

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Removab 10 microgram concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 10 microgram 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 a 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 patients 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.

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.

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

Posology

Removab dosing schedule comprises the following four intraperitoneal infusions:

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

An interval of at least two days must elapse between infusions. The interval between the infusion days can be prolonged in case of relevant adverse reactions. The overall treatment period should not exceed 20 days. No dose reductions of Removab were investigated during clinical trials.

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 patients

Removab is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

Ethnicity

Patients of non-Caucasian origin have not been included in clinical studies.

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.

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 via a constant infusion pump system.

See section 6.6 for detailed instructions on dilution prior to administration and for instructions for administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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, 1000 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. Other or additional standard pre-medication with analgesic / antipyretic / nonsteroidal antiphlogistic medicinal products is recommended.

Systemic Inflammatory Response Syndrome (SIRS), which may also occur uncommonly 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 study procedures such as 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, and, if appropriate, supportive replacement therapy with crystalloids and / or colloids. Conditions such as hypovolaemia, hypoproteinaemia, hypotension, circulatory decompensation and acute renal impairment should 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.

Perfusion system

Only the following material must be used for the application of Removab:

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and lactation

There are no adequate data from the use of Removab in pregnant women. Animal reproduction studies have not been performed with catumaxomab. The potential risk for humans is unknown. Therefore, Removab should not be used during pregnancy unless clearly necessary.

It is unknown whether catumaxomab is excreted in human breast milk. 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

The nature and frequency of adverse reactions described in this section were analysed in an integrated safety analysis on the basis of 5 clinical studies consisting of 258 patients in the indications malignant

ascites (193 patients), peritoneal carcinomatosis (24 patients) and ovarian cancer (41 patients) with intraperitoneal application of Removab.

Approximately 90% of patients experienced adverse reactions. In Table 1, adverse reactions reported with catumaxomab are listed and classified according to frequency and System Organ Class. Frequency groupings are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions with catumaxomab

Blood and lymphatic system disorders	
<i>Very common</i>	Lymphopenia.
<i>Common</i>	Leucocytosis, anaemia, neutrophilia, thrombocythaemia.
Cardiac disorders	
<i>Common</i>	Tachycardia.
Ear and labyrinth disorders	
<i>Common</i>	Vertigo.
Gastrointestinal disorders	
<i>Very common</i>	Abdominal pain*, nausea, vomiting, diarrhoea.
<i>Common</i>	Ileus*, sub-ileus*, constipation, dyspepsia, abdominal distension, flatulence, gastric disorder, gastroesophageal reflux disease, stomatitis.
<i>Uncommon</i>	Gastric haemorrhage*, intestinal obstruction*.
General disorders and administration site conditions	
<i>Very common</i>	Pyrexia*, fatigue, chills, pain.
<i>Common</i>	Asthenia, influenza-like illness, chest pain, oedema, thirst.
<i>Uncommon</i>	Application site inflammation*, extravasation*.
Hepatobiliary disorders	
<i>Common</i>	Hyperbilirubinaemia, cytolytic hepatitis.
Infections and infestations	
<i>Common</i>	Infection, erythema induratum, urinary tract infection.
<i>Uncommon</i>	Catheter-related infection*, skin infection*.
Metabolism and nutrition disorders	
<i>Common</i>	Anorexia, hyponatraemia, hypocalcaemia, hypokalaemia, hypoproteinaemia, dehydration, hyperglycaemia.
Musculoskeletal and connective tissue disorders	
<i>Common</i>	Arthralgia, back pain, myalgia.
Nervous system disorders	
<i>Common</i>	Headache, dizziness.
<i>Uncommon</i>	Convulsion*.
Psychiatric disorders	
<i>Common</i>	Anxiety, insomnia.
Renal and urinary disorders	
<i>Common</i>	Oliguria, leucocyturia, proteinuria, haematuria.
<i>Uncommon</i>	Renal failure acute*.
Respiratory, thoracic and mediastinal disorders	
<i>Common</i>	Dyspnoea*, pleural effusion.
<i>Uncommon</i>	Pulmonary embolism*, pleural effusion*.
Skin and subcutaneous tissue disorders	
<i>Common</i>	Exanthema, dermatitis allergic, skin reaction, erythema, rash, hyperhidrosis, pruritus, urticaria.
<i>Uncommon</i>	Dermatitis allergic*, rash*, skin exfoliation*, skin reaction*.
Vascular disorders	
<i>Common</i>	Hypotension, hypertension, flushing, hot flush.

* were also reported as serious adverse reactions

Adverse reactions of special interest

The following definitions of CTCAE criteria of the US National Cancer Institute apply:

CTCAE grade 1 = mild, CTCAE grade 2 = moderate, CTCAE grade 3 = severe, CTCAE grade 4 = life-threatening

Cytokine release related symptoms:

Very commonly reported acute infusion-related reactions due to release of cytokines included fever, nausea, vomiting and chills. These reactions were frequently observed during and after Removab infusions with a severity of grade 1 and 2 and were fully reversible. Grade 3 pyrexia (5%), vomiting (3.9%), nausea (2.3%), dyspnoea (1.6%) hypotension (1.2%), hypertension (0.8%) and chills (0.8%) were reported. Grade 4 dyspnoea and hypotension were also reported in one patient each. 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 0.8% of the patients symptoms of SIRS were observed within 24 hours after Removab infusion, such as grade 3 tachycardia and fever and grade 4 dyspnoea. These reactions resolved under symptomatic treatment.

Abdominal pain:

In 48.1% of patients abdominal pain was reported as an adverse reaction reaching grade 3 in 9.7% of patients, but it resolved under symptomatic treatment.

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: Other 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. 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.

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 a two-arm, randomised, open-label clinical trial (IP-REM-AC-01) 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).

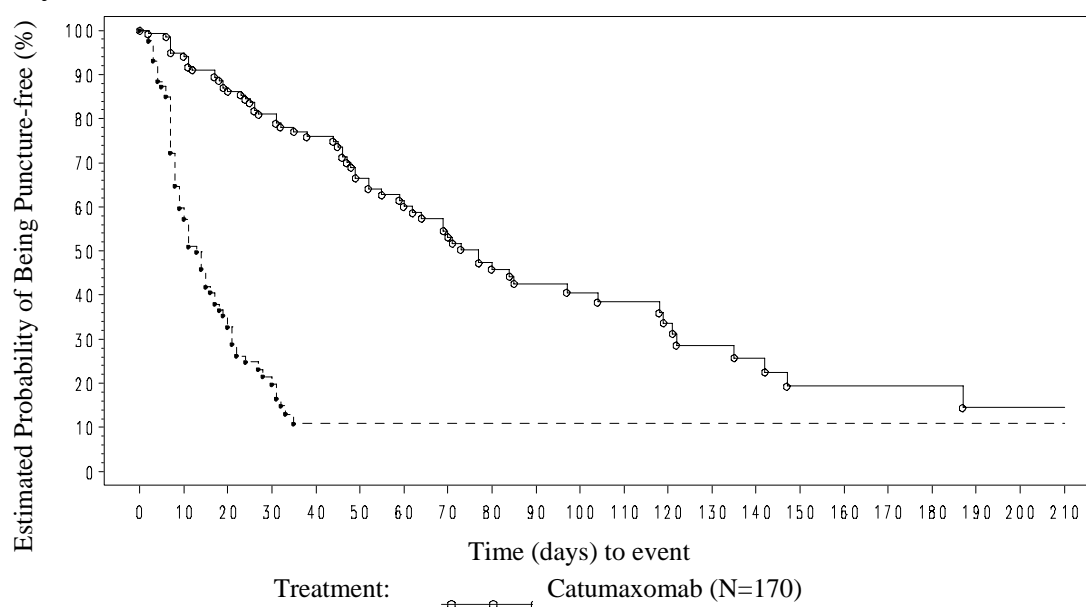
Catumaxomab was applied in patients where standard therapy was not available or no longer feasible and who had a Karnofsky performance status of a least 60. Catumaxomab was administered as four intraperitoneal infusions with increased doses of 10, 20, 50 and 150 micrograms on day 0, 3, 7 and 10, respectively (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 2. Kaplan Meier estimates for time to first need for therapeutic ascites puncture are given in Figure 1.

Table 2 Efficacy results (puncture-free survival and time to first need for therapeutic ascites puncture) of study IP-REM-AC-01 [95% CI]

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



Control (N=88)

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 (post-study phase) in order to assess overall survival (Table 3).

Table 3 Overall survival of study IP-REM-AC-01 in post study phase [95% CI]

	Paracentesis + catumaxomab (N=170)	Paracentesis (control) (N=88)
Overall survival (days)	72	68
95% CI for median (days)	[61;98]	[49;81]
p-value (log-rank test)	0.0846	
Hazard ratio (HR)	0.723	
95% CI for HR	[0.498; 1.048]	

A positive trend for median overall survival after treatment with catumaxomab compared to control was seen.

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% of patients (7/132 patients) were HAMA positive before the 4th infusion. HAMAs were present in 87% of patients one month after the last catumaxomab infusion. No data about clinical effects due to the presence of HAMAs/HARAs are available to date. No hypersensitivity reactions were observed.

5.2 Pharmacokinetic properties

Pharmacokinetics of catumaxomab during and after four intraperitoneal infusions of 10, 20, 50 and 150 microgram 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

24 months

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 of the diluted 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

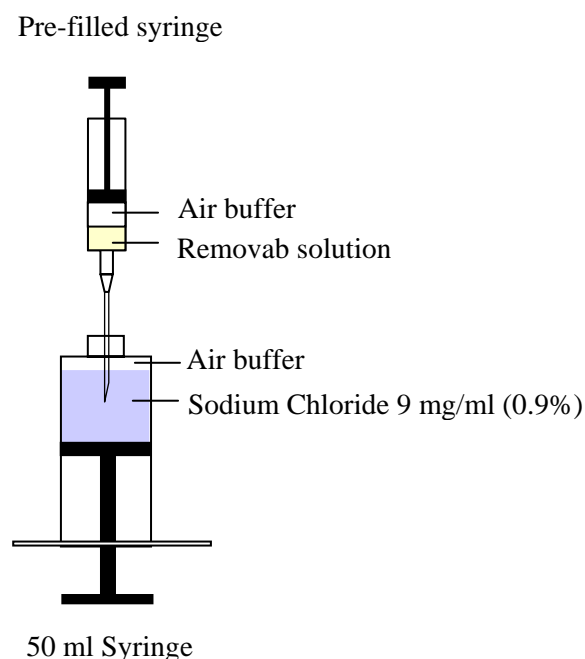
Removab should be prepared by a healthcare professional using appropriate aseptic technique. The outer surface of the pre-filled syringe is not sterile.

- 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 4).
- 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 50 ml syringe is inserted in the infusion pump.

Table 4 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 microgram pre-filled syringe	50 microgram pre-filled syringe			
1 st infusion 10 microgram	1		0.1 ml	10 ml	10.1 ml
2 nd infusion 20 microgram	2		0.2 ml	20 ml	20.2 ml
3 rd infusion 50 microgram		1	0.5 ml	49.5 ml	50 ml
4 th infusion 150 microgram		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:

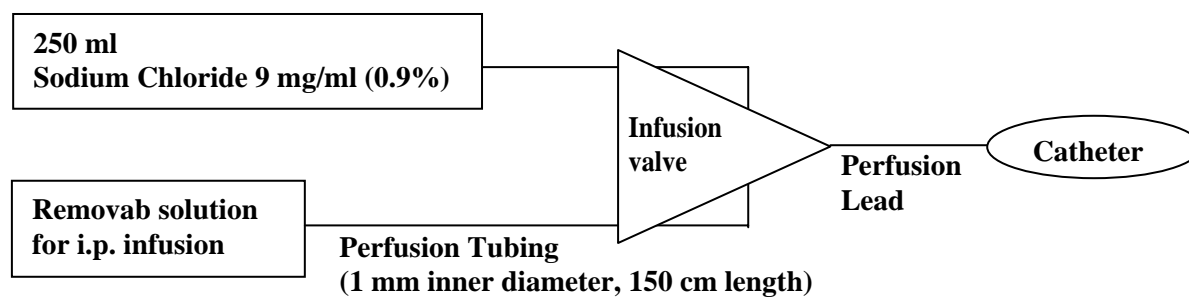
The catheter for intraperitoneal administration should be placed under ultrasound guidance by a physician experienced in intraperitoneal administration procedures. The catheter is used for ascites drainage and infusion of diluted Removab and sodium chloride 9 mg/ml (0.9%) solution for injection. It is 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 (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 6 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 infusion time of 6 hours.
- After completion of the Removab infusion 20 ml sodium chloride 9 mg/ml (0.9%) solution for injection are infused briefly to clear the dead volume in the perfusion lead.
- 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



7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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