FRESENIUS

Press Release

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Fresenius Biotech receives approval for Removab® by European Commission - First Drug worldwide for Treatment of Malignant Ascites

The European Commission has approved Removab (catumaxomab) for the treatment of malignant ascites with immediate effect. It is the first drug worldwide with a regulatory label for the treatment of malignant ascites and provides an important new therapy approach. The approval is based on the results of a large international phase II/III pivotal study which demonstrated a statistically significant improvement of the primary endpoint puncture-free survival. Patients receiving Removab had a four-fold increase in puncture-free survival over a therapy with puncture alone.

The European Commission's decision will apply to all EU member states. Removab will initially be launched in Germany within the next few weeks and will subsequently be introduced in other European countries. With its trifunctional mode of action Removab represents a new generation of antibodies using the body's own immune system to help fight the tumor cells. It is approved for the treatment of malignant ascites in patients with EpCAM positive carcinomas where standard therapy is not available or no longer feasible. The antibody will be administered as four intraperitoneal infusions with ascending doses following a paracentesis.

Malignant ascites is most common in ovarian, pancreatic and gastric cancers with an incidence of 20 to 50% of all cases. Malignant ascites develops late in the course of the cancer disease and regularly has a strong impact on the patient's

quality of life. Removab effectively destroys cancer cells in the peritoneal cavity and therefore attacks the primary cause of ascites formation leading to a significant improvement in the quality of life.

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About the Pivotal Study

The study involved 258 patients with malignant ascites due to carcinomas. Of those, 129 suffered from ovarian cancer while another 129 had non-ovarian cancers.
Patients received paracentesis followed by four intraperitoneal infusions of Removab within 11 days, or paracentesis alone (control group).
The trial met its primary endpoint with high statistical significance. Patients treated with Removab showed a median puncture-free survival (primary endpoint) of 46 days compared with 11 days in the control group ($p < 0.0001$) (Hazard Ratio: 0.254). Puncture-free survival was defined as the period between the last infusion and the first subsequent necessary paracentesis or death, whichever occurred first. The median puncture-free time – a secondary endpoint which did not include the data from patients who died before the next ascites puncture was due – was 77 days versus 13 days ($p < 0.0001$).

The most common side effects observed during the trial, such as fever, nausea and vomiting were all due to Removab's postulated mode of action.
These side effects were predictable, limited, manageable and mostly fully transient.

Malignant Ascites

Malignant ascites can be caused by different carcinomas. Abdominal spread of cancer cells leads to an accumulation of fluid in the abdominal cavity and is associated with a poor prognosis. The most commonly used treatment of malignant ascites is puncture (paracentesis), which has to be carried out on average every one to two weeks and can lead to complications such as infection and fluid or protein deprivation. The trifunctional antibody Removab is known to kill cancer cells in the peritoneal cavity and therefore attacks the primary cause of ascites formation.
The most common carcinomas causing malignant ascites are: ovarian, gastric, colorectal, pancreatic, breast and endometrial.

Epithelial Cell Adhesion Molecule (EpCAM)

EpCAM is a tumor associated antigen expressed on the vast majority of carcinomas (epithelial tumors). EpCAM is expressed on tumor cells in the majority of effusions (ascites) due to carcinomas.

Trifunctional Antibody Removab® (catumaxomab)

Removab with its trifunctional mode of action represents the first antibody of a new generation. The therapeutic objective of Removab is to generate a stronger immune reaction against cancer cells. Removab binds to three different cell types simultaneously: One arm of the antibody recognizes and binds to T cells, the other arm binds EpCAM (epithelial cell adhesion molecule) that is expressed in many types of carcinomas. In addition, immune effector cells with Fc receptors (such as macrophages, monocytes, dendritic cells and natural killer cells) bind to the Fc region of Removab. This simultaneous binding subsequently results in the co-stimulation and activation of T cells and accessory cells, enabling the generation of a strong immune response against cancer cells.

Preclinical data for trifunctional antibodies also suggest a potential long-lasting effect to prevent cancer recurrence. Removab is further developed in various indications (e.g. gastric and ovarian cancer) addressing the underlying cancer. Catumaxomab is a trifunctional antibody licensed from TRION Pharma GmbH.

Fresenius is a German health care group with international operations, providing products and services for dialysis, hospital and outpatient medical care. In 2008, group sales were approx. € 12.3 billion. On December 31, 2008 the Fresenius Group had 122,217 employees worldwide. For more information please visit www.fresenius.com.

Fresenius Biotech, a company of the Fresenius health care group, is focused on the development, marketing and commercialization of biopharmaceuticals in the fields of oncology and transplantation medicine. Fresenius Biotech is a German company with headquarters in Munich. For more information please visit www.fresenius-biotech.com.

Removab® is a registered trade mark by Fresenius Biotech GmbH.

Trion Pharma is a biopharmaceutical company developing trifunctional antibodies in collaboration with Fresenius Biotech. The trifunctional antibodies are produced at TRION's site in Munich, Germany, and are based on a proprietary platform technology for which TRION has secured IP around the world. For more information please visit the company's website at www.trionpharma.com