case narrative numbers were
corrected, as well as an additional table (as
requested) is included in the appendix.

Mark Avigan
9/11/2008 05:43:12 PM
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