M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D030715

DATE: April 15, 2005

FROM: Evelyn R. Farinas, R. Ph., M.G.A.
Post Marketing Safety Evaluator

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation
Office of Drug Safety (ODS), HFD-430

TO: Solomon Iyasu, M.D., M.P.H., Team Leader
Division of Counter-Terrorism and Pediatrics, HFD-960

SUBJECT: ODS POSTMARKETING SAFETY REVIEW
Consult: One-Year Post Pediatric Exclusivity Postmarketing Adverse Events Review
Drug: Fluconazole tablets, injection, oral suspension
NDA: 19-949, 19-950, 20-090, 20-322
Pediatric Exclusivity Approval Date: January 22, 2004

1. EXECUTIVE SUMMARY

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of fluconazole in pediatric patients. Up to the "data lock" date of February 28, 2005, AERS contained 8031 cases for fluconazole (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 6% of the total (444/8031).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, January 22, 2004, to January 22, 2005. We used an AERS data lock date of February 28, 2005, to allow time for reports received up to January 22, 2005, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 395 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 7% of the total number of cases (29/395). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

We reviewed 19 unique pediatric cases reported to the FDA during the pediatric exclusivity period. Note that raw counts indicate 29 cases; however, the excess of 10 reports is due to duplication of cases. The reported adverse events described in the 19 cases included congenital anomalies (4), cardiac events (3), elevation of liver enzymes (3), metabolic events (2), medication errors (2), fungemia (2), and one each of SIDS, neurologic events and hypersensitivity reactions.

Four of the 19 cases listed fatalities associated with neurologic events, elevation of liver enzymes, SIDS and congenital abnormalities, respectively. In two of the four cases where the cause of death was not specified, the pediatric patients received concomitant medications associated with the reported neurologic (somnolence, asthenia, visual disturbances, mental confusion, etc.) and hepatic (elevation of liver enzymes) adverse events. In the other two cases, fluconazole was administered to the infants' mothers. One infant died of asphyxia and SIDS the day after the mother's one time dose of fluconazole. The other was stillborn, and had developed Edwards' syndrome and cardiac abnormalities; its mother had received one dose of fluconazole over 26 weeks before becoming pregnant. Note that the fluconazole label addresses hepatic adverse events, transmission through breast milk, and congenital anomalies.

In the 15 non-fatal cases, the outcome was listed in 13 and described as life-threatening (5), hospitalization (4), congenital anomaly (3) and requiring intervention (1). The five life-threatening reports are associated with cardiac arrhythmias in three and with alterations in glucose metabolism in the other two. It appears that in the hospitalization reports the admissions were most likely related to complications of underlying illnesses (i.e., appendicular peritonitis, catheter infection, palliative care for cancer, and upper respiratory tract infection). The congenital anomaly reports list various abnormalities in three infants; in two the mothers used one dose of fluconazole prior to conception, and in the third the mother was treated with fluconazole during the pregnancy as well as exposed to X-rays during the first trimester of the pregnancy. The required intervention outcome was in a 6-month old infant and consisted of switching antifungal therapy from fluconazole to clotrimazole, with positive resolution of the elevation of liver enzymes.

Our hands-on review of the 19 unique cases showed that, of the most frequently reported adverse events during the pediatric exclusivity period in the pediatric population, eight were reported more than once, but none was reported more than three times. Of the eight, six were listed or addressed in the label. The events reported three times (alanine aminotransferase increased, aspartate aminotransferase increased and electrocardiogram QT prolonged) are listed in the **WARNINGS** and **PRECAUTIONS** sections of the label. Three events reported twice (drug exposure during pregnancy, maternal drugs affecting fetus and overdose) are referred to in the **PRECAUTIONS** and **OVERDOSE** sections of the label. Bronchospasm and medication error (with overdose) were reported twice, but are not listed in the fluconazole label. Bronchospasm was mentioned in association with an allergic reaction to Neupogen in one patient, and with deteriorating respiratory function in another very ill patient. Both medication errors were the result of pharmacist error, one due to misreading the instructions in the prescription and the other with dispensing a higher than prescribed concentration.

Note that and additional 107 events were mentioned only once and thus are included in the list of top 20 events. The majority of these are unlabeled events. Some of these unlabeled events are associated with pre-existing illnesses in the patients, and others are adequately covered by similar terms listed in the labeling. Since these events are mentioned only once it is premature to recommend any labeling changes at this time.

We noticed that occurrence of cardiac adverse events in pediatric patients was not specifically mentioned in the label. Even though QT prolongation is stated in two sections, the label does not indicate clearly if this event can occur in the pediatric population as well. The present label could be construed to mean that QT prolongation, whether alone or due to a drug interaction, has not occurred in the younger population. To avoid such misconception, it may be prudent to include a mention of its occurrence in younger patients under post-marketing events to alert clinicians of such a possibility.

In summary, during the pediatric exclusivity period the 19 unique pediatric cases showed that the events most frequently reported are adequately covered in the fluconazole label. At this time we have not identified new safety concerns in the pediatric population that are not adequately addressed in the label. We will continue to monitor adverse events in the pediatric population and communicate any emerging signal to the review division.

2. PRODUCTS, INDICATIONS, PEDIATRIC FILING HISTORY and PEDIATRIC LABELING

Products:

NDA 19-949 (Tablets) and NDA 20-950 (Injection) were originally approved on January 29, 1990, and shared a combined package insert. NDA 20-090 (Powder for Oral Suspension) was originally approved on December 23, 1993 and then also shared a combined package insert with the other two Diflucan® formulations. The most recent labeling supplement for all three products was approved on October 6, 2004. NDA 20-322 (Tablets) was approved on June 30, 1994 for the treatment of vaginal candidiasis.

Indications:

Fluconazole tablets, injection and powder for oral suspension are indicated for the treatment of vaginal, oropharyngeal and esophageal candidiasis, as well as for cryptococcal meningitis. The labeling also states that fluconazole is effective for the treatment of Candida urinary tract infections, peritonitis and systemic Candida infections. Fluconazole is also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.

Several pediatric studies quoted in the labeling indicate that fluconazole is effective in children. However, the efficacy of fluconazole has not been established in infants less than six months of age.

Pediatric Filing History:

A Written Request for pediatric studies of Diflucan® was issued to Pfizer on December

31, 2001, with an amendment dated June 7, 2002. The requested studies were to include two clinical safety and efficacy studies in pediatric patients with tinea capitis. In response to this Written Request, Pfizer submitted NDA 21-718/Diflucan® for Tinea Capitis to the Division of Dermatologic and Dental Drug Products (DDDDP) on October 28, 2003. This was a Type 6 NDA; the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) continues to hold the parent NDAs.

The studies submitted in NDA 21-718 fulfilled the requirements of the December 31, 2001 Written Request. Thus the sponsor received six months of pediatric exclusivity for the completed studies. However, NDA 21-718 received a non-approval action from DDDDP on April 27, 2004. At that time, DDDDP stated that no new safety concerns were raised by these studies that were not already listed in the Diflucan® product label. DDDDP recommended that no new information needed to be incorporated into the Diflucan® label when the action was taken.

During the NDA 21-718 review, the sponsor submitted Prior Approval labeling supplements on January 20, 2004 to the currently approved NDAs 19-949, 19-950, and 20-090 in DSPIDP (supplements 36, 38 and 18, respectively). The proposed revisions in these supplements are based on studies from NDA 21-718, and include the same proposed changes to the ADVERSE REACTIONS section of the Diflucan® package insert as were included in the Type 6 NDA. These changes consist of tabulated data of pediatric adverse events in treatment groups comparing Diflucan® with an approved comparator (griseofulvin). The tinea capitis indication is not mentioned in the table or elsewhere in the label. The adverse events listed are headache, abdominal pain, and dyspepsia. These adverse events are already identified in the Diflucan label.

The labeling supplements submitted to DSPIDP only included the safety data which (1) do not add new information as the events mentioned are already included in the labeling, (2) show rates that are lower than rates observed in clinical studies of patients with infections for which the product is currently labeled, and (3) mention griseofulvin, a control agent approved only for tinea infections, thereby bringing to mind that indication and possible mis-interpretation that fluconazole be used in tinea.

DSPIDP agreed with the recommendations made by DDDDP and found the sponsor's proposed changes to be unacceptable. A non-approval letter was sent to the sponsor on July 2004.

Pediatric labeling:
Several sections of the labeling address the use of fluconazole in the pediatric population. These sections are reproduced in Appendix One.

3. AERS SEARCH RESULTS

AERS was searched on April 11, 2005, to retrieve reports received by the Agency up to the cut-off date of February 28, 2005, that listed fluconazole as a suspect drug, in adult

and pediatric populations. The search included all sources, foreign and domestic. In the tables below, the *US counts are in parenthesis*.

A. Adverse events through February 28, 2005:

Counts of reports:

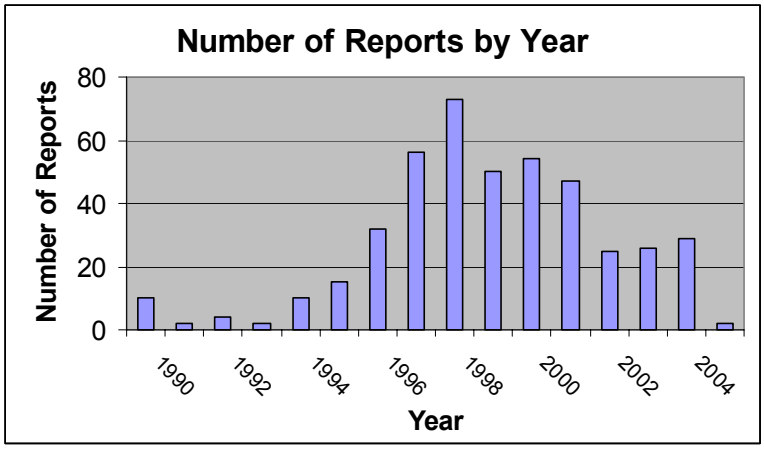
Table 1: Raw counts[1] of total fluconazole reports in AERS through cut-off date of February 28, 2005 (US counts in parentheses)			
	All reports (US)	Serious[2] (US)	Death (US)
All ages[3]	8031 (4588)	6738 (3709)	1359 (247)
Adults (≥ 17 yrs.)	5706 (2849)	4842 (2322)	1113 (185)
Pediatrics (0-16 yrs.)	444 (230)	382 (199)	82 (10)

[1] May include duplicates
[2] Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.
[3] Includes reports where age was not provided

Reporting trend for pediatric reports through February 28, 2005:

Table 2: Reporting trend in AERS reports through February 28, 2005[1]		
Number of cases, all ages [2]	**Year**	**Number of pediatric cases (0-16 years)[3]**
133	1990	10
226	1991	2
139	1992	4
152	1993	2
236	1994	10
351	1995	15
599	1996	32
810	1997	56
1154	1998	73
1312	1999	50
996	2000	54
668	2001	47
483	2002	25
346	2003	26
354	2004	29
71	2005	2

[1] Raw counts, may include duplicates
[2] May include reports where age was not specified
[3] Only includes reports where age was listed in the pediatric age grouping of 0-16 years



Top 20 reported event PTs and labeling status of these events (underlined denotes unlabeled events):

Table 3: Counts of top 20 reported events (preferred terms) through February 28, 2005[1]		
	Top 20 preferred terms	**Counts**
All ages (including reports where no age was provided)	Drug Ineffective	671
	Drug Interaction	533
	Pyrexia	487
	Dermatitis	418
	Condition Aggravated	384
	Fungal Infection	293
	Hepatic Function Abnormal	280
	Nausea	258
	Diarrhea	239
	Vaginitis	239
	Thrombocytopenia	237
	Sepsis	236
	Pruritus	232
	Abdominal Pain	230
	Headache	232
	Vomiting	230
	Pneumonia	212
	Liver Function Test Abnormal	204
	Asthenia	202
	Aspartate Aminotransferase Increased	195
Adults (≥ 17 years)	Pyrexia	429
	Drug Ineffective	393
	Drug Interaction	391
	Condition Aggravated	308
	Dermatitis	296
	Hepatic Function Abnormal	232
	Nausea	211
	Thrombocytopenia	206
	Sepsis	203
	Pruritus	192
	Diarrhea	189
	Pneumonia	179
	Fungal Infection	171
	Abdominal Pain	169

Table 3: Counts of top 20 reported events (preferred terms) through February 28, 2005[1]		
	Top 20 preferred terms	**Counts**
	Headache	167
	Aspartate Amino Transferase Increased	164
	Alanine Aminotransferase Increased	162
	Asthenia	157
	Vaginitis	153
	Vomiting	152
Pediatrics (0-16 years)	Drug Ineffective	33
	Pyrexia	31
	Vomiting	26
	Complications of Maternal Exposure to Therapeutic Drugs	24
	Drug Interaction	23
	Condition Aggravated	20
	Dermatitis	19
	Medication Error	19
	Stevens-Johnson Syndrome	17
	Abdominal Pain	15
	Oral Candidiasis	15
	Toxic Epidermal Necrolysis	15
	Congenital Anomaly	14
	Aspartate Aminotransferase Increased	13
	Fungal Infection	13
	Nausea	13
	Neutropenia	13
	Sepsis	13
	Hepatic Function Abnormal	12
	Liver Function Test Abnormal	12
[1] Raw counts include terms from duplicate reports		

B. Adverse event from pediatric exclusivity approval date, January 22, 2004 through February 28, 2005 (pediatric exclusivity period):

Counts of reports:

Table 4: Raw counts[1] of total fluconazole reports from pediatric exclusivity approval date through cut-off date of February 28, 2005 (US counts in parenthesis)			
	All reports (US)	Serious [2] (US)	Death (US)
All ages [3]	395 (107)	378 (96)	70 (12)
Adults (≥17 yrs.)	331 (76)	320 (71)	59 (10)
Pediatrics (0-16 yrs.)	29 (12)	25 (9)	4 (0)
May include duplicates [2] Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other. [3] Includes reports where age was not specified			

Top 20 reported event PTs and labeling status of these events (underlined indicates unlabeled):

Table 5: Counts of top 20 reported events (preferred terms) derived from line listings[1] - from date of pediatric exclusivity through AERS cut off date of February 28, 2005 [includes events mentioned more than twice][2]		
	Top 20 preferred terms	**Counts**
All ages (including reports where age is not specified) (total number of adverse events reported =820)	Drug Interaction Pyrexia Aspartate Aminotransferase Increased Alanine Aminotransferase Increased Thrombocytopenia Ventricular Tachycardia Condition Aggravated Dyspnea Candidiasis Electrocardiogram Qt Prolonged Blood Alkaline Phosphatase Increased Blood Creatinine Increased Multi-Organ Failure Nausea Convulsion White Blood Cell Count Decreased Blood Bilirubin Increased Dizziness Drug Exposure During Pregnancy Drug Ineffective	42 30 26 25 23 20 18 18 17 16 15 15 15 15 14 14 13 13 13 13
Adults (≥ 17 years) (total number of adverse events reported = 725)	Drug Interaction Pyrexia Aspartate Aminotransferase Increased Alanine Aminotransferase Increased Thrombocytopenia Condition Aggravated Ventricular Tachycardia Candidiasis Nausea Blood Alkaline Phosphatase Increased Blood Creatinine Increased Multi-Organ Failure White Blood Cell Count Decreased Dizziness Electrocardiogram Qt prolonged Erythema Pruritus Gamma-Glutamyltransferase Increased Leukopenia Renal Impairment	38 29 23 22 22 17 17 16 15 14 14 14 13 13 13 13 12 12 12 12
Pediatrics (0-16 years) (total number of adverse events reported = 115)	Bronchospasm Dyspnea Tachycardia Medication Error Oxygen Saturation Decreased Alanine Aminotransferase Increased Aspartate Aminotransferase Increased Dehydration	7 6 6 5 5 3 3 3

Table 5: Counts of top 20 reported events (preferred terms) derived from line listings[1] - from date of pediatric exclusivity through AERS cut off date of February 28, 2005 [includes events mentioned more than twice][2]		
	Top 20 preferred terms	**Counts**
	Electrocardiogram Qt Prolonged	3
	Ventricular Tachycardia	3
	Anesthetic Complication Cardiac	2
	Drug Exposure During Pregnancy	2
	Hemoglobin Decreased	2
	Maternal Drugs Affecting Fetus	2
	Overdose	2
	Tachypnea	2
	Ventricular Extrasystole	2

[1] Raw counts include terms from duplicate reports

[2] The following events were mentioned only once in the pediatric population (0-16 years): Activated Partial Thromboplastin Time Shortened, Anuria, Aspergillosis, Asphyxia, Ataxia, Bacterial Culture Positive, Balance Disorder, Bilirubin Conjugated Increased, Blepharospasm, Blindness Congenital, Blood Alkaline Phosphatase Increased, Blood Bilirubin Abnormal, Blood Creatinine Decreased, Blood Glucose Decreased, Blood Lactated Dehydrogenase Increased, Blood Pressure Decreased, Blood Urea Decreased, Cardiomyopathy, Cataract Congenital, Cholestasis, Coma, Condition Aggravated, Congenital Neurological Disorder, Convulsion, Cytolytic Hepatitis, Developmental Delay, Diabetes Insipidus, Diplopia, Discomfort, Disease Recurrence, Drug Ineffective, Drug Interaction, Drug Level Increased, Dry Skin, Electroencephalogram Abnormal, Encephalitis, Escherichia Infection, Finger Hypoplasia, Fungemia, Gamma-Glutamyltransferase Increased, Gastric Ulcer, General Physical Health Deterioration, Growth Retardation, Hemodynamic Instability, Haptoglobin Increased, Heart Disease Congenital, Heart Rate Increased, Infection, Lethrargy, Leukopenia, Liver Function Test Abnormal, Lymphopenia, Meningitis, Microcephaly, Multi-Organ Failure, Nasopharyngeal Disorder, Nervous System Disorder, Neutropenia, Nystagmus, Esophageal Candidiasis, Procedural Complication, Pseudomonal Infection, Pulmonary Interstitial Emphysema Syndrome, Pulse Pressure Decreased, Pupillary Light Reflex Tests Abnormal, Pyrexia, Radiation Exposure in Utero, Radiation Injury, Rash, Rash Macular, Red Blood Cell Schystocytes Present, Renal Failure, Respiratory Arrest, Respiratory Distress, Respiratory Tract Congestion, Scrotal Disorder,Skin Fissures,Small For Dates Baby, Somnolence, Staphylococcal Infection, Stillbirth, Streptococcal Infection, Stress Syndrome, Sudden Infant Death Syndrome, Supraventricular Tachycardia, Swelling, Syndactyly, Trisomy 18, Vertigo, Fifth (Vith) Nerve Paralysis, Zygomycosis

4. Postmarketing Hands-on Review of All Pediatric Adverse Event Reports From All Sources Received During the Pediatric Exclusivity Period (January 22, 2004 through February 28, 2005)

Demographic characteristics:

Our search of the AERS database yielded 29 pediatric cases. However, hands-on review showed considerable duplication among the cases. After collating the duplicates, we found 19 unique cases of pediatric patients submitted to the Agency during the pediatric exclusivity period. The demographic characteristics for these unique 19 cases are listed in Table 6 below.

Table 6 : Characteristics of pediatric cases reported during the pediatric exclusivity period (January 22, 2004 through February 28, 2005) n=19[1]	
Gender [n=15]	Male: 9 Female: 6
Age [n=15]	1- 24 months: 7 3 to 7 years: 3 8 to 12 years: 2 13 to 16 years: 3 Mean 5.7 years; Median 4 years; Range 1 month to 16 years
Origin [n=19]	8 US, 11 Foreign
Daily dose [n=7]	14 to 50 mg 3 125 to 200 mg 3 6 mg/kg 1 Range 14 mg to 200 mg
Duration of therapy [n=9]	1-10 days 6 11-28 days 1 > 28 days 2 Range 1 day to approximately 2 months
Indications [n=13]	Antifungal prophylaxis 2 Fungal infection 7 Ill-defined disorder 2 Valley fever 1 Infection and fever 1
Outcomes [n=17]	Death: 4 Life threatening 5 Hospitalization: 4 Congenital anomaly: 3 Required intervention: 1
[1] Data is provided for the pediatric patients, not the mothers.	

Labeling status of the top 20 reported adverse events and comparison to adult adverse event profile during the pediatric exclusivity period

Of the 20 most frequently reported adverse events reported during the pediatric exclusivity period in the pediatric population individual review of the 19 unique reports showed that there were eight events mentioned more than once. These were alanine aminotransferase increased, aspartate aminotransferase increased and electrocardiogram QT prolonged with three mentions each; and drug exposure during pregnancy, maternal drugs affecting fetus, overdose, bronchospasm and medication error with two mentions each.

Of the eight adverse events with multiple mentions, six were listed or addressed in the label. The events reported three times (Alanine aminotransferase increased, Aspartate aminotransferase increased and Electrocardiogram QT prolonged) are listed in the **WARNINGS** and **PRECAUTIONS** sections of the label. Of the events reported twice, three (Drug exposure during pregnancy, Maternal drugs affecting fetus and Overdose) are referred to in the **PRECAUTIONS** and **OVERDOSE** sections of the label. However, Bronchospasm and Medication error also reported twice are not listed in the fluconazole label. Bronchospasm was mentioned in association with an allergic reaction to Neupogen in one patient, and with deteriorating respiratory function in another very ill patient. Both

medication errors were the result of pharmacist error, one due to misreading the instructions in the prescription and the other with dispensing a higher than prescribed concentration.

Note that and additional 107 events were mentioned only once and thus are included in the list of top 20 events. The majority of these are unlabeled events. Some of these unlabeled events are associated with pre-existing illnesses in the patients, and others are adequately covered by similar terms listed in the labeling. Since these events are mentioned only once it is premature to recommend any labeling changes at this time.

Fatalities in the pediatric population during the exclusivity period (n=4)

Table 7 – Characteristics of the pediatric fatalities (received during the pediatric exclusivity period)	
Gender (n=1)	1 Female
Age (n=3)	Average: 2.4 years Median: 1.5 months Range: 1 month to 7 years 2 1-3 months 1 7 years
Origin (n=4)	4 Foreign
Daily dose (n=3)	35 mg 150 mg (in the mothers)
Duration of therapy (n=3)	11 days of 35 mg/day one day of 150 mg/day in each of two patients
Indication (n=4)	3 fungal infection 1 ill-defined disorder
Dechallenge (n=1)	Negative
Cause of death (n=1)	SIDS and asphyxia

In this group of four cases, two indicated that patients were treated with several concomitant drugs and in the remaining two fluconazole was administered to the mother. The four reports are summarized below.

a) Concomitant drugs (n=2)
The oldest patient in this group (case # 4177902), a 7-year old female diagnosed with medulloblastoma experienced neurological symptoms (vertigo, nystagmus, diplopia, eye clonism, somnolence, ataxia, deficiency neurologic disorder and coma) subsequent to radiation and fluconazole therapy. In addition to fluconazole, she was also treated with chemotherapeutic drugs (i.e., etoposide, carboplatin, busulfan and thiotepa) that are known for similar neurological toxicities. The cause of death was not stated. "According to the reporting physician, neurological disorders etiologies were either busulfan, fluconazole, or patient-dependent outcome, due to personal sensitivity of the patient."

The six-week old infant (case # 4093853) who experienced elevation of liver enzymes and elevated bilirubin in association with hypertrophy of the liver was also receiving cefozopran, a cephalosporin that can also cause hepatic injury[1]. Liver enzymes values returned to normal after both drugs were discontinued. The cause of death was not

[1] Transient hepatitis and jaundice are mentioned in the **ADVERSE REACTIONS** section of the cefozopran labeling.

provided, but the reporter said that the death and adverse events were not related to the use of fluconazole.

Several of the reported neurological adverse events listed in the first case are described in the labeling for the concomitant products used in these cases in their respective **ADVERSE REACTIONS** section[2]. Thus the toxicities could be due to any one of the drugs administered, to an additive effect or to a sensitivity of the patient, as stated in one of the reports. Hepatic injury is well described in the fluconazole label in the **WARNINGS** and **ADVERSE REACTIONS** sections.

b) Maternal exposure (n=2)
In the two remaining cases, fluconazole was not administered to the infant or fetus. The 40-day old infant (case # 5712549) received fluconazole through breast milk and died of asphyxia and SIDS the day following the mother's intake of one dose of fluconazole. In the reported fetal death (case # 4163094) the mother had taken one dose of fluconazole "over 26 weeks before becoming pregnant".

Transmission through breast milk is addressed in the fluconazole labeling. In the **PRECAUTIONS** section the labeling states that fluconazole is secreted in human milk in concentrations similar to plasma and its use is not recommended in nursing mothers. It could be hypothesized that the infant in case # 5712549 received an overdose of fluconazole through breast milk, although the symptoms listed in this case (asphyxia and frothing at the mouth) are not associated with overdose[3].

The fluconazole label also indicates in the **CLINICAL PHARMACOLOGY** section that the half life of fluconazole is 30 hours, with a maximum of 50 hours. Thus it is unlikely that there would be any remaining fluconazole in the mother available for fetal exposure 26 weeks after dosing.

Our review of these cases could not establish that fluconazole alone was responsible for the adverse events and death experienced by these patients. In two cases patients were treated with concomitant drugs that are associated with neurologic or hepatic injury. In the other two, fluconazole exposure was through the mother. The fluconazole label addresses hepatic adverse events, congenital anomalies and transmission through breast milk.

Non-fatal outcome reports in pediatric population during the exclusivity period (n=15)

Almost all (13/15) of the remaining reports in the pediatric population had a serious outcome by regulatory definition. Five reports listed an outcome of life-threatening,

[2] See the **ADVERSE REACTIONS** section in the etoposide, carboplatin, busulfan, thiotepa and etoposide labeling. (etoposide: somnolence, fatigue, vertigo, mental confusion, asthenia, malaise; thiotepa: fatigue, weakness, blurred vision; busulfan: somnolence, blurred vision, lethargy; carboplatin: asthenia, malaise, visual disturbances)
[3] See the **OVERDOSE** section of the fluconazole label (lists hallucinations and paranoid behavior)

associated with cardiac arrhythmia (n=3), convulsion and diabetes insipidus (n=1), and hypoglycemia (n=1). An additional four indicated an outcome of hospitalization, associated with overdose, on-going fungemia, appendicular peritonitis, and palliative care for cancer (one condition per report). Another three reports described congenital anomalies in patients whose mothers had used fluconazole prior to or during pregnancy, and one more stated that the patient required intervention due to elevation in liver function tests (LFTs). Two of the 15 reports did not indicate an outcome and were associated with an overdose in one and with a rash in the other. In summary, the serious outcomes listed were: five life threatening, four hospitalization, three congenital anomaly and one required intervention to prevent permanent impairment/damage.

Summary of the 15 non-fatal pediatric cases during the pediatric exclusivity period by adverse events

Cardiac events (n=3):

Table 8 – Characteristics of the pediatric cardiac event cases (received during the pediatric exclusivity period)	
Gender (n=3)	3 M
Age (n=3)	Average 9 years Median 11 years Range 15 months to 14 years
Origin (n=3)	1 US, 2 Foreign
Daily dose	Not stated in any of the reports
Duration of therapy (n=1)	1 dose
Indication (n=2)	Ill-defined disorder in both
Dechallenge (n=1)	Positive
Outcome (n=3)	2 Life threatening, 1 Hospitalization
Type of cardiac events:	Tachycardia associated with allergic reaction to Neupogen administration QT prolongation subsequent to co-administration of fluconazole and cisapride SVT secondary to fluconazole therapy

These three patients experienced cardiac arrhythmia most likely associated with drug administration. In the 11-year old patient, tachycardia with bronchospasm, SOB and decreased oxygen saturation occurred 20 minutes post administration of Neupogen intravenously (case # 4138267). In the 14-year old the QT prolongation was associated with concomitant use of cisapride and fluconazole for several days, together with the administration of anesthesia (case # 4113836). In the 15-month old, supraventricular tachycardia occurred on the same day of fluconazole therapy apparently in the absence of concomitant drugs or history of cardiac illness (case # 4180800).

The reactions described in the 11-year old are similar to the allergic reactions described in the **WARNINGS** section of the Neupogen label. The temporal association between Neupogen dosing and appearance of adverse events, dose formulation administered, nature of adverse events and positive dechallenge suggest a closer association to Neupogen therapy than to fluconazole use. This 11-year old was rechallenged with Neupogen, and did not experience adverse events. However, the Neupogen label indicates that symptoms do not reoccur in a minority of rechallenged patients.

QT prolongation is addressed in the fluconazole label in the **CLINICAL PHARMACOLOGY** and in the **ADVERSE REACTIONS** sections. This arrhythmia has been observed during therapy with fluconazole, either by itself or with concomitant use of cisapride. Thus, it is not surprising to see this reaction in the 14-year old report.

Supraventricular tachycardia is not specifically mentioned in the fluconazole label. However, it is not surprising to see this reaction given the fluconazole potential for cardiac rhythm effects.

Cardiac adverse events in pediatric patients are not specifically mentioned in the label. Even though QT prolongation is stated in two sections, the label does not indicate clearly if this event occurs only in adults. The present label could be construed to mean that QT prolongation, whether alone or due to a drug interaction, has not occurred in the younger population. To avoid such misconception, it may be prudent to include a mention of its occurrence in younger patients under post-marketing events to alert clinicians of such a possibility.

Congenital anomalies (n=3)

Table 9– Characteristics of the congenital anomaly cases (received during the pediatric exclusivity period)	
Gender (n=2)	1M, 1 F
Age	Not applicable
Origin	1 US, 2 UK
Daily dose in mother (n=2)	150 mg x 1 dose in both women
Duration of therapy in mother (n=2)	1 dose only in both women
Indication in mother (n=2)	Ill-defined disorder in both women
Dechallenge	Not applicable
Outcome (n=3)	Congenital anomaly in all cases
Type of events	Hypopasdias and bifid scrotum Syndactyly and finger hypoplasia Congenital microcephaly, blindness, cataracts and small body size

The AERS database indicates that there were three infants with congenital anomalies born to women who had used fluconazole. In two cases, the women used fluconazole one time only prior to conception for an ill-defined disorder. The anomalies were described as hypospadias and a bifid scrotum in the infant whose mother took fluconazole eight weeks prior to becoming pregnant (case # 4162504), and syndactyly and finger hypoplasia in the infant whose mother used fluconazole one week prior to conception (case # 4163097).

In the third case (case #5653040) fluconazole was prescribed for use during the pregnancy, but the dose, indication and duration of therapy were not specified. The infant's mother was also treated with isoniazid and pyridoxine and had x-rays at the 10^{th} week of gestation. The infant was born with congenital microcephaly, blindness, cataracts, and small body size. Genetic, chromosomal and infectious disease tests in this infant were negative.

The fluconazole label indicates in the **CLINICAL PHARMACOLOGY** section that the half-life of fluconazole is 30 hours, with a maximum of 50 hours. Thus it is unlikely that in the women treated prior to conception fluconazole exerted an effect in the fetus.

Congenital anomalies seen in animal and clinical studies are described in the **PRECAUTIONS** section. The fluconazole label states in pregnant rats treated with higher doses (25 mg/Kg and higher) there were increases in fetal abnormalities. The same section also states that there have been reports of congenital abnormalities in infants whose mothers were being treated for three or more months with high dose fluconazole therapy for coccidioidomycosis. Even though the woman in case # 5653040 might have used fluconazole for several months, she was also exposed for seven months during the pregnancy to isoniazid, a product considered to be non-teratogenic[4], and to x-rays during the first trimester. Potential adverse outcomes related to radiation exposure during pregnancy include teratogenicity, genetic damage, intrauterine death and increased risk of malignancy[5]. So it is difficult to conclude that the reported congenital anomalies in case # 5653040 were due solely to the patient's exposure to fluconazole.

In **APPENDIX ONE** we have attached a previous ODS consult on congenital abnormalities associated with fluconazole that provides a comprehensive review on this topic.

Metabolic events (n=2)

Table 10 – Characteristics of the pediatric metabolic event cases (received during the pediatric exclusivity period)	
Gender (n=2)	2 M
Age	4 years 5 years
Origin	2 Foreign
Daily dose	50 mg 200 mg
Duration of therapy	Approximately 2 months 9 days
Indication	Fungemia Prophylaxis
Dechallenge	Not stated
Outcome	Life threatening in both reports
Types of events	Hypoglycemia during fluconazole therapy Diabetes insipidus, anuria, hyponatremia and respiratory arrest associated with decreased oxygen saturation

These reports list the occurrence of several unlabeled events; hypoglycemia in a 4-year old and diabetes insipidus, anuria, hyponatremia and respiratory arrest in a 5-year old.

[4] See the **PRECAUTIONS** section of the Rifater® and Rifamate® labels under the **Pregnancy-Teratogenic Effects** subsection ["… isoniazid may exert an embryocidal effect when administered orally during pregnancy, although no isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats, and rabbits). Isoniazid should be prescribed during pregnancy only when therapeutically necessary"]

[5] Lowe SA. Diagnostic radiography in pregnancy: risks and reality. Aust N Z J Obstet Gynaecol. 2004 Jun;44(3):191-6.

No concomitant medications were listed for the younger patient, whereas there were seven concomitant drugs listed in the older patient's report.

The 4-year old initiated fluconazole therapy for fungemia and experienced a decrease in blood sugar from 113 mg/dL (two months prior to therapy) to 40 mg/dL when fluconazole was discontinued (case # 4086895). Laboratory results indicated lower than baseline glucose levels (92mg/dL) a month after fluconazole was discontinued. The reporting pediatrician did not attribute the hypoglycemia to the use of fluconazole.

The 5-year old, treated for fungitis prevention, was diagnosed with diabetes insipidus and also reported hyponatremia, seizures and respiratory arrest subsequent to therapy with multiple concomitant medications (case # 4125746). This patient experienced seizures and respiratory arrest following a decrease in oxygen pressure the day after initiating famotidine therapy and four days after receiving vincristine and initiating therapy with fluconazole and acyclovir. Additional adverse events on that day were hyponatremia, anuria and diabetes insipidus. He was given water and treated with desmopressin. All symptoms abated within the next five days. The reporting physician felt that vincristine "was likely to be responsible" although the reporter also suspected fluconazole and acyclovir.

The **PRECAUTIONS** section of the fluconazole label states that clinically significant hypoglycemia may be precipitated by the concomitant use of fluconazole with oral hypoglycemic agents. However, a decrease in serum glucose in the absence of concomitant use of hypoglycemic agents is not mentioned in the label. The remaining adverse events (i.e., anuria, hyponatremia, diabetes insipidus, and respiratory arrest) are unlabeled events for fluconazole, vincristine and acyclovir.

It is not possible to ascertain if the events in these children were due to the medications administered, existing morbidity or some other unidentified factor. Because these events were mentioned very infrequently we do not recommend a labeling change at this time. However, we will continue to assiduously monitor the post-marketing reports for additional similar reports and communicate emerging signals to the review division.

Overdose/Medication errors (n=2)

Table 11 – Characteristics of the pediatric overdose cases (received during the pediatric exclusivity period)	
Gender	1 M, 1 F
Age (n=2)	3 months in both patients
Origin	2 US
Daily dose (n=1)	25 mg x 3 days
Duration of therapy (n=2)	3 days in one patient; 1 time in the other
Indication (n=2)	Oral thrush in both patients
Dechallenge (n=1)	No
Outcome (n=1)	Hospitalization
Type of events	Overdose associated with medication errors in both patients

In both cases patients received overdoses due to pharmacy errors. In one case, the child received one dose of fluconazole oral suspension at a higher concentration than that

ordered (40 mg/ml instead of 10 mg/ml) resulting in a dose four times greater than the one specified in the prescription (case # 5752876). In the other, the instructions on the label were typed incorrectly directing the patient to take two and half teaspoonfuls instead of two and half milliliters resulting in a dose five times greater than that prescribed (case # 4167774). It appears that the patients did not experience any adverse events as a result of the overdose. The hospitalization in the one patient who received the incorrectly labeled prescription was most likely due to her underlying respiratory tract infections and accompanying dehydration.

In both cases the overdose administered to the patients resulted from human error. Several contributing factors are the availability of two concentrations in oral preparations, potential difficulty in interpreting the prescription, and alleged understaffing. Maybe, as suggested by the reporters, these errors could have been prevented if the prescriptions had been submitted electronically to avoid misunderstanding, and if the pharmacy had been more adequately staffed.

Fungemia (n=2)

Table 12 – Characteristics of the pediatric fungemia cases (received during the pediatric exclusivity period)	
Gender (n=2)	1M, 1F
Age (n=2)	5 months, 13 years
Origin (n=2)	2 US
Daily dose (n=1)	6 mg/Kg
Duration of therapy (n=1)	3 weeks
Indication (n=2)	Fungal infection Antifungal prophylaxis
Dechallenge (n=0)	Not stated in both cases
Outcome (n=2)	Hospitalization in both cases
Type of infections (n=2)	Candida paripsilosis Aspergillosis, Zygomycosis, unidentified infection

In both cases underlying morbidities may have contributed to the failure of fluconazole therapy to cure fungal infections in these patients. The five-month old male being treated for a Candida paripsilosis fungemia did not have sufficient intestinal surface for proper absorption, according to the reporting physician (case # 5680133). The 13-year old female patient being treated for antifungal prophylaxis had a recurrence of an unidentified cancer (case # 5703403). Even though she was treated with fluconazole and Vfend for antifungal prophylaxis, she developed Zygomycosis, Aspergillosis and an infection with another unidentified pathogen. It is possible that therapy with fluconazole was not appropriate in this patient. The fluconazole label indicates that there is fluconazole activity against Aspergillosis in mice, but it has been reported in the literature by Vento and Cainelli that Aspergillosis is not susceptible to fluconazole[6].

It is worth noting that in all the studies quoted in the **CLINICAL STUDIES** section of the labeling none achieved 100% cure (either clinical or therapeutic) after treatment with fluconazole. The label also states that there have been reports of superinfections with

[6] Vento S, Cainelli F. Infections in patients with cancer undergoing chemotherapy: aetiology, prevention and treatment. The Lance Oncology 2003; Oct; 4: 595-604.

Candida species (see **CLINICAL PHARMACOLOGY** section, **Microbiology** subsection).

Hepatic events (n=2)

Table 13 – Characteristics of the pediatric hepatotoxic case (received during the pediatric exclusivity period)	
Gender (n=2)	1 Male 1 Female
Age (n=2)	6 months 16 years
Origin (n=2)	1 US, 1 Foreign
Daily dose (n=1)	26 mg IV (2mg/ml injection) x 1, then 14 mg oral (10 mg/ml suspension) x 3 days
Duration of therapy (n=2)	Average: 4.5 days Range: 4 to 5 days
Indication (n=2)	Prophylaxis for candidemia due to severe fungal diaper dermatitis Persistent fever in severe infection
Dechallenge (n=1)	Positive
Outcome (n=2)	1 Hospitalization 1 Required intervention to prevent permanent impairment or damage
Type of event (n=2)	Elevation of liver enzymes associated with drug therapy Elevation of liver enzymes in association with cholestasis and hepatic cytolysis in the setting of appendicular peritonitis and multiple concomitant antibacterial medications

Increases in transaminases values were reported in two severely ill patients treated with multiple concomitant medications. A six-month old infant was given IV and oral fluconazole to treat severe fungal diaper dermatitis, while on therapy with tobramycin, Timentin, vancomycin, Septra, lansoprazole, albuterol and furosemide (case # 5687896). A 16-year was admitted for appendicular peritonitis and treated with eight antimicrobial medications over the course of six weeks (case # 4075521). She experienced multiple alterations of hematologic and hepatic values that included neutropenia, leukopenia, and increased transaminases together with hepatic cytolysis and cholestasis. In both cases, the elevation in the aminotransferases occurred within one to three days after starting fluconazole.

In the six-month old patient, base line values for liver enzymes were not provided. But the report indicates that this infant experienced considerable elevation of ALT and AST by the fourth day of fluconazole therapy (AST 2221, ALT 12), and that liver enzyme values decreased two days after discontinuing fluconazole (AST 373, ALT 649). Several of the concomitant medications are known to increase liver enzymes (i.e., Septra, tobramycin and Timentin) and may have contributed to the adverse events. Even so, fluconazole was probably the most likely contributor to the adverse events due to the temporal association, positive dechallenge and its history of hepatotoxicity (**WARNINGS** and **ADVERSE REACTIONS** sections).

In addition to the elevated liver enzymes, the 16-year old female was also diagnosed with hepatic cytolysis and cholestasis. She was treated with medications other than fluconazole that are also associated with liver or gallbladder disease (i.e., Rocephin and

gallbladder disease; Tienam and elevation of liver enzymes; Ciflox and cholestatic jaundice and hepatitis). Thus, in this case it is difficult to determine if the events experienced by the patient are related to her underlying illness or if they are adverse events caused by her multiple drug therapy.

Hypersensitivity events (n=1)

Table 14 – Characteristics of the hypersensitivity case	
Gender	Male
Age	12 years
Origin	US
Daily dose	200 mg daily
Duration of therapy	3-4 days
Indication	Valley fever
Dechallenge	Yes
Outcome	Not stated
Type of event	Skin rash and body swelling associated with use of generic product

The patient experienced a rash, generalized body swelling and dryness in the belly button area subsequent to the use of generic fluconazole (case # 5658161). Symptoms resolved after stopping the medication. It was not stated whether the patient had similar reactions with previous or subsequent use of generic or brand name fluconazole. Nevertheless, hypersensitivity reactions are expected and are well described in the **WARNINGS** section of the Diflucan label.

5. Summary

The AERS database was searched on April 11, 2005, for all reports of adverse events (serious and non-serious) occurring with the use of fluconazole in pediatric patients. We focused on the one-year period following the approval of pediatric exclusivity (January 22, 2004 through January 22, 2005), although the cut-off date for data collection was extended to February 28, 2005, to allow for all reports received up to the end of January 2005 to be entered in the database.

Individual review of the cases yielded 19 unique cases, where almost all had a serious outcome (17/19) including four fatalities. The AERS database shows that fluconazole is used in patients as young as one month old, with the majority of the patients in this case series being under 8 years of age. In both US and foreign patients fluconazole was mostly used to treat fungal infections or as prophylaxis for this type of infections. Where stated, the majority of patients received less than 10 days of therapy.

Our review of the four fatalities could not establish that fluconazole alone was responsible for the adverse events and death in these patients. In two cases the patients were treated with concomitant drugs that could have contributed to the adverse events. In the other two, fluconazole was administered to the mother and not to the infant or fetus for which the adverse events were reported.

The majority of the non-fatal outcome cases (13/15) provided the outcome which was described as life-threatening in five, hospitalization in four, congenital anomaly in three, and requiring intervention to prevent permanent impairment/damage. The life-threatening cases were associated with cardiac arrhythmias (3), convulsion and diabetes Insipidus (1) and hypoglycemia (1). The hospitalization cases indicated that admissions were for overdose, on-going fungemia, appendicular peritonitis and palliative care for cancer. The congenital anomalies in infants were reported in infants where the mother had received a dose of fluconazole prior to conception (2) or during pregnancy (1). The intervention required was a change in antifungal therapy due to elevation of liver enzymes. Two of the 15 reports did not list an outcome, and were associated with an overdose in one and with a rash in the other.

The fluconazole label addresses several of these patients' adverse events, such as arrhythmias, hepatotoxicity, congenital anomalies, transmission in breast milk, potential for super infection, and hypersensitivity reactions. The metabolic events are not listed in the label. However, it is not possible to ascertain if the events were due to the concomitant medications, existing morbidity or some other factor. Because these events were mentioned only once we do not recommend a labeling change at this time.

Of the 20 most frequently reported adverse events during the pediatric exclusivity period in the pediatric population only eight were reported more than three times each. Six were listed or addressed in the label. The remaining two adverse events were more closely associated with individual patient responses (bronchospasm) and with human error (medication error). An additional 107 mostly unlabeled events were mentioned only once and thus are included in the list of the top 20 events. Since these events are mentioned only once it is premature to recommend any labeling changes at this time.

We noticed that occurrence of cardiac adverse events in pediatric patients was not specifically mentioned in the label. Even though QT prolongation is stated in two sections, the label does not indicate clearly if this event occurs only in adults. The present label could be construed to mean that QT prolongation, whether alone or due to a drug interaction, has not occurred in the younger population. To avoid such misconception, it may be prudent to include a mention of its occurrence in younger patients under post-marketing events to alert clinicians of such possibility.

In summary, during the pediatric exclusivity period the 19 unique pediatric cases showed that the events most frequently reported are adequately covered in the fluconazole label. At this time we have not identified new safety concerns in the pediatric population that are not adequately addressed in the label. We will continue to monitor adverse events in the pediatric population and communicate any emerging signal to the review division.

Evelyn R. Farinas, R. Ph., M.G.A
Safety Evaluator

Concur: Melissa Truffa, R. Ph., Team Leader

CC: NDA ; HFD-960 Iyasu / Murphy
HFD-430 Avigan / Truffa / Farinas / Birdsong
HFD-590 Albrecht/Ibia/Marques

APPENDIX ONE

1. Fluconazole label – Relevant sections

CLINICAL PHARMACOLOGY
Pharmacokinetics and Metabolism

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Bioequivalence was established between the 100 mg tablet and both suspension strengths when administered as a single 200 mg dose.

Peak plasma concentrations (Cmax) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range: 20-50 hours) after oral administration.

In fasted normal volunteers, administration of a single oral 400 mg dose of DIFLUCAN (fluconazole) leads to a mean Cmax of 6.72 µg/mL (range: 4.12 to 8.08 µg/mL) and after single oral doses of 50-400 mg, fluconazole plasma concentrations and AUC (area under the plasma concentration-time curve) are dose proportional.

Administration of a single oral 150 mg tablet of DIFLUCAN (fluconazole) to ten lactating women resulted in a mean Cmax of 2.61 µg/mL (range: 1.57 to 3.65 µg/mL).

Steady-state concentrations are reached within 5-10 days following oral doses of 50-400 mg given once daily. Administration of a loading dose (on day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11-12%). Following either single- or multiple-oral doses for up to 14 days, fluconazole penetrates into all body fluids studied (see table below). In normal volunteers, saliva concentrations of fluconazole were equal to or slightly greater than plasma concentrations

regardless of dose, route, or duration of dosing. In patients with bronchiectasis, sputum concentrations of fluconazole following a single 150 mg oral dose were equal to plasma concentrations at both 4 and 24 hours post dose. In patients with fungal meningitis, fluconazole concentrations in the CSF are approximately 80% of the corresponding plasma concentrations.

A single oral 150 mg dose of fluconazole administered to 27 patients penetrated into vaginal tissue, resulting in tissue:plasma ratios ranging from 0.94 to 1.14 over the first 48 hours following dosing.

A single oral 150 mg dose of fluconazole administered to 14 patients penetrated into vaginal fluid, resulting in fluid:plasma ratios ranging from 0.36 to 0.71 over the first 72 hours following dosing.

Tissue or Fluid	Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration *
Cerebrospinal fluid **/*	0.5-0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2
Vaginal tissue	1
Vaginal fluid	0.4-0.7

*Relative to concurrent concentrations in plasma in subjects with normal renal function.
**/* Independent of degree of meningeal inflammation.

In normal volunteers, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites.

The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of DIFLUCAN may need to be reduced in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION .) A 3-hour hemodialysis session decreases plasma concentrations by approximately 50%.

In normal volunteers, DIFLUCAN administration (doses ranging from 200 mg to 400 mg once daily for up to 14 days) was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations, and the ACTH-stimulated cortisol response.

Pharmacokinetics in Children

In children, the following pharmacokinetic data {Mean(%cv)} have been reported:

Age Studied	Dose (mg/kg)	Clearance (mL/min/kg)	Half-life (Hours)	Cmax (µg/mL)	Vdss (L/kg)
9 Months-13 years	Single-Oral 2 mg/kg	0.40 (38%) N=14	25.0	2.9 (22%) N=16	--
9 Months-13 years	Single-Oral 8 mg/kg	0.51 (60%) N=15	19.5	9.8 (20%) N=15	--
5-15 years	Multiple IV 2 mg/kg	0.49 (40%) N=4	17.4	5.5 (25%) N=5	0.722 (36%) N=4
5-15 years	Multiple IV 4 mg/kg	0.59 (64%) N=5	15.2	11.4 (44%) N=6	0.729 (33%) N=5
5-15 years	Multiple IV 8 mg/kg	0.66 (31%) N=7	17.6	14.1 (22%) N=8	1.069 (37%) N=7

Clearance corrected for body weight was not affected by age in these studies. Mean body clearance in adults is reported to be 0.23 (17%) mL/min/kg.

In premature newborns (gestational age 26 to 29 weeks), the mean (%cv) clearance within 36 hours of birth was 0.180 (35%, N=7) mL/min/kg, which increased with time to a mean of 0.218 (31%, N=9) mL/min/kg six days later and 0.333 (56%, N=4) mL/min/kg 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six days later and 46.6 hours 12 days later.

Drug Interaction Studies

Oral hypoglycemics: The effects of fluconazole on the pharmacokinetics of the sulfonylurea oral hypoglycemic agents tolbutamide, glipizide, and glyburide were evaluated in three placebo-controlled studies in normal volunteers. All subjects

received the sulfonylurea alone as a single dose and again as a single dose following the administration of DIFLUCAN 100 mg daily for 7 days. In these three studies 22/46 (47.8%) of DIFLUCAN treated patients and 9/22 (40.1%) of placebo treated patients experienced symptoms consistent with hypoglycemia. (See **PRECAUTIONS** .)

Cisapride: A preliminary report from a placebo-controlled, randomized multiple-dose study in subjects given fluconazole 200 mg daily and cisapride 20 mg four times daily starting after 7 days of fluconazole dosing found that fluconazole significantly increased the AUC and Cmax of cisapride both after single (AUC 102% and Cmax 92% increases) and multiple (AUC 192% and Cmax 153% increases) dosing of cisapride. Fluconazole significantly increased the QTc interval in subjects receiving cisapride 20 mg four times daily for 5 days. (See **CONTRAINDICATIONS** and **PRECAUTIONS** .)

CLINICAL STUDIES

Cryptococcal meningitis: In a multicenter study comparing DIFLUCAN (200 mg/day) to amphotericin B (0.3 mg/kg/day) for treatment of cryptococcal meningitis in patients with AIDS, a multivariate analysis revealed three pretreatment factors that predicted death during the course of therapy: abnormal mental status, cerebrospinal fluid cryptococcal antigen titer greater than 1:1024, and cerebrospinal fluid white blood cell count of less than 20 cells/mm ^{3} . Mortality among high risk patients was 33% and 40% for amphotericin B and DIFLUCAN patients, respectively (p=0.58), with overall deaths 14% (9 of 63 subjects) and 18% (24 of 131 subjects) for the 2 arms of the study (p=0.48). Optimal doses and regimens for patients with acute cryptococcal meningitis and at high risk for treatment failure remain to be determined. (Saag, *et al* . N Engl J Med 1992; 326:83-9.)

Vaginal candidiasis: Two adequate and well-controlled studies were conducted in the U.S. using the 150 mg tablet. In both, the results of the fluconazole regimen were comparable to the control regimen (clotrimazole or miconazole

intravaginally for 7 days) both clinically and statistically at the one month post-treatment evaluation.

The therapeutic cure rate, defined as a complete resolution of signs and symptoms of vaginal candidiasis (clinical cure), along with a negative KOH examination and negative culture for *Candida* (microbiologic eradication), was 55% in both the fluconazole group and the vaginal products group.

	Fluconazole PO 150 mg tablet	**Vaginal Product qhs × 7 days**
Enrolled Evaluable at Late Follow-up Clinical cure Mycologic erad. Therapeutic cure	448 347 (77%) 239/347 (69%) 213/347 (61%) 190/347 (55%)	422 327 (77%) 235/327 (72%) 196/327 (60%) 179/327 (55%)

Approximately three-fourths of the enrolled patients had acute vaginitis (<4 episodes/12 months) and achieved 80% clinical cure, 67% mycologic eradication and 59% therapeutic cure when treated with a 150 mg DIFLUCAN tablet administered orally. These rates were comparable to control products. The remaining one-fourth of enrolled patients had recurrent vaginitis (>/=4 episodes/12 months) and achieved 57% clinical cure, 47% mycologic eradication and 40% therapeutic cure. The numbers are too small to make meaningful clinical or statistical comparisons with vaginal products in the treatment of patients with recurrent vaginitis.

Substantially more gastrointestinal events were reported in the fluconazole group compared to the vaginal product group. Most of the events were mild to moderate. Because fluconazole was given as a single dose, no discontinuations occurred.

Parameter	**Fluconazole PO**	**Vaginal Products**
Evaluable patients	448	422
With any adverse event	141 (31%)	112 (27%)
Nervous System	90 (20%)	69 (16%)
Gastrointestinal	73 (16%)	18 (4%)

With drug-related event	117 (26%)	67 (16%)
Nervous System	61 (14%)	29 (7%)
Headache	58 (13%)	28 (7%)
Gastrointestinal	68 (15%)	13 (3%)
Abdominal pain	25 (6%)	7 (2%)
Nausea	30 (7%)	3 (1%)
Diarrhea	12 (3%)	2 (<1%)
Application site event	0 (0%)	19 (5%)
Taste Perversion	6 (1%)	0 (0%)

Pediatric Studies

Oropharyngeal candidiasis: An open-label, comparative study of the efficacy and safety of DIFLUCAN (2-3 mg/kg/day) and oral nystatin (400,000 I.U. 4 times daily) in immunocompromised children with oropharyngeal candidiasis was conducted. Clinical and mycological response rates were higher in the children treated with fluconazole.

Clinical cure at the end of treatment was reported for 86% of fluconazole treated patients compared to 46% of nystatin treated patients. Mycologically, 76% of fluconazole treated patients had the infecting organism eradicated compared to 11% for nystatin treated patients.

	Fluconazole	**Nystatin**
Enrolled Clinical Cure Mycological eradication [*]	96 76/88 (86%) 55/72 (76%)	90 36/78 (46%) 6/54 (11%)

[*] Subjects without follow-up cultures for any reason were considered nonevaluable for mycological response.

The proportion of patients with clinical relapse 2 weeks after the end of treatment was 14% for subjects receiving DIFLUCAN and 16% for subjects receiving nystatin. At 4 weeks after the end of treatment the percentages of patients with clinical relapse were 22% for DIFLUCAN and 23% for nystatin.

CONTRAINDICATIONS

DIFLUCAN (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross-hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing DIFLUCAN to patients with

hypersensitivity to other azoles. Coadministration of terfenadine is contraindicated in patients receiving DIFLUCAN (fluconazole) at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study. Coadministration of cisapride is contraindicated in patients receiving DIFLUCAN (fluconazole). (See CLINICAL PHARMACOLOGY : Drug Interaction Studies and PRECAUTIONS .)

WARNINGS

(1) Hepatic injury: DIFLUCAN has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of DIFLUCAN-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed.

DIFLUCAN hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury. DIFLUCAN should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to DIFLUCAN.

(2) Anaphylaxis: In rare cases, anaphylaxis has been reported.

(3) Dermatologic: Patients have rarely developed exfoliative skin disorders during treatment with DIFLUCAN. In patients with serious underlying diseases (predominantly AIDS and malignancy), these have rarely resulted in a fatal outcome. Patients who develop rashes during treatment with DIFLUCAN should be monitored closely and the drug discontinued if lesions progress.

PRECAUTIONS

General

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. These reports included seriously ill patients with

multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions.

Single Dose

The convenience and efficacy of the single dose oral tablet of fluconazole regimen for the treatment of vaginal yeast infections should be weighed against the acceptability of a higher incidence of drug related adverse events with DIFLUCAN (26%) versus intravaginal agents (16%) in U.S. comparative clinical studies. (See ADVERSE REACTIONS and CLINICAL STUDIES .)

Pregnancy

Teratogenic Effects. Pregnancy Category C: Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60 × the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 × the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 mg/day)

fluconazole therapy for coccidioidomycosis (an unindicated use). The relationship between fluconazole use and these events is unclear. DIFLUCAN should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

Nursing Mothers

Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of DIFLUCAN in nursing mothers is not recommended.

Pediatric Use

An open-label, randomized, controlled trial has shown DIFLUCAN to be effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age. (See CLINICAL STUDIES .)

The use of DIFLUCAN in children with cryptococcal meningitis, *Candida* esophagitis, or systemic *Candida* infections is supported by the efficacy shown for these indications in adults and by the results from several small noncomparative pediatric clinical studies. In addition, pharmacokinetic studies in children (see CLINICAL PHARMACOLOGY) have established a dose proportionality between children and adults. (See DOSAGE AND ADMINISTRATION .)

In a noncomparative study of children with serious systemic fungal infections, most of which were candidemia, the effectiveness of DIFLUCAN was similar to that reported for the treatment of candidemia in adults. Of 17 subjects with culture-confirmed candidemia, 11 of 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure; 13/15 (87%) of evaluable patients had a mycologic cure at the end of treatment but two of these patients relapsed at 10 and 18 days, respectively, following cessation of therapy.

The efficacy of DIFLUCAN for the suppression of cryptococcal meningitis was successful in 4 of 5 children treated in a compassionate-use study of fluconazole for the treatment of life-threatening or serious mycosis. There is no information

regarding the efficacy of fluconazole for primary treatment of cryptococcal meningitis in children.

The safety profile of DIFLUCAN in children has been studied in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1,616 days. (See ADVERSE REACTIONS .)

Efficacy of DIFLUCAN has not been established in infants less than 6 months of age. (See CLINICAL PHARMACOLOGY .) A small number of patients (29) ranging in age from 1 day to 6 months have been treated safely with DIFLUCAN.

ADVERSE REACTIONS

In Patients Receiving a Single Dose for Vaginal Candidiasis:

During comparative clinical studies conducted in the United States, 448 patients with vaginal candidiasis were treated with DIFLUCAN, 150 mg single dose. The overall incidence of side effects possibly related to DIFLUCAN was 26%. In 422 patients receiving active comparative agents, the incidence was 16%. The most common treatment-related adverse events reported in the patients who received 150 mg single dose fluconazole for vaginitis were headache (13%), nausea (7%), and abdominal pain (6%). Other side effects reported with an incidence equal to or greater than 1% included diarrhea (3%), dyspepsia (1%), dizziness (1%), and taste perversion (1%). Most of the reported side effects were mild to moderate in severity. Rarely, angioedema and anaphylactic reaction have been reported in marketing experience.

In Patients Receiving Multiple Doses for Other Infections:

Sixteen percent of over 4000 patients treated with DIFLUCAN (fluconazole) in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%); however, the patterns in HIV infected and non-HIV infected patients were similar. The proportions of patients

discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving DIFLUCAN for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

The following adverse events have occurred under conditions where a causal association is probable:

Hepatobiliary: In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with DIFLUCAN. (See **WARNINGS** .) The spectrum of these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of DIFLUCAN.

In two comparative trials evaluating the efficacy of DIFLUCAN for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking

DIFLUCAN concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

Immunologic: In rare cases, anaphylaxis has been reported.

The following adverse events have occurred under conditions where a causal association is uncertain:

Cardiovascular: QT prolongation, torsade de pointes. (See **PRECAUTIONS** .)

Central Nervous System: Seizures.

Dermatologic: Exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis (see **WARNINGS**), alopecia.

Hematopoietic and Lymphatic: Leukopenia, including neutropenia and agranulocytosis, thrombocytopenia.

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Adverse Reactions in Children:

In Phase II/III clinical trials conducted in the United States and in Europe, 577 pediatric patients, ages 1 day to 17 years were treated with DIFLUCAN at doses up to 15 mg/kg/day for up to 1,616 days. Thirteen percent of children experienced treatment related adverse events. The most commonly reported events were vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%). Treatment was discontinued in 2.3% of patients due to adverse clinical events and in 1.4% of patients due to laboratory test abnormalities. The majority of treatment-related laboratory abnormalities were elevations of transaminases or alkaline phosphatase.

Percentage of Patients With Treatment-Related Side Effects		
	Fluconazole (N=577)	**Comparative Agents (N=451)**

With any side effect	13.0	9.3
Vomiting	5.4	5.1
Abdominal pain	2.8	1.6
Nausea	2.3	1.6
Diarrhea	2.1	2.2

OVERDOSAGE

There has been one reported case of overdosage with DIFLUCAN (fluconazole). A 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behavior after reportedly ingesting 8200 mg of DIFLUCAN. The patient was admitted to the hospital, and his condition resolved within 48 hours.

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if clinically indicated) should be instituted.

Fluconazole is largely excreted in urine. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

In mice and rats receiving very high doses of fluconazole, clinical effects in both species included decreased motility and respiration, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex and cyanosis; death was sometimes preceded by clonic convulsions.

2. Fluconazole congenital abnormalities consult – March 2004

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 29, 2004
FROM: Joyce Weaver, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation, HFD-430
THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430
TO: Jonathan Wilkin, M.D., Director
Division of Dermatological and Dental Drug Products, HFD-540
SUBJECT: Postmarketing Safety Review; PID # D040213
Drug: Fluconazole (Diflucan, NDAs # 019949, 019950, 020090)
Event: Congenital anomalies

EXECUTIVE SUMMARY

We were consulted by the Division of Dermatological and Dental Drug Products (DDDDP) to review the data in the FDA's Adverse Event Reporting System (AERS) reporting congenital anomalies with the use of fluconazole. In pre-clinical testing, the Sponsor found dose-dependent embryolethality and fetal abnormalities including wavy ribs, cleft palate and abnormal craniofacial ossification in rats. Additionally, dose-related abnormalities were found in mouse and rat embryos at the branchial apparatus level. The branchial arches give rise to embryonic craniofacial structures.

Cohort studies have not found an increase in congenital anomalies with the use of fluconazole during pregnancy. However, craniofacial and skeletal abnormalities have been observed in infants whose mothers used fluconazole during pregnancy; 5 such cases have been reported in the medical literature. The cases published in the medical literature report similar craniofacial and skeletal abnormalities as have been reported in rats and in mouse and rat embryos. In addition to craniofacial and skeletal abnormalities, the cases in the medical literature reported cardiac abnormalities. The cases published in the medical literature are included in the AERS database. Among the 62 cases in AERS reporting congenital anomalies with fluconazole, 37 cases reported craniofacial, musculoskeletal, and cardiac abnormalities. Nineteen of the 62 total cases and 10 of the cases reporting craniofacial, musculoskeletal, or cardiac abnormalities represent new cases since our 2001 review of congenital anomalies with fluconazole.

We note that congenital heart and circulation structural defects and congenital musculoskeletal structural defects are common, occurring in 1 in 115 births and in 1 in 130 births, respectively.[1] *Nevertheless, the convergence of the data in AERS, the published case reports, and the Sponsor's pre-clinical testing suggests that fluconazole may be teratogenic, inducing craniofacial, musculoskeletal, and cardiac abnormalities. These effects have been reported even with a single dose of 150mg, the most frequently*

cited regimen in the AERS data. We believe it is appropriate to include the descriptive information (above) in the Pregnancy section of the fluconazole labe1ing. A draft of proposed language for the Pregnancy section of the labeling has been prepared by staff from the Pregnancy Labeling Team. We concur with the drafted language, except that we recommend that information be included about the cases reported to AERS. The proposed language is included in Attachment 1.

INTRODUCTION/BACKGROUND

The Sponsor submitted a pediatric supplement in response to a written request for fluconazole for the treatment of tinea capitis. According to DDDDP, studies for the treatment of tinea capitis did not show statistical significance, and the applicant is not seeking to add the indication; however, safety information from studies will likely be added to the fluconazole product labeling.

ODS was consulted in January 2004 by DDDDP to review the data in AERS reporting congenital anomalies with the use of fluconazole. At that time, we provided copies of three prior reviews on this subject by ODS reviewers, and a copy of case reports received by the Agency since 2001. Our most recent reports were at that time not evaluated with regard to causality, timing of exposure during pregnancy, or other potential factors.
A meeting was subsequently held (February 17, 2004) between the DDDDP, the Division of Division of Special Pathogen and Immunologic Drug Products (DSPIDP), and ODS to discuss whether a Pregnancy Category X is warranted based on the animal findings as well as postmarketing reports of congenital anomalies received to date. At that meeting, a consensus could not be reached as to whether the pregnancy labeling should be modified.

We were asked however, to evaluate the new cases in more detail in order to help guide decision making. This current review provides a comprehensive evaluation of all cases of congenital anomalies received by the Agency as well as a review of the salient medical literature.

DRUG INFORMATION/LABELING

Fluconazole is a synthetic triazole antifungal agent first approved by the FDA in 1/1990. Fluconazole is approved for the following indications:
1. Vaginal candidiasis (vaginal yeast infections due to Candida).
2. Oropharyngeal and esophageal candidiasis.
3. Cryptococcal meningitis.

[1] Data from the March of Dimes, available at URL: www.modimes.org

Fluconazole is a selective inhibitor of fungal cytochrome P-450 sterol C-14 alphademethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14 alpha-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

The medical literature is mixed regarding the potential for fluconazole to cause fetal

damage. Researchers conducting epidemiologic studies have concluded that fluconazole does not appear to increase the prevalence of congenital anomalies. However, both an *in vitro* study and published case reports support a conclusion that fluconazole may cause cardiac, craniofacial, and skeletal abnormalities. Additionally, the Sponsor found doserelated abnormalities in rats in pre-clinical studies.

Fluconazole Pregnancy Labeling
The labeling for fluconazole states the following regarding the potential for teratogenic effects with its use during pregnancy:
Teratogenic Effects. Pregnancy Category C: Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60 × the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 × the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition. There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 mg/day) fluconazole therapy for coccidioidomycosis (an unindicated use). The relationship between fluconazole use and these events is unclear. DIFLUCAN should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

Medical Literature
Epidemiologic Studies

Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. Am J Obstet Gynecol. 1996; 175(6): 1645-50.
This prospective cohort study looked at pregnancy outcomes in women exposed to fluconazole who contacted 3 Italian teratogen information services. The control group comprised 452 women exposed to nonteratogenic agents. Among the 226 pregnancies exposed to fluconazole there were 22 miscarriages, 1 stillbirth, and 7 infants with congenital anomalies. The prevalence of these outcomes and of neonatal growth parameters and the rate of neonatal complications were similar to those in the reference group. No infant had skeletal, cardiac, or facial anomalies. *The authors concluded that first-trimester exposure to fluconazole does not appear to increase the prevalence of miscarriages, congenital anomalies, and low birth weight.*

Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. Pharmacotherapy. 1999; 19(2): 221-2.
This researcher evaluated pregnancy outcomes in 234 women exposed to fluconazole, 492 exposed to a topically administered azole preparation, 88 exposed to an oral azole preparation other than fluconazole, and 1629 not exposed to any of these agents during the first trimester of pregnancy. Ninety-two percent of the women who received oral fluconazole received a single 150-mg dose. Relative risks of having a baby with a congenital disorder for women exposed to fluconazole, oral azoles, and topical azoles in the first trimester of pregnancy compared with those who were unexposed were 1.1 (95% CI 0.4-3.3), 2.1 (95% CI 0.7-6.8), and 0.6 (95% CI 0.2-1.6), respectively. Three infants with congenital anomalies were born to women taking oral fluconazole. The anomalies observed were polydactyly or syndactyly (1), spina bifida (1), and an unspecified heart defect (1). No skeletal disorders were observed in the infants whose mothers used oral fluconazole. *The author concluded that fluconazole exposure in the first trimester of pregnancy does not materially increase the risk of congenital disorders in infants. The cases from this series are in the AERS database.*

Sorensen HT, Nielsen GL, Olesen C, et al. Risk of malformations and other outcomes in children exposed to fluconazole in utero. Br J Clin Pharmacol. 1999; 48(2): 234-8.
The researchers examined the risk of malformations and other birth outcomes following exposure to fluconazole in the first trimester of pregnancy in 121 women. Although information on dose was not presented in the publication, the authors noted that fluconazole is most often prescribed as a single 150-mg dose. Birth outcomes (malformation, low birth weight and preterm delivery) were compared with the outcomes among 13,327 women who did not receive any prescriptions during their pregnancies. The prevalence of malformation was 3.3% (four cases) among the 121 women, who had used fluconazole in the first trimester, and 5.2% (697 cases) in offspring to controls (odds ratio: 0.65, 95% confidence limits: 0.24-1.77). Additionally, the researchers did not find any significantly elevated risk of preterm delivery (odds ratio: 1.17, 95% confidence limits: 0.63-2.17) and low birth weight (odds ratio: 1.19, 95% confidence limits: 0.37-3.79). *The study showed no increased risk of congenital malformations, low birth weight or preterm birth in offspring to women who had used single dose fluconazole before conception or during pregnancy.*

The 4 malformations reported among infants whose mothers took fluconazole in the first trimester of pregnancy were: congenital dislocation of the hip (1), lacrimal stenosis (1), partial syndactyly (1), and ventricular septum defect (1). *The cases from this series are in the AERS database.*

Case Reports/ Case Series
Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. Am J Med Genet. 1997; 72(3): 253-6.
The authors report a case of an infant born to a woman who was treated for *Coccidioides immitis* meningitis with fluconazole 400-800 mg daily until her 9th week of pregnancy. The infant was born by cesarean section after spontaneous rupture of membranes at 31

weeks of gestation. The following anomalies were noted in the infant: multiple skull abnormalities, nose malformation, malformed ears, joint anomalies, radiohumeral synostosis, and hypoplastic nails. *This case is in the AERS database.*

Lee BE, Feinberg M, Abraham JJ, Murthy AR. Congenital malformations in an infant born to a woman treated with fluconazole. Pediatr Infect Dis J. 1992; 11(12): 1062-4.
The authors reported a case of multiple congenital malformations in an infant whose mother had used fluconazole 400-mg daily to treat coccidiomycosis. The infant was born with grossly dysmorphic features, and the infant died shortly after birth. Autopsy revealed that the infant had craniosynostosis, humeroradial fusion, bowed tibia and femur, femoral fractures, hypoplasia of nasal bones, cleft palate, contractures of extremities, cranioschisis, and craniostenosis. *This case is in the AERS database.*

Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole induced congenital anomalies in three infants. Clin Infect Dis. 1996; 22(2): 336-40.
The authors describe 3 infants with craniofacial, skeletal (thin, wavy ribs and ossification defects), and cardiac anomalies born to women who were receiving fluconazole through or beyond the first trimester of pregnancy. The woman were treated with fluconazole for *Coccidioides immitis* meningitis with fluconazole 400-800 mg daily for varying periods of time during their pregnancies; all 3 women received fluconazole through the 6th week of pregnancy. One patient received fluconazole throughout her pregnancy, another woman received fluconazole until her 4th month of pregnancy, and the 3rd woman received fluconazole during the entire pregnancy except during the 7th-9th weeks. Two of the infants died. *These 3 cases are in the AERS database.*

Sanchez JM, Moya G. Fluconazole teratogenicity. Prenat Diagn. 1998; 18(8): 862-3.
An infant with multiple abnormalities was born to a woman who took a single 150-mg dose of fluconazole at about the time of conception to treat vaginal candidiasis. The following anomalies were observed in the infant: encephalocele, hypoplasia of cervical vertebrae, dextrocardia, and anomalies of the great vessels. The infant died 7 days after birth. *This case is in the AERS database.*

***In Vitro* Study**
Menegola E, Broccia ML, Di Renzo F, Giavini E. Antifungal triazoles induce malformations in vitro. Reprod Toxicol. 2001; 15(4): 421-7.
Rat embryos, 9.5 days old were exposed *in vitro* to triazole 500 to 5000 microM, flusilazole 3.125 to 250 microM, or fluconazole 62.5 to 500 microM. After 48 h in culture, the embryos were morphologically examined and processed for histologic and biochemical analysis. Flusilazole and fluconazole showed similar teratogenic effects (abnormalities at the branchial apparatus level and cell death at the level of the branchial mesenchyme) at concentration levels of 6.25 microM and higher for flusilazole and of 125 microM and higher for fluconazole. The branchial arches give rise to embryonic craniofacial structures. Craniofacial abnormalities have been observed in infants whose mothers used fluconazole in pregnancy. *The authors believe that the results of this study confirm the embryotoxic effect of fluconazole.*

SELECTION OF AERS CASE SERIES

We conducted 2 searches of AERS using the following parameters:

Drug Names: fluconazole (active ingredient), Diflucan (tradename);
MedDRA SOC-*Congenital, familial, and genetic disorders*; and
Search dates - no limits.

and

Drug Names: fluconazole (active ingredient), Diflucan (tradename);
No MedDRA terms;
Outcome-congenital anomaly; and
Search dates - no limits

We found 102 cases using the first search strategy, and an additional 9 cases using the second search strategy, for a total of 111 cases. We excluded 49 cases for the following reasons:

the case did not report pregnancy–exposure-related congenital anomalies—25;
the infant had congenital disseminated candidiasis due to maternal-fetal infection (treatment with fluconazole as an alternative to amphotericin was proposed)—1;
second-hand report by a consumer who reported hearing of a pregnant female who delivered a fetus with no arms or legs; she was reportedly treated with fluconazole at an unspecified time—1;
spontaneous abortion or intrauterine death; no malformations noted—3; and
duplicate cases—19.

Ultimately we included 62 cases in this case series. Although we did not include spontaneous abortions or intra-uterine death in the cases reviewed, we conducted an AERS search of the number of cases using the HLGT *Abortions and stillbirth* (89 cases, raw count).

SUMMARY OF CASES

All Congenital Anomalies

The characteristics of the cases are presented in Table 1.

Table 1—Characteristics of 62 Cases Reporting Congenital Anomalies with Fluconazole

Reporter Healthcare practitioner-52, Consumer-6, unk-4

Event year 1990-1
1991-3
1992-3
1993-5
1994-1
1995-2
1996-5
1997-3
1998-2

1999-3
2000-4
2001-3
2002-4
Not reported-23

Report year 1991-1
1992-2
1993-2
1994-2
1995-1
1996-5
1997-16 (includes cases from 2 published case series)
1998-3
1999-10 (includes cases from 2 published case series)
2000-8
2001-6
2002-4
2003-2

Country of origin Non-US-44; US-18

Indication Vaginal candidiasis-25
Coccidioides immitis meningitis-4
HIV-related indications-3
Unspecified vaginitis-3
Unspecified candidiasis-5
Dermatomycosis-1
Empiric for fever, infection-1
Otitis media-1
Trichomonas-1

Table 1—Characteristics of 62 Cases Reporting Congenital Anomalies with Fluconazole

Unspecified recurrent fungal infection-2
Unspecified fungal infection-1
Not reported-15

Timing of exposure during pregnancy
Before conception-1
Weeks 1 through 4-28
Weeks 5 through 8-4
Weeks 9 through 12-2
Other wording describing first trimester-8
Second trimester-1
Third trimester-3
Not reported-11
Throughout pregnancy-3
Throughout pregnancy, except weeks 7 to 9-1

Daily dose
50mg-3

150mg-35
200mg-3
400-800mg-4
Not reported-17

Duration 1 dose-28
2 doses-7
3 doses-3
4 doses-1
Throughout pregnancy-2
Other, or not reported-21

Total exposure 150mg-25
200mg-1
300mg-7
450mg-2
600mg-1
1000mg-1
>100grams-1
Not reported-24

Anomalies **Hypospadias (2)**
Polydactyly/syndactyly (6)
Syndactyly of 3rd and 4th fingers of left hand and partial syndactyly of 3rd and 4th toes of left foot
Poly- or syndactyly
Duplicate thumbs on one hand
Proximal syndactyly of fingers 2-3 of R hand, shortening of proximal phalanx of R 5th finger. Camptodactyly of R 3rd finger and hypoplasia of R arm. (Note this case had questionable mandibular hypoplasia as well.)
Syndactyly, missing phalanges
Partial syndactyly
Renal and/or Urinary Tract Malformations (5)
Megaureter (2)
"Anomaly of the urogenital system"
Hydronephrosis
Multicystic dysplastic kidney 9

Table 1—Characteristics of 62 Cases Reporting Congenital Anomalies with Fluconazole

Cleft lip/palate (3)
Limb defects (7)
Malformed bones in fingers ("pinkies" do not bend)
Severe shortening of all limbs
Phocomelia (absent hand and forearm)
Talipes valgus
Talipes equinovarus
Talipes equinovarus
Missing left foot, malformed right foot, three fingers missing on right hand, two fingers missing on left hand
Cardiac structural defects (4)
Ventricular septal defects
Unspecified heart defect
Ventricular septal defects
Atrial septal defect and atrial wall aneurysm
Multiple anomalies (15)
Multiple malformations of twin fetuses: megabladder, polymalformation

syndrome with omphalocele, malposition of the lower limbs; exomphalos, agenesis of external genitalia, anal agenesia

Encephalocele, hypoplasia of cervical vertebrae, dextrocardia, anomalies of great vessels

Clubfoot, cryptorchidism

Omphalocele, herniated liver, atrial deformity

diaphragmatic hernia, prematurity, respiratory function impairment

Multiple skull abnormalities, nose malformation, malformed ears, joint anomalies, radiohumeral synostosis, hypoplastic nails

Facial malformations, narrow palpebral grooves, large cornea, long digitalized thumb, joint abnormalities

Holoprosencephaly, cleft lip & palate, polydactylism of right hand, enlarged right kidney, right double ureter

frontal bossing and macrocephaly, hypoplastic nipples, hypoplastic toenails, and thin digits

musculoskeletal abnormality (unspecified), facial abnormalities including "upslanted eyes and head is abnormally shaped and slanted"

Craniosynostosis, humeroradial fusion, bowed tibia & femur, femoral fractures, hypoplasia of nasal bones, cleft palate, contractures of extremities, cranioschisis, craniostenosis

Transposition of great arteries, patent ductus arteriosus, atrial septal defect, malformed ears, hepatosplenomegaly

Tetralogy of Fallot, patent ductus arteriosus, pulmonary artery hypoplasia, patent foramen ovale, ventricular septal defect, craniofacial dysproportion, osteopenia with thin fragile bones, exotropia, hydrocephalus, butterfly vertebrae, abnormal ribs

Cleft palate, low ears, tracheomalacia, rudimentary epiglottis, proptosis, bone deformities, ventricular septal defect, pulmonary artery hypoplasia

Encephalopathy, ventricular septal defect

Unspecified abnormalities (3)

Craniofacial abnormalities (5)

"cone-shaped' head

Cerebral atrophy with enlarged ventricles

Dysmorphia and psychomotor retardation

Arrhinia, cryptophthalmos, bilateral microphthalmia

Hydrocephalus

Trisomy 21 (2)

Other (10)

Spina bifida

Pyloric stenosis 10

Table 1—Characteristics of 62 Cases Reporting Congenital Anomalies with Fluconazole

Hirschsprung's disease (congenital megacolon)

"tongue-tied"

brittle primary teeth

thrombocytopenia (respiratory arrest also suffered secondary to meconium)

Congenital hip dislocation

Lacrimal duct stenosis

unspecified congenital anomaly and bone disorder NOS

bilateral hearing impairment

Fetal outcome Live birth-51

Live birth, but death shortly after birth-5

Spontaneous abortion-1

Therapeutic abortion-5

Possible confounding factors-6 cases

HIV+ & receiving antiretroviral drugs-3 cases
Atrial septal defect and atrial wall aneurysm
frontal bossing and macrocephaly, hypoplastic nipples, hypoplastic toenails, and thin digits
Transposition of great arteries, patent ductus arteriosus, atrial septal defect, malformed ears, hepatosplenomegaly
Forceps delivery-1 case
"cone-shaped' head
Concomitant methotrexate-1 case
Facial malformations, narrow palpebral grooves, large cornea, long digitalized thumb, joint abnormalities
Concomitant use of ACE inhibitor-1 case
Multicystic dysplastic kidney

We found 62 cases reporting congenital anomalies with the use of fluconazole during pregnancy. Cases of congenital anomalies have been reported to AERS every year beginning in 1991. Most (52) of the reports were submitted by healthcare practitioners, and were reported from non-US countries (44). The most frequently cited indication for use was vaginal candidiasis (25). Most (43) cases reported exposure during the first trimester of pregnancy, especially in the first 4 weeks of pregnancy (29). Four additional cases reported use throughout, or nearly throughout, the entire pregnancy, including during the first trimester of pregnancy. The most frequently reported dose was 150-mg (35), and the most frequent duration of use cited was one dose (28). The defects reported were largely structural anomalies including limb defects (7), polydactyly/ syndactyly (5), renal and/ or urinary tract malformations (5), craniofacial abnormalities (5), cardiac structural defects (4), cleft lip/palate (3), and hypospadias (2). Fifteen cases reported multiple structural anomalies.

This review includes 19 new cases (not included in our 2001 review). The 19 new cases report the following anomalies:

Polydactyly/syndactyly (1)
Proximal syndactyly of fingers 2-3 of R hand, shortening of proximal phalanx of R 5th finger. Camptodactyly of R 3rd finger and hypoplasia of R arm. (This case had questionable mandibular hypoplasia as well.)
Limb defects (1)
Phocomelia (absent hand and forearm)
Cardiac structural defects (2)
11
Unspecified heart defect
Atrial septal defect and atrial wall aneurysm
Multiple anomalies (5)
Multiple malformations of twin fetuses: megabladder, polymalformation syndrome with omphalocele, malposition of the lower limbs; exomphalos, agenesis of external genitalia, anal agenesia
diaphragmatic hernia, prematurity, respiratory function impairment
frontal bossing and macrocephaly, hypoplastic nipples, hypoplastic toenails, and thin digits
musculoskeletal abnormality (unspecified), facial abnormalities including "upslanted eyes and head is abnormally shaped and slanted"
Encephalopathy, ventricular septal defect
Craniofacial abnormalities (2)
"cone-shaped' head
Dysmorphia and psychomotor retardation
Trisomy 21 (2)

Other (6)
Hirschsprung's disease (congenital megacolon)
"tongue-tied"
brittle primary teeth
thrombocytopenia (respiratory arrest also suffered secondary to meconium)
unspecified congenital anomaly and bone disorder NOS
bilateral hearing impairment

Six of the 62 cases reported possible confounding factors, including HIV infection (a case of cardiac malformations and 2 cases of multiple malformations [including a case with cardiac malformations and a case with craniofacial malformations]), forceps delivery (a case reporting a cone-shaped head), concomitant use of methotrexate (a case reporting multiple malformations including craniofacial and limb defects), and the concomitant use of an angiotensin-converting enzyme inhibitor (a case of multicystic dysplastic kidney). Most (56) of the pregnancies resulted in live births; however, 5 of the infants died shortly after birth. Five pregnancies resulted in therapeutic abortions, and one pregnancy aborted spontaneously.

Attachment 2 presents a line listing of all cases in this series.

Cases Reporting Cardiac, Craniofacial, & Musculoskeletal Anomalies
Pursley, et al described 3 infants with craniofacial, skeletal (thin, wavy ribs and ossification defects), and cardiac anomalies born to women who were receiving fluconazole through or beyond the first trimester of pregnancy. The woman were treated with fluconazole for *Coccidioides immitis* meningitis with fluconazole 400-800 mg daily for varying periods of time during their pregnancies; all 3 women received fluconazole through the 6th week of pregnancy. The anomalies were similar to dose-dependent anomalies observed in cultured mouse embryos and to anomalies observed in rats in studies conducted by the Sponsor. Because craniofacial, skeletal, and cardiac anomalies have been described in both humans and in animal studies, we present data on the subset of cases reporting such anomalies below.

Thirty-seven cases reported cardiac, craniofacial, and musculoskeletal congenital anomalies. The characteristics of the cases are presented in Table 2.

Table 2—Characteristics of 37 Cases Reporting Cardiac, Craniofacial, and Musculoskeletal Congenital Anomalies with Fluconazole
Reporter Healthcare practitioner-31, Consumer-4, unk-2
Event year 1991-3
1992-1
1993-2
1995-1
1996-4
1997-3
1998-1
1999-2
2000-4
2001-2

2002-2
Not reported-12
Report year 1992-2
1993-1
1996-4
1997-9
1999-6
2000-6
2001-5
2002-3
2003-1

Country of origin Non-US-23; US-14

Indication
Vaginal candidiasis-12
Coccidioides immitis meningitis-4
HIV-related indications-3
Unspecified vaginitis-2
Unspecified candidiasis-1
Empiric for fever, infection-1
Trichomonas-1
Unspecified recurrent fungal infection-2
Unspecified fungal infection-1
Otitis media-1
Not reported-9

Timing of exposure
During pregnancy
Before conception-1
Weeks 1 through 4-16
Weeks 5 through 8-1
Weeks 9 through 12-0
Other wording describing first trimester-4
Second trimester-1
Third trimester-2
Not reported-8
Throughout pregnancy-3
Throughout pregnancy, except weeks 7 to 9-1

Daily dose
150mg-20
200mg-2
400-800mg-4
Not reported-11
Duration 1 dose-14
2 doses-5
3 doses-1
Throughout pregnancy-2
Other, or not reported-15

Table 2—Characteristics of 37 Cases Reporting Cardiac, Craniofacial, and Musculoskeletal Congenital Anomalies with Fluconazole

Total exposure	150mg-13 200mg-1 300mg-5 450mg-1 >100grams-1 Not reported-16
Anomalies	**Polydactyly/syndactyly (6)**
	Syndactyly of 3rd and 4th fingers of left hand and partial syndactyly of 3rd and 4th toes of left foot
	Poly- or syndactyly
	Duplicate thumbs on one hand
	Proximal syndactyly of fingers 2-3 of R hand, shortening of proximal phalanx of R 5th finger. Camptodactyly of R 3rd finger and hypoplasia of R arm. (Note this case had questionable mandibular hypoplasia as well.)
	Syndactyly, missing phalanges
	Partial syndactyly
	Limb defects (7)
	Malformed bones in fingers (“pinkies” do not bend)
	Severe shortening of all limbs
	Phocomelia (absent hand and forearm)
	Talipes valgus
	Talipes equinovarus
	Talipes equinovarus
	Missing left foot, malformed right foot, three fingers missing on right hand, two fingers missing on left hand
	Cardiac structural defects (4)
	Ventricular septal defects (2)
	Unspecified heart defect
	Atrial septal defect and atrial wall aneurysm
	Multiple anomalies (14)
	Multiple malformations of twin fetuses: megabladder, polymalformation syndrome with omphalocele, malposition of the lower limbs; exomphalos, agenesis of external genitalia, anal agenesia
	Encephalocele, hypoplasia of cervical vertebrae, dextrocardia, anomalies of great vessels
	Clubfoot, cryptorchidism
	Omphalocele, herniated liver, atrial deformity
	Multiple skull abnormalities, nose malformation, malformed ears, joint anomalies, radiohumeral synostosis, hypoplastic nails
	Facial malformations, narrow palpebral grooves, large cornea, long digitalized thumb, joint abnormalities
	Holoprosencephaly, cleft lip & palate, polydactylism of right hand, enlarged right kidney, right double ureter
	Frontal bossing and macrocephaly, hypoplastic nipples, hypoplastic toenails, and thin digits
	Musculoskeletal abnormality (unspecified), facial abnormalities including “upslanted eyes and head is abnormally shaped and slanted”
	Craniosynostosis, humeroradial fusion, bowed tibia & femur, femoral fractures, hypoplasia of nasal bones, cleft palate, contractures of extremities, cranioschisis, craniostenosis
	Transposition of great arteries, patent ductus arteriosus, atrial septal defect, malformed ears, hepatosplenomegaly
	Tetralogy of Fallot, patent ductus arteriosus, pulmonary artery hypoplasia, patent foramen ovale, ventricular septal defect, craniofacial dysproportion, osteopenia with thin fragile bones, exotropia, hydrocephalus, butterfly vertebrae, abnormal ribs

Cleft palate, low ears, tracheomalacia, rudimentary epiglottis, proptosis, bone deformities, ventricular septal defect, pulmonary artery hypoplasia

Encephalopathy, ventricular septal defect

Craniofacial abnormalities (excluding cleft lip/palate) (4)

"cone-shaped' head

Cerebral atrophy with enlarged ventricles

Dysmorphia and psychomotor retardation

Arrhinia, cryptophthalmos, bilateral microphthalmia

Other (2)

Congenital hip dislocation

unspecified congenital anomaly and bone disorder NOS

Possible confounding factors-5 cases

HIV+ & receiving antiretroviral drugs-3 cases

Atrial septal defect and atrial wall aneurysm

frontal bossing and macrocephaly, hypoplastic nipples, hypoplastic toenails, and thin digits

Transposition of great arteries, patent ductus arteriosus, atrial septal defect, malformed ears, hepatosplenomegaly

Forceps delivery-1 case

"cone-shaped' head

Concomitant methotrexate-1 case

Facial malformations, narrow palpebral grooves, large cornea, long digitalized thumb, joint abnormalities

Fetal outcome Live birth-31

Live birth, but death shortly after birth-3

Therapeutic abortion-3

We found 37 cases reporting cardiac, craniofacial, and musculoskeletal congenital anomalies with the use of fluconazole during pregnancy. Most (31) of the reports were submitted by healthcare practitioners, and were reported from non-US countries (23). The most frequently cited indication for use was vaginal candidiasis (12). Most (22) cases reported exposure during the first trimester of pregnancy, especially in the first 4 weeks of pregnancy (17). Four additional cases reported use throughout, or nearly throughout, the entire pregnancy, including during the first trimester of pregnancy. The most frequently reported dose was 150-mg (20), and the most frequent duration of use cited was one dose (14).

The defects reported were largely structural anomalies including limb defects (7), polydactyly/ syndactyly (5), craniofacial abnormalities (5), cardiac structural defects (4). Fourteen cases reported multiple structural anomalies, including at least one cardiac, craniofacial, or musculoskeletal defect.

This review includes 10 new cases (not included in our 2001 review) reporting cardiac, craniofacial, or musculoskeletal defects:

Polydactyly/syndactyly (1)

Proximal syndactyly of fingers 2-3 of R hand, shortening of proximal phalanx of R 5th finger. Camptodactyly
of R 3rd finger and hypoplasia of R arm. (This case had questionable mandibular hypoplasia as well.)

Limb defects (1)

Phocomelia (absent hand and forearm)

15

Cardiac structural defects (2)

Unspecified heart defect

Atrial septal defect and atrial wall aneurysm
Multiple anomalies (4)
Multiple malformations of twin fetuses: megabladder, polymalformation syndrome with omphalocele,
malposition of the lower limbs; exomphalos, agenesis of external genitalia, anal agenesia
frontal bossing and macrocephaly, hypoplastic nipples, hypoplastic toenails, and thin digits
musculoskeletal abnormality (unspecified), facial abnormalities including "upslanted eyes and head is
abnormally shaped and slanted"
Encephalopathy, ventricular septal defect
Craniofacial abnormalities (2)
"cone-shaped' head
Dysmorphia and psychomotor retardation

Five of the 37 cases reported possible confounding factors, including HIV infection (3 cases of cardiac and multiple malformations), forceps delivery (a case reporting a coneshaped head), and the concomitant use of methotrexate (a case reporting multiple malformations including craniofacial and limb defects). Most (34) of the pregnancies resulted in live births; however, 3 of the infants died shortly after birth. Three pregnancies resulted in therapeutic abortions.

DISCUSSION/ CONCLUSION

In pre-clinical testing, the Sponsor found dose-dependent embryolethality and fetal abnormalities including wavy ribs, cleft palate and abnormal craniofacial ossification in rats. Additionally, dose-related abnormalities were found in mouse and rat embryos at the branchial apparatus level. The branchial arches give rise to embryonic craniofacial structures.
Cohort studies have not found an increase in congenital anomalies with the use of fluconazole during pregnancy. However, craniofacial and skeletal abnormalities have been observed in infants whose mothers used fluconazole during pregnancy. Five such cases have been reported in the medical literature. The cases published in the medical literature report similar craniofacial and skeletal abnormalities as reported in rats and in mouse and rat embryos. These cases reported cardiac abnormalities as well. The cases in the medical literature are included in the AERS database. Among the 62 cases in AERS reporting congenital anomalies with fluconazole, 37 cases reported craniofacial, musculoskeletal, and cardiac abnormalities. Ten new cases (since the 2001 review) reporting craniofacial, musculoskeletal, and cardiac abnormalities are included in this review.

Because the effects were found to be dose-related in animal and *in vitro* studies, we looked at the dose relationship in the AERS cases. Although 4 cases reported use of 400-800mg daily to treat *Coccidioides immitis* meningitis, the most frequently reported drug regimen was a single 150mg dose (25). Congenital heart and circulation structural defects and congenital musculoskeletal structural defects are common, occurring in 1 in 115 births and in 1 in 130 births, respectively. Nevertheless, the convergence of the data in AERS, the published literature, and the Sponsor's pre-clinical testing suggests that fluconazole may be teratogenic, inducing craniofacial, musculoskeletal, and cardiac abnormalities. These effects have been reported even with a single dose of 150mg, the

most frequently cited regimen in the AERS data. The mechanism of possible teratogenic effects is not known. Because fluconazole interacts with membrane phospholipids, one researcher has proposed that fluconazole may interact with growth factor receptors such as fibroblast growth factor receptors.

We recommend inclusion of the data supporting the teratogenicity of fluconazole in the Pregnancy section of the labeling. A draft of proposed language for the Pregnancy section of the labeling has been prepared by staff from the Pregnancy Labeling Team. We concur with the drafted language, except that we recommend that information be included about the cases reported to AERS. The proposed language is included in Attachment 1.

Joyce Weaver, Pharm.D.
Postmarketing Safety Evaluator
Concur:
Claudia B. Karwoski, Pharm.D.
Team Leader

Attachment 1— **PROPOSED PREGNANCY LABELING**
Teratogenic Effects. Pregnancy Category C:
Several epidemiologic studies of *in utero* exposure to fluconazole have been published. These studies provide evidence that a low single dose of fluconazole during pregnancy is unlikely to pose a substantial risk, but the data are insufficient to state that there is no risk. In a cohort study using the UK General Practice Research Database, the frequency of congenital anomalies was not increased among the infants of 234 women who received prescriptions for a single oral dose (mostly 150 mg) of fluconazole in the first trimester of pregnancy.[2] In a Danish record linkage study, no increase in the frequency of congenital anomalies was found among 121 infants of women who received first trimester prescriptions for oral fluconazole (mostly single dose of 150mg).[3] In addition, these investigators did not find evidence of elevated risk of preterm delivery or low birth weight. A prospective cohort study by Italian teratogen information services showed no increase in the frequency of congenital anomalies among the infants of 226 women treated with fluconazole during the first trimester (median dose 200mg, mostly single dose of 150mg, the primary indication for use was vaginal candidiasis).[4] No consistent pattern of anomalies was seen among the affected infants in any of these studies. However, the occurrence of a distinctive and rare pattern of congenital anomalies similar to Antley-Bixler syndrome in four children whose mothers were treated during most or all of the first trimester of pregnancy with high-dose (400-800 mg/d) fluconazole for coccidioidomycosis meningitis makes it likely that chronic high-dose fluconazole treatment in pregnancy may be teratogenic.[5,6,7] The magnitude of teratogenic risk is unknown. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. In post-marketing use, similar events have been reported with low-dose fluconazole as well. These effects are similar to those seen in high-dose rat studies.
Fluconazole was administered orally to pregnant rabbits during organogenesis in two

studies, at 5, 10 and 20 mg/kg and at 5, 25, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60 × the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 × the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.
DIFLUCAN should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

[2] Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. Pharmacotherapy. 1999;19(2):221-2
[3] Sorenson HT, Nielsen GL, Olesen C, et al. Risk of malformations and other outcomes in children exposed
to fluconazole *in utero*. Br J Clin Pharmacol 1999;48:234-9.
[4] Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after firsttrimester
exposure to fluconazole. Am J Obstet Gynecol 1996;175(6):1645-50.
[5] Lee BE, Feinberg M, Abraham JJ, Murthy ARK. Congenital malformations in an infant born to a woman
treated with fluconazole. Pediatr Infect Dis J. 1992;11(12):1062-4.
[6] Pursely TJ, Blomquist IK, Abraham J, et al. Fluconazole-induced congenital anomalies in three infants.
Clin Infect Dis 1996;22:336-40.
[7] Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report
of an additional patient. Am J Med Genet 1997;72:253-6.

Attachment 2—Line Listing of Cases Reporting Congenital Anomalies with Fluconazole

Note: Attachment 2 is a table and could not be reproduced accurately from the PDF document in DFS.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joyce Weaver
3/30/04 02:53:40 PM

DRUG SAFETY OFFICE REVIEWER
Mark Avigan
3/31/04 01:49:40 PM
DRUG SAFETY OFFICE REVIEWER

3. Summary of Pediatric cases received in the 12-months subsequent to pediatric exclusivity approval

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
Fatalities (n=4)					
4177902 7-21-04 Expedited	7 y F D FR	IV > 4 weeks Systemic Candidiasis	Neurological Disorder Eye Movement Disorder Somnolence Coma Candidiasis Infection Death Hypersensitivity Edema Reduced General Condition Dehydration Respiratory Tract Congestion Tongue Disorder Renal Insufficiency Hemoglobin Low Lymphopenia Hyperbilirubinemia Activated Partial Thromboplastin Time Decreased Central Nervous System Lesion C-Reactive Protein Increased Electroencephalogram Abnormal Respiratory Distress Fever Staphylococcus Aureus Bacteremia Infection Pseudomonas Aeruginosa Multi-Organ Failure Vitamin B1 Decreased Vitamin B6 Decreased Hemodynamic instability Blotchy Unevaluable reaction Radiation Therapy Platelet Count Abnormal	Etoposide Carboplatin Busulfan Thiotepa Multiple other products (not specified)	This physician, who is a radiotherapist, reports to a Pfizer sales representative that a 7-year-old female patient, with a history of medulloblastoma initially treated with unspecified chemotherapy (intensification doses) including busulfan (manufacturer unknown), followed two months and half later by decreased doses radiotherapy, on her posterior fossa, her cerebellum, and her cerebral trunk. The radiotherapy intensity was decreased with regards to the usual dosage and the timeline between busulfan administration and radiotherapy was increased to 2 months and half (usually around 10 days), to avoid interaction disorder as radiosensibilization between busulfan and radiotherapy. At the fourth week of radiotherapy, on an unknown date in Apr2004, the patient developed clonism of her eyes, then an important somnolence and deficiency neurologic disorders, followed by coma, leading to her to be transferred to the Resuscitate Unit and start corticoid treatment on 23Apr2004. Tumoral relapse was searched and eliminated. Fluconazole (manufacturer unknown) was administrated before and during radiotherapy. Prior to radiotherapy, fluconazole was given by intravenous route for system candidosis (dosage and start date not specified), then discontinued for unknown reasons. Several days later, the patient developed neurological disorders. Fluconazole was restarted during radiotherapy, first resumed intravenously for an unspecified period of time, then orally for three weeks because of reoccurrence of oesophageal and buccal candidosis. The patient developed infectious syndrome. The child died, date and cause not specified. According to the reporting physician, neurological disorders etiologies were either busulfan, fluconazole, or patient-dependant outcome, due to personal sensitivity of the patient.
4093853 2-17-04 Expedited	1.5 m NS D JP	35 mg IV 10 days Fungal infection	Direct Bilirubin Increased GOT Increased GPT Increased Hepatomegaly Death	Cefozopran hydrochloride	A pediatrician reports to a Pfizer sales representative that a one and a half-month-old baby started receiving Firstcin (cefozopran hydrochloride) intravenously for increased C-reactive protein in early The baby also started receiving Diflucan (fluconazole) 35 mg/day intravenousl cted fungal infection on Laboratory tests

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					on revealed increased direct-bilirubin (D-Bil), GOT and GPT. Hypertrophy of the liver was confirmed as a result of palpation. Diflucan and Firstcin were discontinued on and respectively. GPT subsequently normalized, but D-Bil did not decrease yet (over 10). The pediatrician assessed the increased D-Bil as moderate, the increased GOT and GPT as mild, and the causality of the increased D-Bil with Diflucan as unknown, stating that it was unclear whether the increased D-Bil was due to infection or the drugs because Beta-D-glucan had not been verified. Follow up ( ): This pediatrician reports that direct bilirubin increased (D-Bil) and hypertrophy of the liver were unrelated with Diflucan (fluconazole). The patient died on unrelated with Diflucan, and the cause of death is unspecified. No more information is available at present.
5712549 1-21-05 Expedited	40 d NS D IN	150 mg/d x 1 in the mother Vaginal Candidiasis in the mother	SIDS Drug exposure via breast milk	None	A gynecologist reported to a Pfizer sales representative about the infant of this approximately 32-year-old female patient. This lady patient (nursing mother) came to the reporting gynecologist with symptoms of severe vaginal candidiasis. She was prescribed Fumycin (fluconazole) 150 mg daily, caps stat (single dose). A day after, the patient's almost 40 days old infant died. The patient and her family called the physician reporting the incidence and claiming that the product information on product insert mentioned that use in nursing women is not recommended. The doctor did not hear from the patient after that incident. Follow-up ( ): Additional information from the reporting physician states, the infant was a full term baby and had no concomitant diseases. When the mother took the Fumycin the baby was fine. The baby was taken to a pediatrician. Clinical signs and symptoms manifested at the time, "comprerssed" nose and frothing from the mouth leading to asphyxia. Cause of death asphyxia probably SIDS syndrome. No Autospy was done. Per the reporting physician, the family of the infant is just co-relating the mother taking Fumycin in the evening and the infant's death the next day, she does not think that the infant's death was due to Fumycin.
4163094 6-23-04 Expedited	0 d NS D UK	150 mg/day x 1 in the mother Ill-defined disorder in the mother	Stillbirth Edwards' Syndrome Congenital Anomaly	NS	This is a regulatory authority registry report from the United Kingdom's Medicines and Healthcare products Regulatory Agency (UK-MHRA). A 34-year-old female patient received a single 150 mg dose of fluconazole on an unknown date, route and formulation not specified, for an unknown indication over 26 weeks before becoming pregnant on an

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					unknown date. The child had developed Edwards' syndrome (trisomy 18 and cardiac abnormalities) and was stillborn, date not specified. In the opinion of the UK-MHRA the events were considered serious.
Non-fatal cardiac events (n=3)					
4138267 5-7-04 4139592 5-7-04 4134637 5-18-04 4147215 6-9-04 4157292 6-10-04 4158962 6-21-04 All Expedited	11 y M LT FR	Not stated Ill-defined disorder	Tachycardia Bronchospasm Dyspnea Oxygen saturation decreased	Neupogen Solu-medrol Zovirax Omeprzole Fluconazole Cyclosporine Fortum Targocid Rivotril	Report received from a French Regional Centre for Pharmacovigilance: An 11 year old male patient underwent an unspecified graft for acute lymphoblastic leukaemia and one week later, commenced treatment with NEUPOGEN (210 mcg/day/IV). Eight days later and at the end of an infusion of NEUPOGEN, the patient developed bronchospasm leading to acute decrease in oxygen saturation for 10 minutes with tachycardia and dyspnoea. The events abated after 20 minutes following treatment with salbutamol, dexchlorpheniramine and oxygen, but the patient remained oxygen dependent for the next 24 hours. NEUPOGEN was re-introduced 48 hours later without any further problem. The events were reported to be life-threatening. Methylprednisolone, acyclovir, omeprazole, fluconazole and cyclosporine were reported as co-suspect drugs.
4113836 3-17-04 4100275 3-4-04 4132217 4-21-04 All Expedited	14 y M LT NLD	Not stated Ill-defined disorder	Cisapride Cephalosporin Vancomycin Ondansetron Lactulose Other therapeutic products (not specified) Sufentanil Thiopental Mivacurium Oxygen Nitrous oxide	QT Interval Prolonged Drug Interaction Liver Function Tests Abnormal Hemoglobin Decreased Urea Decreased Creatinine Decreased Ventricular Arrhythmia	This is a follow-up to a report based on the receipt of the English translation of the publication reported to Pfizer by Corporate Translations Inc., on 05Mar2004. Additional information reported to Pfizer on 05Mar2004 changes the classification of this report to serious and determined to be unexpected according to the USPI. This is a literature report from the Tijdschr Kindergeneeskd, 2003, Volume 71(6), pp. 246-248. The English translation has been requested. This physician reports a 14-year-old male with leukemia received general anesthesia for placement of a port-a-cath system. At the end of the procedure, he developed a ventricular tachycardia without output, which resolved after cardiac message and intravenous (IV) Lignocaine (lidocaine). This event was probably related to a prolonged QT interval due to the combination of cisapride and fluconazole (manufacturer unknown) and the volatile anesthetic sevoflurane. Follow-up (05Mar2004): This report is based on the receipt of the English translation of the publication reported to Pfizer by Corporate Translations Inc. on 05Mar2004. This anesthesiologist reports that a 14-year-old male, under the treatment for acute lymphatic leukemia, presented to the authors' hospital for what is called a port-a-cath system (central line with subcutaneous reservoir). Three days before this planned procedure, a similar infected system was removed under

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					general anesthesia without the occurrence of complications. The anesthesia questionnaire listed as medications: cephtazidim (manufacturer unknown), vancomycin (manufacturer unknown), cisapride (manufacturer unknown), ondansetron (manufacturer unknown), and lactulose (manufacturer unknown). A consolidation course of treatment with cytostatics was recently stopped in connection with liver function disturbances, Pre-operative laboratory tests showed the following values: Hemoglobin (Hb) 6.4mmol/L (range 8.2-10.2mmol/L), sodium 138mmol/L (range 135-146mmol/L), potassium 3.8mmol/L(range 3.5-5.0mmol/L), urea 0.7mmol/L (range 2.5-8.0mmol/L), creatinine 51micromol/L (range 60-110micromol/L), lactate dehydrogenase (LD) 743U/L (range 160-320U/L), aspartate aminotransferase (AST) 91U/L (range 5-30U/L), alanine aminotransferase (ALT) 173U/L (range 5-30U/L), alkaline phosphatase 122U/L (range 25-75U/L), and gamma-glutamyltransferase 153U/L (range less than 45U/L). Upon connection of the electrocarcliogram (EKG) monitor before introduction of the anesthesia, a bigeminy of ventricular extrasystoles was visible. In view of the normal results of electrolytes and the anesthesias that had been uncomplicated up until now, it was decided to continue the procedure anyway. There followed an intravenous introduction of sufentanil, thiopental and mivacurium. The trachea was intubated and the anesthesia was continued with sevoflurane (manufacturer unknown) in a mixture of oxygen and nitrous oxide. There was normoventilation during the entire procedure. After introduction, the frequency of the extrasystoles decreased. The central line was correctly positioned on the transition from the vena cava superior to the right atrium. No rhythm problems occurred with this. Upon completion of the procedure, the sevoflurane was stopped and there was a switchover to 100% oxygen. There again occurred a bigeminy of ventricular extrasystoles that changed to a regular sawtooth-shaped rhythm without output, appropriate to ventricular tachycardia. Heart massage was started immediately while the defibrillator was placed in readiness. After 60 seconds of heart massage, the patient again had cardiac output with sinus rhythm and still with the bigeminy. Initially, a possible cardiomyopathy caused by cytostatics was thought to be the cause of the problems. The sevoflurane was resumed. No indications for a pneumothorax or hematothorax were

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					seen on a quickly made chest X-ray. After 2 doses of 1mg/kg of lidocaine, the sevoflurane was again stopped. After the return of spontaneous respiration and consciousness, the trachea was extubated and the patient transported to intensive care for further diagnostics and treatment. On the EKG, a lengthened QT interval of 540ms was seen (normal value up to 440ms). There were no indications for ischemia observable on the EKG. No neurological residual phenomena from this incident were noted, On laboratory examination in intensive care, the serum electrolytes were normal. Upon further study of the patient file, it turned out that, two days before the procedure, fluconazole (manufacturer unknown) was started within the framework of selective bowel decontamination. The combination of cisapride with fluconazole was quickly connected to the ventricular tachycardia. These medications were stopped. On echocardiography, a normal heart was seen with good shortening fraction. The further course was uncomplicated. The QT interval was ultimately normalized to a value of 410ms six days after this incident. The authors' note that in connection with dyspepsia, this patient had been taking cisapride for a half a year in relatively high doses daily. It is known that cisapride lengthens the AT interval on the EKG dose-dependently as a result of lengthening the cardiac repolarization time. If cisapride is combined with medications that inhibit liver enzymes such as macrolide antibiotics, HIV protease inhibitors and anti-mycotics, especially imidazoles and triazoles, higher plasma levels are reached, and because of this, the cardiac, repolarization time further increases. Fluconazole, an anti-mycotic of the triazole group, inhibits biotransformation (via the P450 system), which results in higher plasma levels of cisapride. Simultaneous administration of these drugs is contraindicated at all times, in connection with the risk of the occurrence of life-threatening arrhythmias. It is also known that various volatile anesthetics can lengthen QT interval. In this patient, there existed no electrolyte disturbances and there was no cardiacischemia as a cause of the rhythm problems. The decrease in ventricular extrasystoles after introduction of the anesthesia can be explained by a decrease in stress. This was also the reason for resuming the sevoflurane upon the occurrence of ventricular tachycardia. The authors feel that in this patient, the combination of cisapride and fluconazole caused a lengthening of the cardiac

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					repolarization, This increase in seriousness because of liver function disturbances through which the plasma levels of both drugs was increased, in addition to adding the vaporized anesthetic sevoflurane, of which lengthening of the QT interval, has also been described as a side effect. The increased stress on stopping sevoflurane functioned as a trigger for the occurrence of ventricular tachycardia. It is of great importance to be informed about medications that lengthen the QT interval. A combination of these drugs should be especially avoided.
4180800 7-27-04 Direct	15 m M LT US	Not stated One dose Not stated	Supraventricular tachycardia Lethargy	Not stated	SVT secondary to fluconazole Pt received dose 17:30 - Mom noticed lethargic and felt tachy to ER - HR 280BPM Adenosine x 3 - with recurrence oral propranolol Pt converted when ice towel to face applied D/Ced home 7-24 with F/U for cardiac testing
Non-fatal congenital anomaly (n=3)					
4162504 6-23-04 Expedited	1 d M CA UK 150	150 mg/d x 1 in the mother Ill-defined disorder in the mother	Hypospadias Scrotal disorder Congenital Anomaly	None	This is a regulatory authority registry report from the United Kingdom's Medicines and Healthcare products Regulatory Agency (UK-MHRA), authority ID number 473606. This healthcare professional reports that a female patient of unknown age and weight received a single 150mg dose of fluconazole (brand unspecified) with formulation and indication unknown, approximately eight weeks before getting pregnant on an unknown date. Her male child of unknown weight was born on an unknown date with proximal hypospadias and a bifid scrotum (scrotal disorder). The outcome of the events is unknown. It is reported that the mother was not receiving any other drugs during her first trimester of pregnancy. In the opinion of the UK-MHRA the events were assessed as serious (reasons unspecified).
4163097 6-23-04 Expedited	Not stated UK	150 mg x1 in mother Ill-defined disorder in the mother	Syndactyly Finger hypoplasia Congenital Anomaly	None	This is a regulatory authority registry report form the Uninted Kingdom's Medicines and Healthcare products Regulatory Agency (UK-MHRA), authority ID number 473608. This healthcare professional reports that a female patient of unknown age and weight received a single 150 mg dose of fluconazole (formulation not specified) on an unknown date for an unknown indication one week prior to becoming pregnant on an unknown date. Her child of unknown sex and weight was born on an unknown date with minor webbing of two finger (syndactily)and three short fingers on the other hand (finger hypoplasia). It is reported that the mother was not receiving any other drugs during the first trimester of her pregnancy. In the opinion of the UK-MHRA the events were assessed as serious (reasons unspecified)

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
5653040 10-18-04 Direct	Few days US	Not stated Not stated	Congenital microcephaly Blindness Cataract Small body size	Isoniazid Pyridoxine Other medications not identified	Female baby was born on 1 in at 38 tation with weight only 3lb. Diagnosed with congenital microcephaly few days after birth. Pregnancy was normal and stated on all prenatal documentations. Genetic, chromosomal and infections testing were done at the hospital and came back all negative. No cause was found. Since it appeared in is not genetic problem, the treatment during the pregnancy had to be reviewed more closely. As a pregnant mother I received Tuberculin test which was recorded as positive by the nurse. The previous testings were all negative. Being raised in Europe I have BCG vaccine in my past which the hospital knew about since it is recorded in their records. The tuberculin test was never repeated. Medications were prescribed right away without further testing or any kind of safety counseling. Mediations including isoniazid, Diflucan, Pyridoxine + other. If Isoniazid is in CATEGORY C, why it would be prescribed to a fully healthy woman and putting the fetus at risk? Another drug prescribed DIFLUCAN is NEVER STUDIED IN PREGNANT WOMEN???[As stated in most medical literature] If a drug is never studied during pregnancy, how do you know the outcome? Why prescribe it? What am I? How can someone test a drug on my unborn baby? May be this is a question for the person who prescribed it? X-Rays were done TWICE IN THE SAME DAY at 10th week of gestation during pregnancy X-Rays were NEGATIVE. Everywhere is stated between 8th and 15th week X-Rays are not performed unless necessary. Why should a healthy pregnant woman have X-RAYS and put her unborn child at risk? Medications that are NOT PROVEN TO BE SAFE given during pregnancy for NO REASON??? Female baby girl born at 38 weeks with weight 3 lb. having congenital microcephaly, blindness , cataracts, small body size, which means she is not growing, mentally disabled, physically disabled, socially disabled currently 3 years and 3 months having the size of a newborn baby, her head size is even smaller then a newborn baby, not able to crawl, sit, turn, eat on her own, walk talk, nothing. Nothing at all. Disabled at the most severe degree you can imagine. More then 33% delays in every activity examined twice by Early Intervention Program and many doctors. Does someone care about that? Medications not proven to be safe given during pregnancy? Thank you for reading this, Hope you can help. Thank you.
Non-fatal metabolic events (n=2)					

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
4086895 2-25-04 Expedited	4 y M LT JP	50mg Fungemia	None	Blood sugar decreased	This is a follow-up report based on information reported to Pfizer on . The initial report wa submitted to the Us FDA on A pediatrician reported to a Pfizer sales representative that a 4-year-old male patient with a current history of Hirschsprung's disease was started in the beginning of Nov 2003 on treatment with intravenous "diflucan (fluconazole) 50 mg/day for a fungaemia. In Dec 2003 his blood sugar tended to decrease g/dL to 70 mg/dL. Around his blood sugar stayed about 40mg/dL to 80 mg/dL for about a week. Diflucan treatment was continued. No accompanying signs or symptoms were noted. At the time of the report he had not recovered from the adverse event. The reporting pediatrician considered the severity of the adverse event as mild and the event as unlikely to be related to Diflucan. No more information is available. Follow-up : The pediatrician reports that Diflucan (fluconazole) was stopped on the _____ The event was reported as ing and the patient recovered. Patient's history includes Hirschspring's disease and enterostomy. Laboratory tests revealed on a blood sugar result of 113 mg/dL, on a result of 62 mg/dL, on a result of 52 mg/dL, on a result of 41 mg/dL, on a result of 40mg/dL, and on a result of 92mg/dLl. The reporter assessed the event as unrelated to Diflucan. No more information is available at present.
4125746 4-15-04 Expedited	5 y M LT JP	200 mg qd x 9 days Prophylaxis	Zovirax Carbenine Pepcid Flucytosine NIdran Baktar Oncovin	Anuria Convulsion Diabetes Insipidus Encephalitis Gastric Ulcer Herpes Zoster Hyponatremia Meningitis Respiratory Arrest	Information has been received from a physician via Yamanouchi Pharmaceutical Co. Ltd (manufacturer control # 200305946) as part of a business agreement concerning a 5 year old hospitalized male with medulloblastoma, severe hydrocephalus (from , and severe neutropenia (from) and a history of tumorectomy of the cerebral tumor (on), radiation therapy (and chemotherapy who on was placed on therapy with famotidine, injection (form), 10 mg, twice a day for the treatment of a gastric ulcer. Concomitant suspect therapy included vincristine sulfate (ONCOVIN) 1.1 mg on or the treatment of cerebral tumor; fluconazole (DIFLUCAN), 200 mg daily for Fungitis prevention from 4 and acyclovir (Zovirax), 540 mg daily from for the treatment of herpes zoster. Other concomitant therapy included betamipron (+) panipenem (CARBENIN), nimustine hydrochloride

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					(NIDRAN), flucytosine, and sulfamethoxazole (+) trimethoprim (BAKTAR). At 5:00 am on 04 the patient's SpO2 dropped to the 80's%. Oxygen therapy was initiated. At 6:35 am, he developed clonic contraction in the right lower limb then systemic seizure. At 6:45 am, chloral hydrate (ESCRE) suppository was administered. At 7:00 am, the seizure was terminated with diazepam (CERCINE). At the same time, respiratory arrest occurred. It was considered that the patient's respiratory arrest was due to the seizure. The patient's sodium was 117 mEq/L. There was no change in CT and the patient was accommodated in the ICU. The patient did not produce any urine between the hours of 6:00 and 10:00 am. However, at 10:00 am urine output was resumed with a color of "pretty light". At 12:00 noon, urine output was 200-300 ml/hour and urinary osmolarity was 28 and serum sodium was 128 mEq/L. The patient was diagnosed with diabetes insipidus and water was supplemented. At 8:00 pm, vasopressin (PITRESSIN) was loaded and then desmopressin was administered twice. The symptom gradually abated, not needing desmopressin any longer and the patient's sodium level improved. On , therapy with famotidine was discontinued (reason not specified). On therapy with midazolam (DORMICUM) was discontinued. The patient's serum sodium was 139 mEq/L. he was extubated a ed from ICU the next day. He did not speak as much as before. The movement of the four limbs gradually abated although weak. It was judged that the symptoms abated on . Hyponatremia, seizures, diabetes insipidus and respiratory arrest were considered to be immediately life-threatening. The reporter felt that hyponatremia, seizures and diabetes insipidus were not related to therapy with famotidine. The reporter felt that vincristine sulfate was likely to be responsible. The reporting physician wants to ascertain a suspect drug, as treatment will continue. The reporting physician stated that probably famotidine has no causal relationship. Vincristine sulfate (Oncovin) is likely to be responsible. The three possible causes were suspected, (1) meningitis, (2) encephalitis/encephalopathy and (3) drug. As there was no change in MRI, CT and CSF test and herpes zoster was improving on , meningitis and enc phalopathy are unlikely although not completely deniable. Among the drugs administered vincristine sulfate is most suspected. Fluconazole

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					(DIFLUCAN) and (ZOVIRAX) are also suspected. However, famotidine is unlikely to be responsible. Recovery of diabetes insipidus, although temporarily, may be related with reserve capacity of the patient. Additional information is not expected.
Non-fatal overdose/medication errors (n=2)					
5752876 2-28-05 Direct	3 m M Not stated US	Not stated x 1 dose Thrush	Not stated	Not stated	Prescription faxed to pharmacy filled in the wrong concentration. Correct concentration 10 mg/ml filled as 40 mg/ml. Medication delivered in the evening and sent to Group Home. Dose given correctly but because of wrong concentration overdose given.
4167774 6-28-04 Expedited 4107600 3-12-04 Direct 4158902 6-17-04 Direct 4089856 2-10-04 Direct	3 m F H US	2.5 teaspoons (125 mg) x 3 days Thrush	Medication error Dehydration Discomfort	Not stated	This 3-month old female with a 3 week history of upper respiratory tract infection, nausea, vomiting and diarrhea, was directed to take Diflucan (fluconazole) 2.5 teaspoons once per day instead of the prescribed 2.5 mls once per day. The child required hospitalization later that week, but it is unclear whether the overdose of Diflucan was the sole reason, since she was already suffering from an upper respiratory tract infection, otitis media and nausea/vomiting before the script was written. The dosing error may have "pushed her over the edge" to get admitted. While hospitalized the patient was treated with IV fluids on Thursday and Friday of the same weeks for dehydration and was receiving Tylenol (acetaminophen) for her discomfort. This is a medication error by the pharmacy (a national community chain). The store apparently did not have enough medication to fill the prescription completely; therefore the patient was given a partially filled prescription with instructions to return for the remaining. Three days later the consumer returned for the remainder of the prescription which the store failed to obtain. So she went to another store, which the pharmacist initially refused to fill an already partially filled prescription. However, the pharmacist acquiesced and agreed to fill the remainder of the prescription. In doing so, the pharmacist discovered that he instructions on the prescription were incorrect.
Non-fatal fungemia (n=2)					
5703403 12-27-04 Expedited	13 y F H, OT US	NS Antifungal prophylaxis	Cancer Zygomycosis	VFend	This physician reported to a Pfizer sales representative that this 13-year-old female with a history of cancer, had a relapse of her cancer in early October. At an unknown time this child was started on Diflucan (fluconazole) for antifungal prophylaxis and then was switched (reason not reported) to a low dose of Vfend (voriconazole) also for antifungal prophylaxis. The patient developed a dual fungal infection, zygomycosis, one of the

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					pathogens is Aspergillosis and other pathogen is unknown. It is not known when the zygomycosis began. The child is currently hospitalized under palliative care. Follow-up : The Quality Analysis, mplaints group provided the national drug code, 0049-3410-00, for Diflucan 50mg tablet. Follow-up : The Quality Analysis, Product Complaints group provided the national drug code, 0049-3180-30, for Vfend 200mg tablet.
5680133 11-12-04 Expedited	5 m M H US	6mg/ Kg x 3 wks Fungemia	Fungemia Drug ineffective	Not stated	This physician reports a 5-month-old male infant was started on Diflucan (fluconazole) 6mg/kg (therapy dates, formulation and exact dosage unknown) for a Candida paripsilosis fungemia due to an infected catheter. The duration of the therapy was 3 weeks, and patient is still fungemic at an unknown date. Physician stated that he did not believe Diflucan was inefficacious. Follow-up (: This is a follow-up from the same physician who reports that the lot number and expiration date are unknown. The NDC number is 0049-3440-19. Follow-up (This physician reports that the patient treated with oral fluconazole experienced a failure to cure fungemia. The patient had repeated positive blood cultures for a sensitive fungus when given oral fluconazole. The reason for the failure was the patient's history of malrotation, extensive intestinal re-section, short gut, and did not have enough gut surface to absorb. The failure to cure fungemia resolved with one treatment. The outcome was prolonged hospitalization.
Non-fatal hepatic events (n=2)					
5687896 11-24-04 Direct	6 m M RI US	28 mg x1, then 14 mg q d x 3 d Prophylaxis for candidemia	LFTs abnormal	Tobramycin Timentin Vancomycin Septra	A 6 month old male experienced significant elevation in LFTs following treatment with fluconazole for severe fugal diaper dermatitis. Fluconazole was used to prevent Candidemia since patient had to have femoral access line placed. When problem was detected fluconazole was discontinued and clotrimazole cream initiated. Fluconazole doses were listed a 28 mg IV once x 1 day (, then 14 mg orally daily x 3 days (hrough AST and ALT values on were 2221 and 1291, respectively.
4075521 1-30-04 Expedited	16 F H FR	5 days Fever associated with infection	Alanine aminotrasnferase inc. Aspartate aminotransferase inc. Cholestasis Cytolytic hepatitis Escherichia infection Leukopenia Neutropenia Pyrexia Streptococcal infection	Amiklin inj Tazocilline Vancomycin Rocephin'Flagyl Tienam Ciflox	A physician reported to BMS France (2004-0104) via the French Health Authority (TS0300474) that a 16 year old female patient experienced neutropenia, leucopenia, increased serum glutamic oxaloacetic transaminase and increased serum glutamic pyruvic transaminase, and hepatic cytolysis and cholestasis while receiving amikacin, piperacillin + tazobactam, fluconazole and vancomycin therapies. On , the patient was hospitalized for surgical treatment of

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receipt date Report type	**Age Sex Out Country**	**Dose Duration of therapy Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
					appendicular peritonitis. She received treatment at that time with intravenous ceftriaxone and metronidazole. On - she developed a sub-phrenic abscess caused by Enterococcus faecalis and Vellonella species. On , ceftriaxone and metronidaz discontinued, treatment with intravenous piperacillin + tazobactam and intravenous amikacin were initiated. On intravenous vancomycin was initiated and on amikacin was discontinued. The patient still had a persistent fever so on piperacillin + tazobactam was discontinued, cilastatin + imipenem and metronidazole therapies were initiated. Laboratory information showed a white blood cell count (WBC) of 10.6 x10E9/L and neutrophil count of 7.66 10E9/L. On she underwent a laparotomy ed streptococcus argyrosus, escherichia coli and anaerobic germs. Because of persistent fever, ciprofloxacin and fluconazole were added on _____ Laboratory tests from tha re ive for cytomegalovirus and Epstein-Barr virus. On , the patient developed leuc epatic cytolysis. Laboratory information from showed a WBC of 3.4 trophil at 2.67 x10E9/L, aspartate aminotransferase (ASAT) at 3 xULN, and alanine aminotransferase (ALAT) of 2.5 xULN. The events worsened on with laboratory va 2.2 x10E9/L, neutrophils at 0.97 x10E9/L, ASAT at 5.4 xULN, ALAT at 1.7 xULN, and gamma-glutamyl transpeptidase (gamma-GT) at 8xULN. She also experienced cholestasis. All treatments were discontinued, and she was admitted to the intensive care unit of the hospital. On treatment with metronidazole, cilastatin/imipenem and ciprofloxacin were restarted. On her condition was improving. tests from that day showed a WBC of 2.1 x10E9/L, neutrophil at 0.44 x10E9/L, ASAT at 9 xULN, ALAT at 37 xULN, and gammaGT at 15 xULN. By she had almost completely cording to the French methodology of causality assessment, drug relationship was "unable to determine" for amikacin, piperacillin + tazobactam, fluconazole and vancomycin therapies.
Non-fatal hypersensitivity events (n=1)					
5658161 10-27-04 Direct	12 y M NS US	200 mg /d 3-4 days Valley fever	Rash Generalized body swelling Dry skin Skin fissures	NS	Was given generic Diflucan broke out with a rash. Belly button area got dry and caked, and body became swollen stopped taking generic rash went away.

Country abbreviations: FR= France, IN=India; JP=Japan; NLD= Netherlands; UK= United Kingdom; US=United States

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Evelyn Farinas
4/20/05 04:16:09 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
4/22/05 10:10:02 AM
DRUG SAFETY OFFICE REVIEWER