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Capecitabine
Potentially fatal interaction with Brivudine

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate which is indicated as adjuvant therapy for various neoplastic conditions. It works as a precursor of the cytotoxic portion of 5-flurouracil (5-FU). Brivudine is an antiviral agent indicated for the early treatment of herpes zoster infections. Patients submitted to antineoplastic therapy have a depressed immune system. This potentiates viral infections. A patient with a herpetic infection is at risk of being given both medicines.

Four fatal cases of capecitabine-brivudine interaction were reported during routine pharmacovigilance activities. This interaction results from irreversible inhibition of bromovinyluracil, brivudine's main metabolite, which in turn inhibits di-hydropyrimidine dehydrogenase, leading to **increased therapeutic effect of capecitabine and hence to raised serum levels of 5-fluorouracil**. In high concentrations, 5-fluorouracil is toxic and can cause adverse reactions, including fatal blood and GI reactions.

In order to avoid potential interactions, the following **washout times** need to be ensured:

- If the patient is taking capecitabine, **24 hours should elapse before brivudine is administered**;
- If the patient is taking brivudine, **2 weeks** should elapse between the last dose of brivudine and the **start of therapy with capecitabine**.

Risk minimization measures have already been implemented, including a Dear Healthcare Professional Communication **(DHPC)** and a warning on the packaging of medicinal products containing brivudine. However, those measures have proved to be insufficient. Interaction warnings will therefore be reinforced by changes to the SPC of medicinal products containing capecitabine, namely to sections 4.3 Contraindications, 4.4 Warnings and special precautions for use, and 4.5 Interaction with other medicinal products and other forms of interaction. Section 2 of the PL will be updated accordingly.

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Biotin
possible interference with lab tests

Quick Read
Biotin, especially in high doses, in children and/or patients with renal impairment, may interfere with the results of laboratory tests, namely with troponin (risk of false negatives) and thyroid function tests.

Biotin (also known as vitamin B7 or formerly as vitamin H) is a water-soluble vitamin that acts as a co-factor for various carboxylases. In doses between 12.5 µg and 20 mg, it is used as a food supplement (usually for hair and nail health) and as a medicine, namely in high doses in off-label treatment of multiple sclerosis and in children with congenital metabolic conditions.

The first safety communication regarding potential interference of biotin with laboratory tests came from the US Food and Drug Administration (FDA) in 2017. The FDA stressed that biotin in the blood or other biological samples taken from patients who ingested high quantities of the supplement could cause clinically incorrect lab test results. In January 2018 Denmark validated this safety signal in the EU.

Biotin may interfere with clinical laboratory tests at single doses of ≥ 150 µg (oral use) or of ≥ 60 µg (parenteral use).

Taking the available data into account, the PRAC has recommended changes to the wording of the SPCs (and corresponding PLs):

4.4. Special warnings and precautions for use

Interference with clinical laboratory tests

Biotin may interfere with laboratory tests that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results, depending on the assay. The risk of interference is higher in children and patients with renal impairment and increases with higher doses. When interpreting results of laboratory tests, possible biotin interference has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed (e.g. thyroid test results mimicking Graves' disease in asymptomatic patients taking biotin or false negative troponin test results in patients with myocardial infarction taking biotin). Alternative tests not susceptible to biotin interference should be used, if available, in cases where interference is suspected. The laboratory personnel should be consulted when ordering laboratory tests in patients taking biotin.

Maria Manuel Teixeira, Margarida Duarte

ADRs in the Literature

DTPa vaccine not associated with autism

There are not many studies on the effects in mother and child of prenatal anti-tetanus, diphtheria and acellular Pertussis (DTPa) vaccination. These authors looked retrospectively at a cohort of post-partum mother-child pairs in a sample of California hospitals. An autism-spectrum disorder was reported in 1.5% (1,341) of the children – the incidence rate was 3.78 per 1,000 person*years in vaccinated pairs and 4.05 per 1,000 person*years in non-vaccinated pairs. Prenatal immunization was therefore not associated with a higher risk of occurrence of autism-spectrum disorder. This **reinforces recommendations to vaccinate pregnant women to protect their babies**, who are at greater risk of fatal complications from pertussis.

Becerra-Culqui TA et al. Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination and Autism Spectrum Disorder. Pediatrics. 2018 Sep;142(3).doi: 10.1542/peds.2018-0120

ADR risk factors at the start of antiretroviral therapy

The authors of this study assessed the prevalence of ADRs in 399 patients being started on Highly Active Antiretroviral Therapy (**HAART**) in three Brazilian public health services specialized in HIV/AIDS. The most frequently found reactions were **neurological**. In general, patients with the lowest probability of sustaining ADRs were over 33 years of age, had CD4 counts of more than 200 cells/mm3 and/or quality of life characteristics with greater physical command or greater autonomy. **Female gender** and the use of **illicit drugs** were associated with a **higher probability** of ADRs.

Mendes JC et al. Adverse reactions associated with first-line regimens in patients initiating antiretroviral therapy. Eur J Clin Pharmacol. doi: 10.1007/s00228-018-2472-y.

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics

Communications to Healthcare Professionals published on the Infarmed website

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INN Medicinal product	Target	Comunication Online publication date
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Hydroxyethyl starch (HES) Tetraspan Volulyte Voluven	**Physicians:** directors of anaesthesiology, emergency and intensive care services **Pharmacists:** directors of pharmaceutical services **Nurses:** head nurses in anaesthesiology, emergency and intensive care services	Additional measures to reinforce existing restrictions, namely need for specific qualification of healthcare units and for training of professionals who prescribe or administer HES 15/02/2019
Thiamazole Metibasol	**Physicians:** endocrinology, internal medicine, gastroenterology, gynaecology/obstetrics, paediatrics **Pharmacists:** community	Risk of acute pancreatitis and recommendation to use effective contraception 15/02/2019

Compiled by Fernanda Marques

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Inotersen Tegsedi	**Patients**	Alert card 28-02-2019

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