M E M O R A N D U M SERVICES

#### DEPARTMENT OF HEALTH AND HUMAN

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

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DATE:	April 15, 2005
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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

#### **<u>1. EXECUTIVE SUMMARY</u>**

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

<sup>1</sup> May include duplicates

<sup>2</sup> Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

<sup>3</sup> 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 <sup>1</sup>		
Number of cases, all ages <sup>2</sup>	Year	Number of pediatric cases (0-16 years) <sup>3</sup>
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
<sup>1</sup> Raw counts, may include duplicates	•	·

 $^{2}$  May include reports where age was not specified

<sup>3</sup> Only includes reports where age was listed in the pediatric age grouping of 0-16 years



#### <u>Top 20 reported event PTs and labeling status of these events (underlined denotes</u> <u>unlabeled events):</u>

Table 3: Counts of top 20 reported events (preferred terms) through February 28, 2005 <sup>1</sup>		
	Top 20 preferred terms	Counts
All ages (including reports where	Drug Ineffective	671
no age was provided)	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 ( $\geq 17$ 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 <sup>1</sup>		
	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	24
	Therapeutic Drugs	
	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
<sup>1</sup> Raw counts include terms from dur	licate 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 <sup>1</sup> 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 <sup>2</sup> (US)	Death (US)
All ages <sup>3</sup>	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 <sup>2</sup> Serious outcomes per regulatory definition, which includes death, hospitalization, life threatening			

Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other. <sup>3</sup> Includes reports where age was not specified

#### <u>Top 20 reported event PTs and labeling status of these events (underlined indicates</u> <u>unlabeled):</u>

Table 5: Counts of top 20 reported events (preferred terms) derived from line listings<sup>1</sup> - from date of pediatric exclusivity through AERS cut off date of February 28, 2005 [includes events mentioned more than twice]<sup>2</sup>

	Ton 20 preferred terms	Counts
All ages (including reports where	Drug Interaction	42
age is not specified )	Drug interaction	30
(total number of adverse events	Aspartate Aminotransferase Increased	26
(total number of adverse events) reported = $820$ )	Alanine Aminotransferase Increased	20
reported 620)	Thrombocytopenia	23
	Ventricular Techycardia	20
	Condition Aggravated	18
	Dyspnea	18
	Condidiasis	17
	Electrocardiogram Ot Prolonged	17
	Blood Alkaline Phosphatase Increased	15
	Blood Creatining Increased	15
	Multi Organ Failure	15
	Nousce	15
	Convulsion	13
	White Plead Call Count Decreased	14
	Plood Diliguhin Increased	14
	Digginage	13
	Dizzilless Drug Exposure During Bragnoney	13
	Drug Exposure During Pregnancy	13
$\mathbf{A} = \mathbf{A} + $	Drug Interestion	15
Adults $(\geq 1 / \text{years})$	Drug Interaction	38
(total number of adverse events $-725$ )	<u>Pyrexia</u>	29
reported = 725)	Aspartate Aminotransferase Increased	25
	Throw he system on is	22
	Condition A grounted	17
	Ventricular Techycordia	17
	<u>Ventricular Tachycardia</u>	1/
	Neuros	10
	Dlood Allealing Dhognhotoga Ingrouped	13
	Diood Aikaine Phosphatase increased	14
	Blood Creatinine increased	14
	White Diagd Call Count Deersond	14
	Dimine Blood Cell Could Decleased	13
	Dizzilless Electropordiogram Otherelanged	13
	Enectrocardiogram Qt protonged	13
	Bruritus	13
	Commo Clutomultronsforaço Increased	12
	L aukanonia	12
	Devel Impoirment	12
Dediatrias (0, 16 years)	Renai inipariment	12
(total number of adverse events)	Dusphen	6
(101a1  humber of adverse events)	Techycordia	6
reported – 113)	<u>I activitation</u>	5
	Ovugen Saturation Degraged	5
	Alapina Aminotransforma Increased	
	Againet Aminou ansierase Increased	
	Aspanate Annouansierase increased	
		5

Table 5: Counts of top 20 reported events (preferred terms) derived from line listings' - from date of		
pediatric exclusivity through AERS cut off date of February 28, 2005 [includes events mentioned more than		
twice	TE 20 6 14	<u> </u>
	1 op 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
1	Ventricular Extrasystole	2
<sup>1</sup> Raw counts include terms from	n duplicate reports	
$^{2}$ The following events were me	entioned only once in the pediatric populati	on (0-16 years):
Activated Partial Thromboplastin Tin	ne Shortened, Anuria, Aspergillosis, Asphyxia, Atax	xia, Bacterial Culture
Positive, Balance Disorder, Bilirubin	Conjugated Increased, Blepharospasm, Blindness C	Congenital, Blood
Alkaline Phosphatase Increased, Bloc	d Bilirubin Abnormal, Blood Creatinine Decreased	, Blood Glucose
Decreased, Blood Lactated Dehydrog	enase Increased, Blood Pressure Decreased, Blood	Urea Decreased,
Cardiomyopathy, Cataract Congenita	l, Cholestasis, Coma, Condition Aggravated, Conge	nital Neurological
Disorder, Convulsion, Cytolytic Hepa	atitis, Developmental Delay, Diabetes Insipidus, Dip	olopia, Discomfort,
Disease Recurrence, Drug Ineffective, Drug Interaction, Drug Level Increased, Dry Skin, Electroencephalogram		
Abnormal, Encephalitis, Escherichia	Infection, Finger Hypoplasia, Fungemia, Gamma-G	lutamyltransferase
Increased, Gastric Ulcer, General Phy	vsical Health Deterioration, Growth Retardation, He	modynamic Instability,
Haptoglobin Increased, Heart Disease Congenital, Heart Rate Increased, Infection, Lethrargy,		
Leukopenia, Liver Function Test Abr	ormal, Lymphopenia, Meningitis, Microcephaly, M	lulti-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 <sup>1</sup>		
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 patien	ts. not the mothers.	

#### <u>Labeling status of the top 20 reported adverse events and comparison to adult</u> <u>adverse event profile during the pediatric exclusivity period</u>

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.

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	

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

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<sup>1</sup>. Liver enzymes values returned to normal after both drugs were discontinued. The cause of death was not

<sup>&</sup>lt;sup>1</sup> 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<sup>2</sup>. 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<sup>3</sup>.

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,

<sup>&</sup>lt;sup>2</sup> 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)

<sup>&</sup>lt;sup>3</sup> 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.

#### <u>Summary of the 15 non-fatal pediatric cases during the pediatric exclusivity period</u> <u>by adverse events</u>

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	

#### Cardiac events (n=3):

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.

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	

#### Congenital anomalies (n=3)

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<sup>th</sup> 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<sup>4</sup>, 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<sup>5</sup>. 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.

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	

#### Metabolic events (n=2)

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.

<sup>&</sup>lt;sup>4</sup> 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"]

<sup>&</sup>lt;sup>5</sup> 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.

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	

#### Overdose/Medication errors (n=2)

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.

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	

#### Fungemia (n=2)

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<sup>6</sup>.

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

<sup>&</sup>lt;sup>6</sup> 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)
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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.

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

#### Hypersensitivity events (n=1)

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.

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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  $\mu$ g/mL (range: 4.12 to 8.08  $\mu$ g/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  $\mu$ g/mL (range: 1.57 to 3.65  $\mu$ g/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 multipledose 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 <sup>3</sup>. 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

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intravaginally for 7 days) both clinically and statistically at the one month posttreatment 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.

	<u>Fluconazole</u>	<u>Nystatin</u>
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)

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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 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

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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 Vomiting Abdominal pain Nausea Diarrhea	13.0 5.4 2.8 2.3 2.1	9.3 5.1 1.6 1.6 2.2
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#### 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.

#### 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 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.

#### 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.
- 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  $20-60 \times$  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  $20-60 \times$  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: 0.37-3.79). *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

Event year

#### 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

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
1 0	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 or	igin 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
Duratio	1  dose-28
Durutte	2 doses-7
	2 doses-3
	1 doses 1
	4 uoses-1 Throughout programmy 2
	of the second pregnancy-2
TT ( 1	Other, or not reported-21
l otal e	xposure 150mg-25
	200mg-1
	300mg-7
	450mg-2
	600mg-1
	1000mg-1
	>100grams-1
	Not reported-24
Anomalies	Hynosnadias (2)
1 momunes	Polydactyly/syndactyly (6)
	Syndactyly of 3rd and 4th fingers of left hand and partial syndactyly of 3 <sup>rd</sup> and 4th toes of left
	foot
	Poly- or syndactyly
	Duplicate thumbs on one hand
	nhalanx 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 progenital system"
	Hydronenhrosis
	Multicystic dysplastic kidney 9
Table 1—Cha	practeristics of 62 Cases Reporting Congenital Anomalies with
Fluconazole	in acteristics of 02 Cases reporting Congenitar Anomanes with
Fluconazoic	Cleft lin/nalate (3)
	Limb defects (7)
	Malformed bones in fingers ("pinkies" do not bend)
	Severe shortening of all limbs
	Phocomelia (absent hand and forearm)
	l alipes valgus
	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
	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, andMusculoskeletal 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 N	on-US-23 <sup>.</sup> US-14
Indication	Vaginal candidiasis-12
Individuation	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 0
Timing of ovnosura	Not reported-9
T ming of exposure	During programay
	During pregnancy Defers concention 1
	Weeks 1 through 4 16
	Weeks I unough 4-10
	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
<b>D</b> 11 1	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, andMusculoskeletal Congenital Anomalies with FluconazoleTotal exposure150mg-13

Total exposure	150mg-13
1	200mg-1
	300mg-5
	450m ~ 1
	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
	Faitial Syndactyry
	Malformed bones in fingers ("ninkies" do not hend)
	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
	agenesis of external genitalia, anal agenesia
	Encenhalocele 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
	and thin digits
	Musculoskeletal abnormality (unspecified) facial abnormalities including
	"unslanted eves 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 toramen ovale, ventricular septal detect, craniofacial dysproportion,
	osteopenia with thin fraghe bones, exotropia, nydrocephaius, 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.

<sup>2</sup> Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. Pharmacotherapy. 1999;19(2):221-2

<sup>3</sup> 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.

<sup>4</sup>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.

<sup>s</sup> 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.

<sup>6</sup> Pursely TJ, Blomquist IK, Abraham J, et al. Fluconazole-induced congenital anomalies in three infants.

Clin Infect Dis 1996;22:336-40.

<sup>7</sup> 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.

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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 #	Age	Dose	Adverse Events	Concomitant	Comments/Summary of case	
Receipt	Sex	Duration of		drugs		
date	Out	therapy				
Report type	Country	Indication				
Fatalities (n=	4)					
4177902	7у	IV	Neurological Disorder	Etoposide	This physician, who is a radiotherapist,	
7-21-04	F	>4 weeks	Eye Movement	Carboplatin	reports to a Pfizer sales representative that	
Expedited	D	Systemic	Disorder	Busulfan	a 7-year-old female patient, with a history	
	FR	Candidiasis	Somnolence	Thiotepa	of medulloblastoma initially treated with	
			Coma	Multiple other	unspecified chemotherapy (intensification	
			Candidiasis	products (not	doses) including busulfan (manufacturer	
			Infection	specified)	unknown), followed two months and half	
			Death		later by decreased doses radiotherapy, on	
			Hypersensitivity		her posterior fossa, her cerebellum, and	
			Edema		her cerebral trunk. The radiotherapy	
			Reduced General		intensity was decreased with regards to the	
			Condition		usual dosage and the timeline between	
			Deliyulation Despiratory Treat		busunan administration and radiotierapy	
			Congestion		(usually around 10 days) to avoid	
			Tongue Disorder		interaction disorder as radiosensibilization	
			Renal Insufficiency		between busulfan and radiotherany At	
			Hemoglobin Low		the fourth week of radiotherapy on an	
			Lymphopenia		unknown date in Apr2004, the patient	
			Hyperbilirubinemia		developed clonism of her eyes, then an	
			Activated Partial		important somnolence and deficiency	
			Thromboplastin Time		neurologic disorders, followed by coma,	
			Decreased		leading to her to be transferred to the	
			Central Nervous		Resuscitate Unit and start corticoid	
			System Lesion		treatment on 23Apr2004. Tumoral relapse	
			C-Reactive Protein		was searched and eliminated. Fluconazole	
			Increased		(manufacturer unknown) was	
			Electroencephalogram		administrated before and during	
			Abnormal		radiotherapy. Prior to radiotherapy,	
			Respiratory Distress		<u>Iluconazole was given by intravenous</u>	
			Stanhylasasaya		start data not aposified), then discontinued	
			Aureus Bacteremia		for unknown reasons. Several days later	
			Infection		the patient developed neurological	
			Pseudomonas		disorders Eluconazole was restarted	
			Aeruginosa		during radiotherapy first resumed	
			Multi-Organ Failure		intravenously for an unspecified period of	
			Vitamin B1		time, then orally for three weeks because	
			Decreased		of reoccurrence of oesophageal and buccal	
			Vitamin B6		candidosis. The patient developed	
			Decreased		infectious syndrome. The child died, date	
			Hemodynamic		and cause not specified. According to the	
			instability		reporting physician, neurological disorders	
			Blotchy		etiologies were either busulfan,	
			Unevaluable reaction		fluconazole, or patient-dependant	
			Radiation Therapy		outcome, due to personal sensitivity of the	
			A hnormal		patient.	
			Autorina			
4093853	15m	35 mg IV	Direct Bilirubin	Cefozonran	A nediatrician reports to a Dfizer sales	
2-17-04	NS	10 days	Increased	hydrochloride	representative that a one and a half-month-	
Expedited	D	Fungal	GOT Increased	nyuroemonue	old baby started receiving Firstein	
Expedited	IP	infection	GPT Increased		(cefozopran hydrochloride) intravenously	
		meenon	Hepatomegalv		for increased C-reactive protein in early	
			Death		The baby also started receiving	
					Diflucan (fluconazole) 35 mg/dav	
					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 #	Age	Dose	Adverse Events	Concomitant	Comments/Summary of case
Receipt	Sex	Duration of		drugs	
date Demonstrations	Out	therapy			
Report type	Country	Indication			on revealed increased direct
					on revealed increased direct- bilirubin (D-Bil), GOT and GPT. Hypertrophy of the liver was confirmed as a result of palpation. <u>Diflucan and</u> <u>Firstcin were discontinued on</u> <u>and respectively</u> . 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
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	available at present.         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, "compressed" 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 III-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). <u>A 34-</u> year-old female patient received a single <u>150 mg dose of fluconazole on an</u> <u>unknown date, route and formulation not</u> 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
	country	multation			<u>unknown date</u> . 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 car	diac events	(n=3)			1
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
4113836 3-17-04 4100275 3-4-04 4132217 4-21-04 All Expedited	14 y M LT NLD	Not stated III-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	Were reported as co-suspect arugs.This is a follow-up to a report based onthe receipt of the English translation of thepublication reported to Pfizer byCorporate Translations Inc., on05Mar2004. Additional informationreported to Pfizer on 05Mar2004 changesthe classification of this report to seriousand determined to be unexpectedaccording to the USPI. This is a literaturereport from the Tijdschr Kindergeneeskd,2003, Volume 71(6), pp. 246-248. TheEnglish translation has been requested.This physician reports a 14-year-old malewith leukemia received general anesthesiafor placement of a port-a-cath system. Atthe end of the procedure, he developed aventricular tachycardia without output,which resolved after cardiac message andintravenous (IV) Lignocaine (lidocaine).This event was probably related to aprolonged QT interval due to thecombination of cisapride and fluconazole(manufacturer unknown) and the volatileanesthetic sevoflurane. Follow-up(05Mar2004): This report is based on thereceipt of the English translation of thepublication reported to Pfizer byCorporate Translations Inc. on05Mar2004. This anesthesiologist reportsthat a 14-year-old male, under thetreatment for acute lymphatic leukemia,presented to the authors' hospital for whatis called a port-a-cath system (central linewith subcutaneous reservoir). Three daysbefore this planned procedure, a similar

Table 1A – Su	ummary of A	AERS pediatric	cases received during th	ne 1-year following a	pproval of pediatric exclusivity
Case #	Age	Dose	Adverse Events	Concomitant	Comments/Summary of case
Receipt	Sex	Duration of		drugs	
date	Out	therapy			
Report type	Country	Indication			
iteport type	country	multution			general anesthesia without the occurrence
					of complications. The anesthesia
					questionnaire listed as medications:
					application (manufacturer university)
					veneemuein (manufacturer unknown),
					vancomych (manufacturer unknown),
					cisapride (manufacturer unknown),
					ondansetion (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
					135-146 mmol/L), potassium
					3.8mmol/L(range 3.5-5.0mmol/L), urea
					0./mmol/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

Case #         Age Dose         Dose therapy         Adverse Events         Concomiant         Comments/Summary of case           Receipt date         Out         Indication         seen on a quickly made chest X-ray. After 2 dose of Imp/kg of lidocaine, the creation of populareous respination conscionsess, the trachea was extubated and the patient transported to intensive care for further dignostics and treatment. On the EKG, a lengthened QT intensive intensive of the trachea was extubated and the patient transported to intensive care for further dignostics and treatment. On the EKG, a lengthened QT intensive intensive was another on the second date was neared. On about on the second date was neared. On about on the second date was neared. In about on the second date was neared. In about on the procedure fluctuations for inschem about on the date of the second date phonoment must includent was neared. On labout on the care of the second cannot fluctuate the procedure fluctuations for inschem about on the date of the base form the patient fluctuations for inschem about the track of the base form the procedure fluctuations for inschem about on the track of the base form the patient fluctuation for inschem about the track of the base form the procedure fluctuation for inschem about the track of the base form the patient fluctuation for inschem about the second the track of connecting the second the second transmitter makeware tracked in the second the second transmitter further corres: was uncomplicated. The tracked of the start was an the EKG dose-dependently as a result of the date of a half a year in relation at an intensity of the start of the corres of the further at an intense of a second anti-invortion in the EKG dose-dependently in the Start the author's not that in connected at inschem and anti-invortion, the dependent the the stare of the start and the trat of the corres of this, the	Table 1A – Su	ummary of A	AERS pediatric	cases received during th	e 1-year following a	pproval of pediatric exclusivity
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return of spontaneous regimtion and consciousness, the trachen was extributed and the patient transported in diamonal Constructions and treatment. On the EKG, a lengthened (7) interval of 540ms was seen (normal value up to 440ms). There were no indications for ischemic and period and the test of the test of the test of the test of the test of the test of examination in intensive care, the serum electrolytes were normal. Upon further study of the patient file, it turned out that, wo dave before the pracedure. Inconzolet furnification discontrol of the seruit study of the patient file, it turned out that, wo dave before the pracedure. Inconzolet furnification of cisaparide with fluconzole was aquickly connected to the ventricular tachycandia. These medications were stopped on electorytes was started within the framework of selective bowed docontamination. The combination of cisaparide with fluconzole was aquickly connected to the ventricular tachycandia. These medications were stopped on electorative was uncomplicated. The Q1 interval was ultimately noncerion with dyspesia, in patient had been taking cisaparide for a hair a year in relatively high dosss days after this incident. The authors' note that in conscription rule cisaparide is combined with medications that a year in classical high doss days along that a year in classical biotransformation in the EKG dose-dependently, as a result of lengthems the AT interval on the EKG dose-dependently, as a result of lengthems the AT interval on the EKG dose-dependently, as a result of lengthems the AT interval on the EKG dose-dependently as a result of lengthems the AT interval on the EKG dose-dependently as a result of lengthems the AT interval and an in- mycortic of the trizzole groupination time. If cisaparities in higher playmating as the as may along the result and be matching and as a result of the dose and microse, in connection with the risk of at all interval. The authors feel that in this play test for the playmane here the another and the reverase no cardit						sevoflurane was again stopped. After the
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combination of cisapride and fluconazole						autions reer that in this patient, the
caused a langthaning of the cardiac						caused a lengthening of the cardiac

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case #	Age	Dose	Adverse Events	Concomitant	Comments/Summary of case
Receipt	Sex	Duration of		drugs	
date	Out	therapy			
Report type	Country	Indication			
					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
					lengthening of the OT 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	15 m	Not stated	Supraventricular	Not stated	SVT secondary to fluconazole Pt received
7-27-04	M	One dose	tachycardia		dose 17:30 - Mom noticed lethargic and
Direct	LT	Not stated	Lethargy		felt tachy to ER - HR 280BPM
	US				Adenosine x 3 - with recurrence oral
					propranoioi Pt converted when ice towel
					F/U for cardiac testing
Non fatal con	gonital ana	maly (n-3)			170 for cardiac testing
4162504	1 d	150  mg/d x	Hypospadias	None	This is a regulatory authority registry
6-23-04	M	1 in the	Scrotal disorder	rione	report from the United Kingdom's
Expedited	CA	mother	Congenital Anomaly		Medicines and Healthcare products
1	UK	Ill-defined	0 ,		Regulatory Agency (UK-MHRA),
	150	disorder in			authority ID number 473606. This
		the mother			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
					unknown date with provinal 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	Not	150 mg x1	Syndactyly	None	This is a regulatory authority registry
6-23-04	stated	in mother	Finger hypoplasia		report form the Uninted Kingdom's
Expedited	UK	Ill-defined	Congenital Anomaly		Medicines and Healthcare products
		disorder in			Regulatory Agency (UK-MHRA),
		the mother			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
					tinger (syndactily) and three short fingers
					on the other hand (linger hypoplasia). It is
					any other drugs during the first trimestor
					of her pregnancy. In the opinion of the
					UK-MHRA the events were assessed as
					serious (reasons unspecified)

Table 1A – St	Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity					
Case # Receint	Age Sex	Dose Duration of	Adverse Events	Concomitant drugs	Comments/Summary of case	
date	Out	therapy		ur ugo		
Report type	Country	Indication				
5653040	Few	Not stated	Congenital	Isoniazid	Female baby was born on 1 in	
10-18-04	days	Not stated	microcephaly	Pyridoxine	at 38 tation	
Direct	US		Blindness	Other	with weight only 3lb. Diagnosed with	
			Cataract	medications not	congenital microcephaly few days after	
			Small body size	identified	birth. Pregnancy was normal and stated on	
					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	
					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, Diffical, Fyfidoxine + other. If	
					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	
					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	
					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 REASON222 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	
					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	
					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 – St	Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity						
Case #	Age	Dose	Adverse Events	Concomitant	Comments/Summary of case		
Receipt	Sex	Duration of		drugs			
date	Out	therapy					
Report type	Country	Indication					
4086895	4 y	50mg	None	Blood sugar	This is a follow-up report based on		
2-25-04	М	Fungemia		decreased	information reported to Pfizer on		
Expedited	LT				. The initial report wa submitted to		
	JP				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 $/0 \text{ mg/dL}$ .		
					Around nis blood sugar stayed		
					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		
					result of $113 \text{ mg/dL}$ on		
					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	5 y	200 mg qd x	Zovirax	Anuria	Information has been received from a		
4-15-04	M	9 days	Carbenine	Convulsion	physician via Yamanouchi Pharmaceutical		
Expedited	LT	Prophylaxis	Pepcid	Diabetes	Co. Ltd (manufacturer control #		
	JP		Flucytosine	Insipidus	200305946) as part of a business		
			NIdran	Encephalitis	agreement concerning a 5 year old		
			Baktar	Gastric Ulcer	hospitalized male with medulloblastoma,		
			Oncovin	Herpes Zoster	severe hydrocephalus (from		
				Hyponatremia	, and severe neutropenia (from		
				Respiratory	of the acrebral tumor (on		
				Arrest	radiation therapy (		
				Allest	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		
					tor Fungitis prevention from		
					$\frac{4}{540}$ and acyclovir (Zovirax),		
					540 mg daily mom		
					zoster. Other concomitant therapy		
					included betamipron (+) panipenem		
					(CARBENIN), nimustine hydrochloride		

Case #         Osce         Osce         Outmation of therapy         Concomiant         Comments/Summary of case           Report type         Country         Indication         (NIDRAN), flucytosine, and summary of case         (NIDRAN), flucytosine, and summary of case           Report type         Country         Indication         (NIDRAN), flucytosine, and summary of case           Report type         Country         Indication         (NIDRAN), flucytosine, and summary of case           Report type         Country         Indication         (NIDRAN), flucytosine, and summary of case           Report type         Country         Indication         (A           Report type         Country summary of case         (A           Report type         Country summary of case         (A           Report type         Country summary of case         (Case Case)           Report type         Country summary of case         (Case)           Report type         Country summary of case         (Case)	Table 1A – St	ummary of A	AERS pediatric	cases received during th	ne 1-year following a	pproval of pediatric exclusivity
Receipt data         Sex built         Duration of the trapy         drugs           Report type         Country         Indication         (NIDEAN), flucytosine, and sulfamethorazole (+) trimelhoptim (BAKTAN, 14, 155 0am on 04 to patients \$\phi02\$ dropped in 04 to patient \$\phi03\$ accommadel in the 120 to 04 to patient \$\phi03\$ accommadel in the 120 to 04 to 04 to 04 to 04 sectars. The patient \$\phi03\$ accommadel in the 120 to 04 to 04 to 04 to 04 sectars. The patient \$\phi03\$ dropped in 04 to patient \$\phi03\$ accommadel in 04 the 120 droop, rune output \$\phi03\$ dropped in 04 the patient \$\phi03\$ accommadel in 04 the 120 droop, rune output \$\phi03\$ dropped in 04 the patient \$\phi03\$ accommadel in 04 the 120 droop output \$\phi03\$ dropped in 04 the patient \$\phi03\$ accommadel and in 04 the patient \$\phi03\$ accommadel and in 04 the 120 droop output \$\phi03\$ dropped in 04 the patient \$\phi03\$ accommadel and in 04 the 120 dropped in 04 the patient \$\phi03\$ accommadel and in 04 the 120 dropped in 04 the 120 droppe	Case #	Age	Dose	Adverse Events	Concomitant	Comments/Summary of case
date         Out         Increase           Report type         County         Indication         (NIDRAN), flucytosine, and suffamehozarub (+) trimethoprim (BAKTAR), A15:00 am on 04 the patient's SQU apped to the 80% Oxygen theory was initiated. A16:33 nn, he developed clonic contraction in the right lower limb then system course. At disappearing was initiated. A16:33 nn, he developed clonic contraction in the right lower limb then system course. At disappearing was initiated. A16:33 nn, he setzure was terminated with diazepara (CFRCINF). A14 the same time, response are sub-response of the same time, response are sub-response of the same time, response or response of the same time, response are sub-response of the same time, response and serving same are sub-response of the same time, response and serving same are sub-response of the same time, response and serving same are sub-response of the same time, response and serving same are sub-response of the same are sub-response of the same time and the same are sub-response of the same time are same are sub-response of the same time are same are sub-response of the same are sub-response bare sub-response are sub-response are sub-response o	Receipt	Sex	Duration of		drugs	
Report type         Country         Indication           (NIDRAN), flucytosine, and sulfamethoxazole (+) immediately and (RAKTRR). At 50 an non 04 the patient's SpO2 deroped to the 80%. Oxygent therapy was initiated. At 6.35 an, he developed clonic contraction in the right lower limb then systemic setzare. At 6.45 am, chloral bydate (ESRE) suppository was administered. At 700 an, the same was estimated. At 6.53 cm, he developed clonic contraction in the suppository was administered. At 700 an, the same was estimated. At 6.65 am, the grant set settimates and the same was administered. (CRE oNP) for same time, comparison (CRE oNP) and social for some time between the hours of 6.00 and 10.00 am. However, at 10.00 am time the comparison (CRE TRE SIN) was loaded and the desonpressin was administered was comparison (CRE SIN) was loaded and the desonpressin was administered was comparison (CRE SIN) was loaded and the desonpressin was administered was comparison of the four immover any longer and the patient's softime low constrained the case actualized and though was discussing and sector. The onversent of the that hyponatrening, sectores and tablets insipadus was exe tracked to dispates insipadus wasen	date	Out	therapy			
(NIDRAN), flueytosine, and suffamethoxazole (+) trimethoprim (IRAUTAR), At 5:00 arm on 04 the patient's SpO2 dropped to the 89%. Oxygen therapy was initiated. At 6:33 ann, the developed clonic contraction in the right lower limb then systemic seizner. At 6:43 ann, chloral hydrain (ESCRE) or superimetry was triminated with diargam (CFRCINF). At the same time, respiratory arest occurred. It was considered that the patient's respiratory arrest was due to the seizner, was terminated with diargam (CFRCINF). At the same time, respiratory arrest occurred. It was considered that the patient's respiratory arrest was due to the seizner, was accommodated in the ICU. The patient did not produce any urine between the hours of 6:000 and 10:00 am. However, at 10:00 am urine output was resumed with a color of "Pitty light". At 12:00 non, urine output was 200-800 mil.hour and urinary osmolarity was 28 and serum sospressin (PITRIESEN) was loaded and then desamperessin was administered wivec. The symptom gradually abated, not needing desamperssin any longer and the patient's sodium level improved. On therapy with financiality was 12 and as the study of the discontinued (reason not specified). On therapy with financiality was discontinued (reason not specified). On therapy with indicaloun (DORMICUM) was discontinued a def from ICU the act day. If edid not speak as much as before. The royonring hyperite week. It was vitual at the symptom seizures, diadated the respiratory arrest were considered to the respiratory arrest were considered to the respiratory arrest due at the symptomic was tabated in IER serum sodium was 13 m flagt. The was extubated a del from ICU the act day. If edid not speak as much as before. The royonring that was to assect in significal serue sodia due to physician was to assect the immediately the drug as dimense in significal serue sodia due to physician assect the that winerstine significal serue in respiratory are the responsible. The reporting thigh is physician stated that probably finantidine has no cu	Report type	Country	Indication			
suffamethosanole (-) immethyrine (RAKTRB), X5:00 am on 04 the patients \$p02 dropped to the 80% Oxygen therapy was initiated At 6:35 am, he developed clonic contraction in the right lower lumb then systemic setzure. At 6:45 am, chicral hydrate (CSRR) suppository was administered. At 7:00 am, the sizure was terminated with diazepam (CFRCNB). At the same time, respiratory arrest occurred. It was considered that the patient was accommodate in the ICU. The patient did not produce any unite between the hours of 6:00 and 1:000 am. However, at 10:00 am time output was 12 and the patient was accommodate in the ICU. The patient did not produce any unite between the hours of 6:00 and 1:000 am. However, at 10:00 am time output was 12 and second with diabetes insipidus and water was supplemented. At 8:00 pm, suspension (PTRESSIN) was loaded and then desongressin was administered write. The symptom gradually abated, not needing desongressin any longer and the patient's solution was 129 m. figure. The patient did not produce the symptom gradually abated, not needing desongressin any longer and the patient's solution was 139 m. figure. The patient's secun solution the responsible. The reporting this that the responsible. The reporting by solution was to socere on tradied to the symptoms abated on more than the produced and theses insinglaws were not related to the symptoms abated of (10) rung, account of the figure. The theory solitis and responsible. The reporting by solution was to socere on tradied to the symptomis abated of (2) rung. As there was ine						(NIDRAN), flucytosine, and
(BACTAR), At 5:00 am of 04 the patients SpC2 dropped to the 80%s. Oxygen therapy was initiated. At 6:35 am, the developed columic contraction in the right lower timb then system seizure. At 6:453 am, chloral hydrafe (ESCRE) suppository was administered. At 7:00 am, the seizure was estimated with diazepart (CERCINE). At the same twice due to be seizure. The patients' sodium was 117 mEq.1. There was no change in CT and the patient's adjuster of the seizure of the patient's odjuant of the seizure. The patient's sodium was 117 mEq.1. There was no change in CT and the patient was accommodated in the ICU. The patient did not produce any urine between the bases of 6:00 and 10:00 am. However, at 10:00 am united with diazetes michae and or the seizure. The patient's distance any urine between the bases of 6:00 and 10:00 am. However, at 10:00 am united with diazetes michae and urinary computing was 28 and serms adjurne was 218 mEq.1. The patient was diagnosed with was 28 and serms adjurne was 218 mEq.1. The patient was diagnosed with was 28 and serms adjurne was adjurned to the form of sodium level improved. On therapy with framotidine was discontineed (reason on togenified). On therapy with diazetes insigned and the patient's sodium level insigned and the patient's serum sodium was 139 mEq.1. he was extubated a cel from ICU the next day. He did not speak as much as before. The movement of the four limbs gradually abated serue was the was indiged that the symptoms abated on the hory solital the symptoms abated on the reporting physician was to ascertain a support leng, as treatment with continue. The reporting thysician was to ascertain a support leng, as treatment with continue. The reporting physician stand that probably famotidine bare ophalopathy						sulfamethoxazole (+) trimethoprim
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Table 1A – Su	Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity						
Case # Receipt date	Age Sex Out	Dose Duration of therapy	Adverse Events	Concomitant drugs	Comments/Summary of case		
Keport type	Country	Indication			(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 ove	rdose/medi	cation 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, <u>was</u> <u>directed to take Diflucan (fluconazole) 2.5</u> teaspoons once per day instead of the <u>prescribed 2.5 mls once per day</u> . 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. <u>Three days later</u> the consumer returned for the remainder of the prescription with instructions to return for the remaining. <u>Three days later</u> the consumer returned for the remainder of the prescription with 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 fun	gemia (n=2)	)		-	1		
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. <u>At an</u> <u>unknown time this child was started on</u> <u>Diflucan (fluconazole) for antifungal</u> <u>prophylaxis and then was switched</u> (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 #	Age	Dose	Adverse Events	Concomitant	Comments/Summary of case
date	Sex Out	Duration of therapy		arugs	
Report type	Country	Indication			
					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 <u>started on Diflucan</u> (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
Non-fatal her	atic events	(n=?)			hospitalization.
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 – St	ummary of A	AERS pediatric	cases received during th	ne 1-year following a	pproval of pediatric exclusivity
Case #	Age	Dose	Adverse Events	Concomitant	Comments/Summary of case
Receipt	Sex	Duration of		drugs	
date	Out	therapy			
Report type	Country	Indication			
					appendicular peritonitis. She received
					treatment at that time with intravenous
					centriaxone and metronidazole. On -
					she developed a sub-phrenic
					abscess caused by Enterococcus faecans
					ceffriaxone and metronidaz
					discontinued treatment with intravenous
					niperacillin + 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,
					Pageusa of parsistant favor, aiproflavorin
					and fluconazole were added on
					Laboratory tests from tha
					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
					$\frac{1}{2.2 \times 10E9/L},$
					neutrophils at 0.97 x10E9/L, ASA1 at 5.4
					<u>XULN, ALAT at 1.7 XULN, and gamma-</u>
					SVIII N. 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
					tazabaatam flyaanazala an 1
					tazooactam, nuconazole and vancomycin
Non fatal here	arsonsitivit	v ovonte (n-1)	l	I	uiciapies.
5658161	12 v	200  mg/d	Rash	NS	Was given generic Diflucan broke out
10-27-04	M	3-4 days	Generalized hody	110	with a rash. Belly button area got dry and
Direct	NS	Valley fever	swelling		caked, and body became swollen stopped
2	US		Dry skin		taking generic rash went away
	~~		Skin fissures		Benerie rash went usury.

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

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

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