

Temsirolimus: risk of myocardial infarction

Since 2016, the EU summary of product characteristics (SPC) for Torisel[®], which contains the cytotoxic immunosuppressant *temsirolimus*, states that "the known association of *temsirolimus* with hyperlipaemia may predispose to myocardial infarction" (1,2). This information was added following the European Pharmacovigilance Risk Assessment Committee's (PRAC) analysis of 17 cases of myocardial infarction, 3 of which were fatal, that occurred between 1 day and 9 months after starting *temsirolimus* therapy. In 8 cases, *temsirolimus* was the only drug suspected (3,4). *Temsirolimus* is known to provoke hyperlipaemia, hypercholesterolaemia and hypertension (1,2).

In the European Union, *temsirolimus* is authorised for use in metastatic renal cell carcinoma and mantle cell lymphoma. After intravenous administration, it is rapidly metabolised to *sirolimus*, another immunosuppressant, which is authorised for the prevention of organ rejection in certain transplant recipients (1,2,5).

In practice The risk of myocardial infarction is another addition to *temsirolimus*'s already long list of adverse effects (1,2). As of 7 June 2017, this risk is not mentioned in either the EU SPC or patient leaflet for *sirolimus*, despite adverse effects that are largely shared by *temsirolimus* and *sirolimus* (5,6).

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 - 2- European Commission "SPC + package leaflet + annex IV-Torisel" 14 January 2016 + "SPC-Torisel" 15 October 2015: 69 pages.
 - 3- EMA - PRAC "Minutes of the meeting on 07-10 April 2015" 7 May 2015: 78 pages.
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Pholcodine: anaphylactic reactions to neuromuscular blockers

Pholcodine, an opioid used as a cough suppressant for decades, appears to be implicated in the occurrence of sometimes fatal anaphylactic shock during anesthesia as a result of cross-reactivity to neuromuscular blocking agents, such as *suxamethonium* (1).

In Norway, *pholcodine* was withdrawn from the market in 2007, and within 3 years the number of anaphylactic reactions to neuromuscular blockers had decreased (1).

In late 2016, six years after market withdrawal of *pholcodine*, a Norwegian team published a follow-up study (2). The frequency of anaphylactic reactions to neuromuscular blockers has decreased by about one-third since 2007. No deaths resulting from anaphylactic reactions to neuromuscular blockers were recorded during the last 3-year period studied, versus 5 deaths during the first 3 years when *pholcodine* was on the market. The prevalence of anti-*suxamethonium* antibodies in 300 serum samples from so-called allergic patients dropped to zero percent in 2012.

The situation in Norway seems to be approaching that of Sweden, where the last syrup containing

pholcodine was withdrawn from the market at the end of the 1980s. Anaphylactic reactions to neuromuscular blockers are now very rare, with one case reported every 1 or 2 years. In Denmark, *pholcodine* has never been available, and anaphylactic reactions to neuromuscular blockers are extremely rare (2).

In practice *Pholcodine* is still available in many cough suppressants. Despite the known harms of a drug that is not useful, health authorities and pharmaceutical companies have not taken a decision to withdraw *pholcodine* from the market in order to protect patients. Faced with this dangerous inertia, it is up to healthcare professionals to protect patients by routinely avoiding the use of *pholcodine* and offering better solutions.

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 - 2- De Pater GH "Six years without pholcodine; Norwegians are significantly less IgE-sensitized and clinically more tolerant to neuromuscular blocking agents" *Allergy* 2016: 20 pages.