פייזר פי אף אי פרמצבטיקה ישראל בע"מ
רח' שנקר 9, ת.ד. 12133
הרצליה פיתוח, ישראל 46725
טל: 972-9-9700500 פקס: 972-9-9700501

אפריל 2021

רופא/ה, רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלון לרופא של **Dilantin 125mg** :
קו תחתי משמעו תוספת טקסט, קו חוצה משמעו מחיקת טקסט, הדגשה משמעה החמרה.

חוזק: Phenytoin 125 mg in each 5 mL of oral suspension

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

להלן העדכונים העיקריים בעלון לרופא:

5 WARNINGS AND PRECAUTIONS
5.3 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. 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. In addition, retrospective, case-control, genome-wide association studies in patients of southeast Asian ancestry have also identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant, which has also been associated with decreased clearance of phenytoin. Consider avoiding phenytoin as an alternative to carbamazepine in patients who are positive for HLA-B*1502 or in CYP2C9*3 carriers.
The use of HLA-B*1502 or CYP2C9 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.

~~**5.13 Slow Metabolizers of Phenytoin**~~
~~A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be caused by limited enzyme availability and lack of induction; it appears to be genetically determined. If early signs of dose-related central nervous system (CNS) toxicity develop, serum levels should be checked immediately.~~

7 DRUG INTERACTIONS
Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme~~s~~ CYP2C9 and to a lesser extent by CYP2C19 and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism.

8 USE IN SPECIFIC POPULATIONS
8.7 Use in Patients with Decreased CYP2C9 Function
Patients who are intermediate or poor metabolizers of CYP2C9 substrates (e.g., *1/*3, *2/*2, *3/*3) may exhibit increased phenytoin serum concentrations compared to patients who are normal metabolizers (e.g., *1/*1). Thus, patients who are known to be intermediate or poor metabolizers may ultimately require lower doses of phenytoin to maintain similar steady-state concentrations compared to normal metabolizers. If early signs of dose-related central nervous system (CNS) toxicity develop, serum concentrations should be checked immediately.

12 CLINICAL PHARMACOLOGY
12.5 Pharmacogenomics
CYP2C9 activity is decreased in individuals with genetic variants such as the CYP2C9*2 and CYP2C9*3 alleles. Carriers of variant alleles, resulting in intermediate (e.g., *1/*3, *2/*2) or poor metabolism (e.g., *2/*3, *3/*3) have decreased clearance of phenytoin. Other decreased or nonfunctional CYP2C9 alleles may also result in decreased clearance of phenytoin (e.g., *5, *6, *8, *11).
The prevalence of the CYP2C9 poor metabolizer phenotype is approximately 2-3% in the White population, 0.5-4% in the Asian population, and <1% in the African American population. The CYP2C9 intermediate phenotype prevalence is approximately 35% in the White population, 24% in the African American population, and 15-36% in the Asian population.

העלון לרופא נשלח למשרד הבריאות לצורך פרסומם במאגר התרופות שבאתר משרד הבריאות:
http://www.health.gov.il/units/pharmacy/trufot/index.asp לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פי אף אי פרמצבטיקה ישראל בע"מ, שנקר 9, ת.ד. 12133 הרצליה פיתוח, 46725.

בברכה,
גילי קבשה
רוקחת ממונה