Pfizer Hellas S.A.
243, Messoghion Avenue,
GR-154 51, Neo Psychiko,
Athens, Greece

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Direct Healthcare Professional Communication

Epanutin 30mg/5ml oral suspension (Phenytoin): Lead content potentially exceeding that specified by International Conference on Harmonization Guideline for Elemental Impurities

Dear Healthcare professional,

Pfizer Hellas S.A., in agreement with the Medicines Authority would like to inform you of the following safety information for phenytoin 30mg/5ml oral suspension (OS):

Summary

- **The International Conference on Harmonization (ICH) Guideline for Elemental Impurities specifies a permitted daily exposure (PDE) for lead of 5µg/day.**
- **Some batches of phenytoin 30mg/5ml OS have been found to exceed the ICH PDE for lead at the maximum daily phenytoin dose of 300 mg/day in pediatric patients. All batches of phenytoin 30mg/5ml OS have been found to exceed the ICH PDE for lead at the maximum daily phenytoin dose of 500 mg/day in adults.**
- **Patients receiving up to 210 mg/day of phenytoin will not be exposed to an amount of lead that exceeds the ICH PDE.**
- **Given the known potential for lead-related toxic effects, initiation or continuation of treatment with phenytoin 30mg/5ml OS in pediatric patients should be carefully considered in light of other treatment alternatives and overall benefit/risk.**
- **Treatment initiation with phenytoin 30mg/5ml OS in adults is not recommended. Continuation of treatment with this product in adults should be carefully considered in light of other treatment alternatives and overall benefit/risk.**
- **Epanutin is indicated for the control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. Epanutin has also been employed in the treatment of trigeminal neuralgia but it should only be used as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine. Phenytoin is listed as an essential medicine by the World Health Organization.**

Background on the safety issue

Phenytoin 30mg/5ml OS and Lead Exposure

On the 1st December 2017, the revised International Conference on Harmonization (ICH) Q3D Guideline for Elemental Impurities in Drug Products became effective for authorised medicinal products in the EU, which specified a permitted daily exposure (PDE) for lead of 5µg/day.

Lead is known to be present in one of the excipients used in phenytoin 30mg/5ml OS. The amount of lead exposure to a patient will depend on the dose of phenytoin 30mg/5ml OS that the patient receives.

In humans and animals, exposure to lead may cause neurological, reproductive, developmental, immune, cardiovascular and renal health effects. In general, sensitivity to lead toxicity is greater when there is exposure in utero and in children compared to adults. No safe levels of lead exposure have been established.

Phenytoin 30mg/5ml OS in Pediatric Patients

In pediatric patients, the maximum phenytoin daily dose is 300 mg/day. Some batches of phenytoin 30mg/5ml OS have been found to exceed the ICH PDE for lead at the maximum daily phenytoin dose. Pediatric patients receiving up to 210 mg/day of phenytoin will not be exposed to an amount of lead that exceeds the ICH PDE.

Given the known potential for lead-related toxic effects, treatment initiation with phenytoin 30mg/5ml OS in children who are not currently taking this product should be carefully considered in light of other treatment alternatives and overall benefit/risk. In children who are already maintained on this medication, the benefits of treatment continuation must be weighed against the risks. Prescribers should consider alternative phenytoin formulations and/or alternative antiepileptic drugs.

Phenytoin 30mg/5ml OS in Adult Patients

In adult patients, the maximum phenytoin daily dose is 500 mg/day. All batches of phenytoin 30mg/5ml OS have been found to exceed the ICH PDE for lead at the maximum daily phenytoin dose. Patients receiving up to 210 mg/day of phenytoin will not exceed the ICH PDE for lead.

Given the known potential for lead-related toxic effects, initiation of treatment with phenytoin 30mg/5ml OS in adults who are not currently taking this medication is not recommended. In adults who are already maintained on this medication, the benefits of treatment continuation must be weighed against the risks. Prescribers should consider alternative phenytoin formulations and/or alternative antiepileptic drugs.

Ongoing Mitigation Strategy

Benefit/Risk Assessment and Ongoing Mitigation Strategy

Given that ICH PDE for lead is not exceeded at phenytoin 30mg/5ml OS doses up to 210 mg/day, given that phenytoin is classified as an essential medicine by the World Health Organization, and in light of the established antiepileptic effects of the drug, Pfizer believes that the benefit-risk profile for phenytoin 30mg/5ml OS remains positive. Concurrently, Pfizer recognizes that lead exposure has been shown to have negative health impacts, including behavioral and academic effects in children. The measures recommended in this communication, including consideration of alternative antiepileptic drugs, particularly in patients not currently maintained on phenytoin 30mg/5ml OS, are aimed at reducing the risks of potential lead exposure.

While the formulation of phenytoin 30mg/5ml OS has not changed, publication of ICH elemental impurity guidance has prompted Pfizer to examine the lead content in this product. Pfizer is monitoring the lead content of all batches of phenytoin 30mg/5ml OS prior to batch release to minimize the potential release of those batches that exceed PDE for lead in pediatric patients, while maintaining supply of this essential medicine. In parallel, Pfizer is actively evaluating options to minimize lead content in phenytoin 30mg/5ml OS. Pfizer will keep you informed as these efforts progress.

Phenytoin is indicated for the control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. Epanutin has also been employed in the treatment of trigeminal neuralgia but it should only be used as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine. Phenytoin is listed as an essential medicine by the World Health Organization.

Call for reporting

Healthcare professionals are reminded to report suspected adverse reactions associated with the use of Epanutin in accordance with the national spontaneous system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Malta Medicines Authority Post-licensing, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt

Company contact point

Product name	Company	Email	Phone	Fax
Epanutin 30mg/5ml oral	Pfizer Hellas S.A, Greece	GRC.AEReporting@pfizer.com	+30 210 6785800	+30 210 8199096

suspension	Local representative: V.J. Salomone Pharma Ltd.	Local contact: regvjsp@vjsalomone.com	Local number: +356 99644126 +356 21220174	Local number: +356 21243026

Yours sincerely,

Damianos Menegas
Medical Director
Greece, Cyprus and Malta