

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Removab 10 micrograms concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 10 micrograms of catumaxomab* in 0.1 ml solution, corresponding to 0.1 mg/ml.

*rat-mouse hybrid IgG2 monoclonal antibody produced in a rat-mouse hybrid-hybridoma cell line

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Removab is indicated for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

4.2 Posology and method of administration

Removab must be administered under the supervision of a physician experienced in the use of anti-neoplastic medicinal products.

Posology

Prior to the intraperitoneal infusion, pre-medication with analgesic / antipyretic / non-steroidal antiphlogistic medicinal products is recommended (see section 4.4).

Removab dosing schedule comprises the following four intraperitoneal infusions:

1 st dose	10 micrograms on day 0
2 nd dose	20 micrograms on day 3
3 rd dose	50 micrograms on day 7
4 th dose	150 micrograms on day 10

Removab has to be administered as constant rate intraperitoneal infusion with an infusion time of at least 3 hours. In clinical studies infusion times of 3 hours and 6 hours were investigated. For the first of the four doses an infusion time of 6 hours may be considered depending on the patient's health condition.

An interval of at least two infusion free calendar days must elapse between infusion days. The interval between the infusion days can be prolonged in case of relevant adverse reactions. The overall treatment period should not exceed 20 days.

Monitoring

Adequate monitoring of the patient after end of Removab infusion is recommended. In the pivotal study patients were monitored for 24 h after each infusion.

Special populations

Hepatic impairment

Patients with hepatic impairment of a higher severity grade than moderate and / or with more than 70% of the liver metastasised and / or portal vein thrombosis / obstruction have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk (see section 4.4).

Renal impairment

Patients with renal impairment of a higher severity grade than mild have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk (see section 4.4).

Paediatric population

There is no relevant use of Removab in the paediatric population in the granted indication.

Method of administration

Removab must be administered as an **intraperitoneal infusion only**.

Removab **must not** be administered by intraperitoneal bolus or by any other route of administration. For information on the perfusion system to be used see section 4.4.

Precautions to be taken before administering the medicinal product

Before administration of Removab the concentrate for solution for infusion is diluted in sodium chloride 9 mg/ml (0.9%) solution for injection. The diluted Removab solution for infusion is administered intraperitoneally as constant rate infusion using an adequate pump system.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to murine (rat and / or mouse) proteins.

4.4 Special warnings and precautions for use

Removab **must not** be administered as a bolus or by any route other than intraperitoneally.

Cytokine release related symptoms

As release of pro-inflammatory and cytotoxic cytokines is initiated by the binding of catumaxomab to immune and tumour cells, cytokine release related clinical symptoms such as fever, nausea, vomiting and chills have been very commonly reported during and after the Removab administration (see section 4.8). Dyspnoea and hypo-/ hypertension are commonly observed. In the clinical studies in patients with malignant ascites, 1,000 mg paracetamol intravenously was routinely administered prior to Removab infusion for pain and pyrexia control. Despite this premedication, patients experienced the adverse reactions described above with an intensity of up to grade 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the US National Cancer Institute, version 3.0. Other or additional standard pre-medication with analgesic / antipyretic / nonsteroidal antiphlogistic medicinal products is recommended.

Systemic Inflammatory Response Syndrome (SIRS), which may also occur commonly due to the mechanism of action of catumaxomab, develops, in general, within 24 hours after Removab infusion, showing symptoms of fever, tachycardia, tachypnoea and leucocytosis (see section 4.8). Standard therapy or premedication, e.g. analgesic / antipyretic / nonsteroidal antiphlogistic is appropriate to limit the risk.

Abdominal pain

Abdominal pain was commonly reported as an adverse reaction. This transient effect is considered partially a consequence of the intraperitoneal route of administration.

Performance status and BMI

A solid performance status expressed as Body Mass Index (BMI) > 17 (to be assessed after drainage of ascites fluid) and Karnofsky Index > 60 is required prior to Removab therapy.

Acute infections

In presence of factors interfering with the immune system, in particular acute infections, the administration of Removab is not recommended.

Ascites drainage

Appropriate medical management of ascites drainage is a prerequisite for Removab treatment in order to assure stable circulatory and renal functions. This must at least include ascites drainage until stop of spontaneous flow or symptom relief, and, if appropriate, supportive replacement therapy with crystalloids and / or colloids.

Patients with hemodynamic insufficiency, oedema or hypoproteinaemia

Blood volume, blood protein, blood pressure, pulse and renal function should be assessed before each Removab infusion. **Conditions such as hypovolaemia, hypoproteinaemia, hypotension, circulatory decompensation and acute renal impairment must be resolved prior to each Removab infusion.**

Hepatic impairment or portal vein thrombosis / obstruction

Patients with hepatic impairment of a higher severity grade than moderate and / or with more than 70% of the liver metastasised and / or portal vein thrombosis / obstruction have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.

Renal impairment

Patients with renal impairment of a higher severity grade than mild have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of catumaxomab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Removab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether catumaxomab/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue / abstain from Removab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data on the effect of catumaxomab on fertility are available.

4.7 Effects on ability to drive and use machines

Removab has minor to moderate influence on the ability to drive and use machines. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions are derived from an integrated safety analysis including 12 clinical studies. 728 patients received catumaxomab intraperitoneally, 293 patients as 6 hour - and 435 patients as 3 hour infusions.

The overall safety profile of Removab is characterised by cytokine-release related symptoms and gastrointestinal reactions.

Cytokine-release related reactions: SIRS a potentially life-threatening combination of tachycardia, fever and/or dyspnoea, can develop within 24 hours after a catumaxomab infusion and resolves under symptomatic treatment. Other cytokine-release related reactions such as fever, chills, nausea, and vomiting are very commonly reported reactions in intensity of CTCAE grade 1 and 2 (US National Cancer Institute, version 4.0). These symptoms reflect the mechanism of action of catumaxomab and are in general fully reversible.

Gastrointestinal reactions like abdominal pain, nausea, vomiting and diarrhoea are very common and occur mostly with CTCAE grade 1 or 2, but were also observed in higher grades, and respond to adequate symptomatic treatment.

The safety profile of catumaxomab using a 3h versus a 6h infusion time is in general comparable in regards to nature, frequency and severity. An increased frequency of some adverse reactions was seen in relation to 3h administration including chills and hypotension (grades 1 / 2), diarrhoea (all grades) and fatigue (grade 1 / 2).

Tabulated list of adverse reactions

In Table 1, adverse reactions are listed by organ class. Frequency groupings are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$).

Table 1 Adverse reactions reported from patients receiving catumaxomab treatment

Infections and infestations	
<i>Common</i>	Infection.
<i>Uncommon</i>	Erythaema induratum*, device-related infection*.
Blood and lymphatic system disorders	
<i>Common</i>	Anaemia*, lymphopenia, leukocytosis, neutrophilia.
<i>Uncommon</i>	Thrombocytopenia*, coagulopathy*.
Immune system disorders	
<i>Common</i>	Cytokine release syndrome*, hypersensitivity*.
Metabolism and nutrition disorders	
<i>Common</i>	Decreased appetite* / anorexia, dehydration*, hypokalaemia, hypoalbuminaemia, hyponatraemia*, hypocalcaemia*, hypoproteinaemia.
Psychiatric disorders	
<i>Common</i>	Anxiety, insomnia.
Nervous system disorders	
<i>Common</i>	Headache, dizziness.
<i>Uncommon</i>	Convulsion*.
Ear and labyrinth disorders	
<i>Common</i>	Vertigo.
Cardiac disorders	
<i>Common</i>	Tachycardia*, incl. sinus tachycardia.
Vascular disorders	
<i>Common</i>	Hypotension*, hypertension*, flushing.

Respiratory, thoracic and mediastinal disorders	
<i>Common</i>	<u>Dyspnoea*</u> , pleural effusion*, cough.
<i>Uncommon</i>	Pulmonary embolism*, hypoxia*.
Gastrointestinal disorders	
<i>Very common</i>	<u>Abdominal pain*</u> , <u>nausea*</u> , <u>vomiting*</u> , diarrhoea*.
<i>Common</i>	Constipation*, dyspepsia, abdominal distension, sub-ileus*, flatulence, gastric disorder, ileus*, gastroesophageal reflux disease, dry mouth.
<i>Uncommon</i>	Gastrointestinal haemorrhage*, intestinal obstruction*.
Hepatobiliary disorders	
<i>Common</i>	Cholangitis*, hyperbilirubinaemia.
Skin and subcutaneous tissue disorders	
<i>Common</i>	Rash*, erythaema*, hyperhidrosis, pruritus.
<i>Uncommon</i>	Skin reaction*, dermatitis allergic*.
Musculoskeletal and connective tissue disorders	
<i>Common</i>	Back pain, myalgia, arthralgia.
Renal and urinary disorders	
<i>Common</i>	Proteinuria.
<i>Uncommon</i>	Renal failure acute*.
General disorders and administration site conditions	
<i>Very common</i>	<u>Pyrexia*</u> , <u>fatigue*</u> , <u>chills*</u> .
<i>Common</i>	Pain, asthenia*, <u>Systemic inflammatory response syndrome*</u> , oedema incl. oedema peripheral*, general physical health deterioration*, chest pain, influenza-like illness, malaise*, catheter site erythema.
<i>Uncommon</i>	Extravasation*, application site inflammation*.

* were also reported as serious adverse reactions
underlined: see section ‘Description of selected adverse reactions’

Description of selected adverse reactions

The following definitions of CTCAE criteria of the US National Cancer Institute (version 4.0) apply: CTCAE grade 1 = mild, CTCAE grade 2 = moderate, CTCAE grade 3 = severe, CTCAE grade 4 = life-threatening

Cytokine release related symptoms with higher intensities

In 5.1% of patients pyrexia reached an intensity of CTCAE grade 3 as it was the case with cytokine release syndrome (1.0%), chills (0.8%), nausea (3.4%), vomiting (4.4%), dyspnoea (1.6%) and hypo-/hypertension (2.1% / 0.8%). In one patient (0.1%) dyspnoea and in 3 patients (0.4%) hypotension was reported in CTCAE grade 4 intensity. Symptoms of pain and pyrexia can be ameliorated or avoided by pre-medication (see sections 4.2 and 4.4).

Systemic Inflammatory Response Syndrome (SIRS)

In 3.8% of the patients symptoms of SIRS were observed within 24 hours after catumaxomab infusion. In three patients (0.4%) an intensity of CTCAE grade 4 was observed. These reactions resolved under symptomatic treatment.

Abdominal pain

In 43.7% of patients abdominal pain was reported as an adverse reaction reaching grade 3 in 8.2 % of patients, but it resolved under symptomatic treatment.

Hepatic enzymes

Transient increase in hepatic enzymes was commonly observed after the administration of Removab. In general, the changes in laboratory parameters were not clinically relevant and mostly returned to baseline after end of treatment.

Only in case of clinically relevant or persisting increase further diagnostics or therapy should be considered.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

No case of overdose has been reported. Patients receiving a higher than recommended dose of catumaxomab experienced more severe (grade 3) adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC09

Mechanism of action

Catumaxomab is a trifunctional rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule (EpCAM) and the CD3 antigen.

The EpCAM antigen is overexpressed on most carcinomas (Table 2). CD3 is expressed on mature T-cells as a component of the T-cell receptor. A third functional binding site in the Fc-region of catumaxomab enables interaction with accessory immune cells via Fcγ receptors.

Due to catumaxomab's binding properties, tumour cells, T-cells and accessory immune cells come in close proximity. Thereby, a concerted immunoreaction against tumour cells is induced which includes different mechanisms of action such as T-cell activation, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and phagocytosis. This results in destruction of tumour cells.

Table 2 EpCAM expression in most relevant ascites causing cancer types

Cancer Type	Literature data		Retrospective data from study IP-CAT-AC-03
	Percentage of tumors expressing EpCAM	Percentage of EpCAM positive effusions	Percentage of EpCAM positive effusions
Ovarian	90-92	79-100	98
Gastric	96	75-100	100
Colon	100	87-100	100
Pancreatic	98	83-100	80
Breast	45*-81	71-100	86
Endometrial	94	100	100

*= lobular breast cancer

Pharmacodynamic effects

The anti-tumour activity of catumaxomab has been demonstrated *in vitro* and *in vivo*. Effective catumaxomab-mediated killing of tumour cells *in vitro* was observed for target cells with low and high expression of the EpCAM antigen, independent of the primary tumour type. The *in vivo* anti-tumour activity of catumaxomab was confirmed in an immunologically compromised mouse model of ovarian carcinoma, where tumour development was delayed by an intraperitoneal treatment with catumaxomab and human peripheral blood mononuclear cells.

Clinical efficacy

The efficacy of catumaxomab was demonstrated in two phase III clinical studies. Patients of non-Caucasian origin have not been included in these clinical studies.

IP-REM-AC-01

A pivotal, two-arm, randomised, open-label, phase II/III clinical trial in 258 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas of whom 170 were randomised to catumaxomab treatment. This study compared paracentesis plus catumaxomab *versus* paracentesis alone (control).

Catumaxomab was applied in patients where standard therapy was not available or no longer feasible and who had a Karnofsky performance status of at least 60. Catumaxomab was administered as four intraperitoneal infusions with increased doses of 10, 20, 50 and 150 micrograms on day 0, 3, 7 and 10, respectively (see section 4.2). In the pivotal study IP-REM-AC-01 98.1% of patients were hospitalised for a median of 11 days.

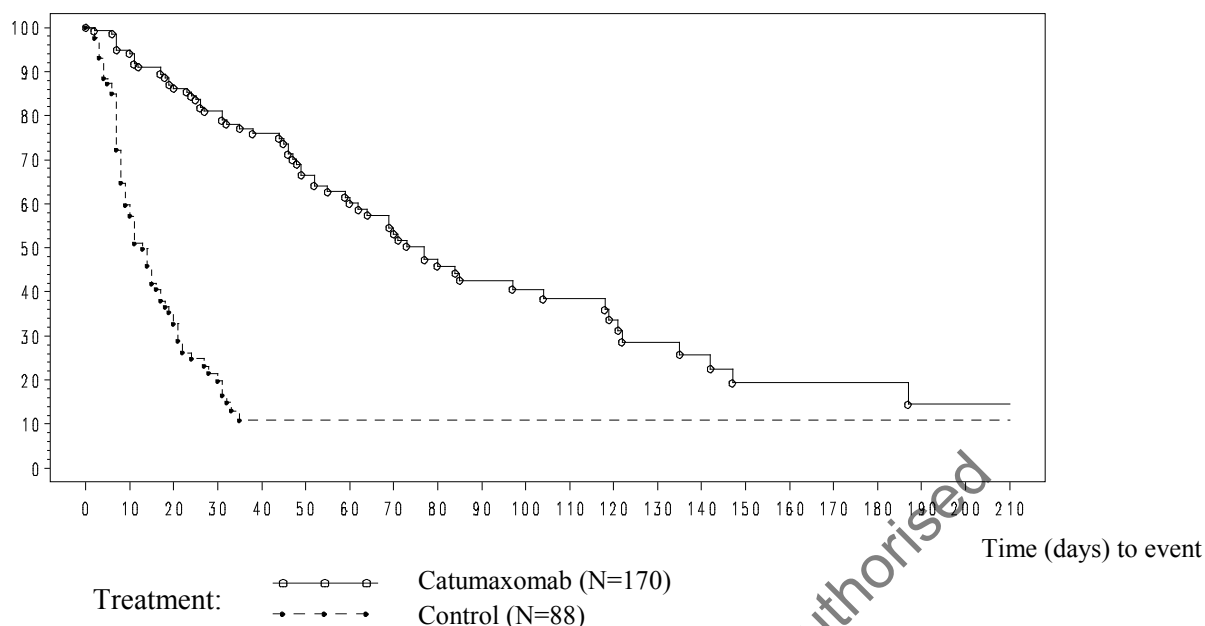
In this study, the primary efficacy endpoint was puncture-free survival, which was a composite endpoint defined as the time to first need for therapeutic ascites puncture or death, whichever occurred first. The results for puncture-free survival and time to first need for therapeutic ascites puncture in terms of medians and hazard ratios are presented in Table 3. Kaplan Meier estimates for time to first need for therapeutic ascites puncture are given in Figure 1.

Table 3 Efficacy results (puncture-free survival and time to first need for therapeutic ascites puncture) of study IP-REM-AC-01

Variable	Paracentesis + catumaxomab (N=170)	Paracentesis (control) (N=88)
Puncture free survival		
Median puncture-free survival (days)	44	11
95% CI for median (days)	[31; 49]	[9; 16]
p-value (log-rank test)	< 0.0001	
Hazard ratio (HR)	0.310	
95% CI for HR	[0.228; 0.423]	
Time to first need for therapeutic ascites puncture		
Median time to first need for therapeutic ascites puncture (days)	77	13
95% CI for median (days)	[62;104]	[9; 17]
p-value (log-rank test)	< 0.0001	
Hazard ratio (HR)	0.169	
95% CI for HR	[0.114; 0.251]	

Figure 1 Kaplan-Meier estimates of time to first need for therapeutic ascites puncture of study IP-REM-AC-01

Estimated Probability of Being Puncture-free (%)



N: number of patients in a treatment group.

The efficacy of the treatment with paracentesis and catumaxomab in patients with malignant ascites due to EpCAM-positive carcinomas was statistically significantly superior to that with paracentesis alone in terms of puncture-free survival and time to first need for therapeutic ascites puncture.

After completion of the study, patients were further observed until the end of their lifetime to assess overall survival (Table 4).

Table 4 Overall survival of study IP-REM-AC-01 in post study phase

	Paracentesis + catumaxomab (N=170)	Paracentesis (control) (N=88)
Hazard ratio (HR)	0.798	
95% CI for HR	[0.606; 1.051]	
6 months survival rate	27.5%	17.1%
1 year survival rate	11.4%	2.6%
Median overall survival (days)	72	71
95% CI for median (days)	[61; 98]	[54; 89]
p-value (log-rank test)	0.1064	

Altogether 45 out of 88 (51%) patients in the control arm crossed-over to achieve active treatment with catumaxomab.

IP-CAT-AC-03

This confirmatory two-arm, randomized, open label, phase IIIb study in 219 epithelial cancer patients with symptomatic malignant ascites requiring therapeutic ascites puncture investigated treatment with catumaxomab plus 25 mg prednisolone premedication vs. catumaxomab alone. Catumaxomab was administered as four 3-hour constant-rate i.p. infusions in doses of 10, 20, 50 and 150 micrograms on day 0, 3, 7 and 10, respectively, in both groups. The patient population was comparable to the pivotal study.

In order to assess the impact of prednisolone premedication on safety and efficacy the primary safety endpoint “composite safety score” and the co-primary efficacy endpoint “puncture-free survival” were investigated.

The composite safety score evaluated the frequency and severity of the main known adverse reactions pyrexia, nausea, vomiting and abdominal pain in both treatment groups. Administration of prednisolone as premedication did not result in a reduction of these adverse reactions.

The primary efficacy endpoint, puncture-free survival, was a composite endpoint defined as the time to first need for therapeutic ascites puncture or death, whichever occurred first (identical to the pivotal study).

Table 5 Efficacy results (puncture-free survival and time to first need for therapeutic ascites puncture) of study IP-CAT-AC-03

Variable	Catumaxomab + prednisolone (N=111)	Catumaxomab (N=108)	Pooled population (N=219)
Puncture free survival			
Median puncture-free survival (days)	30	37	35
95% CI for median (days)	[23; 67]	[24; 61]	[26; 59]
p-value (log-rank test)	0.402		
Hazard ratio (HR) (Catumaxomab versus Catumaxomab + Prednisolone)	1.130		
95% CI for HR	[0.845; 1.511]		
Time to first need for therapeutic ascites puncture			
Median time to first need for therapeutic ascites puncture (days)	78	102	97
95% CI for median (days)	[30; 223]	[69; 159]	[67; 155]
p-value (log-rank test)	0.599		
Hazard ratio (HR) (Catumaxomab versus Catumaxomab + Prednisolone)	0.901		
95% CI for HR	[0.608; 1.335]		

As secondary efficacy endpoint overall survival (Table 6) was assessed.

Table 6 Overall survival of study IP-CAT-AC-03 in post study phase

	Catumaxomab + prednisolone (N=111)	Catumaxomab (N=108)	Pooled population (N=219)
Median overall survival (days)	124	86	103
95% CI for median (days)	[97.0; 169.0]	[72.0; 126.0]	[82; 133]
p-value (log-rank test)	0.186		
Hazard ratio (HR) (Catumaxomab versus Catumaxomab + Prednisolone)	1.221		
95% CI for HR	[0.907 ;1.645]		

Immunogenicity

The induction of human anti-murine (rat and / or mouse) antibodies (HAMAs/HARAs) is an intrinsic effect of murine monoclonal antibodies. Current data on catumaxomab derived from the pivotal study show that only 5.6% of patients (7/124 patients) were HAMA positive before the 4th infusion. HAMAs were present in 94% of patients one month after the last catumaxomab infusion. No hypersensitivity reactions were observed.

Patients who developed HAMAs 8 days after catumaxomab treatment showed better clinical outcome, as measured by puncture-free survival, time to next puncture and overall survival, compared with HAMA-negative patients.

In a feasibility study evaluating a second i.p. infusion cycle consisting of 10, 20, 50 and 150 micrograms of catumaxomab in 8 patients with malignant ascites due to carcinoma (IP-CAT-AC-04)

ADA was detectable in all available ascites and plasma samples at screening. The patients remained ADA positive during treatment phase and follow-up. Despite pre-existing ADA values all patients received all 4 catumaxomab infusions. The median puncture-free survival time was 47.5 days, median time to first therapeutic puncture 60.0 days and median overall survival 406.5 days. All patients experienced symptoms related to catumaxomab mode of action with a safety profile comparable in nature to the first i.p. treatment cycle. No hypersensitivity reactions were observed.

5.2 Pharmacokinetic properties

Pharmacokinetics of catumaxomab during and after four intraperitoneal infusions of 10, 20, 50 and 150 micrograms catumaxomab were investigated in 13 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas.

The variability between subjects was high. The geometric mean plasma C_{max} was approximately 0.5 ng/ml (range 0 to 2.3), and the geometric mean plasma AUC was approximately 1.7 day* ng/ml (range < LLOQ (lower limit of quantification) to 13.5). The geometric mean apparent terminal plasma elimination half-life ($t_{1/2}$) was approximately 2.5 days (range 0.7 to 17).

Catumaxomab was detectable in the ascites fluid and in plasma. The concentrations increased with the number of infusions and the doses applied in most patients. Plasma levels tended to decline after achieving a maximum after each dose.

Special populations

No studies have been conducted.

5.3 Preclinical safety data

Administration of catumaxomab in animal models did not result in any signs of abnormal or drug-related acute toxicity or signs of local intolerance at the injection/infusion site. However, these findings are of limited value due to the high species-specificity of catumaxomab.

Repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid monohydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After dilution

The prepared solution for infusion is physically and chemically stable for 48 hours at 2°C to 8°C and for 24 hours at a temperature not above 25°C. From a microbiological point of view, the product

should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze. Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.1 ml concentrate for solution for infusion in a pre-filled syringe (type I glass, siliconised) with plunger stopper (bromobutyl rubber) and luer lock system (polypropylene siliconised and polycarbonate) with tip cap (styrene butadiene rubber) with a cannula; pack size of 1.

6.6 Special precautions for disposal and other handling

Disposal

No special requirements.

Material and equipment required

The following components must be used for the dilution and administration of Removab as Removab is only compatible with:

- 50 ml polypropylene syringes
- polyethylene perfusion tubings with an inner diameter of 1 mm and a length of 150 cm
- polycarbonate infusion valves / Y connections
- polyurethane, polyurethane silicon coated catheters

In addition the following is required:

- Sodium chloride 9 mg/ml (0.9%) solution for injection
- Precision perfusion pump

Instructions for dilution prior to administration

Removab should be prepared by a healthcare professional using appropriate aseptic technique. The outer surface of the pre-filled syringe is not sterile.

- Based on the dose, the appropriate amount of sodium chloride 9 mg/ml (0.9%) solution for injection is extracted with a 50 ml syringe (Table 7).
- An additional air buffer of at least 3 ml is included in the 50 ml syringe.
- The tip cap from the Removab pre-filled syringe is removed with the tip pointing up.
- The enclosed cannula is attached to the Removab pre-filled syringe. For each syringe a new cannula is used.
- The pre-filled syringe cannula is inserted through the 50 ml syringe opening so that the cannula is immersed in the sodium chloride 9 mg/ml (0.9%) solution for injection (Figure 2).
- The entire content of the syringe (Removab concentrate plus air buffer) is injected from the pre-filled syringe directly into the sodium chloride 9 mg/ml (0.9%) solution for injection.
- The plunger rod MUST NOT be drawn back to rinse the pre-filled syringe, in order to avoid contamination and to ensure that the correct volume is ejected.
- The 50 ml syringe is closed with a cap and shaken gently to mix the solution. Any air bubble(s) from the 50 ml syringe is eliminated.
- The peelable sticker, which is provided on the inner side of the Removab carton box, displaying the text "Diluted Removab. Intraperitoneal use only." must be attached to the 50 ml syringe

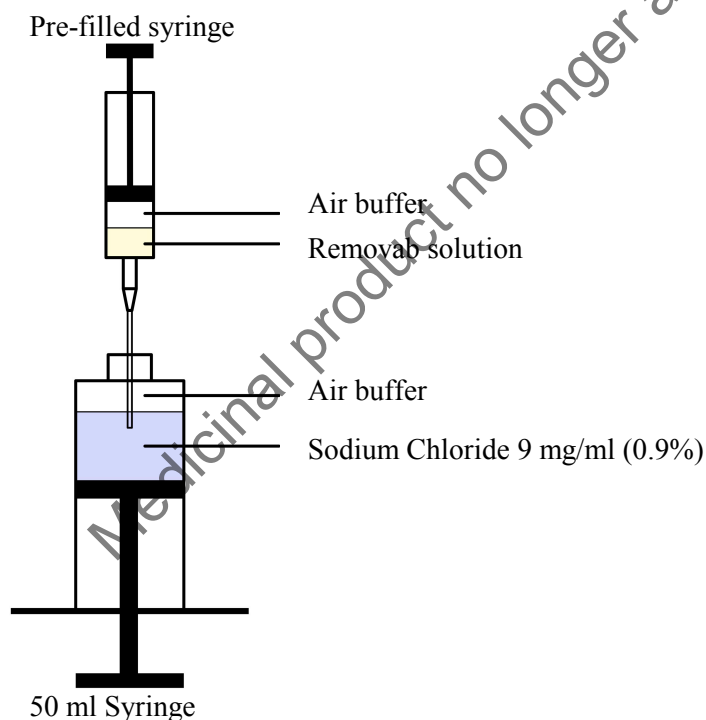
containing the diluted Removab solution for intraperitoneal infusion. This is a precautionary measure to ensure that Removab is infused only via the intraperitoneal route of administration.

- The 50 ml syringe is inserted in the infusion pump.

Table 7 Preparation of Removab solution for intraperitoneal infusion

Number of infusion / Dose	Number of Removab pre-filled syringe(s)		Total volume of Removab concentrate for solution for infusion	Sodium chloride 9 mg/ml (0.9%) solution for injection	Final volume for administration
	10 micrograms pre-filled syringe	50 micrograms pre-filled syringe			
1 st infusion 10 micrograms	1		0.1 ml	10 ml	10.1 ml
2 nd infusion 20 micrograms	2		0.2 ml	20 ml	20.2 ml
3 rd infusion 50 micrograms		1	0.5 ml	49.5 ml	50 ml
4 th infusion 150 micrograms		3	1.5 ml	48.5 ml	50 ml

Figure 2 Illustration of the transfer of Removab from the pre-filled syringe to the 50 ml syringe



Method of administration

The catheter for intraperitoneal administration should be placed under ultrasound guidance by a physician experienced in intraperitoneal administration procedures. The catheter is used for ascites drainage and infusion of diluted Removab and sodium chloride 9 mg/ml (0.9%) solution for injection. It is recommended that the catheter remains in the abdominal cavity during the entire treatment period. It can be removed the day after the last infusion.

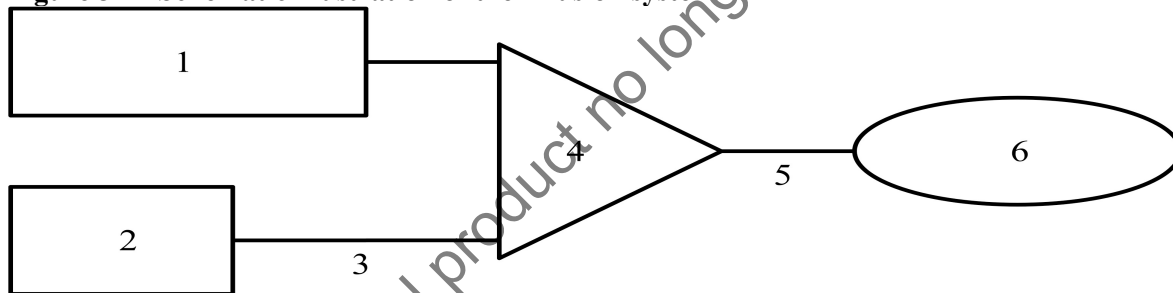
Prior to each Removab administration the ascites fluid must be drained until stop of spontaneous flow or symptom relief (see section 4.4). Subsequently, prior to each Removab administration 500 ml

sodium chloride 9 mg/ml (0.9%) solution for injection shall be infused to support distribution of the antibody in the abdominal cavity.

Removab must be administered intraperitoneally over an infusion time of at least 3 hours via a constant infusion pump system as described below:

- The 50 ml syringe containing the diluted Removab solution for infusion is installed in the precision pump.
- The connected perfusion tubing equipment of the precision pump is prefilled with the diluted Removab solution for infusion. A perfusion tubing of an inner diameter of 1 mm and a length of 150 cm must be used.
- The perfusion tubing is connected to the Y-connection.
- Parallel to each Removab application 250 ml sodium chloride 9 mg/ml (0.9%) solution for injection are infused via an infusion valve / Y connection in the perfusion lead of the catheter.
- The pump speed is adjusted according to the volume to be administered and the scheduled infusion time.
- When the 50 ml syringe containing the diluted Removab solution for infusion is empty it is replaced with a 50 ml syringe containing 20 ml sodium chloride 9 mg/ml (0.9%) solution for injection until the end of the scheduled infusion time to clear the dead volume in the perfusion lead (approximately 2 ml) under unchanged conditions. The remaining sodium chloride 9 mg/ml (0.9%) solution for injection can be discarded.
- The catheter is kept closed until the next infusion.
- The day after the last infusion a drainage of ascites until stop of spontaneous flow is performed. Subsequently, the catheter can be removed.

Figure 3 Schematic illustration of the infusion system



- 1 250 ml Sodium Chloride 9 mg/ml (0.9%)
- 2 Removab solution for i.p. infusion
- 3 Perfusion Tubing (1 mm inner diameter, 150 cm length)
- 4 Infusion valve
- 5 Perfusion Lead
- 6 Catheter

7. MARKETING AUTHORISATION HOLDER

Neovii Biotech GmbH
Am Haag 6-7
82166 Graefelfing
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/512/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2009
Date of latest renewal: 18 December 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: <http://www.ema.europa.eu>.

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Removab 50 micrograms concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 50 micrograms of catumaxomab* in 0.5 ml solution, corresponding to 0.1 mg/ml.

*rat-mouse hybrid IgG2 monoclonal antibody produced in a rat-mouse hybrid-hybridoma cell line

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Removab is indicated for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

4.2 Posology and method of administration

Removab must be administered under the supervision of a physician experienced in the use of anti-neoplastic medicinal products.

Posology

Prior to the intraperitoneal infusion, pre-medication with analgesic / antipyretic / non-steroidal antiphlogistic medicinal products is recommended (see section 4.4).

Removab dosing schedule comprises the following four intraperitoneal infusions:

1 st dose	10 micrograms on day 0
2 nd dose	20 micrograms on day 3
3 rd dose	50 micrograms on day 7
4 th dose	150 micrograms on day 10

Removab has to be administered as constant rate intraperitoneal infusion with an infusion time of at least 3 hours. In clinical studies infusion times of 3 hours and 6 hours were investigated. For the first of the four doses an infusion time of 6 hours may be considered depending on the patient's health condition.

An interval of at least two infusion free calendar days must elapse between infusion days. The interval between the infusion days can be prolonged in case of relevant adverse reactions. The overall treatment period should not exceed 20 days.

Monitoring

Adequate monitoring of the patient after end of Removab infusion is recommended. In the pivotal study patients were monitored for 24 h after each infusion.

Special populations

Hepatic impairment

Patients with hepatic impairment of a higher severity grade than moderate and / or with more than 70% of the liver metastasised and / or portal vein thrombosis / obstruction have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk (see section 4.4).

Renal impairment

Patients with renal impairment of a higher severity grade than mild have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk (see section 4.4).

Paediatric population

There is no relevant use of Removab in the paediatric population in the granted indication.

Method of administration

Removab must be administered as an **intraperitoneal infusion only**.

Removab **must not** be administered by intraperitoneal bolus or by any other route of administration. For information on the perfusion system to be used see section 4.4.

Precautions to be taken before administering the medicinal product

Before administration of Removab the concentrate for solution for infusion is diluted in sodium chloride 9 mg/ml (0.9%) solution for injection. The diluted Removab solution for infusion is administered intraperitoneally as constant rate infusion using an adequate pump system.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to murine (rat and / or mouse) proteins.

4.4 Special warnings and precautions for use

Removab **must not** be administered as a bolus or by any route other than intraperitoneally.

Cytokine release related symptoms

As release of pro-inflammatory and cytotoxic cytokines is initiated by the binding of catumaxomab to immune and tumour cells, cytokine release related clinical symptoms such as fever, nausea, vomiting and chills have been very commonly reported during and after the Removab administration (see section 4.8). Dyspnoea and hypo-/ hypertension are commonly observed. In the clinical studies in patients with malignant ascites, 1,000 mg paracetamol intravenously was routinely administered prior to Removab infusion for pain and pyrexia control. Despite this premedication, patients experienced the adverse reactions described above with an intensity of up to grade 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the US National Cancer Institute, version 3.0. Other or additional standard pre-medication with analgesic / antipyretic / nonsteroidal antiphlogistic medicinal products is recommended.

Systemic Inflammatory Response Syndrome (SIRS), which may also occur commonly due to the mechanism of action of catumaxomab, develops, in general, within 24 hours after Removab infusion, showing symptoms of fever, tachycardia, tachypnoea and leucocytosis (see section 4.8). Standard therapy or premedication, e.g. analgesic / antipyretic / nonsteroidal antiphlogistic is appropriate to limit the risk.

Abdominal pain

Abdominal pain was commonly reported as an adverse reaction. This transient effect is considered partially a consequence of the intraperitoneal route of administration.

Performance status and BMI

A solid performance status expressed as Body Mass Index (BMI) > 17 (to be assessed after drainage of ascites fluid) and Karnofsky Index > 60 is required prior to Removab therapy.

Acute infections

In presence of factors interfering with the immune system, in particular acute infections, the administration of Removab is not recommended.

Ascites drainage

Appropriate medical management of ascites drainage is a prerequisite for Removab treatment in order to assure stable circulatory and renal functions. This must at least include ascites drainage until stop of spontaneous flow or symptom relief, and, if appropriate, supportive replacement therapy with crystalloids and / or colloids.

Patients with hemodynamic insufficiency, oedema or hypoproteinaemia

Blood volume, blood protein, blood pressure, pulse and renal function should be assessed before each Removab infusion. **Conditions such as hypovolaemia, hypoproteinaemia, hypotension, circulatory decompensation and acute renal impairment must be resolved prior to each Removab infusion.**

Hepatic impairment or portal vein thrombosis / obstruction

Patients with hepatic impairment of a higher severity grade than moderate and / or with more than 70% of the liver metastasised and / or portal vein thrombosis / obstruction have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.

Renal impairment

Patients with renal impairment of a higher severity grade than mild have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of catumaxomab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Removab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether catumaxomab/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue / abstain from Removab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data on the effect of catumaxomab on fertility are available.

4.7 Effects on ability to drive and use machines

Removab has minor to moderate influence on the ability to drive and use machines. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions are derived from an integrated safety analysis including 12 clinical studies. 728 patients received catumaxomab intraperitoneally, 293 patients as 6 hour - and 435 patients as 3 hour infusions.

The overall safety profile of Removab is characterised by cytokine-release related symptoms and gastrointestinal reactions.

Cytokine-release related reactions: SIRS a potentially life-threatening combination of tachycardia, fever and/or dyspnoea, can develop within 24 hours after a catumaxomab infusion and resolves under symptomatic treatment. Other cytokine-release related reactions such as fever, chills, nausea, and vomiting are very commonly reported reactions in intensity of CTCAE grade 1 and 2 (US National Cancer Institute, version 4.0). These symptoms reflect the mechanism of action of catumaxomab and are in general fully reversible.

Gastrointestinal reactions like abdominal pain, nausea, vomiting and diarrhoea are very common and occur mostly with CTCAE grade 1 or 2, but were also observed in higher grades, and respond to adequate symptomatic treatment.

The safety profile of catumaxomab using a 3h versus a 6h infusion time is in general comparable in regards to nature, frequency and severity. An increased frequency of some adverse reactions was seen in relation to 3h administration including chills and hypotension (grades 1 / 2), diarrhoea (all grades) and fatigue (grade 1 / 2).

Tabulated list of adverse reactions

In Table 1, adverse reactions are listed by organ class. Frequency groupings are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$).

Table 1 Adverse reactions reported from patients receiving catumaxomab treatment

Infections and infestations	
<i>Common</i>	Infection.
<i>Uncommon</i>	Erythema induratum*, device-related infection*.
Blood and lymphatic system disorders	
<i>Common</i>	Anaemia*, lymphopenia, leukocytosis, neutrophilia.
<i>Uncommon</i>	Thrombocytopenia*, coagulopathy*.
Immune system disorders	
<i>Common</i>	Cytokine release syndrome*, hypersensitivity*.
Metabolism and nutrition disorders	
<i>Common</i>	Decreased appetite* / anorexia, dehydration*, hypokalaemia, hypoalbuminaemia, hyponatraemia*, hypocalcaemia*, hypoproteinaemia.
Psychiatric disorders	
<i>Common</i>	Anxiety, insomnia.
Nervous system disorders	
<i>Common</i>	Headache, dizziness.
<i>Uncommon</i>	Convulsion*.
Ear and labyrinth disorders	
<i>Common</i>	Vertigo.
Cardiac disorders	
<i>Common</i>	Tachycardia*, incl. sinus tachycardia.
Vascular disorders	
<i>Common</i>	Hypotension*, hypertension*, flushing.

Respiratory, thoracic and mediastinal disorders	
<i>Common</i>	<u>Dyspnoea*</u> , pleural effusion*, cough.
<i>Uncommon</i>	Pulmonary embolism*, hypoxia*.
Gastrointestinal disorders	
<i>Very common</i>	<u>Abdominal pain*</u> , <u>nausea*</u> , <u>vomiting*</u> , diarrhoea*.
<i>Common</i>	Constipation*, dyspepsia, abdominal distension, sub-ileus*, flatulence, gastric disorder, ileus*, gastroesophageal reflux disease, dry mouth.
<i>Uncommon</i>	Gastrointestinal haemorrhage*, intestinal obstruction*.
Hepatobiliary disorders	
<i>Common</i>	Cholangitis*, hyperbilirubinaemia.
Skin and subcutaneous tissue disorders	
<i>Common</i>	Rash*, erythaema*, hyperhidrosis, pruritus.
<i>Uncommon</i>	Skin reaction*, dermatitis allergic*.
Musculoskeletal and connective tissue disorders	
<i>Common</i>	Back pain, myalgia, arthralgia.
Renal and urinary disorders	
<i>Common</i>	Proteinuria.
<i>Uncommon</i>	Renal failure acute*.
General disorders and administration site conditions	
<i>Very common</i>	<u>Pyrexia*</u> , <u>fatigue*</u> , <u>chills*</u> .
<i>Common</i>	Pain, asthenia*, <u>Systemic inflammatory response syndrome*</u> , oedema incl. oedema peripheral*, general physical health deterioration*, chest pain, influenza-like illness, malaise*, catheter site erythema.
<i>Uncommon</i>	Extravasation*, application site inflammation*.

* were also reported as serious adverse reactions
underlined: see section ‘Description of selected adverse reactions’

Description of selected adverse reactions

The following definitions of CTCAE criteria of the US National Cancer Institute (version 4.0) apply: CTCAE grade 1 = mild, CTCAE grade 2 = moderate, CTCAE grade 3 = severe, CTCAE grade 4 = life-threatening

Cytokine release related symptoms with higher intensities

In 5.1% of patients pyrexia reached an intensity of CTCAE grade 3 as it was the case with cytokine release syndrome (1.0%), chills (0.8%), nausea (3.4%), vomiting (4.4%), dyspnoea (1.6%) and hypo-/hypertension (2.1% / 0.8%). In one patient (0.1%) dyspnoea and in 3 patients (0.4%) hypotension was reported in CTCAE grade 4 intensity. Symptoms of pain and pyrexia can be ameliorated or avoided by pre-medication (see sections 4.2 and 4.4).

Systemic Inflammatory Response Syndrome (SIRS)

In 3.8% of the patients symptoms of SIRS were observed within 24 hours after catumaxomab infusion. In three patients (0.4%) an intensity of CTCAE grade 4 was observed. These reactions resolved under symptomatic treatment.

Abdominal pain

In 43.7% of patients abdominal pain was reported as an adverse reaction reaching grade 3 in 8.2 % of patients, but it resolved under symptomatic treatment.

Hepatic enzymes

Transient increase in hepatic enzymes was commonly observed after the administration of Removab. In general, the changes in laboratory parameters were not clinically relevant and mostly returned to baseline after end of treatment.

Only in case of clinically relevant or persisting increase further diagnostics or therapy should be considered.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

No case of overdose has been reported. Patients receiving a higher than recommended dose of catumaxomab experienced more severe (grade 3) adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC09

Mechanism of action

Catumaxomab is a trifunctional rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule (EpCAM) and the CD3 antigen.

The EpCAM antigen is overexpressed on most carcinomas (Table 2). CD3 is expressed on mature T-cells as a component of the T-cell receptor. A third functional binding site in the Fc-region of catumaxomab enables interaction with accessory immune cells via Fcγ receptors.

Due to catumaxomab's binding properties, tumour cells, T-cells and accessory immune cells come in close proximity. Thereby, a concerted immunoreaction against tumour cells is induced which includes different mechanisms of action such as T-cell activation, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and phagocytosis. This results in destruction of tumour cells.

Table 2 EpCAM expression in most relevant ascites causing cancer types

Cancer Type	Literature data		Retrospective data from study IP-CAT-AC-03
	Percentage of tumors expressing EpCAM	Percentage of EpCAM positive effusions	Percentage of EpCAM positive effusions
Ovarian	90-92	79-100	98
Gastric	96	75-100	100
Colon	100	87-100	100
Pancreatic	98	83-100	80
Breast	45*-81	71-100	86
Endometrial	94	100	100

*= lobular breast cancer

Pharmacodynamic effects

The anti-tumour activity of catumaxomab has been demonstrated *in vitro* and *in vivo*. Effective catumaxomab-mediated killing of tumour cells *in vitro* was observed for target cells with low and high expression of the EpCAM antigen, independent of the primary tumour type. The *in vivo* anti-tumour activity of catumaxomab was confirmed in an immunologically compromised mouse model of ovarian carcinoma, where tumour development was delayed by an intraperitoneal treatment with catumaxomab and human peripheral blood mononuclear cells.

Clinical efficacy

The efficacy of catumaxomab was demonstrated in two phase III clinical studies. Patients of non-Caucasian origin have not been included in these clinical studies.

IP-REM-AC-01

A pivotal, two-arm, randomised, open-label, phase II/III clinical trial in 258 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas of whom 170 were randomised to catumaxomab treatment. This study compared paracentesis plus catumaxomab *versus* paracentesis alone (control).

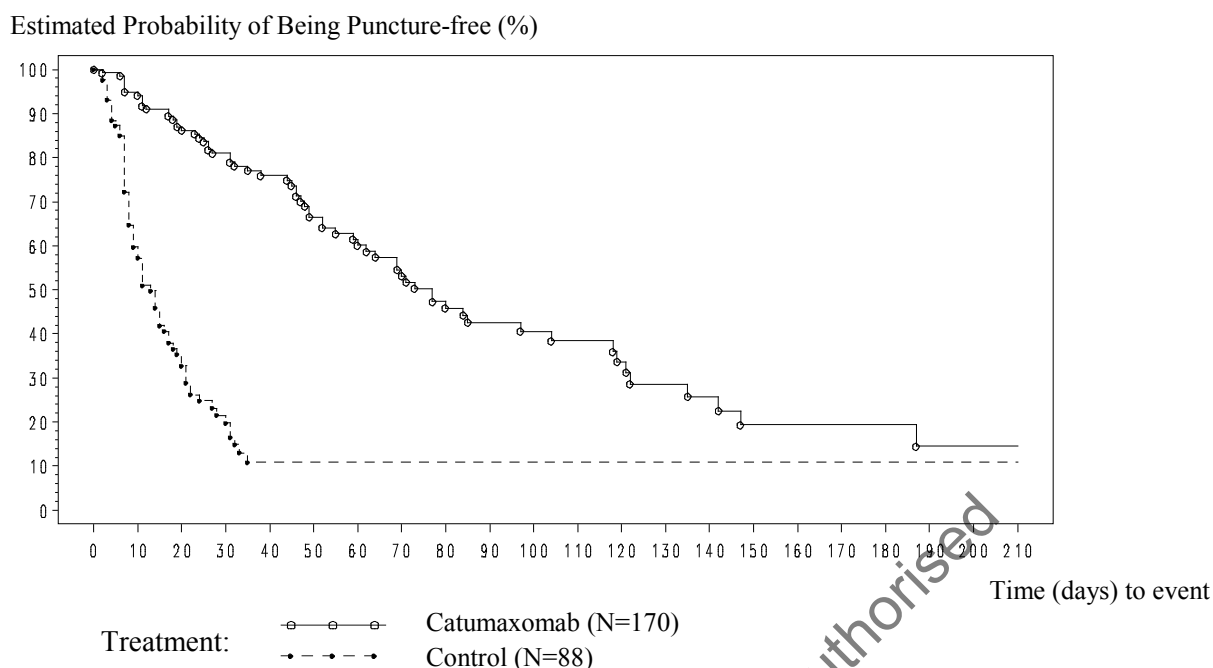
Catumaxomab was applied in patients where standard therapy was not available or no longer feasible and who had a Karnofsky performance status of at least 60. Catumaxomab was administered as four intraperitoneal infusions with increased doses of 10, 20, 50 and 150 micrograms on day 0, 3, 7 and 10, respectively (see section 4.2). In the pivotal study IP-REM-AC-01 98.1% of patients were hospitalised for a median of 11 days.

In this study, the primary efficacy endpoint was puncture-free survival, which was a composite endpoint defined as the time to first need for therapeutic ascites puncture or death, whichever occurred first. The results for puncture-free survival and time to first need for therapeutic ascites puncture in terms of medians and hazard ratios are presented in Table 3. Kaplan Meier estimates for time to first need for therapeutic ascites puncture are given in Figure 1.

Table 3 Efficacy results (puncture-free survival and time to first need for therapeutic ascites puncture) of study IP-REM-AC-01

Variable	Paracentesis + catumaxomab (N=170)	Paracentesis (control) (N=88)
Puncture free survival		
Median puncture-free survival (days)	44	11
95% CI for median (days)	[31; 49]	[9; 16]
p-value (log-rank test)	< 0.0001	
Hazard ratio (HR)	0.310	
95% CI for HR	[0.228; 0.423]	
Time to first need for therapeutic ascites puncture		
Median time to first need for therapeutic ascites puncture (days)	77	13
95% CI for median (days)	[62;104]	[9; 17]
p-value (log-rank test)	< 0.0001	
Hazard ratio (HR)	0.169	
95% CI for HR	[0.114; 0.251]	

Figure 1 Kaplan-Meier estimates of time to first need for therapeutic ascites puncture of study IP-REM-AC-01



N: number of patients in a treatment group.

The efficacy of the treatment with paracentesis and catumaxomab in patients with malignant ascites due to EpCAM-positive carcinomas was statistically significantly superior to that with paracentesis alone in terms of puncture-free survival and time to first need for therapeutic ascites puncture.

After completion of the study, patients were further observed until the end of their lifetime to assess overall survival (Table 4).

Table 4 Overall survival of study IP-REM-AC-01 in post study phase

	Paracentesis + catumaxomab (N=170)	Paracentesis (control) (N=88)
Hazard ratio (HR)	0.798	
95% CI for HR	[0.606; 1.051]	
6 months survival rate	27.5%	17.1%
1 year survival rate	11.4%	2.6%
Median overall survival (days)	72	71
95% CI for median (days)	[61; 98]	[54; 89]
p-value (log-rank test)	0.1064	

Altogether 45 out of 88 (51%) patients in the control arm crossed-over to achieve active treatment with catumaxomab.

IP-CAT-AC-03

This confirmatory two-arm, randomized, open label, phase IIIb study in 219 epithelial cancer patients with symptomatic malignant ascites requiring therapeutic ascites puncture investigated treatment with catumaxomab plus 25 mg prednisolone premedication vs. catumaxomab alone. Catumaxomab was administered as four 3-hour constant-rate i.p. infusions in doses of 10, 20, 50 and 150 micrograms on day 0, 3, 7 and 10, respectively, in both groups. The patient population was comparable to the pivotal study.

In order to assess the impact of prednisolone premedication on safety and efficacy the primary safety endpoint “composite safety score” and the co-primary efficacy endpoint “puncture-free survival” were investigated.

The composite safety score evaluated the frequency and severity of the main known adverse reactions pyrexia, nausea, vomiting and abdominal pain in both treatment groups. Administration of prednisolone as premedication did not result in a reduction of these adverse reactions.

The primary efficacy endpoint, puncture-free survival, was a composite endpoint defined as the time to first need for therapeutic ascites puncture or death, whichever occurred first (identical to the pivotal study).

Table 5 Efficacy results (puncture-free survival and time to first need for therapeutic ascites puncture) of study IP-CAT-AC-03

Variable	Catumaxomab + prednisolone (N=111)	Catumaxomab (N=108)	Pooled population (N=219)
Puncture free survival			
Median puncture-free survival (days)	30	37	35
95% CI for median (days)	[23; 67]	[24; 61]	[26; 59]
p-value (log-rank test)	0.402		
Hazard ratio (HR) (Catumaxomab versus Catumaxomab + Prednisolone)	1.130		
95% CI for HR	[0.845; 1.511]		
Time to first need for therapeutic ascites puncture			
Median time to first need for therapeutic ascites puncture (days)	78	102	97
95% CI for median (days)	[30; 223]	[69; 159]	[67; 155]
p-value (log-rank test)	0.599		
Hazard ratio (HR) (Catumaxomab versus Catumaxomab + Prednisolone)	0.901		
95% CI for HR	[0.608; 1.335]		

As secondary efficacy endpoint overall survival (Table 6) was assessed.

Table 6 Overall survival of study IP-CAT-AC-03 in post study phase

	Catumaxomab + prednisolone (N=111)	Catumaxomab (N=108)	Pooled population (N=219)
Median overall survival (days)	124	86	103
95% CI for median (days)	[97.0; 169.0]	[72.0; 126.0]	[82; 133]
p-value (log-rank test)	0.186		
Hazard ratio (HR) (Catumaxomab versus Catumaxomab + Prednisolone)	1.221		
95% CI for HR	[0.907 ;1.645]		

Immunogenicity

The induction of human anti-murine (rat and / or mouse) antibodies (HAMAs/HARAs) is an intrinsic effect of murine monoclonal antibodies. Current data on catumaxomab derived from the pivotal study show that only 5.6% of patients (7/124 patients) were HAMA positive before the 4th infusion. HAMAs were present in 94% of patients one month after the last catumaxomab infusion. No hypersensitivity reactions were observed.

Patients who developed HAMAs 8 days after catumaxomab treatment showed better clinical outcome, as measured by puncture-free survival, time to next puncture and overall survival, compared with HAMA-negative patients.

In a feasibility study evaluating a second i.p. infusion cycle consisting of 10, 20, 50 and 150 micrograms of catumaxomab in 8 patients with malignant ascites due to carcinoma (IP-CAT-AC-04)

ADA was detectable in all available ascites and plasma samples at screening. The patients remained ADA positive during treatment phase and follow-up. Despite pre-existing ADA values all patients received all 4 catumaxomab infusions. The median puncture-free survival time was 47.5 days, median time to first therapeutic puncture 60.0 days and median overall survival 406.5 days. All patients experienced symptoms related to catumaxomab mode of action with a safety profile comparable in nature to the first i.p. treatment cycle. No hypersensitivity reactions were observed.

5.2 Pharmacokinetic properties

Pharmacokinetics of catumaxomab during and after four intraperitoneal infusions of 10, 20, 50 and 150 micrograms catumaxomab were investigated in 13 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas.

The variability between subjects was high. The geometric mean plasma C_{max} was approximately 0.5 ng/ml (range 0 to 2.3), and the geometric mean plasma AUC was approximately 1.7 day* ng/ml (range < LLOQ (lower limit of quantification) to 13.5). The geometric mean apparent terminal plasma elimination half-life ($t_{1/2}$) was approximately 2.5 days (range 0.7 to 17).

Catumaxomab was detectable in the ascites fluid and in plasma. The concentrations increased with the number of infusions and the doses applied in most patients. Plasma levels tended to decline after achieving a maximum after each dose.

Special populations

No studies have been conducted.

5.3 Preclinical safety data

Administration of catumaxomab in animal models did not result in any signs of abnormal or drug-related acute toxicity or signs of local intolerance at the injection/infusion site. However, these findings are of limited value due to the high species-specificity of catumaxomab.

Repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid monohydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After dilution

The prepared solution for infusion is physically and chemically stable for 48 hours at 2°C to 8°C and for 24 hours at a temperature not above 25°C. From a microbiological point of view, the product

should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze. Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.5 ml concentrate for solution for infusion in a pre-filled syringe (type I glass, siliconised) with plunger stopper (bromobutyl rubber) and luer lock system (polypropylene siliconised and polycarbonate) with tip cap (styrene butadiene rubber) with a cannula; pack size of 1.

6.6 Special precautions for disposal and other handling

Disposal

No special requirements.

Material and equipment required

The following components must be used for the dilution and administration of Removab as Removab is only compatible with:

- 50 ml polypropylene syringes
- polyethylene perfusion tubings with an inner diameter of 1 mm and a length of 150 cm
- polycarbonate infusion valves / Y connections
- polyurethane, polyurethane silicon coated catheters

In addition the following is required:

- Sodium chloride 9 mg/ml (0.9%) solution for injection
- Precision perfusion pump

Instructions for dilution prior to administration

Removab should be prepared by a healthcare professional using appropriate aseptic technique. The outer surface of the pre-filled syringe is not sterile.

- Based on the dose, the appropriate amount of sodium chloride 9 mg/ml (0.9%) solution for injection is extracted with a 50 ml syringe (Table 7).
- An additional air buffer of at least 3 ml is included in the 50 ml syringe.
- The tip cap from the Removab pre-filled syringe is removed with the tip pointing up.
- The enclosed cannula is attached to the Removab pre-filled syringe. For each syringe a new cannula is used.
- The pre-filled syringe cannula is inserted through the 50 ml syringe opening so that the cannula is immersed in the sodium chloride 9 mg/ml (0.9%) solution for injection (Figure 2).
- The entire content of the syringe (Removab concentrate plus air buffer) is injected from the pre-filled syringe directly into the sodium chloride 9 mg/ml (0.9%) solution for injection.
- The plunger rod MUST NOT be drawn back to rinse the pre-filled syringe, in order to avoid contamination and to ensure that the correct volume is ejected.
- The 50 ml syringe is closed with a cap and shaken gently to mix the solution. Any air bubble(s) from the 50 ml syringe is eliminated.
- The peelable sticker, which is provided on the inner side of the Removab carton box, displaying the text "Diluted Removab. Intraperitoneal use only." must be attached to the 50 ml syringe

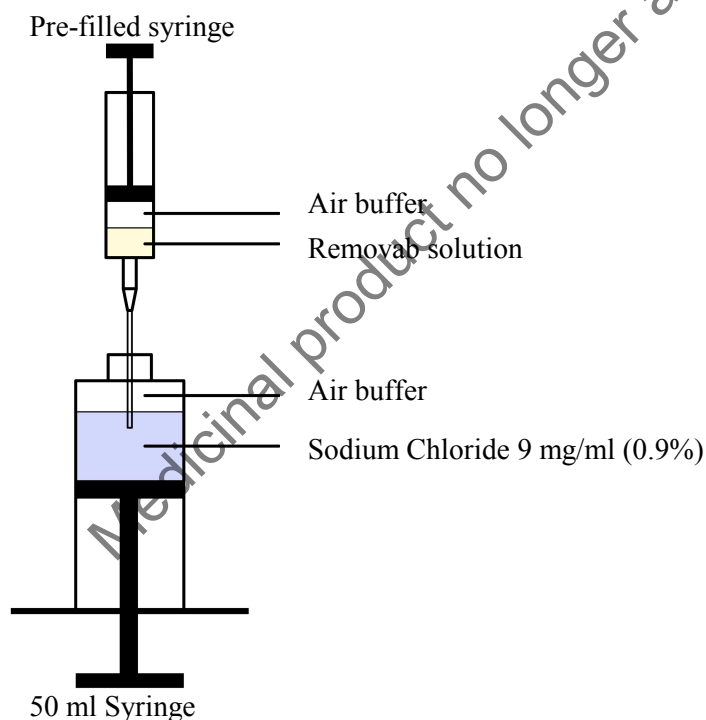
containing the diluted Removab solution for intraperitoneal infusion. This is a precautionary measure to ensure that Removab is infused only via the intraperitoneal route of administration.

- The 50 ml syringe is inserted in the infusion pump.

Table 7 Preparation of Removab solution for intraperitoneal infusion

Number of infusion / Dose	Number of Removab pre-filled syringe(s)		Total volume of Removab concentrate for solution for infusion	Sodium chloride 9 mg/ml (0.9%) solution for injection	Final volume for administration
	10 micrograms pre-filled syringe	50 micrograms pre-filled syringe			
1 st infusion 10 micrograms	1		0.1 ml	10 ml	10.1 ml
2 nd infusion 20 micrograms	2		0.2 ml	20 ml	20.2 ml
3 rd infusion 50 micrograms		1	0.5 ml	49.5 ml	50 ml
4 th infusion 150 micrograms		3	1.5 ml	48.5 ml	50 ml

Figure 2 Illustration of the transfer of Removab from the pre-filled syringe to the 50 ml syringe



Method of administration

The catheter for intraperitoneal administration should be placed under ultrasound guidance by a physician experienced in intraperitoneal administration procedures. The catheter is used for ascites drainage and infusion of diluted Removab and sodium chloride 9 mg/ml (0.9%) solution for injection. It is recommended that the catheter remains in the abdominal cavity during the entire treatment period. It can be removed the day after the last infusion.

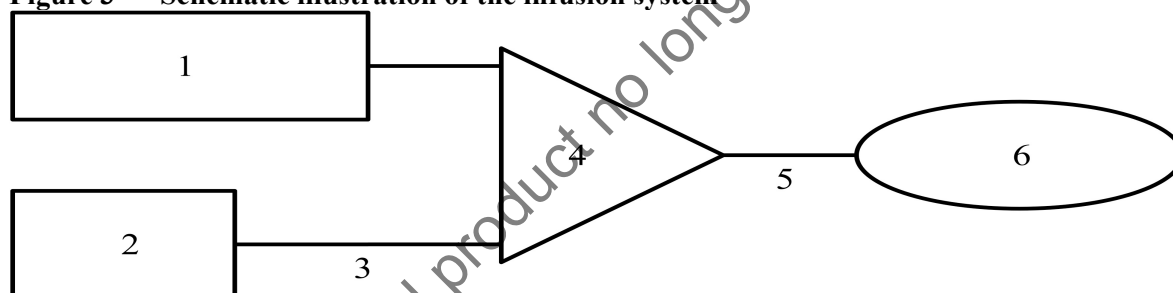
Prior to each Removab administration the ascites fluid must be drained until stop of spontaneous flow or symptom relief (see section 4.4). Subsequently, prior to each Removab administration 500 ml

sodium chloride 9 mg/ml (0.9%) solution for injection shall be infused to support distribution of the antibody in the abdominal cavity.

Removab must be administered intraperitoneally over an infusion time of at least 3 hours via a constant infusion pump system as described below:

- The 50 ml syringe containing the diluted Removab solution for infusion is installed in the precision pump.
- The connected perfusion tubing equipment of the precision pump is prefilled with the diluted Removab solution for infusion. A perfusion tubing of an inner diameter of 1 mm and a length of 150 cm must be used.
- The perfusion tubing is connected to the Y-connection.
- Parallel to each Removab application 250 ml sodium chloride 9 mg/ml (0.9%) solution for injection are infused via an infusion valve / Y connection in the perfusion lead of the catheter.
- The pump speed is adjusted according to the volume to be administered and the scheduled infusion time.
- When the 50 ml syringe containing the diluted Removab solution for infusion is empty it is replaced with a 50 ml syringe containing 20 ml sodium chloride 9 mg/ml (0.9%) solution for injection until the end of the scheduled infusion time to clear the dead volume in the perfusion lead (approximately 2 ml) under unchanged conditions. The remaining sodium chloride 9 mg/ml (0.9%) solution for injection can be discarded.
- The catheter is kept closed until the next infusion.
- The day after the last infusion a drainage of ascites until stop of spontaneous flow is performed. Subsequently, the catheter can be removed.

Figure 3 Schematic illustration of the infusion system



- 1 250 ml Sodium Chloride 9 mg/ml (0.9%)
- 2 Removab solution for i.p. infusion
- 3 Perfusion Tubing (1 mm inner diameter, 150 cm length)
- 4 Infusion valve
- 5 Perfusion Lead
- 6 Catheter

7. MARKETING AUTHORISATION HOLDER

Neovii Biotech GmbH
Am Haag 6-7
82166 Graefelfing
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/512/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2009

Date of latest renewal: 18 December 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: <http://www.ema.europa.eu>.

Medicinal product no longer authorised

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Trion Pharma GmbH
Frankfurter Ring 193a
DE-80807 Munich
Germany

Name and address of the manufacturer responsible for batch release

Neovii Biotech GmbH
Am Haag 6-7
82166 Graefelfing
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton: Removab 10 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Removab 10 micrograms concentrate for solution for infusion
catumaxomab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 10 micrograms catumaxomab in 0.1 ml solution, corresponding to 0.1 mg/ml.

3. LIST OF EXCIPIENTS

Sodium citrate, citric acid monohydrate, polysorbate 80, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.
1 pre-filled syringe.
1 sterile cannula

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intraperitoneal use only, after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Neovii Biotech GmbH
Am Haag 6-7
82166 Graefelfing
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/512/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister: Removab 10 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Removab 10 micrograms concentrate for solution for infusion
catumaxomab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Neovii Biotech GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

1 pre-filled syringe.

Intraperitoneal use only, after dilution. Read the package leaflet before use.

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe: Removab 10 micrograms

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Removab 10 micrograms concentrate for solution for infusion
catumaxomab
Intraperitoneal use only, after dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.1 ml

6. OTHER

Neovii Biotech GmbH

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton: Removab 50 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Removab 50 micrograms concentrate for solution for infusion
catumaxomab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 50 micrograms catumaxomab in 0.5 ml solution, corresponding to 0.1 mg/ml.

3. LIST OF EXCIPIENTS

Sodium citrate, citric acid monohydrate, polysorbate 80, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.
1 pre-filled syringe.
1 sterile cannula

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intraperitoneal use only, after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Neovii Biotech GmbH
Am Haag 6-7
82166 Graefelfing
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/512/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister: Removab 50 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Removab 50 micrograms concentrate for solution for infusion
catumaxomab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Neovii Biotech GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

1 pre-filled syringe.

Intraperitoneal use only, after dilution. Read the package leaflet before use.

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe: Removab 50 micrograms

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Removab 50 micrograms concentrate for solution for infusion
catumaxomab
Intraperitoneal use only, after dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Neovii Biotech GmbH

Medicinal product no longer authorised

**WARNING TEXT FOR PEELABLE STICKER TO BE ATTACHED TO 50ml SYRINGE
CONTAINING THE DILUTED REMOVAB SOLUTION FOR INFUSION**

(Part of the Outer Carton)

Diluted Removab.
Intraperitoneal use only.

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package leaflet: Information for the patient

Removab 10 micrograms concentrate for solution for infusion catumaxomab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Removab is and what it is used for
2. What you need to know before you use Removab
3. How to use Removab
4. Possible side effects
5. How to store Removab
6. Contents of the pack and other information

1. What Removab is and what it is used for

Removab contains the active substance catumaxomab, a monoclonal antibody. It recognises a protein on the surface of cancer cells and recruits immune cells to destroy them.

Removab is used to treat malignant ascites, when standard treatment is not available or no longer feasible. Malignant ascites is an accumulation of fluid in the abdominal space (peritoneal cavity) resulting from certain types of cancer.

2. What you need to know before you use Removab

Do not use Removab

- if you are allergic to catumaxomab or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to murine proteins (from rat and / or mouse)

Warnings and precautions

Talk to your doctor or nurse before using Removab. It is important to tell your doctor if you have any of the following:

- undrained fluid in your abdominal cavity
- cold hands and feet, light headedness, difficulty passing urine, increased heart rate, and weakness (symptoms of low blood volume)
- weight gain, weakness, shortness of breath and fluid retention (symptoms of low blood protein levels)
- feeling dizzy and faint (symptoms of low blood pressure)
- problems with your heart and circulation
- kidney or liver problems
- an infection.

Before you start using Removab your doctor will check your:

- Body Mass Index (BMI), which depends on your height and weight
- Karnofsky Index, a measure of your general performance status.

You are required to have a BMI above 17 (after drainage of the ascites fluid) and a Karnofsky Index above 60 to use this medicine.

Infusion-related side effects and abdominal pain are very common (see section 4). You will be given other medicines to reduce fever, pain or inflammation caused by Removab (see section 3).

Children and adolescents

Removab should not be used in children and adolescents under 18 years of age.

Other medicines and Removab

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. You should not use Removab if you are pregnant unless clearly necessary.

Driving and using machines

If you experience side effects such as dizziness or chills during or after administration, you should not drive or use machines until they disappear.

3. How to use Removab

You will be given Removab under the supervision of a doctor experienced in treating cancer. After the Removab infusion you will be observed as decided by your doctor.

Before starting and during treatment, you will be given other medicines to reduce fever, pain or inflammation caused by Removab.

Removab is given as 4 intraperitoneal infusions with increasing dose (10, 20, 50 and 150 micrograms), separated at least by 2 infusion-free calendar days (for example you will receive infusion on day 0, 3, 7, 10). The infusion must be administered at constant rate with duration time of at least 3 hours. The overall treatment period should not exceed 20 days.

A catheter will be placed in your abdominal space (intraperitoneal) for the whole treatment period, until the day after your last infusion.

If you have any further questions on the use of this product, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common serious side effects of Removab are infusion-related side effects and side effects related to the gastrointestinal system (stomach and gut).

Infusion-related side effects

During and after infusion with Removab more than 1 in 10 patients (very common) will probably experience infusion-related side effects. The most common infusion-related side effects, which are mostly mild to moderate, are fever, chills, feeling sick and vomiting.

If such symptoms occur, please inform your doctor as soon as possible. Your doctor may consider reducing the infusion rate of Removab or giving you additional treatment to reduce these symptoms.

A complex of symptoms including very fast heartbeat, fever and shortness of breath can develop in up to 4 out of 100 patients. These symptoms occur mainly within 24 hours after a Removab infusion and can become life-threatening, but can be treated well with additional therapy.

If such symptoms occur, speak to a doctor immediately, as these side effects require immediate attention and treatment.

Side effects related to the gastrointestinal system

Gastrointestinal reactions like abdominal pain, feeling sick, vomiting and diarrhoea occur in more than 1 in 10 patients (very common), but are mostly mild to moderate and respond well to additional treatment.

If such symptoms occur, please inform your doctor as soon as possible. Your doctor may consider reducing the infusion rate of Removab or giving you additional treatment to reduce these symptoms.

Other serious side effects

Very common serious side effects (may affect more than 1 in 10 people):

- Tiredness

Common serious side effects (may affect up to 1 in 10 people):

- Loss of appetite
- Dehydration
- Reduction in red blood cells (anaemia)
- Decreased blood levels of calcium and sodium
- A very fast heart beat
- High or low blood pressure
- Abdominal pain accompanied by difficulty or blockage passing stools, constipation
- Shortness of breath
- Accumulation of fluid around the lungs which cause chest pain and breathlessness
- Inflammation of the bile ducts
- Skin redness, rash
- Very fast heartbeat, fever, shortness of breath, feeling faint or light-headed
- Complex of reactions due to the release of mediators of inflammation
- Worsening of general state of health, generally feeling unwell and weak
- Fluid retention
- Hypersensitivity

Uncommon serious side effects (may affect up to 1 in 100 people):

- Lumps under the skin on the back of the legs that may become sores and leave scars
- Inflammation and pain or burning and stinging in the area around the catheter
- Reduction in number of blood platelets, blood clotting problems
- Bleeding in the stomach or gut, shown by the vomiting of blood or the passage of red or black stools
- Skin reaction, severe allergic skin reaction (dermatitis)
- Fits
- Lung problems including blood clot in the lungs
- Low blood oxygen levels
- Severe kidney problems
- Extravasation (inadvertent leakage of administered medicinal product from the intraperitoneal catheter system into surrounding tissue)

If such symptoms occur, please inform your doctor as soon as possible. Some of these side effects may require medical treatment.

Other side effects

Common side effects (may affect up to 1 in 10 people):

- Pain
- Reduction or increase in number of white blood cells
- Decreased blood levels of potassium
- Decreased blood protein levels
- Increase of bilirubin in blood
- Spinning sensation
- Indigestion, stomach problems, heartburn, feeling bloated, passing wind, dry mouth
- Flu-like symptoms
- Dizziness or headache
- Chest pain
- Increased sweating
- Infections
- Increased protein levels in urine
- Back pain, aching muscles and joints
- Feeling anxious and having difficulty sleeping
- Itchy rash or hives
- Redness of the skin in the area around the catheter
- Flushing
- Cough

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Removab

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

The prepared infusion solution should be used immediately.

6. Contents of the pack and other information

What Removab contains

- The active substance is catumaxomab (10 micrograms in 0.1 ml, corresponding to 0.1 mg/ml).
- The other ingredients are sodium citrate, citric acid monohydrate, polysorbate 80 and water for injections.

What Removab looks like and contents of the pack

Removab is presented as a clear and colourless concentrate for solution for infusion in a pre-filled syringe with a cannula. Pack size of 1.

Marketing Authorisation Holder and Manufacturer

Neovii Biotech GmbH
Am Haag 6-7

82166 Graefelfing
Germany

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in MM/YYYY.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

For information on dilution and administration of Removab please refer to section 6.6 of the Summary of Product Characteristics (SmPC) included in each package of Removab 10 micrograms and Removab 50 micrograms, respectively.

Medicinal product no longer authorised

Package leaflet: Information for the patient

Removab 50 micrograms concentrate for solution for infusion catumaxomab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Removab is and what it is used for
2. What you need to know before you use Removab
3. How to use Removab
4. Possible side effects
5. How to store Removab
6. Contents of the pack and other information

1. What Removab is and what it is used for

Removab contains the active substance catumaxomab, a monoclonal antibody. It recognises a protein on the surface of cancer cells and recruits immune cells to destroy them.

Removab is used to treat malignant ascites, when standard treatment is not available or no longer feasible. Malignant ascites is an accumulation of fluid in the abdominal space (peritoneal cavity) resulting from certain types of cancer.

2. What you need to know before you use Removab

Do not use Removab

- if you are allergic to catumaxomab or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to murine proteins (from rat and / or mouse)

Warnings and precautions

Talk to your doctor or nurse before using Removab. It is important to tell your doctor if you have any of the following:

- undrained fluid in your abdominal cavity
- cold hands and feet, light headedness, difficulty passing urine, increased heart rate, and weakness (symptoms of low blood volume)
- weight gain, weakness, shortness of breath and fluid retention (symptoms of low blood protein levels)
- feeling dizzy and faint (symptoms of low blood pressure)
- problems with your heart and circulation
- kidney or liver problems
- an infection.

Before you start using Removab your doctor will check your:

- Body Mass Index (BMI), which depends on your height and weight
- Karnofsky Index, a measure of your general performance status.

You are required to have a BMI above 17 (after drainage of the ascites fluid) and a Karnofsky Index above 60 to use this medicine.

Infusion-related side effects and abdominal pain are very common (see section 4). You will be given other medicines to reduce fever, pain or inflammation caused by Removab (see section 3).

Children and adolescents

Removab should not be used in children and adolescents under 18 years of age.

Other medicines and Removab

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. You should not use Removab if you are pregnant unless clearly necessary.

Driving and using machines

If you experience side effects such as dizziness or chills during or after administration, you should not drive or use machines until they disappear.

3. How to use Removab

You will be given Removab under the supervision of a doctor experienced in treating cancer. After the Removab infusion you will be observed as decided by your doctor.

Before starting and during treatment, you will be given other medicines to reduce fever, pain or inflammation caused by Removab.

Removab is given as 4 intraperitoneal infusions with increasing dose (10, 20, 50 and 150 micrograms), separated at least by 2 infusion-free calendar days (for example you will receive infusion on day 0, 3, 7, 10). The infusion must be administered at constant rate with duration time of at least 3 hours. The overall treatment period should not exceed 20 days.

A catheter will be placed in your abdominal space (intraperitoneal) for the whole treatment period, until the day after your last infusion.

If you have any further questions on the use of this product, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common serious side effects of Removab are infusion-related side effects and side effects related to the gastrointestinal system (stomach and gut).

Infusion-related side effects

During and after infusion with Removab more than 1 in 10 patients (very common) will probably experience infusion-related side effects. The most common infusion-related side effects, which are mostly mild to moderate, are fever, chills, feeling sick and vomiting.

If such symptoms occur, please inform your doctor as soon as possible. Your doctor may consider reducing the infusion rate of Removab or giving you additional treatment to reduce these symptoms.

A complex of symptoms including very fast heartbeat, fever and shortness of breath can develop in up to 4 out of 100 patients. These symptoms occur mainly within 24 hours after a Removab infusion and can become life-threatening, but can be treated well with additional therapy.

If such symptoms occur, speak to a doctor immediately, as these side effects require immediate attention and treatment.

Side effects related to the gastrointestinal system

Gastrointestinal reactions like abdominal pain, feeling sick, vomiting and diarrhoea occur in more than 1 in 10 patients (very common), but are mostly mild to moderate and respond well to additional treatment.

If such symptoms occur, please inform your doctor as soon as possible. Your doctor may consider reducing the infusion rate of Removab or giving you additional treatment to reduce these symptoms.

Other serious side effects

Very common serious side effects (may affect more than 1 in 10 people):

- Tiredness

Common serious side effects (may affect up to 1 in 10 people):

- Loss of appetite
- Dehydration
- Reduction in red blood cells (anaemia)
- Decreased blood levels of calcium and sodium
- A very fast heart beat
- High or low blood pressure
- Abdominal pain accompanied by difficulty or blockage passing stools, constipation
- Shortness of breath
- Accumulation of fluid around the lungs which cause chest pain and breathlessness
- Inflammation of the bile ducts
- Skin redness, rash
- Very fast heartbeat, fever, shortness of breath, feeling faint or light-headed
- Complex of reactions due to the release of mediators of inflammation
- Worsening of general state of health, generally feeling unwell and weak
- Fluid retention
- Hypersensitivity

Uncommon serious side effects (may affect up to 1 in 100 people):

- Lumps under the skin on the back of the legs that may become sores and leave scars
- Inflammation and pain or burning and stinging in the area around the catheter
- Reduction in number of blood platelets, blood clotting problems
- Bleeding in the stomach or gut, shown by the vomiting of blood or the passage of red or black stools
- Skin reaction, severe allergic skin reaction (dermatitis)
- Fits
- Lung problems including blood clot in the lungs
- Low blood oxygen levels
- Severe kidney problems
- Extravasation (inadvertent leakage of administered medicinal product from the intraperitoneal catheter system into surrounding tissue)

If such symptoms occur, please inform your doctor as soon as possible. Some of these side effects may require medical treatment.

Other side effects

Common side effects (may affect up to 1 in 10 people):

- Pain
- Reduction or increase in number of white blood cells
- Decreased blood levels of potassium
- Decreased blood protein levels
- Increase of bilirubin in blood
- Spinning sensation
- Indigestion, stomach problems, heartburn, feeling bloated, passing wind, dry mouth
- Flu-like symptoms
- Dizziness or headache
- Chest pain
- Increased sweating
- Infections
- Increased protein levels in urine
- Back pain, aching muscles and joints
- Feeling anxious and having difficulty sleeping
- Itchy rash or hives
- Redness of the skin in the area around the catheter
- Flushing
- Cough

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Removab

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

The prepared infusion solution should be used immediately.

6. Contents of the pack and other information

What Removab contains

- The active substance is catumaxomab (50 micrograms in 0.5 ml, corresponding to 0.1 mg/ml).
- The other ingredients are sodium citrate, citric acid monohydrate, polysorbate 80 and water for injections.

What Removab looks like and contents of the pack

Removab is presented as a clear and colourless concentrate for solution for infusion in a pre-filled syringe with a cannula. Pack size of 1.

Marketing Authorisation Holder and Manufacturer

Neovii Biotech GmbH
Am Haag 6-7

82166 Graefelfing
Germany

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in MM/YYYY.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

For information on dilution and administration of Removab please refer to section 6.6 of the Summary of Product Characteristics (SmPC) included in each package of Removab 10 micrograms and Removab 50 micrograms, respectively.

Medicinal product no longer authorised

Medicinal product no longer authorised

ANNEX IV

GROUNDS FOR ONE ADDITIONAL RENEWAL

- **Grounds for one additional renewal**

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Removab remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

- Uncertainty in the knowledge about the rare unfavourable effects since the safety database is still very limited due to the low number of patients treated with Removab.

Therefore, based upon the safety profile of Removab, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.

Medicinal product no longer authorised