U.S. Food and Drug Administration
Protecting and Promoting Public Health

DRUG SAFETY NEWSLETTER

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IN THIS ISSUE

THE NEWSLETTER'S MISSION

This publication provides postmarketing information to healthcare professionals to enhance communication of new drug safety information, raise awareness of reported adverse events, and stimulate additional adverse event reporting. For more information, visit the FDA Drug Safety Newsletter Fact Sheet at *www.fda.gov/cder/dsn/factsheet.htm*

REPORTING ADVERSE EVENTS

FDA encourages the reporting of all suspected adverse reactions to all drugs, all suspected drug interactions, and all suspected reactions resulting in death, life-threatening outcomes, hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defects.

Report serious adverse events to FDA's MedWatch reporting system by completing a form online at *www.fda.gov/medwatch/report.htm*, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

WELCOME FROM THE COMMISSIONER

Knowledge not communicated almost invariably is knowledge wasted, and if the information can help better protect and promote the health of our public, the waste is intolerable. At the Food and Drug Administration, we are acutely conscious that this is especially true about the wealth of data that are developed or received by our Agency about the safety of new or widely used medications. Communicating the right facts in the right way to those who need to know them–the nation's healthcare professionals–is therefore an integral part of our mission. I regard this task to be as vital as any other purpose of our Agency.

This *Drug Safety Newsletter* is a new means toward this objective and an important addition to FDA's various communication tools for disseminating helpful and reliable information about the products we regulate. The role of this *Newsletter* is to keep our medical community posted–including physicians, dentists, nurses, and pharmacists–about selected postmarketing drug safety reviews, important emerging drug safety issues, and recently approved pharmaceutical products. We expect to publish it quarterly and e-mail it for free to all subscribers.

We're launching this publication to help healthcare professionals make better decisions about the medicines they use in their practice and stimulate their reporting of adverse events. The *Newsletter* is another FDA contribution to our nation's greatest strength, which is the good health and vigor of our people.

Andrew C. von Eschenbach, M.D.
Commissioner of Food and Drugs

EDITOR'S NOTE

Welcome to the first issue of the *Drug Safety Newsletter*. Every year, FDA receives more than 400,000 reports of adverse events associated with the use of drugs marketed in the United States. We review these reports regularly to identify signals of potential drug risks. Spontaneous adverse event reports are one basis for updating product labeling and communicating new information about risks associated with medicines to healthcare professionals and patients. Some articles in the *Drug Safety Newsletter* will report safety findings identified in the course of reviewing these adverse event reports. Other articles will report findings identified in clinical trials and epidemiology studies. We also plan to feature topics of special interest, such as interesting clinical or methodological approaches to drug safety questions. In addition, the *Drug Safety Newsletter* will list recent advisories on drug safety that have been posted on FDA's Web site, with related links.

How do we select topics for the *Drug Safety Newsletter*? We base our coverage on factors such as (1) the likely importance of a topic for patient care and public health, (2) the seriousness of an adverse event, and (3) the timeliness of a topic, given other publications or events of public interest.

In this first issue, one article describes the occurrence of a rare, life-threatening clinical condition called progressive multifocal leukoencephalopathy (PML), in association with the use of rituximab. With the development and use of increasingly powerful and long-acting immunosuppressants, such as rituximab, cases of serious (sometimes fatal), reactivated latent viral infections and exacerbated, or new, infections have been reported. As the article describes, the reported cases often have a complex clinical background that may present interpretative challenges (e.g., patients are often receiving, or have received, multiple drugs that suppress the immune system).

An article on modafinil provides a summary of our updated review of cases of modafinil-associated serious skin reactions (i.e., Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)).

The temozolomide article describes a rare, life-threatening postmarketing adverse event, aplastic anemia. Even in a drug known to cause myelosuppression and for which cases of pancytopenia have been reported in clinical studies, it is important to be vigilant for other similar serious adverse events. Such is the case for aplastic anemia and temozolomide, a drug used to treat newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma.

Finally, in every issue, we intend to routinely report on postmarketing findings for a recently approved new molecular entity. In this issue, we present an overview of reported adverse events of interest associated with the use of deferasirox, an oral chelating agent used to treat iron overload due to multiple blood transfusions.

It is our hope that this inaugural issue of *Drug Safety Newsletter* will convey to its readers valuable drug safety information and will encourage healthcare professionals to report additional cases to the FDA.

Renan A. Bonnel, Pharm.D., M.P.H.
Senior Scientific Editor

RITUXIMAB (marketed as Rituxan)

Progressive Multifocal Leukoencephalopathy (PML)

A safety review on rituximab identified an association of the drug with a serious adverse event, progressive multifocal leukoencephalopathy (PML), a viral infection of the central nervous system (see Box 1). The product labeling has been updated to reflect this new safety information, and a public health advisory and information for healthcare professionals have been posted on FDA's Web site. This article, based upon the review of the first 12 cases of PML identified, describes the postmarketing data that prompted the revisions to product labeling and provides recommendations to healthcare professionals and patients regarding this serious adverse event. As of December 2006, FDA has received a total of 24 reports of PML in patients who received rituximab treatment.

Rituximab is a monoclonal antibody approved for the treatment of patients with non-Hodgkin's lymphoma and patients with moderate-to-severe, active rheumatoid arthritis when there has been inadequate response to other treatments. Rituximab is a powerful immunosuppressant that eliminates mature circulating B-cells for up to nine months.[1] In the United States, rituximab has been marketed since November 1997.

Since marketing approval, FDA has been reviewing serious adverse events reported in association with rituximab treatment. This review summarizes the initial evaluation of 12 cases of PML reported to FDA through August 2005, including two cases identified in a review of the medical literature.[2,3]

REPORTED CASES OF PML

The initial 12 cases involved patients ranging in age from 32 to 76 years (median age 53). The gender distribution was equal. All patients received rituximab for an approved indication, treatment of non-Hodgkin's lymphoma, except for two patients, one who had chronic lymphocytic leukemia (CLL) and the other, Hodgkin's disease. Two of the 12 patients were hospitalized, and death occurred in 9 patients. Ten of the 12 patients tested positive for the JC virus and 1 patient had confirmed BK virus. JC-viral load quantification was not conducted prior to and after rituximab therapy. All patients developed PML while receiving or, in many cases, within a plausible timeframe after discontinuation of rituximab. Many patients received high-dose chemotherapy with hematopoietic stem cell transplant (HSCT), corticosteroids, and/or other chemotherapy agents (alkylating agents and purine analogs), in addition to rituximab. Any of these treatments may have contributed to the risk for developing PML. In addition, one patient was positive for the human immunodeficiency virus (HIV).

BOX 1

What is PML?

PML is a rare fatal demyelinating disease that is caused by a viral infection of the brain following reactivation of the JC or BK polyomavirus (also known as papovavirus) present in about 80 percent of adults.[4,5]

Diseases and conditions (e.g., leukemia, AIDS, lymphoma, and organ transplantation) and medications (e.g., nataluzimab, fludarabine, and tacrolimus) that affect cell-mediated immunity have been associated with PML development. The JC papovaviruses bind to primary glial cells, stromal cells, and B lymphocytes. The virus penetrates the brain when B cells cross the blood-brain barrier, and immunosuppression may create conditions suitable for virus expansion, leading to varying biologic activity.[6] There is no known effective treatment for PML.

Although the exact mechanism is unclear, it is postulated that PML may occur after the recovery of infected lymphocytes following a period of immunosuppression such as following rituximab administration. The average half-life of rituximab is 208 hours, and the median recovery time of B lymphocytes is about 12 months.[1] This postulated mechanism is consistent with the observation in the case series that PML appeared approximately four months on average after discontinuation of rituximab therapy.

TWO CASE HISTORIES

Two cases that suggest a role for rituximab in the development of PML are summarized below (see Box 2). These two cases were selected as the patients were HIV-negative and not on chemotherapy at the time of the initial manifestations of PML, and these cases illustrate the temporal relationship between discontinuation of rituximab and the early manifestations of PML.

In the first case, the patient with a 20-year history of multiple sclerosis was treated for non-Hodgkin's lymphoma with rituximab for about 3 years before presenting with symptoms of JC virus-induced PML 6 months after discontinuation of rituximab. At the time of PML presentation, her only risk factors for PML were non-Hodgkin's lymphoma and treatment with prednisone.

In the second case, the patient was started on a treatment protocol consisting of CHOP+R (cyclophosphamide, doxorubicin, vincristine, and prednisone + rituximab) for non-Hodgkin's lymphoma. Four months after finishing CHOP+R regimen, she presented with signs and symptoms of PML and died. The pathology seen on brain biopsy revealed PML.

In addition to rituximab therapy, the cases in this series had other possible contributory factors that caused decreased cell-mediated immunity and may have predisposed the patients to PML. These included:

- HIV disease
- Hematopoietic stem cell transplant
- High-dose chemotherapy
- Corticosteroids
- Chemotherapy (purine analogs (fludarabine) and alkylating agents (cyclophosphamide, ifosfamide, carmustine))

Despite the fact that these contributory factors may have played a role in the development of PML, a temporal relationship with PML and rituximab appeared to exist.

CURRENT STATUS

Two recent cases of PML submitted to the FDA postmarketing database involved patients treated with Rituxan for systemic lupus erythematosus (SLE), an unapproved indication. A boxed warning was added to the product labeling in February 2007 to reflect current information. In addition, a *Public Health Advisory* and an *Information for Healthcare Professionals* sheet have been issued to alert the public and healthcare professionals of this serious and potentially fatal adverse event. FDA encourages:

- Physicians to maintain a high index of suspicion for the development of PML in patients receiving Rituxan and to consider evaluation for PML when new neurological signs or symptoms appear
- Patients being treated with Rituxan to report any new neurological signs or symptoms to their physician

BOX 2

Case 1

A 63-year-old female with a history of multiple sclerosis (MS) since 1978 was started on rituximab for maintenance therapy in 2001 for treatment of non-Hodgkin's lymphoma (NHL). She was diagnosed with NHL in 1999 and received two rounds of fludarabine treatment before beginning rituximab therapy in 2001. She received rituximab intermittently every 6 months for approximately 3 years. The last dose was administered in mid-2004. Six months after the last dose of rituximab, the patient experienced progressive right hemiplegia. Subsequently, the patient's physical condition further deteriorated, affecting both speech and language. Cranial nerve tests performed six months later showed impairment of volitional eye movement and bilateral gaze. Right upper extremity spasticity with the elbow and wrist held in semi-flexed position was observed. According to the treating neurologist, the slow decline in functional status with aphasia and hemiplegia were felt to be atypical of MS, and PML was suspected. Her laboratory results were positive for JC virus detected in the CSF, which is consistent with PML, negative for BK virus, and negative for cryptococcal antigen. Her MRI revealed an area of ischemia in the left hemisphere and a possible area of demyelination in the pons. In addition to a history of MS, she had bladder dysfunction, emphysema, and multiple episodes of pneumonia. Concomitant medications included albuterol, amitriptyline, baclofen, docusate, fluticasone, hyoscyamine, prednisone, salmeterol, tiotropium, and warfarin. She died in mid-2005.

Case 2

A 44-year-old female with a diagnosis of non-Hodgkin's lymphoma was started on a treatment protocol consisting of CHOP+R in 2004. The CHOP chemotherapy was given concurrently with rituximab. Rituximab dose was 560 mg (375 mg/m^2) weekly for eight cycles. Four months after completing rituximab therapy, she was hospitalized with complaints of headache, nausea, vomiting, and pain. An MRI of the brain at admission showed a large area of abnormal uptake in the left parietal region, more compatible with primary CNS lymphoma than PML. A month prior to hospitalization, an MRI revealed a probable left occipital lobe infarction with no hemorrhage or evidence of lymphoma. The patient subsequently died. The patient's cause of death based on the results of an autopsy of the brain was PML; no tumor or lymphoma were seen.

FDA will continue to follow the issue closely due to the serious nature and high mortality rate associated with this event.

RELEVANT WEB SITES:

www.fda.gov/medwatch/safety/2006/safety06.htm#Rituxan
www.fda.gov/cder/drug/infopage/rituximab/default.htm
www.fda.gov/cder/drug/InfoSheets/HCP/rituximab.pdf
www.fda.gov/cder/drug/advisory/rituximab.htm

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6. Goldberg SL, Pecora AL, Alter RS, et al. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood. 2002; 99 (4): 1486-1488.

MODAFINIL (marketed as Provigil)

SERIOUS SKIN REACTIONS

FDA has been monitoring cases of serious skin reactions, including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), in its postmarketing reviews of adverse event reports associated with the use of modafinil. The product labeling for modafinil has been recently updated to include a bolded warning for serious rash, including SJS.[1] Based on postmarketing data for modafinil, a recently approved drug with a similar chemical structure, armodafinil, includes a similar bolded warning in the product labeling.[2] Healthcare professionals and patients should be watchful for skin reactions associated with the use of modafinil and armodafinil and report cases to FDA's MedWatch.

Modafinil (Provigil) is an oral wakefulness-promoting agent to treat patients with excessive sleepiness (ES) associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD).[1] Modafinil is a controlled substance (C-IV) and has been available in the United States since 1998. The safety and efficacy in children under the age of 16 has not been established.

From the date of initial marketing, December 1998, to January 30, 2007, FDA received six cases of severe cutaneous adverse reactions associated with modafinil, including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) involving adult and pediatric patients.

The 6 cases from the United States occurred in four females and two males aged 49, 42, 17, 27, 15, and 7 years old, respectively. The median time-to-onset of adverse dermatologic effects following initiation of modafinil therapy was 17.5 days, ranging from 5 days to 5 weeks (see Table). Patients presented with a rash to either body extremities (arms, hands, and legs) or to the whole body with some experiencing eruptions in the mouth (lips, tongue), eyes, or genitals. In addition, some patients developed skin pigment changes, pruritus, ulcers, burning of the skin, mild skin scaling, sloughing, and/or fever. Skin biopsies from four patients confirmed TEN, SJS/TEN, SJS/EM, and eosinophilia with unspecified findings consistent with a drug hypersensitivity syndrome.[3,4]

There were no deaths. Five of 6 patients required hospital admission for management, including one patient with TEN who was admitted to the surgical burn unit 20 days after starting modafinil at recommended doses to treat a sleep disorder. In this case, the rash affected 50% of the total body surface area (BSA), with 20 to 30% of the skin denuded. Although this patient had an extensive medication history, modafinil was the primary suspect drug because it was the last agent added to the patient's drug regimen. In addition, modafinil discontinuation upon hospital admission coincided with patient improvement,

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Case summaries of serious skin reactions (SJS, TEN, EM, and DRESS) following use of modafinil				
AGE/SEX	EVENT	TIME TO ONSET	BIOPSY	CASE SUMMARY
49/F	TEN	20 days	Yes	A patient who initiated recommended doses of modafinil for a sleep disorder was hospitalized on day 20 in the burn unit for a severe life-threatening exfoliating skin reaction. Although the patient had an extensive medication history, modafinil was the primary suspect drug because it was the last agent added to the drug regimen. The patient improved, despite the continuation of several concomitant medications, some of which, such as celecoxib and propranolol, have labeled warnings for TEN.
42/F	SJS/TEN	14 days	Yes	A patient received concomitant medications since 2005 before adding modafinil for a sleep disorder in 2006. The patient's extensive body rash (30% BSA) with the confirmation of biopsy led to the final SJS/TEN diagnosis.
17/F	SJS	45 days	Not reported	A patient received both modafinil 300 mg daily for the treatment of attention deficit disorder (ADD) and Lamictal (labeled warnings for SJS) for about 2 months. The patient was hospitalized over 5 days for SJS. Both drugs were discontinued. One to 2 months later, the patient received one dose of modafinil 50 mg and developed a skin rash that also involved the patient's mouth. Modafinil was discontinued.
27/F	SJS/EM	5 days	Yes	A patient had received 5 days of modafinil when she presented to the hospital with a sore throat, which progressed to swelling of the oral cavity and difficulty swallowing, fever, and sloughing of the oral and vaginal mucosa. A biopsy confirmed SJS/EM.
7/M	SJS	15 days	None	A child received modafinil for ADHD and presented with oral lesions (believed to be a Coxsackie viral infection), followed by an extensive body rash. At some later date, a dermatologist diagnosed SJS based on case history and clinical presentation that included eruptions on the skin, genitals, mouth, and lips. The dermatologist could not rule out a possible viral contribution to the event.
15/M	DRESS	5 weeks	Yes	A patient was initiated on modafinil with increasing doses up to 400 mg daily for the treatment of ADHD. Five weeks later, the patient presented with an extremity rash that progressed to a generalized body rash with fever (38°C). Over the following days, the patient developed fatigue, myalgia, vomiting, rhinorrhea, and dry cough. Subsequently, the patient was hospitalized and all medications, including Luvox, Zyprexa, and Abilify, which were prescribed since 2005, and modafinil, were discontinued. On admission, the patient's medical work-up revealed fever, fatigue, and generalized maculopapular rash. There was no evidence that the rash involved the genitals or scalp. There were no target lesions or mucous membrane involvement. Petechiae were observed on the soft palate, and facial edema was noted. Admission laboratory values revealed 37% eosinophils, 25,000 WBCs, and BUN/creatinine levels suggesting a pre-renal state. During hospitalization, the patient's condition worsened with multiple organ system involvement, including the cardiac, renal, respiratory, and pancreatic systems. A dermatologist diagnosed DRESS syndrome based on a skin biopsy (site unspecified), that showed eosinophilia and unspecified findings consistent with a drug hypersensitivity syndrome.

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despite continuation of other concomitant medications, such as celecoxib and propranolol, which have labeled warnings for TEN.

In one case of SJS, although potentially confounded with Lamictal therapy (labeled warning for SJS), rechallenge with modafinil resulted in recurrence of the rash including oral mucosal involvement, which supported a causal association with modafinil use. Modafinil was subsequently discontinued. In the SJS/TEN case, a 42-year-old female received concomitant medications (including escitalopram, which has a labeled warning for TEN) since 2005 without incidence before adding modafinil for sleep disorder in 2006. The patient's extensive body rash (30% of the body surface area), skin biopsy, and clinical presentation all aided the dermatologist in diagnosing SJS with overlapping TEN.

One case of DRESS syndrome was reported in a 15-year-old who was started on modafinil for attention deficit hyperactivity disorder (ADHD), an unapproved indication. After 5 weeks of therapy, the patient developed a skin rash that progressed with multiple organ system involvement, including the cardiac, renal, respiratory, and pancreatic systems. Based on the clinical presentation, increased eosinophil count, and skin biopsy results, the consulting dermatologist diagnosed DRESS syndrome.

Although some cases were potentially confounded by drugs known to be associated with serious skin reactions, all cases had features that implicate modafinil. The cases described a temporal relationship with detailed clinical descriptions, relevant laboratory data, dermatologist-substantiated diagnoses, skin biopsy confirmation, positive dechallenges, and/or a positive rechallenge, all of which support an association between modafinil use and serious cutaneous skin reactions. FDA

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TEMOZOLOMIDE (marketed as TEMODAR)

APLASTIC ANEMIA

A safety review of temozolomide identified cases of aplastic anemia, some fatal, associated with use of the drug. Healthcare professionals should be alert to the possibility of aplastic anemia in the setting of refractory or prolonged myelosuppression in patients receiving temozolomide and report cases to FDA's MedWatch.

Temozolomide, marketed in the United States since 1999, is an oral alkylating agent that is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme. It is used concomitantly with radiotherapy and then as maintenance treatment. It is also indicated for the treatment of refractory anaplastic astrocytoma that progresses despite treatment with a nitrosourea and procarbazine. Temozolomide is not active until converted at physiologic pH to a metabolite, which alkylates DNA, disrupting its synthesis.[1]

From August 11, 1999, to November 3, 2006, FDA received 18 (domestic-14, foreign-4) reports of aplastic anemia among patients receiving temozolomide. Product labeling currently includes a warning regarding myelosuppression and describes pancytopenia among reported adverse events.

The mean age of patients described in the case reports was 48 years (range 4 to 75). Gender distribution was slightly greater for males (56%). Ten patients received temolozomide for the approved indications of glioblastoma multiforme (5) and anaplastic astrocytoma (5). The remainder of the cases involved patients with the following reported tumors: oligodendroma (3), ependymoma (1), glioma (1), medulloblastoma (1), unspecified brain tumor (1), and in one case the underlying condition information was unknown. Eight patients received concurrent radiation treatment. The median time to onset of aplastic anemia from the start of temozolomide therapy was 36 days (range 5 to 578). Nine cases occurred in treatment-naïve patients receiving temozolomide according to the labeled dose. Time of onset for these cases was 1 to 3 months after initiating therapy.

No cases described a prior history of pancytopenia or aplastic anemia. Eleven cases of aplastic anemia were confirmed by biopsy.

Six cases reported prior or concurrent exposure to medications that have been associated with aplastic anemia. These medications include alkylating agents (busulfan, cyclophosphamide, chloromethane, melphalan, nitrosourea, and dacarbazine), antiepileptics, and antibiotics. The timing of the medications was not provided, and definitive attribution for the aplastic anemia to receipt of temozolomide for these six cases cannot be made.

The serious outcomes included death (8) and hospitalization (8). Of the eight patients who died, three patients died from complications arising from aplastic anemia secondary to temozolomide, two patients died secondary to bone marrow transplant complications, and three patients died of disease progression.[2] Five patients recovered following discontinuation of temozolomide with a recovery time reported in two cases of 1 month and 4 months. The severity (moderate, severe, or very severe) of many cases of aplastic anemia were difficult to characterize based on the information provided in the postmarketing reports. In several cases, although other medications associated with aplastic anemia were used concomitantly, our analyses could not exclude the possible contributory role of temozolomide.

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2. Villano JL, Collins CA, Manasanch EE, et al. Aplastic anaemia in patient with glioblastoma multiforme treated with temozolomide. Lancet Oncol. 2006; 7(5): 436-438.

This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging drug safety issue. Nor does it mean that FDA is advising healthcare professionals to discontinue prescribing the product. FDA is considering, but has not reached a conclusion about, whether this information warrants any regulatory action.

NEW MOLECULAR ENTITY (NME) – Early Safety Findings

DEFERASIROX (marketed as Exjade)

Deferasirox is an orally active chelating agent that is selective for iron (Fe^{3+}) and was approved for marketing in the United States in November 2005 in accordance with the regulations governing accelerated approval of new drugs for serious or life-threatening illnesses. Deferasirox is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients two years of age and older. Deferasirox is a tridentate ligand that binds iron with high affinity in a 2:1 ratio.[1]

Deferasirox is distributed by a limited number of specialty pharmacies in the U.S., and many of the suspected adverse drug reaction reports described below are based on these pharmacies' telephone inquiries to patients and healthcare professionals.

Between November 2, 2005, and June 20, 2006, FDA received 115 reports of suspected adverse drug reactions in association with the use of deferasirox (the number of reports represents crude counts that may reflect duplicates). Of these 115 reports, 108 reported a serious outcome including death (19; 17 unduplicated), hospitalization (74), life-threatening (6), disabled (4), and/or required intervention (1). For cases with an outcome of death, the cause of death reported in many cases was due to progression or complication of the underlying disease. The number of males was slightly greater than females (54% versus 46%), and the source of the reports was mainly domestic (86%). The ages ranged from 6 to 91 years, and 37% (43 of 115 cases) of the patients were 65 years of age or older. Thus far, the adverse events reported in the pediatric population (17 unduplicated cases) have been of no greater severity than those described in the adult population. No fatal events were reported in pediatric patients.

Of the 115 reports, commonly reported adverse event terms involved the gastrointestinal (including hepatic), renal, and hematological systems (see Table). Selected hepatic, renal, and hematological events are discussed below.

Hepatic events: 24 unduplicated reports involved hepatic adverse events, which augmented preapproval hepatotoxicity signals, described in product labeling, of increased serum transaminase and drug-induced hepatitis. The reported events include increased aminotransferases, increased bilirubin, jaundice, ascites, subclinical and clinical hepatitis, liver failure, hepatic encephalopathy, and cholecystitis. Three cases of hepatic failure were reported in patients with significant hepatic history and/or use of concomitant medication with known hepatic adverse events. The contribution of deferasirox therapy to hepatic failure is unclear in these cases.

Renal events: 16 unduplicated reports described renal adverse events, including renal failure, acute renal failure,

glomerulonephritis, interstitial nephritis, and renal tubulopathy. Four patients had a history of renal disease. Seven patients improved after discontinuation of deferasirox. In the seven cases of acute renal failure, time to onset was 15 days (range 5 to 58) after initiation of deferasirox therapy; and 2 cases were fatal, two required treatment with hemodialysis, and four improved or recovered.

Hematologic events: There have been postmarketing reports (both spontaneous (15 unduplicated reports) and from clinical trials) of cytopenias, including agranulocytosis, neutropenia, and thrombocytopenia, in patients treated with deferasirox. Some of these patients died. Although most of these patients had preexisting hematologic disorders that are frequently associated with bone marrow failure, a contributory role for deferasirox cannot be excluded.

Healthcare professionals are requested to report any suspect serious adverse reactions in association with deferasirox therapy, particularly:

- Hepatic adverse events
- Renal failure, including fatal renal failure
- Cytopenias, including agranulocytosis, neutropenia, and thrombocytopenia

Recently, the product labeling has been updated to reflect the current information regarding the cases of acute renal failure and cytopenias in the Warnings and the Adverse Reactions sections, and to provide recommendations to healthcare professionals for monitoring patients. Additionally, a Dear Healthcare Professional Letter has been issued to alert the public to these serious adverse events.[2] FDA continues to receive reports of suspected adverse drug reactions in association with use of deferasirox and is evaluating and closely monitoring these reports. As a condition of approval, in accordance with the regulations governing accelerated approval of new drugs for serious or life-threatening illnesses, further studies are being performed to determine the long-term benefits and risks of deferasirox. FDA

Deferasirox - Commonly Reported Reaction Terms
n=115 reports

MedDRA* Preferred Terms	Total Case/Event Count
Gastrointestinal:	
Alanine aminotransferase increased	17
Blood bilirubin increased	16
Diarrhea	17
Nausea	16
Renal:	
Blood urea increased	14
Blood creatinine increased	17
Renal failure acute	7
Hematological:	
Hemoglobin decreased	18
Platelet count decreased	11
Hematocrit decreased	9
Sickle cell anemia with crisis	7
Other:	
Pyrexia	27
Dyspnea	10
Fatigue	10
Rash	9
Dehydration	9
Malaise	8
Asthenia	7

** MedDRA (Medical Dictionary of Regulatory Activities) Preferred Terms are not mutually exclusive; one report may contain an unlimited number of preferred terms.*

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1. Deferasirox (Exjade) product label. *www.fda.gov/cder/foi/label/2007/021882s002lbl.pdf*
2. Dear Healthcare Professional Letter. *www.fda.gov/medwatch/safety/2007/Exjade_DHCPL_May2007.pdf*

REMINDER: HOW TO REPORT ADVERSE REACTIONS

Report serious adverse events to FDA's MedWatch reporting system by completing a form online at www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

DRUG SAFETY COMMUNICATIONS

Posted by FDA from January 1, 2007, to June 1, 2007 (advisories are available at www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm)

Date	Product(s)	Safety Issue and Web Address
May 23, 2007	Gadolinium-Containing Contrast Agents [Magnevist (gadopentate dimeglumine), Omniscan (gadodiamide), OptiMARK (gadoversetamide), MultiHance (gadobenate dimeglumine), and Prohance (gadoteridol)]	Reports of nephrogenic systemic fibrosis (NSF); *www.fda.gov/cder/drug/infopage/gcca*
May 21, 2007	Avandia, Avandemet, and Avandaryl (rosiglitazone maleate)	Pooled analysis of controlled clinical trials describing increased risks of heart attack and heart-related deaths; *www.fda.gov/cder/drug/infopage/rosiglitazone/default.htm*
March 30, 2007	Zelnorm[1] (tegaserod maleate)	Increased risk of heart attack, stroke, and worsening heart chest pain; *www.fda.gov/cder/drug/advisory/tegaserod.htm*
March 29, 2007	Permax[2] (pergolide mesylate)	Increased risk of heart valve damage; *www.fda.gov/cder/drug/infopage/pergolide/default.htm*
March 16, 2007	Zyvox (linezolid)	Increased risk of death when used for intravascular catheter-related infections where there is a gram negative or no organism at time of study entry; *www.fda.gov/cder/drug/infopage/linezolid/default.htm*
March 9, 2007	Erythropoiesis Stimulating Agents [Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa)]	Increased risk of death, non-fatal heart attacks, strokes, heart failure, blood clots, and tumor progression; *www.fda.gov/cder/drug/infopage/RHE*
March 9, 2007	Actimmune (interferon gamma-1b)	Early termination of clinical trial evaluating Actimmune for treatment of idiopathic pulmonary fibrosis (IPF) due to lack of benefit; *www.fda.gov/cder/drug/infopage/interferon_gamma_1b*
February 21, 2007	Xolair (omalizumab)	Reports of delayed anaphylaxis; *www.fda.gov/cder/drug/infopage/omalizumab*
February 9, 2007	Topical Anesthetic Creams	Reports of life-threatening adverse events, such as an irregular heartbeat, seizures, and death; *www.fda.gov/cder/drug/advisory/topical_anesthetics.htm*

NOTES:

1. Withdrawn from marketing March 30, 2007.

2. Withdrawn from marketing March 29, 2007.

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