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.

**REFERENCES**


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 temozolomide 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-naive 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 deferasirox 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. 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.

**REFERENCES**


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,