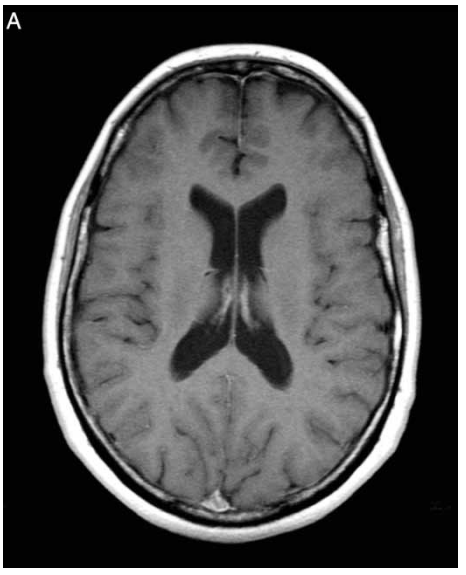

Figure A. Axial T1 MRI with contrast shows no evidence of a brain tumor.

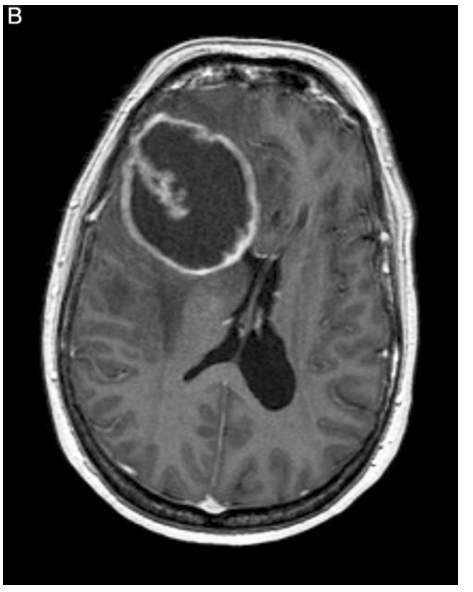

Figure B. Eight months later, a large glioblastoma has developed.

have followed a 58-year-old female patient with multiple sclerosis whose monitoring MRI in August 2007 is shown in Figure A. Because of worsening of her condition with apathy, the MRI was repeated in April 2008. T1-weighted MRI with gadolinium revealed a large right frontal lesion with ring enhancement which turned out to be a glioblastoma (Figure B). This 6.5 cm glioblastoma was not detectable in August 2007 even in retrospect and thus must have developed *de novo* within less than 8 months.

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Fatal drug-drug interaction of brivudine and capecitabine

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To The Editor,

Drug-drug interactions (DDI) are well known risk factors for adverse drug reactions (ADR) and are an important issue in drug safety. ADR may be severe and require hospitalization, some cases might even be fatal. ADR cause 3–15% of hospitalizations and represent an important public health problem. We report the clinical course of a drug-drug interaction with capecitabine and brivudine, resulting in fatal outcome. We also describe the mechanism of this interaction.

A 80-year-old female patient with metastatic colorectal cancer (CRC) was treated by her medical oncologist with capecitabine (Roche Pharma) 3 g daily for 14 days, followed by a 1 week drug-free

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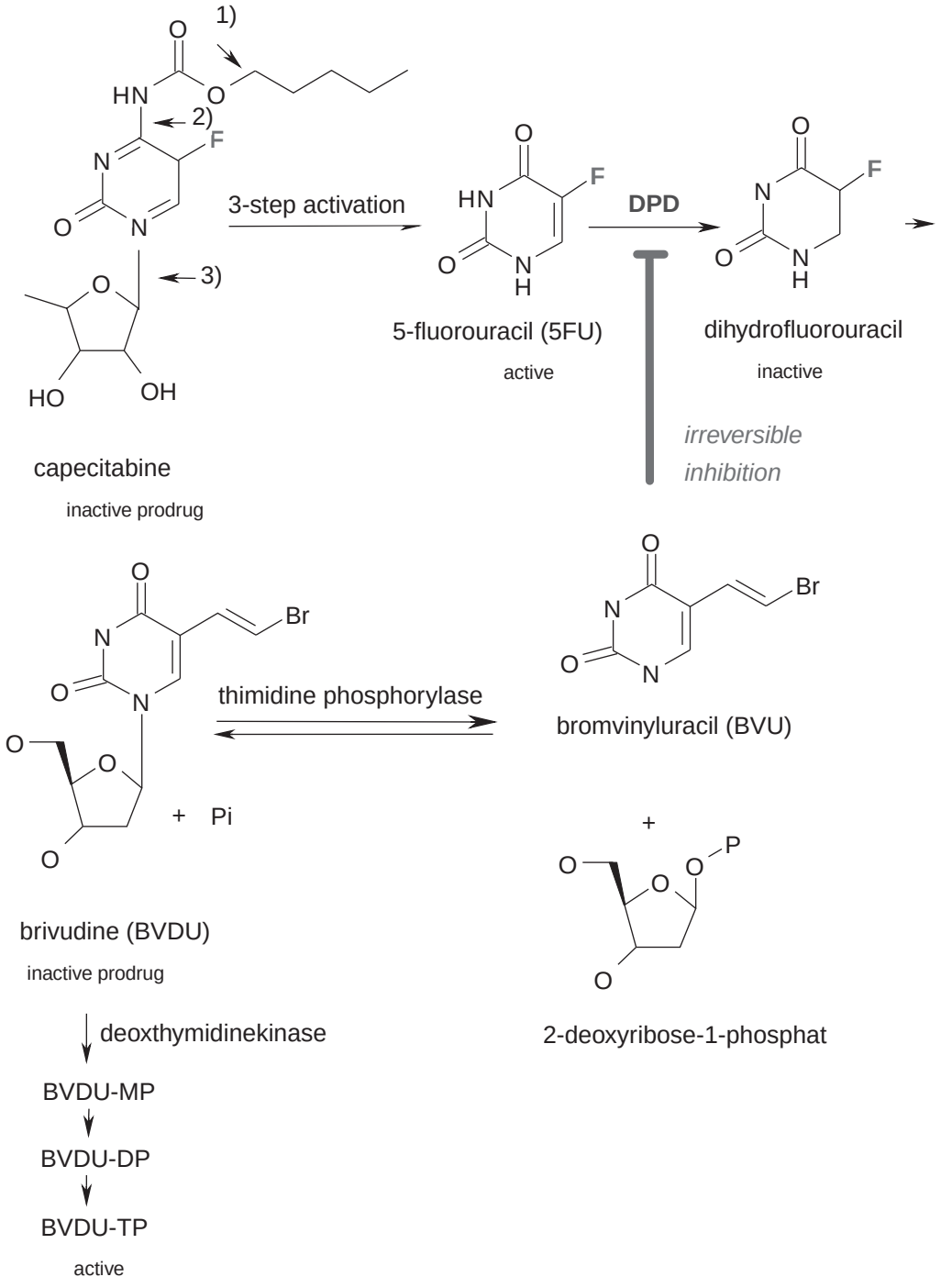

Figure 1. Metabolism of capecitabine and interaction with brivudine ((E)-5-(2-bromovinyl)-2′-deoxyuridine; BVDU). The activation of capecitabine to 5-FU involves 3 steps. 5-FU is metabolized to dihydrofluorouracil by dihydropyrimidine-dehydrogenase (DPD). Brivudine is metabolized by pyrimidine-nucleosidphosphorylase to bromovinyluracil (BVU), an irreversible inhibitor of DPD.
BVDU-MP: brivudine monophosphate; BVDU-BP: brivudine biphosphate; BVDU-TP: brivudine triphosphate. (Adapted according to De Clercq) [5]

interval. Three months later, her general practitioner prescribed brivudine (Menarini Pharma) 125 mg daily for herpes zoster. After the first brivudine dose, she developed a rash, edema of her lips and inflammation of the oral mucosa. She stopped brivudine after the second tablet. Two weeks later, she was hospitalized with an exanthema, painful mucositis, vomiting and diarrhea. Laboratory investigations showed a hemoglobin of 103 g/L (120–160 g/L), leucocytes 11.1×10^9/L ($3.2 - 10\ 0 \times 10^9$/L), CRP 11 g/L (<10 g/L), INR 1.32 (<1.17), creatinine clearance 34 ml/min. Capecitabine was stopped immediately and pain was treated with opiates. Despite antihistaminic and steroid treatment, skin

lesions enlarged and finally progressed to Stevens-Johnson Syndrome. She developed severe leucopenia (0.1×10^9/L) and thrombocytopenia (10×10^9/L) and was treated with filgrastim and thrombocyte-substitution, respectively. She became febrile and, despite empiric broad spectrum antibiotics, developed septic shock resistant to vaso-active agents. After a comatose state, she finally died on the 12th day of hospitalization, 3 weeks after onset of her first symptoms.

Capecitabine is an oral 5-fluorouracil (5-FU) prodrug mainly used for the treatment of CRC and breast cancer. The drug is activated in a 3-step process, yielding the active agent 5-FU (Figure 1). The final step of activation into 5-FU occurs preferentially in malignant cells. Main adverse reactions of 5-FU are myelotoxicity, mucositis and a hand-foot-syndrome. More than 80% of 5-FU is metabolized by dihydropyrimidine-dehydrogenase (DPD), the rate limiting step of 5-FU inactivation (Figure 1) [1].

Brivudine ((E)-5-(2-bromovinyl)-2′-deoxyuridine; BVDU) is a thymidine analogue for treatment of herpes zoster virus infections. Brivudine is hepatically converted to bromovinyluracil (BVU) and 2-deoxyribose-1-phosphate (Figure 1). Non-metabolized brivudine is phosphorylated by viral deoxythymidinekinase to BVDU monophosphate (BVDU-MP) and BVDU diphosphate (BVDU-DP). The latter is trapped in infected cells and is activated to BVDU triphosphate (BVDU-TP), inhibiting viral replication. Of note, BVU is an irreversible inhibitor of DPD, decreasing DPD activity by ≥ 90, which normalizes only within 18 days. This inhibition is associated with a 5-15 fold increase in 5-FU-concentrations [2,3]. Due to enhanced 5-FU toxicity, the combination of these drugs is absolutely contraindicated. In 1993, fifteen fatal DDI with the antiviral sorivudine, another irreversible DPD-inhibitor, and the 5-FU-prodrug tegafur were reported in Japan [4].

In our patient, the combination of brivudine and capecitabine occurred despite clearly visible warning labels on the package. This is the first report of a fatal DDI between capecitabine and brivudine and the only case reported to the Swiss National Pharmacovigilance Center Swissmedic [6]. Alertness of the prescribers and optimal communication between health care providers are essential to prevent concomitant prescription of these drugs.

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Mangafodipir as a cytoprotective adjunct to chemotherapy – a case report

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To the Editor

The contrast agent mangafodipir (Teslascan®, GE Healthcare) for MRI of the liver has been in clinical use with a low profile of side effects for more than a decade. As a chelate of mangenese ion bound to fodipir, it also posesses superoxide dismutase (SOD)

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