Dilantin (phenytoin)

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WHAT IS DILANTIN?

- **Dilantin** is **phenytoin**, and phenytoin is also marketed under the name Phenytek. Fosphenytoin is marketed under these name Cerebyx.
- **Dilantin** is an antiepileptic drug which can be useful in the treatment of epilepsy
- **Dilantin** is indicated for the control of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures
- The plasma half-life averages 22 hours, with a range of 7 to 42 hours.
- Steady-state therapeutic levels are achieved at least 7 to 10 days (5–7 half-lives) after initiation of therapy with recommended doses of 300 mg/day.

WHAT ADVERSE EVENT DOES DILANTIN CAUSE?

Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

WHAT IS SJS/TEN?

FDA drug safety newsletter **volume 1 | Issue 4 | summer 2008**

BOX 2

What are Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme (EM)?

SJS and TEN are two related, and potentially life-threatening, acute skin disorders that may result from drug exposure. SJS and TEN are characterized by varying degrees of blistering with detachment of the epidermis. For SJS, 10-30% of the body surface area is affected. For TEN, greater than 30% of the body surface area is affected.[3] The mortality resulting from these reactions is reported to be between 1-3% for SJS and 10-70% for TEN.[4] In industrialized countries, the estimated annual incidence of these adverse events is reported to be 1-2 cases/one million people/year.[5]

The prodromal phase of SJS/TEN may begin with symptoms of fever, malaise, headache, cough, and rhinorrhea. These initial symptoms may last for 1-3 days before the appearance of flat atypical or purpuric macular lesions. These lesions may then progress to blistering, erosions, and epidermal detachment. The mucosal membranes of the mouth, eye, and genital areas are affected in most patients. Respiratory and gastrointestinal tract lesions may also be present.

Skin lesions may be tender and mucosal lesions may be painful. Early lesions show scattered necrotic keratinocytes in the epidermis. Late lesions show confluent "full-thickness" epidermal necrosis and may eventually form subepidermal bullae.[6]

SJS/TEN are most often caused by drugs (e.g., anti-infective sulfonamides, non-steroidal anti-inflammatory drugs, anticonvulsants, and allopurinol). Vaccinations, exposure to chemicals and fumigants, and infection with mycoplasma pneumonia are also associated with SJS.[6] The greatest risk for developing SJS or TEN is during the first two months of drug therapy.[7] Drug causality is usually suspected if the time between the initiation of drug therapy and the onset of SJS and TEN is 4–28 days.[6]

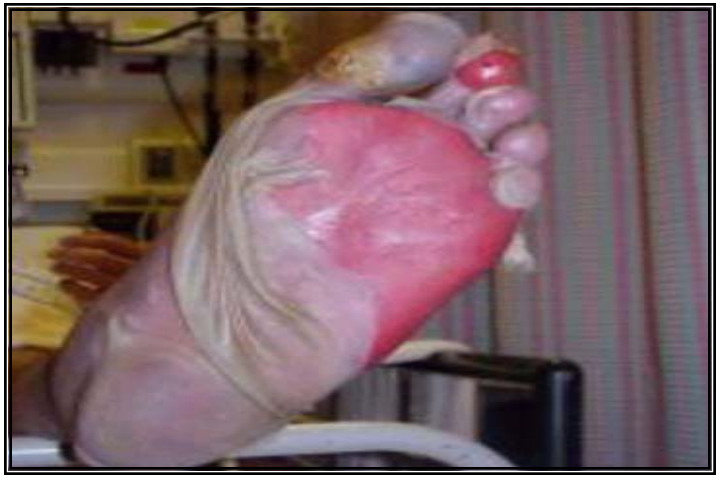
There are no definitive treatments for SJS and TEN. Supportive care and treatment of specific symptoms are critical. SJS- and TEN-associated mortality may be reduced by early identification and immediate discontinuation of the suspect drug.[6] Patients often do better if the discontinued drug has a short half-life (< 24 hours). Corticosteroids, intravenous immunoglobulins, plasmapheresis, cyclophosphamide, cyclosporine, and thalidomide† have been used in the treatment of TEN.[7]

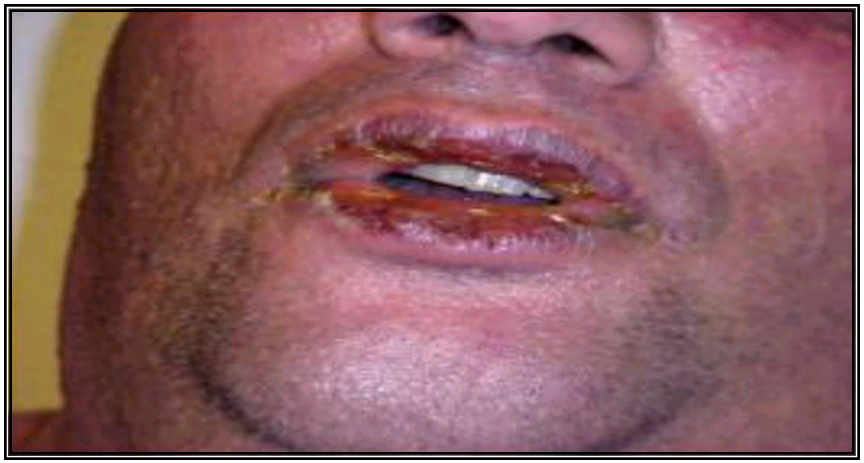
Erythema multiforme (EM), in contrast to SJS and TEN, is most often caused by the herpes simplex virus. It is a recurrent condition characterized by a limited number of typical or raised target lesions. Blisters may also develop with EM. There is limited oral mucosa involvement. The condition has low morbidity and no mortality.[4,6]

Footnote

† The study assessing the safety and efficacy of thalidomide in treating TEN was terminated due to a higher mortality with thalidomide compared with the placebo group.[7] Thalidomide itself is labeled for SJS/TEN and hypersensitivity reactions.

SJS/TEN





- **Stevens-Johnson syndrome - A "minor form of TEN," with less than 10% body surface area (BSA) detachment**
- **Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) - Detachment of 10-30% BSA**
- **Toxic epidermal necrolysis - Detachment of more than 30% BSA**

PREVALENCE

Frequency	Mortality/Morbidity	Race	**Sex**	**Age**
Cases tend to have a propensity for the early spring and winter.	**Mortality is determined primarily by the extent of skin sloughing. When BSA sloughing is less than 10%, the mortality rate is approximately 1-5%. However, when more than 30% BSA sloughing is present, the mortality rate is between 25% and 35%.** **Lesions may continue to erupt in crops for as long as 2-3 weeks. Mucosal pseudomembrane formation may lead to mucosal scarring and loss of function of the involved organ system. Esophageal strictures may occur when extensive involvement of the esophagus exists. Mucosal shedding in the tracheobronchial tree may lead to respiratory failure.** **Ocular sequelae may include corneal ulceration and anterior uveitis. Blindness may develop secondary to severe keratitis or panophthalmitis in 3-10% of patients. Vaginal stenosis and penile scarring have been reported. Renal complications are rare.**	**Caucasian predominance has been reported**	**The male-to-female ratio is 2:1**	**Most patients are in the second to fourth decade of their lives; however, cases have been reported in children as young as 3 months**

TREATMENT FOR SJS/TEN

- **Withdrawal of the suspected offending agent is critically important. Timing of withdrawal has been linked to outcome.**
- **Care in the ED must be directed to fluid replacement and electrolyte correction.**
- **Skin lesions are treated as burns.**
- **Patients with SJS/TEN should be treated with special attention to airway and hemodynamic stability, fluid status, wound/burn care, and pain control.**
- **Treatment is primarily supportive and symptomatic. Some have advocated cyclophosphamide, plasmapheresis, hemodialysis, and immunoglobulin. Most authorities believe that corticosteroids are contraindicated.**
  - **Manage oral lesions with mouthwashes.**
  - **Topical anesthetics are useful in reducing pain and allowing the patient to take in fluids.**
  - **Areas of denuded skin must be covered with compresses of saline or Burow solution.**
- **Underlying diseases and secondary infections must be identified and treated. Offending drugs must be stopped.**
- **The use of systemic steroids is controversial. Some authors believe that they are contraindicated. Treatment with systemic steroids has been associated with an increased prevalence of complications.**
- **In a large European study designed to evaluate the efficacy of various treatments, the EuroSCAR Study "found no sufficient evidence of a benefit for any specific treatment."8 The group looked at mortality in patients treated with IV immunoglobulins and corticosteroids.**
- **Address tetanus prophylaxis.**

HOW DID THE FDA LEARN ABOUT THE PHENYTOIN-SJS/TEN PROBLEM?

- **An article in the May 2008 issue of *Epilepsia* (Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population) reported that the HLA-B*1502 allele was found in 4 out of 4 patients with SJS associated with phenytoin treatment in a Thai population. In contrast, the frequency of HLA-B*1502 in the phenytoin-tolerant control group was much lower (18%). Based on that article, a preliminary estimate of the risk for SJS in Thai patients who are new users of phenytoin and are positive for HLA-B*1502 is approximately 3%. This compares to a risk estimate at the same epilepsy treatment center of approximately 0.3% in all new phenytoin users. A previous article in the May 2007 issue of *Epilepsia* (Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese) reported a single case of phenytoin-associated SJS in a Chinese patient in Hong Kong who was positive for HLA-B*1502.**

- **Because of these new data suggesting a possible association between HLA-B*1502 and phenytoin-induced SJS/TEN, and the known association between phenytoin and SJS/TEN, consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.**

- **Phenytoin is an antiepileptic drug with some structural similarity to another antiepileptic drug, carbamazepine. Labeling for carbamazepine was recently updated to reflect an increased risk of serious skin reactions, including SJS/TEN, in Asian patients who had recently started taking carbamazepine and who tested positive for HLA-B*1502.**

- **New preliminary data suggests that phenytoin may carry a risk of serious skin reactions in some Asian patients who tested positive for HLA-B*1502, similar to the risk carried by carbamazepine. Because fosphenytoin is a prodrug and is converted to phenytoin after administration, any concern regarding this association with phenytoin is also applicable to fosphenytoin.**

- **Of carbamazepine-treated patients who experience a serious skin reaction, over 90% have this reaction within the first few months of treatment. Patients who have been taking carbamazepine for more than a few months, without developing skin reactions, are at low risk of developing this reaction. Similarly, the risk for serious skin reaction with phenytoin therapy appears to be greatest in the first few months of therapy.**

Information for Healthcare Professionals sheet (12/12/2007)

DILANTIN-SJS/TEN DOES *NOT* ONLY AFFECT ASIANS

- Two rare, related, and potentially life-threatening adverse dermatological events associated with the use of the anticonvulsant drug CBZ (marketed as Carbatrol, Equetro, Tegretol, and generics) are SJS and TEN. Both SJS and TEN have similar pathophysiologies and symptoms (e.g., erythema, with varying degrees of blisters, skin erosions and detachment) and affect both skin and mucosal membranes. Differential diagnosis of SJS and/or TEN is based on the degree of skin surface area detachment (SJS affects 10% or less of skin surface area; SJS/TEN affects 10-30% of skin surface area; TEN affects 30% or greater skin surface area with high morbidity and mortality). For this article, these diagnoses are referred to as SJS/TEN.

- **Traditionally, the likelihood of developing CBZ-associated SJS/TEN has been considered low.1,2 Recent reports, however, indicate that certain populations may be at increased risk for developing these conditions. For instance, *these reactions are estimated to occur in 1 to 6 per 10,000 new users of CBZ in countries with mainly Caucasian populations*. The risk in some Asian countries is estimated to be about 10 times higher.**

- Based on the accumulation of data provided by the scientific literature and other available sources, the potential risk for SJS/TEN in individuals carrying the HLA-B*1502 allele has now been described in a *Boxed Warning*, and in the *Warning and Precautions, Laboratory Tests* and *Geriatric Use* sections of the CBZ product labeling.

Postmarketing Reviews - Volume 1, Number 3, Spring 2008
Carbamazepine (marketed as CARBATROL, EQUETRO, TEGRETOL and generics): **Stevens-Johnson syndrome**, toxic epidermal necrolysis, and HLA-B*1502

FDA ACTION:
FDA ALERT [11/24/2008]

FDA is investigating new preliminary data regarding a potential increased risk of serious skin reactions including **Stevens Johnson syndrome (SJS)** and **toxic epidermal necrolysis (TEN)** from **phenytoin** therapy in Asian patients positive for a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais. ***Because fosphenytoin is a prodrug and is converted to phenytoin after administration, any concern regarding this association is also applicable to fosphenytoin.*** Phenytoin and fosphenytoin are used to control tonic-clonic (grand mal) and complex-partial seizures in epilepsy.

FDA ACTION:

Drug Safety Communications
Volume 2, Number 1, 2009

(Dilantin, Phenytek, and generics) and Fosphenytoin Sodium (Cerebyx and generics)

- **New data suggest a potential increased risk of phenytoin or fosphenytoin-induced serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) in patients with the human leukocyte antigen allele, HLA-B*1502**.

FDA ACTION:

FDA "Show #84", March 2009

Serious Skin Reactions in Asian Patients on Phenytoin and Fosphenytoin

FDA is investigating new preliminary data suggesting an increased risk of serious skin reactions from the anti-epileptic drugs phenytoin and fosphenytoin if they are taken by Asian patients who are positive for the human leukocyte antigen allele HLA-B*1502. These reactions include Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). Phenytoin is marketed as Dilantin, Phenytek and generics. Fosphenytoin sodium is marketed as Cerebyx and generics.

It is estimated that in parts of China, Taiwan, Thailand, Malaysia, Indonesia and the Philippines, 15 percent or more of the population may carry the HLA-B*-1502 allele. The frequency in South Asia, including India, is somewhat lower, and in Japan and Korea it is under one percent.

It was previously established that another anti-epileptic drug, carbamazepine, increases the risk of these skin reactions in Asian patients with the HLA-B*1502 allele. FDA has recommended screening patients of Asian ancestry for this allele before prescribing carbamazepine and not starting the drug unless the expected benefit clearly outweighs the risk.

In the case of phenytoin and fosphenytoin, the possible risk is still being studied, and there is not enough information at this point to recommend testing for the allele before starting therapy. However, FDA is recommending that physicians avoid using phenytoin as a substitute for carbamazepine in patients who test positive for the HLA-B*1502 allele.

With carbamazepine, over 90 percent of serious skin reactions occur during the first few months of treatment. Patients who have taken the drug for longer than this without having a skin reaction are at low risk for developing one. Likewise, the risk for serious skin reactions with phenytoin seems to be greatest during the first few months of treatment.

WHAT DID PFIZER DO?

APRIL 2009 DILANTIN-SJS LABEL CHANGES DO NOT REFERENCE ASIANS ONLY

ADVERSE REACTIONS

- **Central Nervous System:**
- **Gastrointestinal System:**
- **Integumentary System:**

  Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see PRECAUTIONS section).

PRECAUTIONS

Phenytoin should be discontinued if a skin rash appears (see WARNINGS section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See ADVERSE REACTIONS section.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

PFIZER 2009 Dilantin Label: Adverse Reactions

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see PRECAUTIONS section).

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PFIZER 2009 Dilantin Label: Precautions

Phenytoin should be discontinued if a skin rash appears (see WARNINGS section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See ADVERSE REACTIONS.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

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DILANTIN CASES BEING ACCEPTED BY BAILEY & GALYEN

1. PATIENT OF ANY NATIONALITY WHO WAS PRESCRIBED AND TOOK DILANTIN PRIOR TO APRIL, 2009
2. DIAGNOSED WITH STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS WHILE TAKING DELANTIN
3. RECEIVED MEDICAL ATTENTION FOR STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS
4. NEED MEDICAL RECORDS SHOWING 1-3