Pharmacotherapeutic report, summary
Catumaxomab (Removab®) for the indication 'malignant ascites'

Approved by the Medicinal Products Reimbursement Committee (CFH)

Medicine. Catumaxomab concentrate for solution for infusion

Registered indication. "Intraperitoneal treatment of malign ascites in patients with EpCAM-positive cancers where standard therapy is not available or no longer feasible.

Posology. 10, 20, 50 and 150 μg on day 0, 3, 7 and 10 respectively via intraperitoneal infusion.

Mechanism of action. Catumaxomab is a rat/mouse hybrid monoclonal antibody that specifically targets the epithelial cell adhesion molecule (EpCAM) that is overexpressed in most cancers, and the CD3 antigen, which is present on ripe T cells as component of the T-cell receptor. A third functional binding location in the Fc-region makes interaction possible with antigen-presenting cells (APC) via Fcγ receptors. Due to the binding properties, tumour cells, T-cells and antigen-presenting cells are brought into close proximity, thus inducing a combined immune response to tumour cells, e.g., T-cell activation, *antibody-dependent cell-mediated cytotoxicity,* complement-dependent cytotoxicity and phagocytosis, which can result in tumour cell destruction.

Specific details. Premedication with analgesics/antipyretics/non-steroidal antiflogistics is recommended prior to infusion. The ascites fluid must be drained before each catumaxomab infusion, and also one day after the last infusion.

Summary of the therapeutic value

Intended effects. Too much uncertainty exists about the result of the phase II/III research of Heiss et al. and the clinical relevance of the endpoint 'puncture-free survival' to be able to reliably estimate the size and the relevance, in daily practice, of the effect of catumaxomab in combination with paracentesis in comparison with paracentesis alone. The available data on quality of life are too uncertain to be involved in the clinical relevance of catumaxomab.

Unintended effects. The addition of catumaxomab to paracentesis leads to a considerable increase in grade 3 treatment-related adverse events.

Experience. Experience with catumaxomab is limited.

Applicability. The applicability of catumaxomab in combination with paracentesis is less broad as that of paracentesis alone.

Ease of use. The ease of use of catumaxomab, when added to paracentesis, is considerably less than when using paracentesis alone

Final conclusion on therapeutic value.

The most important effect of catumaxomab in clinical research is a statistically significant 35-day extension in 'puncture-free survival', however without any statistically significant effects on general survival in the entire study population or in the prospectively specified subgroups.

Catumaxomab leads to an increase in severe side effects. The clinical relevance, in daily practice, of the primary efficacy endpoint 'puncture-free survival' is not clear and cannot be confirmed by findings on quality of life due to different limitations in the set-up of the study into this. Furthermore, the most important clinical study has important shortcomings, i.e., the open label set-up, crossover (as a result of which the total number of paracentesis that can be avoided cannot be properly estimated) and imbalance between the two arms with regard to number of paracenteses. In view of the uncertainties mentioned, it is not possible to issue a substantiated therapeutic assessment of catumaxomab. As a result, due to insufficient evidence, the therapeutic value of treating malign ascites with catumaxomab in combination with paracentesis is lower than that of paracentesis.

*The original text of this excerpt from a **CFH-Report** of CVZ was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of CVZ's CFH-Report.*
Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.