Approval Package for:

APPLICATION NUMBER: NDA 08-762/S-039

Name: Dilantin Suspension

Sponsor: Pfizer Inc

Approval Date: December 14, 2011

APPLICATION NUMBER: NDA 08-762/S-039

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APPLICATION NUMBER: NDA 08-762/S-039

APPROVAL LETTER



Food and Drug Administration Silver Spring MD 20993

NDA 008762/S-032/S-039/S-040/S-41

SUPPLEMENT APPROVAL

Pfizer Inc Attention: Carol Haley Director, Worldwide Regulatory Strategy 235 East 42nd Street New York, NY 10017-5755

Dear Ms. Haley:

Please refer to your Supplemental New Drug Application (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dilantin-125® (phenytoin) Oral Suspension.

Application	Submitted on:	Received on:	
NDA 008762/S-032	November 25, 2003	November 26, 2003	
NDA 008762/S-039	August 28, 2009	August 28, 2009	
NDA 008762/S-040	January 18, 2011	January 18, 2011	
NDA 008762/S-041	January 18, 2011	January 18, 2011	
NDA 008762/S-043	June 30, 2011	June 30, 2011	
These "Changes Being Effected" supplements provide for:			
• Package insert update of safety information including:			
1) Contraindications section- addition of hypersensitivity to inactive ingredients			
2) Drug Interactions section -edit to include additional information.			
3) Adverse Reactions section- edit to include additional information			

- Package insert revision to include additional information in the Warnings and Precautions sections regarding serious skin reactions, hypersensitivity, and Anticonvulsant Hypersensitivity Syndrome.
- Package insert addition of fluorouracil to the Precautions/Drug Interactions section.
- Revise package insert language about osteomalacia in the Precautions section.
- Revision of Medication Guide

We acknowledge receipt of your amendment dated November 8, 2011.

We have completed our review of these supplemental applications, and our review of labeling revisions for NDA 008726, as amended, as follows: updating information regarding CYP450-mediated metabolism, adding a Contraindication to coadministration with delavirdine, additional revisions to the Drug Interactions section, to the Warnings section, and to the Adverse Reactions section. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U http://www.fda.gov/downloads/DrugsGuidance http://www.fda.gov/downloads/DrugsGuidance http://www.fda.gov/downloads/DrugsGuidance <a href="http://www.fda.gov/

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(1)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration Center for Drug Evaluation and Research Division of Drug Marketing, Advertising, and Communications 5901-B Ammendale Road Beltsville, MD 20705-1266 You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <u>http://www.fda.gov/opacom/morechoices/fdaforms/cder.html</u>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <u>http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm</u>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

OTHER

We request that you perform a comprehensive literature search and a comprehensive safety database search (of cases after June 30, 2001) to determine whether the Drug Interactions and Adverse Reactions sections of labeling should be further updated. Please submit an analysis of your findings and proposed related labeling changes as a Prior Approval Supplement within 3 months of the date of this letter.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Su-Lin Sun, PharmD, Regulatory Project Manager, at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D. Division Director Division of Neurology Products Office of Drug Evaluation I Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

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

/s/

RUSSELL G KATZ 12/14/2011

APPLICATION NUMBER: NDA 08-762/S-039

LABELING

Dilantin-125[®]

(Phenytoin Oral Suspension, USP) (FOR ORAL ADMINISTRATION ONLY; NOT FOR PARENTERAL USE)

DESCRIPTION

Dilantin (phenytoin) is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is 5,5-diphenyl-2,4 imidazolidinedione, having the following structural formula:



Each 5 ml of suspension contains 125 mg of phenytoin, USP; alcohol, USP (maximum content not greater than 0.6 percent); banana flavor; carboxymethylcellulose sodium, USP; citric acid, anhydrous, USP; glycerin, USP; magnesium aluminum silicate, NF; orange oil concentrate; polysorbate 40, NF; purified water, USP; sodium benzoate, NF; sucrose, NF; vanillin, NF; and FD&C yellow No. 6.

CLINICAL PHARMACOLOGY

Mechanism of Action

Phenytoin is an antiepileptic drug which can be useful in the treatment of epilepsy. The primary site of action appears to be *the motor cortex* where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to *stabilize* the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of posttetanic potentiation at synapses. Loss of posttetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

Pharmacokinetics and Drug Metabolism

The plasma half-life in man after oral administration of phenytoin 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.

When serum level determinations are necessary, they should be obtained at least 5-7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. For Dilantin-125 Suspension, peak levels occur $1\frac{1}{2}-3$ hours after administration.

Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20 mcg/mL, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver

disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but, more importantly, by tubular secretion. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high plasma levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

Special Populations

Patients with Renal or Hepatic Disease: Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see DOSAGE AND ADMINISTRATION). Unbound phenytoin concentrations may be more useful in these patient populations.

Age: Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see DOSAGE AND ADMINISTRATION).

Gender and Race: Gender and race have no significant impact on phenytoin pharmacokinetics.

Pediatrics: Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dose (300 mg/day).

INDICATIONS AND USAGE

Dilantin (phenytoin) is indicated for the control of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY sections).

CONTRAINDICATIONS

Dilantin is contraindicated in those patients with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins.

Coadministration of Dilantin is contraindicated with delavirdine due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.

WARNINGS

Effects of Abrupt Withdrawal

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When in the judgment of the clinician the need for dosage reduction, discontinuation, or substitution of alternative anticonvulsant medication arises, this should be done gradually. In the event of an allergic or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant not belonging to the hydantoin chemical class.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Dilantin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be

monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Dilantin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days, but can occur later. Dilantin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (see **DRESS/Multiorgan hypersensitivity** below).

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.

The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including Dilantin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Dilantin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity

Dilantin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see CONTRAINDICATIONS). Additionally, consider alternatives to structurally similar drugs such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in these same patients. Similarly, if there is a history of hypersensitivity reactions to these structurally similar drugs in the patient or immediate family members, consider alternatives to Dilantin.

Hepatic Injury

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with Dilantin. These events may be part of the spectrum of DRESS or may occur in isolation. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, Dilantin should be immediately discontinued and not readministered.

Hematopoietic System

Hematopoietic complications, some fatal, have occasionally been reported in association with administration of Dilantin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma,

lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs of DRESS.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Effects on Vitamin D and Bone

The chronic use of phenytoin in patients with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, and osteomalacia) and bone fractures. Phenytoin induces hepatic metabolizing enzymes. This may enhance the metabolism of vitamin D and decrease vitamin D levels, which may lead to vitamin D deficiency, hypocalcemia, and hypophosphatemia. Consideration should be given to screening with bone-related laboratory and radiological tests as appropriate and initiating treatment plans according to established guidelines.

Effects of Alcohol Use on Phenytoin Serum Levels

Acute alcoholic intake may increase phenytoin serum levels, while chronic alcoholic use may decrease serum levels.

Exacerbation of Porphyria

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy:

Clinical:

Risks to Mother. An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see PRECAUTIONS, Laboratory Tests). However, postpartum restoration of the original dosage will probably be indicated.

Risks to the Fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two- to three-fold that in the general population. However, the relative contributions of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy.

Postpartum Period. A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Preclinical:

Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m² basis) to pregnant rabbits.

PRECAUTIONS

General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined. If early signs of dose-related CNS toxicity develop, plasma levels should be checked immediately.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See WARNINGS section.)

Information for Patients:

Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking Dilantin. Instruct patients to take Dilantin only as prescribed.

Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, e.g., surgery, etc.

Patients should be instructed to use an accurately calibrated measuring device when using this medication to ensure accurate dosing.

Patients should be made aware of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Patients, their caregivers, and families should be counseled that AEDs, including Dilantin, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS: Pregnancy section).

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments. Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10 to 20 μ g/mL (unbound phenytoin concentrations of 1 to 2 μ g/mL).

Drug Interactions: Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 enzymes CYP2C9 and CYP2C19, and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

The most commonly occurring drug interactions are listed below:

Note: The list is not intended to be inclusive or comprehensive. Individual drug package inserts should be consulted.

Drugs that affect phenytoin concentrations:

- Drugs, which may increase phenytoin serum levels, include: acute alcohol intake, amiodarone, anti-epileptic agents (felbamate, topiramate, oxcarbazepine), azoles (fluconazole, ketoconazole, itraconazole, voriconazole), chloramphenicol, chlordiazepoxide, cimetidine, diazepam, disulfiram, estrogens, ethosuximide, fluorouracil, fluoxetine, fluvoxamine, H₂-antagonists, halothane, isoniazid, methylphenidate, omeprazole, phenothiazines, salicylates, sertraline, succinimides, sulfonamides, ticlopidine, tolbutamide, trazodone, and warfarin.
- Drugs, which may decrease phenytoin levels, include: carbamazepine, chronic alcohol abuse, nelfinavir, reserpine, ritonavir, and sucralfate.
- Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.
- Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid, and sodium valproate serum levels is unpredictable.
- The addition or withdrawal of these agents in patients on phenytoin therapy may require an adjustment of the phenytoin dose to achieve optimal clinical outcome.

Drugs affected by phenytoin:

- Drugs that should not be coadministered with phenytoin: Delavirdine
- Drugs whose efficacy is impaired by phenytoin include: azoles (fluconazole, ketoconazole, itraconazole, voriconazole), corticosteroids, doxycycline, estrogens, furosemide, irinotecan, oral contraceptives, paclitaxel, paroxetine, quinidine, rifampin, sertraline, teniposide, theophylline, vitamin D, and warfarin.
- Increased and decreased PT/INR responses have been reported when phenytoin is coadministered with warfarin.
- Phenytoin decreases plasma concentrations of certain HIV antivirals (amprenavir, efavirenz, Kaletra (lopinavir/ritonavir), indinavir, nelfinavir, ritonavir, saquinavir), and anti-epileptic agents (felbamate, topiramate, oxcarbazepine, quetiapine).
- The addition or withdrawal of phenytoin during concomitant therapy with these agents may require adjustment of the dose of these agents to achieve optimal clinical outcome.

Drug Enteral Feeding/Nutritional Preparations Interaction: Literature reports suggest that patients who have received enteral feeding preparations and/or related nutritional supplements have lower than

expected phenytoin plasma levels. It is therefore suggested that phenytoin not be administered concomitantly with an enteral feeding preparation. More frequent serum phenytoin level monitoring may be necessary in these patients.

Drug/Laboratory Test Interactions: Phenytoin may decrease serum concentrations of T4. It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations.

Carcinogenesis: See WARNINGS section for information on carcinogenesis.

Pregnancy:

Pregnancy Category D; See WARNINGS section.

To provide information regarding the effects of *in utero* exposure to Dilantin, physicians are advised to recommend that pregnant patients taking Dilantin enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Nursing Mothers: Infant breast feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

Pediatric Use: See DOSAGE AND ADMINISTRATION section.

Geriatric Use: Phenytoin clearance tends to decrease with increasing age (see CLINICAL PHARMACOLOGY: Special Populations).

ADVERSE REACTIONS

Body As a Whole: Allergic reactions in the form of rash and rarely more serious forms (see Skin and Appendages paragraph below) and DRESS (see WARNINGS) have been observed. Anaphylaxis has also been reported.

There have also been reports of coarsening of facial features, systemic lupus erythematosus, periarteritis nodosa, and immunoglobulin abnormalities.

Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination, somnolence, and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, paresthesias, and headaches have also been observed. There have also been rare reports of phenytoin-induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Digestive System: Nausea, vomiting, constipation, enlargement of the lips, gingival hyperplasia, toxic hepatitis and liver damage.

Skin and Appendages: 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, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see WARNINGS section). There have also been reports of hypertrichosis.

Hematologic and Lymphatic System: Hematopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported (see WARNINGS section).

Special Senses: Altered taste sensation including metallic taste.

Urogenital: Peyronie's disease

OVERDOSAGE

The lethal dose in pediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL; dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric patients.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

DOSAGE AND ADMINISTRATION

FOR ORAL ADMINISTRATION ONLY; NOT FOR PARENTERAL USE

Serum concentrations should be monitored and care should be taken when switching a patient from the sodium salt to the free acid form. Dilantin® Kapseals® is formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in Dilantin-125 Suspension and Dilantin Infatabs. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and vice versa.

General: Dosage should be individualized to provide maximum benefit. In some cases serum blood level determinations may be necessary for optimal dosage adjustments—the clinically effective serum level is usually 10–20 mcg/mL. With recommended dosage, a period of seven to ten days may be required to achieve steady-state blood levels with phenytoin and changes in dosage (increase or decrease) should not be carried out at intervals shorter than seven to ten days.

Adult Dose: Patients who have received no previous treatment may be started on one teaspoonful (5 mL) of Dilantin-125 Suspension three times daily, and the dose is then adjusted to suit individual requirements. An increase to five teaspoonfuls daily may be made, if necessary.

Dosing in Special Populations

Patients with Renal or Hepatic Disease: Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution. Unbound phenytoin concentrations may be more useful in these patient populations.

Elderly Patients: Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

Pediatric: Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dose (300 mg/day).

HOW SUPPLIED

N 0071-2214-20—Dilantin-125[®] Suspension (phenytoin oral suspension, USP), 125 mg phenytoin/5 mL with a maximum alcohol content not greater than 0.6 percent, an orange suspension with an orange-vanilla flavor; available in 8-oz bottles.

Store at controlled room temperature $20^{\circ}-25^{\circ}C$ ($68^{\circ}-77^{\circ}F$). [See USP.] Protect from freezing and light.

Distributed by



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MEDICATION GUIDE

DILANTIN-125[®] (Dī LAN' tĭn-125) (Phenytoin Oral Suspension, USP)

Read this Medication Guide before you start taking DILANTIN and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about DILANTIN, ask your healthcare provider or pharmacist.

What is the most important information I should know about DILANTIN?

Do not stop taking DILANTIN without first talking to your healthcare provider. Stopping DILANTIN suddenly can cause serious problems.

DILANTIN can cause serious side effects including:

1. Like other antiepileptic drugs, DILANTIN may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability

- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase activity and talking (mania)
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop taking DILANTIN without first talking to a healthcare provider.

Stopping DILANTIN suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

2. Dilantin may harm your unborn baby.

- If you take DILANTIN during pregnancy, your baby is at risk for serious birth defects.
- Birth defects may occur even in children born to women who are not taking any medicines and do not have other risk factors
- If you take DILANTIN during pregnancy, your baby is also at risk for bleeding problems right after birth. Your healthcare provider may give you and your baby medicine to prevent this.
- All women of child-bearing age should talk to their healthcare provider about using other possible treatments instead of DILANTIN. If the decision is made to use DILANTIN, you should use effective birth control (contraception) unless you are planning to become pregnant.
- Tell your healthcare provider right away if you become pregnant while taking DILANTIN. You and your healthcare provider should decide if you will take DILANTIN while you are pregnant.
- **Pregnancy Registry:** If you become pregnant while taking DILANTIN, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- 3. Swollen glands (lymph nodes)
- 4. Allergic reactions or serious problems which may affect organs and other parts of your body like the liver or blood cells. You may or may not have a rash with these types of reactions. Symptoms can include any of the following:
 - swelling of your face, eyes, lips, or tongue
 - trouble swallowing or breathing
 - a skin rash
 - hives
 - fever, swollen glands (lymph nodes), or sore throat that do not go away or come and go

- painful sores in the mouth or around your eyes
- yellowing of your skin or eyes
- bruising or bleeding
- severe fatigue or weakness
- severe muscle pain
- frequent infections or an infection that does not go away
- loss of appetite (anorexia)

• nausea or vomiting

Call your healthcare provider right away if you have any of the symptoms listed above.

What is DILANTIN?

DILANTIN is a prescription medicine used to treat tonic-clonic (grand mal), complex partial (psychomotor or temporal lobe) seizures, and to prevent and treat seizures that happen during or after brain surgery.

Who should not take DILANTIN?

Do not take DILANTIN if you:

- are allergic to phenytoin or any of the ingredients in DILANTIN. See the end of this leaflet for a complete list of ingredients in DILANTIN.
- have had an allergic reaction to CEREBYX (fosphenytoin), PEGANONE (ethotoin), or MESANTOIN (mephenytoin).
- take delavirdine

What should I tell my healthcare provider before taking DILANTIN?

Before you take DILANTIN, tell your healthcare provider if you:

- Have or had liver disease
- Have or had porphyria
- Have or had diabetes
- Have or have had depression, mood problems, or suicidal thoughts or behavior
- Are pregnant or plan to become pregnant. If you become pregnant while taking DILANTIN, the level of DILANTIN in your blood may decrease, causing your seizures to become worse. Your healthcare provider may change your dose of DILANTIN.
- Are breast feeding or plan to breastfeed. DILANTIN can pass into breast milk. You and your healthcare provider should decide if you will take DILANTIN or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including

prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking DILANTIN with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take DILANTIN?

- Take DILANTIN exactly as prescribed. Your healthcare provider will tell you how much DILANTIN to take.
- Your healthcare provider may change your dose. Do not change your dose of DILANTIN without talking to your healthcare provider.
- DILANTIN can cause overgrowth of your gums. Brushing and flossing your teeth and seeing a dentist regularly while taking DILANTIN can help prevent this.
- If you take too much DILANTIN, call your healthcare provider or local Poison Control Center right away.
- Do not stop taking DILANTIN without first talking to your healthcare provider. Stopping DILANTIN suddenly can cause serious problems.

What should I avoid while taking DILANTIN?

- Do not drink alcohol while you take DILANTIN without first talking to your healthcare provider. Drinking alcohol while taking DILANTIN may change your blood levels of DILANTIN which can cause serious problems.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how DILANTIN affects you. DILANTIN can slow your thinking and motor skills.

What are the possible side effects of DILANTIN?

See "What is the most important information I should know about DILANTIN?"

DILANTIN may cause other serious side effects including:

• Softening of your bones (osteopenia, osteoporosis, and osteomalacia). This can cause broken bones.

Call your healthcare provider right away, if you have any of the symptoms listed above.

The most common side effects of DILANTIN include:

- problems with walking and coordination
- slurred speech
- confusion
- dizziness
- trouble sleeping
- nervousness

- tremor
- headache
- nausea
- vomiting
- constipation
- rash

These are not all the possible side effects of DILANTIN. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DILANTIN?

• Store DILANTIN-125 Suspension at room temperature between 68°F to 77°F (20°C to 25°C). Protect from light. Do not freeze.

Keep DILANTIN and all medicines out of the reach of children.

General information about DILANTIN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DILANTIN for a condition for which it was not prescribed. Do not give DILANTIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about DILANTIN. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about DILANTIN that was written for healthcare professionals.

For more information about DILANTIN, visit <u>http://www.pfizer.com</u> or call 1-800-438-1985.

What are the ingredients in DILANTIN-125?

<u>Oral Suspension</u> Active ingredient: phenytoin, USP Inactive ingredients: alcohol, USP (maximum content not greater than 0.6 percent); banana flavor; carboxymethylcellulose sodium, USP; citric acid, anhydrous, USP; glycerin, USP; magnesium aluminum silicate, NF; orange oil concentrate; polysorbate 40, NF; purified water, USP; sodium benzoate, NF; sucrose, NF; vanillin, NF; and FD&C yellow No. 6.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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APPLICATION NUMBER: NDA 08-762/S-039

OTHER REVIEW(S)

Clinical Safety Review

Drug:	Phenytoin	
NDA:	08-762 Dilantin-125 [®] (phenytoin, USP) oral suspension	
Sponsor:	Pfizer	
Material reviewed:	: CBE Labeling Supplement (S39) submitted 8/28/09	
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Date:	04/12/11	
Reviewer:	Mary Doi, M.D., M.S., Medical Officer, DNP Safety Team	
Team Leader:	Sally Yasuda, Pharm D., M.S., DNP Safety Team	

Dilantin CBE Labeling Supplement

1. Executive Summary

This review evaluates a CBE labeling supplement for oral Dilantin® in which the Sponsor proposed the following four changes to the safety information:

- Strengthen the warning concerning serious skin reactions.
- Add language concerning the association of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) events with HLA-B*1502 in Asian patients.
- Add language concerning anticonvulsant hypersensitivity syndrome.
- Add language concerning the

(b) (4)

Following evaluation of the Sponsor's submission and of the literature, this review recommends the following:

- Strengthen the warning concerning serious skin reactions and include this information in the Warnings section of labeling.
- Include in the Warnings sections of labeling information concerning the association of SJS/TEN with HLA-B*1502 in patients of Asian ancestry.
- Include in the Warnings section of the labeling information regarding multiorgan hypersensitivity reactions/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and that this information should be consistent with such language being written in other AED labels. Information about DRESS should be added to "Information for Patients."
- Language regarding (b) (4) should not be added to the labeling as there is insufficient evidence to support this association.
- In addition to those changes, this review recommends adding general information on genetic variations in P450-mediated metabolism of phenytoin as a risk for unusually high plasma concentrations, rather than referring to a "congenital enzyme deficiency."

The Division and the Sponsor have agreed upon labeling.

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2. Review of Current Submission

On August 28, 2009, in accordance with 21 CFR §314.70 (c)(6)(iii) Pfizer submitted a Change Being Effected (CBE) Supplement to advise the agency of changes made to the package insert for Dilantin®. The Sponsor proposed four main changes to the safety information:

- 1) strengthen the warning concerning serious skin reactions.
- and add language concerning
- 2) the association of phenytoin-induced Stevens -Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) with HLA-B*1502 in patients of Asian ancestry
- 3) anticonvulsant hypersensitivity syndrome
- 4) (b) (4)

3. Strengthening the Warning Concerning Serious Skin Reactions

3.1 Background

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCARs) to medications characterized by widespread detachment of epidermis and erosions of mucous membranes. Based on the European Study of SCAR (EuroSCAR-study), the use of phenytoin is strongly associated with SJS/TEN with a multivariate relative risk of 17 (95% CI 4.1-68).¹ In other studies, the incidence of SJS/TEN due to phenytoin has been reported as 8.3 per 10,000 new users.² Even though rare, SJS and TEN have a significant impact on public health because of high mortality (20-25%), high morbidity, and need for alternative therapies. Typically, the onset of SJS/TEN is 4 to 28 days after starting the drug, which is usually earlier than other drug hypersensitivity reactions (see section 5 below).³ This temporal information is also important to emphasize in the labeling to aid in assessing the causality of medications in SJS or TEN and in distinguishing these reactions from other hypersensitivity reactions.

According to the information provided in the CBE, review of the Sponsor's safety database for cases reported as of 31 January 2008 found 628 cases reporting an event contained in the MedDRA (v. 10.1) Severe Cutaneous Adverse Reactions SMQ (narrow). Because of these cases, the Sponsor's opinion is to include this information regarding SCAR, not only in the Precautions and Adverse Reactions section, but also in the Warnings section.

3.2 Current phenytoin labeling PRECAUTIONS General: ...

¹ Mockenhaupt M et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: Assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR Study. J Investigative Dermatol. 2008; 128: 35-44.

² Mockenhaupt M et al. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Neurology. 2005; 64: 1134-8.

³ Mockenhaupt M et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: Assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR Study. J Investigative Dermatol. 2008; 128: 35-44.

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.

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).

3.3 Sponsor's proposed additions to phenytoin labeling

WARNINGS (b) (4)

3.4 Comments on Sponsor's proposed label

SJS and TEN are addressed in the currently approved labeling only in the Precautions and Adverse Reactions section. However, as discussed above, sufficient information exists in the literature and in the Sponsor's database to confirm the occurrence of SJS/TEN associated with phenytoin and to support a causal relationship. Therefore, information regarding SJS and TEN should be added to the Warnings section and removed from the Precautions section in order to emphasize these serious reactions. These paragraphs should be added directly after the subsection on Suicidal Behavior and Ideation instead of at the end of the Warnings section. The paragraph heading should be changed from ^{(b) (4)} to Serious Dermatologic Reactions, similar to in the Tegretol® labeling. The reviewer recommends changing the first part of the Sponsor's paragraph to use language in the Tegretol® labeling along with adding the temporal information regarding the onset of SJS/TEN. The reviewer would delete the last two sentences of the Sponsor's paragraph: "

" These same

morbilliform eruptions can also occur initially in the multiorgan hypersensitivity reactions

associated with phenytoin.⁴ Therefore, these rashes, although most often benign, can be the first sign of more serious hypersensitivity reactions in which further phenytoin would be

contraindicated. Finally, because severe cutaneous reactions can also be seen as a component of multiorgan hypersensitivity, the label should emphasize the need to also check for more systemic signs and symptoms of hypersensitivity if a rash is present.⁵ Multiorgan hypersensitivity will be discussed later in this review.

3.5 Reviewer's recommended phenytoin labeling changes

The sponsor's proposed additions are shown in <u>green underline</u>. Medical reviewer's proposed additions are shown in <u>red underline</u> with deletions as <u>strikethrough</u>.

WARNINGS

^{(b) (4)}-Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days, but can occur later. Dilantin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (see **DRESS/Multiorgan hypersensitivity** below).

(b) (4)

(b) (4)

PRECAUTIONS General: ...

⁴ Bachot N, Roujeau JC. Differential Diagnosis of Severe Cutaneous Drug Eruptions. Am J Clin Dermatol. 2003; 4(8): 561-572.

⁵ Knowles SR et al. Anticonvulsant hypersensitivity syndrome: incidence, prevention, and management. Drug Safety. 1999; 21(6): 489-501.

4. The Association of SJS and TEN with HLA-B*1502 in Patients of Asian Ancestry

4.1 Background

Ever since observations were made of a familial pattern of severe drug hypersensitivity, investigators have been searching for genetic markers for SJS and TEN.⁶ In 2004, a study presented a strong link between carbamazepine (CBZ)-induced SJS/TEN and the HLA-B*1502 allele.⁷ Further studies confirmed these results and also reported that this relationship was specific to certain ethnicities, in only certain groups of Asian ancestry (strongest in China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan) but not in Japanese, Koreans, or Caucasians.⁸ It is still unclear whether this allele is directly involved in eliciting the CD8+ T-cell mediated cytotoxic response or if this allele is in strong linkage disequilibrium with the causative polymorphism (that is only in Asians).⁹

In 2007, the FDA performed a review of carbamazepine associated SJS/TEN in Asians and concluded that there was an increased risk of this condition in individuals with the HLA-B*1502 allele. Changes were made to Tegretol® labeling that included this information in the boxed warning and that recommended testing for this allele in specific Asian populations. Later studies examined a possible association of SJS/TEN induced by other antiepileptic drugs (AEDs) and the HLA-B*1502 allele. In November of 2008, the FDA issued a new "Information for Healthcare Professionals to Consider when Prescribing Phenytoin or Fosphenytoin" that reported a possible association between HLA-B*1502 and phenytoin or fosphenytoin-induced SJS/TEN.¹⁰ Healthcare providers were recommended to consider avoiding phenytoin and fosphenytoin as alternatives for carbamazepine in patients who test positive for HLA-B*1502.

As noted above in section 3.1, 628 cases reporting an event contained in the MedDRA (v. 10.1) Severe Cutaneous Adverse Reactions SMQ (narrow) were identified in the Sponsor's safety database as of January 31, 2008. Eighty-four cases reported race/ethnicity as black (50 cases) or Asian (34 cases). However, none of the cases included results of genetic testing relevant to phenytoin metabolism or HLA-B*1502.

4.2 Published studies of the association between phenytoin-induced SJS/TEN and HLA-B*1502

¹⁰ Accessed on November 19, 2010.

⁶ Edwards et al. Concordance of primary generalized epilepsy and carbamazepine hypersensitivity in monozygotic twins. Postgrad Med J. 1999; 75(889): 680-1.

 ⁷ Chung WH et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature. 2004; 428(6982): 486.
 ⁸ Lonjou C et al. A marker for Stevens-Johnson syndrome: ethnicity matters. Pharmacogenomics J. 2006; 6(4): 265-8.

⁹ Man CBL et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia. 2007; 48(5): 1015-18.

http://www_fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124788.htm

The reviewer performed an independent, extensive search of Medline, Embase, and Web of Science for published studies investigating the association between phenytoin-induced SJS/TEN and HLA-B*1502. Three case-control studies were found along with one abstract of another case-control study. The studies are discussed below listed in the order that the studies were published.

4.2.1 Man CBL et al., Hong Kong 2007¹¹

- Case-control study
- 'Ethnic Han Chinese' patients treated in public hospitals in Hong Kong
- Cases developed cutaneous adverse reactions < 8 weeks of starting an AED
- Cases were compared 1:2 to controls
- Controls were patients without cutaneous reactions on the respective AED for > 3 months
 0 14.5% positive for HLA-B*1502
- 24 cutaneous adverse drug reactions
 - o 6 with SJS/TEN
 - 4 CBZ (carbamazepine)-induced, 100% positive for HLA-B*1502
 - 1 PHT (phenytoin)-induced, positive for HLA-B*1502
 - 1 LTG (lamotrigine)-induced, positive for HLA-B*1502
 - o 2 with HSS (drug hypersensitivity syndrome), all negative for HLA-B*1502
 - o 16 with MPE (maculopapular eruption), 12.5% positive for HLA-B*1502
- Authors concluded that the study was limited by its small sample size and further studies needed to be performed to further test this association between PHT-induced SJS/TEN and HLA-B*1502.
- 4.2.2 Locharernkul C et al., Thailand 2008¹²
 - Case-control study
 - 31 cases recruited from a university-based tertiary epilepsy surgery center in Bangkok.
 - "Only reliable temporal relation and clinical manifestation of the drug to the cutaneous reactions were included."
 - 50 controls without cutaneous reactions on the respective AED for > 3 months
 - 31 cutaneous adverse drug reactions
 - o 10 with SJS/TEN
 - 6 CBZ-induced, 100% positive for HLA-B*1502
 - Compared to 19% (8) of controls positive for HLA-B*1502
 - OR = 25.5 (95% CI 2.68-242.61, p=0.0005)
 - 3 patients were tolerant to PHT
 - 4 PHT-induced, 100% positive for HLA-B*1502
 - Compared to 18% (8) of controls positive for HLA-B*1502
 - OR = 18.5 (95% CI 1.82-188.40, p=0.005)
 - 1 patient was tolerant to CBZ
 - o 21 with MPE

¹¹ Man CBL et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia. 2007; 48(5): 1015-18.

¹² Locharernkul C et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia. 2008; 49(12): 2087-91.

- Authors concluded that both CBZ- and PHT-induced SJS are associated with the HLA-B*1502 allele in this Thai population.
- Authors also concluded that because patients who had the HLA-B*1502 allele could be tolerant to a particular AED but then develop SJS/TEN from another AED, the allele may be necessary but not sufficient to cause SJS/TEN.

4.2.3 Hung S et al., Taiwan 2010¹³

- Case-control study from 2002-2008 (the group's earlier study on CBZ from 1996-2003)
- 35 Han Chinese patients from 4 different hospitals in Taiwan/China
- Cases developed SJS/TEN within 8 weeks of starting an AED (and symptoms resolved upon withdrawal of the drug)
- 180 controls (113 PHT and 67 LTG) without cutaneous reactions on the respective AED for > 3 months. For OXC (oxcarbazepine) controls, 93 healthy subjects randomly selected from a biobank were used.
- Total of 51 HLA alleles A, B, C and DRB1 were assayed
- 26 PHT-induced SJS/TEN cases were found
 - 30.8% (8) positive for HLA-B*1502
 - Compared to 8% (9) of phenytoin controls positive for HLA-B*1502
 - OR = 5.1 (95% CI 1.8-15.1, p=0.0041)
 - None of the 3 patients with TEN were positive for the HLA-B*1502 allele.
 - Other alleles with "significant" [see comment below] associations with PHT:
 - HLA-B*1301 (OR 3.7, 95% CI 1.4-10.0, p=0.015)
 - Of note, HLA-B*1301 is strongly associated with trichloroethylene-induced hypersensitivity dermatitis (including SJS/TEN) among exposed workers in China.¹⁴
 - HLA-DRB1*1602 (OR 4.3, 95% CI 1.4-12.8, p=0.0128)
 - C_w*0801 (OR 3.0, 95% CI 1.1-7.8, p=0.028)
 - C_w*0801 is within the haplotype of B*1502
- 6 LTG-induced SJS/TEN cases were found
 - 33.3% (2) positive for HLA-B*1502
 - Compared to 9% (6) of controls positive for HLA-B*1502
 - \circ OR = 5.1 (95% CI 0.8-33.8, p=0.1266)
- 3 OXC-induced SJS/TEN cases were found
 - o 100% positive for HLA-B*1502
 - Compared to 8% (7) controls positive for HLA-B*1502
 - o $OR = 80.7 (95\% CI 3.8-1714.4, p=8.4x10^{-4})$
- The authors concluded that aromatic AEDs, including CBZ, OXC, and PHT should be avoided in patients with the HLA-B*1502 allele.

Comments: In the statistical methods, this study did not use Bonferroni's method in which a correction factor is applied to the p value when comparisons between multiple groups are

¹³ Hung S et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics. 2010; 11(3): 349-356.

¹⁴ Li H et al. HLA-B*1301 as a biomarker for genetic susceptibility to hypersensitivity dermatitis induced by trichloroethylene among workers in China. Environmental Health Perspectives. 2007; 115(11) 1553-6.

studied. Each of the p values needed to be multiplied by the total number of alleles tested which equals 51 alleles (8 HLA-A, 16 HLA-B, 10 HLA-C_w, and 17 HLA-DRB1). Once these correction factors are applied to the p values, none of the allele associations reach any statistical significance. The closest p value to 0.05 is the association with HLA-B*1502 with a corrected p value of 0.21. The authors did make a comment in the discussion section that the "results of this study were not corrected for multiple comparisons because of the small sample size and because some of the alleles were present in very low frequencies." However, these are not valid reasons to forgo applying this correction factor. Therefore, the authors' conclusion that phenytoin should be avoided in patients with the HLA-B*1502 allele is too strong of a conclusion to make from this study that in actuality did not reveal a statistically significant association between PHT-induced SJS/TEN and the HLA-B*1502 allele. Instead, the study was useful only in the generation of hypotheses that there may be possible associations between PHT-induced SJS/TEN and some alleles, particularly the HLA-B*1502, HLA-B*1301, and HLA-DRB1*1602 alleles. Future studies need to be performed to further analyze these associations.

It would have also been informative for the study to have included patients with CBZinduced SJS/TEN so that a direct comparison can be made with patients with these other AED-induced SJS/TEN. Out of all of the AEDs, OXC has the most structural similarity with CBZ and with this study's result that OXC-induced SJS/TEN had the strongest association (OR 80.7) with HLA-B*1502, this association should be further investigated.

4.2.4 Tassaneeyakul W et al., Thailand 2010 (abstract only)¹⁵

- Case-control study
- Cases developed SJS/TEN or SCADR (severe cutaneous adverse drug reactions which include SJS, TEN, and HSS)
- CBZ-induced SJS/TEN patients
 - 89.6% (45) cases positive for HLA-B*1502
 - Compared to 10.4% (5) controls positive for HLA-B*1502
- PHT-induced SCADR patients
 - 27.8% (5) cases positive for HLA-B*1502
 - Compared to 19.4% (7) controls positive for HLA-B*1502
- The authors concluded that the HLA-B*1502 allele is not a good marker for PHTinduced SCADR in this Thai population.

Comment: This abstract reports allele results for PHT-induced SCADR patients instead of PHT-induced SJS/TEN patients. Prior studies revealed different relationships between AED-induced SJS/TEN and AED-induced HSS, therefore grouping together SJS/TEN patients with HSS patients may bias this association towards the null.

4.3 Sponsor's review of the literature

The sponsor discussed only the first study by Man et al. in their clinical overview that was submitted along with these labeling changes in Aug of 2009.¹⁶ Their conclusions were the

¹⁵ Tassaneeyakul W et al. Association of HLA-B1502 and severe cutaneous adverse reactions caused by aromatic antiepileptic drugs. Abstract. Drug Metabolism Reviews. 2010; 42(S1): 255.

¹⁶ Man CBL et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia. 2007; 48(5): 1015-18.

following: "Given the small sample size and lack of supporting data, no conclusive statement can be made about this association." "Although the current literature sample size is quite small, the potential seriousness of these hypersensitivity reactions warrants including the following statement to the Warnings section of the phenytoin prescribing information."

4.4 Reviewer discussion of the literature

The first study by Man CBL et al had such a small sample size (only one case of PHT-induced SJS/TEN) that it is difficult to make any conclusions of the association between PHT-induced SJS/TEN and the HLA-B*1502 allele. With the high allele frequency of HLA-B*1502 in this region (15%), these results might have occurred by chance alone. However, although the study by Locharernkul C et al also had a small sample size, it is harder to attribute all four cases of PHT-induced SJS/TEN positive for HLA-B*1502 due to chance alone (the OR was 18.5 with a p value that was statistically significant). The Hung et al. study did have a larger sample size and tested for multiple alleles. This study reported a possible association; the OR for patients carrying the HLA-B*1502 allele to develop SJS/TEN was 5.1 but with a p value (after the Bonferroni correction) that does not reach statistical significance (see comment above in section 4.2.3). This study was also useful in revealing that there may be associations between PHT-induced SJS/TEN with other alleles.

At this point, the evidence is not strong enough to make a recommendation to perform screening for the presence of the HLA-B*1502 allele prior to initiating treatment with phenytoin, although, this decision may change once more information is available regarding this association with this allele. Other medications that have recommendations for genetic screening included in the labeling have much stronger relationships between their drug-induced hypersensitivity reactions and the respective alleles (abacavir and HLA-B*5701 and CBZ and HLA-B*1502). For example, the OR for patients carrying the HLA-B*1502 allele to develop CBZ-induced SJS/TEN was 1357 (95% CI 193-8838, $p_c = 1.6 \times 10^{-41}$).¹⁷ Similarly, the OR for patients carrying the HLA-B*5701 allele to develop abacavir-induced hypersensitivity was 117 (95% CI 29-481, $p_c < 0.0001$).¹⁸

There is however enough evidence currently to conclude that there may be an association between SJS/TEN induced by phenytoin and the HLA-B*1502 allele. Therefore, it would be prudent to add information to the phenytoin labeling to consider avoiding the use of phenytoin in HLA-B*1502 positive patients when alternative therapies are otherwise equally available.

Further studies need to be performed with direct comparisons made between multiple AEDs (particularly CBZ, PHT, and OXC) using expanded HLA genotyping to specifically include the HLA-B*1301 and HLA-B*1502 alleles with the correct use of the Bonferroni correction factor.

4.5 Sponsor's proposed additions to phenytoin labeling

WARNINGS

¹⁷ Hung S et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenetics and Genomics. 2006; 16(4): 297-306.

¹⁸ Mallal S et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002; 359: 727-732.

(b) (4)

...

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using (^{(b) (4)}. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking (^{(b) (4)})

4.6 Comments on Sponsor's proposed label

The reviewer agrees with the addition of this information regarding HLA-B*1502 to the phenytoin labeling which is similar to the information already included in the Tegretol® labeling. However, the last sentence of the paragraph should be changed to the sentence that was included in the 2008 FDA Alert: "Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502."¹⁹ Also, information needs to be added to the phenytoin labeling regarding the limitations of genotyping, analogous to the information included already in the Tegretol® labeling.

4.7 Reviewer's recommended changes to phenytoin labeling

The sponsor's proposed additions are shown in <u>green underline</u>. Medical reviewer's proposed additions are shown in <u>red underline</u> with deletions as <u>strikethrough</u>.

WARNINGS

^{(b) (4)}-Serious Dermatologic Reactions

•••

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine- ^{(b) (4)}. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin.

<u>—Consideration should be given to avoiding phenytoin as an alternative for</u> carbamazepine in patients positive for HLA-B*1502.

The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

¹⁹ Accessed on November 19, 2010.

http://www_fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124788.htm

5. Anticonvulsant Hypersensitivity Syndrome

5.1 Safety Review of Multiorgan hypersensitivity/DRESS syndrome with antiepileptic drugs by Lourdes Villalba, MD (1/16/09)

Dr. Villalba found that zonisamide (EB05=43.6), carbamazepine (EB05=28.6), and phenytoin (EB05=14.2) were among the drugs with the highest number of reports of drug hypersensitivity and DRESS in the FDA Adverse Events Report System. However despite the strong association between phenytoin and DRESS, the phenytoin label itself only briefly mentions phenytoin hypersensitivity in the WARNINGS and PRECAUTIONS sections without the mention of fatal reactions. After reviewing the labels of the anticonvulsants, she noted that although most of these labels contain some information about multiorgan hypersensitivity reactions, they varied on the language, location, and degree of detail. In her opinion, multiorgan hypersensitivity reactions (hypersensitivity/DRESS) should be part of class labeling for most antiepileptic drugs and that the specific term DRESS with the emphasis that these are potentially fatal reactions should be included within the WARNINGS and PRECAUTIONS section in all of these labels. The Division has already taken steps to address this need in the labels for lacosamide, lamotrigine, and gabapentin and has drafted

gabapentin (draft).

5.2 Other anticonvulsant labels with the specific term DRESS

5.2.1 Lacosamide (Vimpat®)

WARNINGS

5.6 Multiorgan Hypersensitivity Reactions

One case of symptomatic hepatitis and nephritis was observed among 4011 subjects exposed to VIMPAT during clinical development. The event occurred in a healthy volunteer, 10 days after stopping VIMPAT treatment. The subject was not taking any concomitant medication and potential known viral etiologies for hepatitis were ruled out. The subject fully recovered within a month, without specific treatment. The case is consistent with a delayed multiorgan hypersensitivity reaction. Additional potential cases included 2 with rash and elevated liver enzymes and 1 with myocarditis and hepatitis of uncertain etiology.

Multiorgan hypersensitivity reactions (also known as <u>Drug Reaction with Eosinophilia and</u> <u>Systemic Symptoms</u>, or DRESS) have been reported with other anticonvulsants and typically, although not exclusively, present with fever and rash associated with other organ system involvement, that may or may not include eosinophilia, hepatitis, nephritis, lymphadenopathy, and/or myocarditis. Because this disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. If this reaction is suspected, VIMPAT should be discontinued and alternative treatment started.

5.2.2 Gabapentin (Neurontin®) Capsules

The Division has made recommendations to Pfizer to include information about the risk for multiorgan hypersensitivity, or DRESS, in the labeling of Neurontin® (gabapentin) Capsules. The Division requested the addition of the following as the last paragraph to the Warnings section.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including Neurontin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Neurontin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.3 Current phenytoin labeling

CONTRAINDICATIONS

Dilantin is contraindicated in those patients with a history of hypersensitivity to phenytoin or other hydantoins.

WARNINGS

Lymphadenopathy

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, e.g., fever, rash, and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

PRECAUTIONS

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see CONTRAINDICATIONS). Additionally, caution should be exercised if using structurally similar (e.g., barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

ADVERSE REACTIONS [last paragraph]

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, periarteritis nodosa and immunoglobulin abnormalities.

5.4 Sponsor's proposed additions to phenytoin labeling



5.5 Comments on Sponsor's proposed label

In accordance with the other anticonvulsant labels and Dr. Villalba's safety review, the specific term DRESS should be added to the phenytoin labeling (and the old terminology of "serum sickness" should be removed). Furthermore, the possibility that this condition can be fatal or life-threatening should be emphasized with the need for the patient to be evaluated immediately if the signs or symptoms are present. Also, the information that this syndrome can have a variety of different presentations should be included, emphasizing the possibility that the initial signs of fever, rash, and lymphadenopathy may or may not be associated with other organ involvement, such as hepatitis, hepatic failure, blood dyscrasias, myocarditis, myositis, or acute multiorgan failure. And the early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even without a rash.

Comments on the following sentences from the Sponsor's proposed label:

a) " ^{(b) (4)}."

Although the exact pathophysiology is unknown, there is strong evidence that this syndrome is an immunologic adverse drug event associated with a relative excess of reactive metabolites

(b) (4)

(arene oxides) which causes direct cytotoxic effects and induces type IV hypersensitivity reactions.²⁰ Therefore, this statement should not be included in the labeling at this time.

It is important to include this sentence that emphasizes the temporal relationship between initiation of treatment and appearance of symptoms which is typically later than most other serious skin reactions.²¹ This interval between first drug exposure and symptoms appears to be different for different AEDs. A retrospective chart review of 10 patients using phenytoin reported a mean interval of drug intake and onset of the syndrome of 24.6 days (SD = 11.6 days)²² which is roughly equal to an interval of 2-5 weeks. There was a statistically significant difference (p=0.01) in this mean interval between patients using phenytoin and carbamazepine (mean 45 ± 24.1 SD days). [Of note, other anticonvulsant labeling such as for valproate and oxcarbazepine include information regarding this interval as "median time to detection 21 days: range 1 to 40 days" and "median time to detection 13 days: range 4-60", respectively.]



One of the articles cited by the sponsor did state that the incidence of skin rashes has been estimated between 1% and 10% (up to 19%) of exposures.²³ However, this statement should not be included in the labeling because it may minimize the patient's need to be evaluated if a rash develops.

d) "	(b) (4)
	²⁷ .

Please see Section 6 for further details on

Studies have reported that patients with first-degree relatives who developed DRESS may have a higher risk of also developing DRESS.^{24,25} These studies mainly used an in vitro lymphocyte toxicity (LTA) assay which measures the ability of the patient's lymphocytes to detoxify the oxidative metabolites (arene oxides) thought to be the cause of DRESS. A positive LTA result means that significant lymphocyte cell death occurred i.e. the patient lacked the enzyme (microsomal epoxide hydroxylase) that converts the arene oxides to nontoxic metabolites. In the

²⁰ Bohan, KH et al. Anticonvulsant hypersensitivity syndrome: Implications for pharmaceutical care. Pharmacotherapy. 2007; 27(10): 1425-1439.

²¹ Bachot N, Roujeau JC. Differential Diagnosis of Severe Cutaneous Drug Eruptions. Am J Clin Dermatol. 2003; 4(8): 561-572.

²² Mansur AT et al. Anticonvulsant hypersensitivity syndrome: clinical and laboratory features. Int J Dermatol. 2008; 47: 1184-1189.

²³ Sierra NM et al. Cross hypersensitivity syndrome between phenytoin and carbamazepine. Pharm World Sci. 2005; 27: 170-174.

²⁴ Gennis MA et al. Familial occurrence of hypersensitivity to phenytoin. Am J Med. 1991; 91(6): 631-4.

²⁵ Shear NH, Speilberg SP. Anticonvulsant hypersensitivity syndrome: in vitro risk assessment. Jour of Clin Investigation. 1988; 82: 1826-1832.

study by Gennis et al., three siblings from a family of 12 siblings developed hypersensitivity reactions to phenytoin. In vitro studies demonstrated abnormal metabolite detoxification in these 3 patients and several of their siblings. These studies concluded that first-degree relatives of an afflicted individual may have a risk that approaches 1 in 4^{26} (versus the reported incidence of 1 in 1000 to 1 in 10,000 exposures in the general population).²⁷ Even though these are mainly in vitro studies and specific genetic defects have not yet been identified, it is important to counsel family members of this increased risk in order to choose safer alternatives (see next paragraph) or to more closely monitor for symptoms and signs.

Patients who have experienced this syndrome in the past do indeed have a higher risk of developing DRESS. This is important to emphasize especially when choosing an alternative AED. Studies have shown that cross-sensitivity occurs between aromatic (and possibly nonaromatic) AEDs. These studies which looked primarily at the development of rashes as a marker of hypersensitivity demonstrated a cross-sensitivity of 40-58% between phenytoin and carbamazepine.²⁸ In a retrospective chart review, cross-sensitivity for the development of DRESS between phenytoin and carbamazepine was observed in 9 out of 20 cases (45%).²⁹ Therefore, it would be prudent for this information regarding cross-sensitivity to be included in the Warnings section specifically listing carbamazepine.

[Of note, the Trileptal® (oxcarbazepine) label contains the following recommendation: WARNINGS

"Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25%-30% of them will experience hypersensitivity reactions with Trileptal. For this reason patients should be specifically questioned about any prior experience with carbamazepine, and patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with Trileptal only if the potential benefit justifies the potential risk."]

The sponsor cited a reference which stated that risk factors for DRESS included HIV infection and cancer while reporting a case of a patient with lung adenocarcinoma treated with chemotherapy/radiation who was also on phenytoin for anticonvulsive prophylaxis for her brain metastases and later developed DRESS.³⁰ This reference also cited a source that presented a case report of a patient with cancer, specifically glioblastoma multiforme treated with chemotherapy, dexamethasone, and phenytoin who later developed DRESS.³¹ This paper also referred to an article published in 1993 that reported 3 cases of DRESS, none with the comorbidities of HIV or cancer.³² Therefore, there are a number of case reports of patients with cancer status post immunosuppressive therapy who have developed DRESS, however, it is

²⁶ Gennis MA et al. Familial occurrence of hypersensitivity to phenytoin. Am J Med. 1991; 91(6): 631-4.

²⁷ Gogtay NJ et al. Anticonvulsant hypersensitivity syndrome: a review. Expert Opin. Drug Saf. 2005; 4(3): 571-

²⁸ Hyson C, Sadler M. Cross sensitivity of skin rashes with antiepileptic drugs. Can J Neurol Sci. 1997; 24: 245-9. ²⁹ Sierra NM et al. Cross hypersensitivity syndrome between phenytoin and carbamazepine. Pharm World Sci.

^{2005; 27: 170-174.}

³⁰ Kaminsky A et al. Anticonvulsant hypersensitivity syndrome. Int J of Derm. 2005; 44: 594-598.

³¹ Redondo P et al. Drug-induced hypersensitivity syndrome and toxic epidermal necrolysis. Treatment with Nacetylcysteine. Br J Dermatol. 1997; 136: 645-646.

³² Handfield-Jones SE et al. The anticonvulsant hypersensitivity syndrome. Br J Dermatol. 1993; 129 (2): 175-7.

unclear whether this is a true risk factor or related to a higher incidence of phenytoin use among cancer patients with brain metastases for seizure prophylaxis.

Furthermore, it is unclear that immunosuppression, specifically HIV infection is a true risk factor for DRESS. It has been postulated in the literature that there is higher incidence of hypersensitivity reactions in these patients because of HIV-related glutathione deficiency, which could impair the detoxification of the reactive metabolites.³³ However, studies have failed to identify an association between drug hypersensitivity and glutathione levels in these patients.³⁴ Therefore, ^{(D) (4)} and this

information should not be included in the labeling at this time until further studies are available.

e) " ^{(b) (4)}."

Studies did reveal that in previously sensitized individuals, the syndrome presents more quickly (may occur within one day on rechallenge)³⁵ and that there is an acceleration of the natural disease progression.³⁶ However, it was unclear that this represents a difference in actual severity in these individuals and therefore, this information should not be included in the labeling at this time.

5.6 Reviewer's recommended changes to phenytoin labeling

The sponsor's proposed additions are shown in <u>green underline</u>. Medical reviewer's proposed additions are shown in <u>red underline</u> with deletions as <u>strikethrough</u>.



³³ Chosidow O et al. Drug rashes. What are the targets of cell-mediated cytotoxicity? Archives of Dermatology. 1994; 130: 627-629.

³⁴ Eliaszewicz M et al. Prospective evaluation of risk factors of cutaneous drug reactions to sulfonamides in patients with AIDS. Journal of the Am Academy of Derm 2002; 47: 40-46.

³⁵ Knowles SR et al. Anticonvulsant hypersensitivity syndrome: incidence, prevention, and management. Drug Safety. 1999; 21(6): 489-501.

³⁶ Sierra NM et al. Cross hypersensitivity syndrome between phenytoin and carbamazepine. Pharm World Sci. 2005; 27: 170-174.

[paragraph after Serious Dermatologic Reactions]

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including Dilantin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved.

(b) (4)

. It is important to

note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Dilantin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

[Move the following paragraph from PRECAUTIONS to WARNINGS within the DRESS paragraph]

Phenytoin-Dilantin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity (see CONTRAINDICATIONS). Additionally, <u>consider alternatives</u> to <u>eaution should be exercised if using structurally similar drugs such as carboxamides (e.g., carbamazepine), (e.g., barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) and other related compounds) in these same patients. <u>Similarly, if there is a positive history of hypersensitivity reactions to these structurally similar drugs in the patient or immediate family members, consider alternatives to Dilantin.</u></u>

[Finally, within the Information for Patients section, add symptoms and signs of DRESS to skin rash]

Information for Patients:

Patients should be instructed to call their physician if skin rash develops.

Patients should be made aware of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

(b) (4)

6.

6.1 Background

Phenytoin is metabolized by the cytochrome P450 enzymes, CYP2C9 and CYP2C19, with CYP2C9 responsible for the majority of phenytoin inactivation.³⁷ The allelic frequencies vary between racial groups. In Caucasians, CYP2C9*2 and CYP2C9*3 alleles dominate, while in blacks, CYP2C9*5 and CYP2C9*11 dominate.³⁸ These alleles result in reduced function.^{39,40} With phenytoin's narrow therapeutic index, impairments in CYP2C9 activity may result in severe toxicity.⁴¹ Some data are suggestive of

but the clinical consequences are unclear.

6.2 Sponsor's review of the literature

The sponsor referenced two case reports to support their statement that (b) (4) hypersensitivity reactions, including

SJS/TEN and DRESS.

In one case report, a black female was prescribed phenytoin 100 mg tid for status epilepticus and within 2 weeks of discharge from the hospital, presented with slurred speech, mental status changes, memory loss, and inability to stand.⁴² Plasma phenytoin concentrations were found to be almost 2.5 times the maximum therapeutic concentration of 20 μ g/ml. She was also noted to have a significantly reduced clearance of phenytoin (17% that of the theoretical extensive metabolizer). The patient was homozygous for the CYP2C9 null mutation (specifically a new CYP2C9*6 allele). The frequency of this allele was estimated to be 0.6% in African Americans, but 0% in Caucasians (however, with overlapping confidence intervals). However, although signs of dose-related adverse reactions of phenytoin intoxication were noted, no signs or symptoms of any hypersensitivity reactions (specifically rash, SCAR, DRESS) were noted.

In the second case report, a 31 year old woman (race was not identified) was treated with oral phenytoin 100 mg tid to prevent posttraumatic seizures.⁴³ On day 10 of treatment, she developed dysarthria, nystagmus, dysmetria, left hemifacial dyskinesia, and mental status changes. Labs revealed a serum phenytoin concentration greater than the upper limit of the assay method (>100 mg/L) with an elimination half-life of 103 hours, far above the normal range of 7-60 hours. The patient was then genotyped and was found to be homozygous for the CYP2C9*3 allele and

³⁷ Loscher, W et al. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia. 2009; 50(1): 1-23.

³⁸ Allabi AC et al. Genetic polymorphisms of CYP2C9 and CYP2C19 in the Beninese and Belgian populations. Br J Clin Pharmacol. 2003; 56: 653-657.

³⁹ Yasuda SU, Zhang L, Huang S-M. The role of ethnicity in variability in response to drugs: Focus on clinical pharmacology studies. Clin Pharmacol Ther. 2008; 84 (3):417-423.

⁴⁰ Tai, G et al. In-vitro and in-vivo effects of the CYP2C9*11 polymorphism on warfarin metabolism and dose. Pharmacogenetics and Genomics. 2005; 15(7):475-481.

⁴¹ Lee CR et al. Cytochrome P450 3C9 polymorphisms: a comprehensive review of the in-vitro and human data. Pharmacogenetics. 2002; 12: 251-263.

⁴² Kidd RS et al. Identification of a null allele of CYP2C9 in an African-American exhibiting toxicity to phenytoin. Pharmacogenetics. 2001; 11: 803-808.

⁴³ Brandolese R et al. Severe phenytoin intoxication in a subject homozygous for CYP2C9*3. Clin Pharmacol Ther 2001; 70: 391-4.

heterozygous for the CYP2C19*2 allele. However, again there was no mention of the patient developing signs or symptoms of actual hypersensitivity to phenytoin.

Sponsor's conclusion from the literature review

"While the available literature suggests ^{(b) (4)} with respect to allelic expression, phenytoin clearance, and severe adverse reactions, the limited published data do not allow definitive conclusions.

Because of the potential seriousness of these hypersensitivity reactions, however, the Sponsor suggests adding the following statement to the Warnings and Precautions section of the phenytoin prescribing information."

6.3 Reviewer discussion of the literature

These case reports represent cases of phenytoin intoxication and not phenytoin hypersensitivity reactions and therefore do not provide evidence that mutations in the CYP2C9 enzyme are risk factors for DRESS or SJS/TEN, nor provide evidence that ^{(b) (4)} of these reactions.





6.4 Sponsor's proposed additions to phenytoin labeling



6.5 Comments on Sponsor's proposed label

The reviewer does not agree with the above additions as there is not strong evidence in the literature that ^{(b) (4)} is a risk factor for hypersensitivity reactions. However, this issue

⁴⁴ Chang D, Shear N. Cutaneous reactions to anticonvulsants. Semin Neurol. 1992; 12: 329-37.

⁴⁵ Hussain SA et al. Incidence of epilepsy in a racially diverse, community-dwelling, elderly cohort: results from the Einstein aging study. Epilepsy Res. 2006; 71(2-3): 195-205.

⁴⁶ Cowan LD et al. Prevalence of the epilepsies in children and adolescents. Epilepsia. 1989; 30: 94-106.

did help to highlight details known about the metabolic pathways of phenytoin, information which is missing from the current phenytoin labeling. Therefore, the reviewer would recommend adding the name of the specific cytochrome P450 enzymes in the Clinical Pharmacology and Drug Interactions section and would also emphasize the need for early plasma levels in these slow metabolizers in the Precautions section.

6.6 Reviewer's recommended changes to phenytoin labeling

Medical reviewer's proposed additions are shown in <u>red underline</u> with deletions as strikethrough.

CLINICAL PHARMACOLOGY [fifth paragraph]

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, <u>variant CYP2C9 and CYP2C19 alleles</u> congenital enzyme deficiency, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

PRECAUTIONS

General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined. If early signs of dose-related CNS toxicity develop, plasma levels should be checked immediately.

•••

Drug Interactions: Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 enzymes <u>CYP2C9 and CYP2C19</u>, and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected.

7. Summary of Recommended Changes to Complete Phenytoin Labeling

Please see the final agreed upon labeling that is attached to the approval letter.

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

/s/

MARY DOI 08/11/2011

SALLY U YASUDA 08/12/2011

APPLICATION NUMBER: NDA 08-762/S-039

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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Pfizer Global Research & Development

August 28, 2009

Carol Haley Worldwide Regulatory Affairs & Quality Assurance

Russell Katz, MD Director Division of Neurology Products ATTN: Central Document Room Food and Drug Administration Center for Drug Evaluation and Research 5901-B Ammendale Rd. Beltsville, MD 20705-1266 THIS DOCUMENT CONTAINS CONFIDENTIAL AND/OR TRADE SECRET INFORMATION THAT IS DISCLOSED ONLY IN CONNECTION WITH THE LICENSING AND/OR REGISTRATION OF PRODUCTS FOR PFIZER INC OR ITS AFFILIATED COMPANIES. THIS DOCUMENT SHOULD NOT BE DISCLOSED OR USED, IN WHOLE OR IN PART, FOR ANY OTHER PURPOSE WITHOUT THE PRIOR WRITTEN CONSENT OF PFIZER INC.

SUBJECT: NDA 08-762 – DILANTIN-125® (phenytoin, USP) ORAL SUSPENSION

*ANDA 84-349 - DILANTIN® (extended phenytoin sodium capsules, USP)

*ANDA 84-427 - DILANTIN® (phenytoin tablets, USP) INFATABS

Changes-being-effected labeling supplement

(b) (4)

Dear Dr. Katz:

Please refer to Pfizer's

and is submitting the enclosed changes-being-effected labeling

supplements.

We are submitting revised labeling to each of the subject applications to include additional information in the **Warnings and Precautions** sections of the prescribing information with respect to skin reactions and Anticonvulsant Hypersensitivity Syndrome. A clinical overview describing the supportive information for this label revision was provided in



(b) (4)

Module 2.5 (b) (4) and should be used in support of this new submission as well. References in the clinical overview will be provided on request. The revised labeling, in Microsoft Word using Track Changes to show the revised language, and label content in structured product labeling (SPL) are provided in this submission. There are two labels for ANDA 84-349, one each for the 30 mg and 100 mg product. In order to comply with the FDA requirement that only one SPL file be included per submission, we are submitting only the 30 mg SPL with this changes-being-effected supplement for ANDA 84-349 and will submit the SPL file for the 100 mg capsule version under separate cover as a General Correspondence.

Application Number	Submission Sequence	Approximate Size of Submission	Index of Media Units
008762	0010	2 MB	Gateway
084349	0019	2 MB	Gateway
084427	0010	2 MB	Gateway

The submission is being submitted in electronic common technical document (eCTD) format, in accordance with the ICH and FDA guidance on electronic submissions. The submission has been scanned for viruses using McAfee VirusScan Enterprise Version 8.5.0i and is virus free. For issues regarding the technical use of this electronic submission, please contact Alan Davis at 212-733-6175 or email at WRONY-esubmissions@pfizer.com.

If you have any questions regarding this submission, please contact me at 212-733-4787 or by e-mail at carol.haley@pfizer.com

Sincerely,

Carol.J.Haley Reason: I am approving this document. Location: New

Carol Haley Director

*cc: Gary J. Buehler, R.Ph., Director Office of Generic Drugs, Food and Drug Administration