ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Korjuny 10 micrograms concentrate for solution for infusion
Korjuny 50 micrograms concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Korjuny 10 micrograms concentrate for solution for infusion

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

Excipients with known effect
One pre-filled syringe contains 21.6 micrograms of polysorbate 80.

For the full list of excipients, see section 6.1.

Korjuny 50 micrograms concentrate for solution for infusion

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

Excipients with known effect
One pre-filled syringe contains 108 micrograms of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Korjuny is indicated for the intraperitoneal treatment of malignant ascites in adults with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, who are not eligible for further systemic anticancer therapy.

4.2 Posology and method of administration

Korjuny must be administered under the supervision of a physician experienced in the use of anti-cancer medicinal products

EpCAM testing

EpCAM positivity (≥ 400 EpCAM- positive cells/10^6 analysed ascites cells) should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see section 5.1).

Posology

Prior to the intraperitoneal infusion, medication for the prophylactic treatment of cytokine release symptoms, including analgesic, antipyretic and non-steroidal antiphlogistic medicinal products is recommended (see sections 4.4 and 5.1).
Side effects of catumaxomab treatment should be treated as medically indicated and according to the current standard of care.

Korjuny dosing schedule comprises the 4 intraperitoneal infusions listed in table 1.

Table 1 Korjuny dosing schedule

Infusion number	Dose	Day
1	10 micrograms	0
2	20 micrograms	3
3	50 micrograms	7
4	150 micrograms	10

Patients should remain under close medical supervision for at least 24 hours after the first infusion of Korjuny. For the remaining doses, patients may be hospitalised for at least 6 hours or for a longer time after infusions of Korjuny at the discretion of the treating physician to safeguard patient safety.

The interval between the infusion days can be prolonged at the discretion of the treating physician if needed in order to minimise the risk of adverse reactions. The overall treatment period should not exceed 21 days.

Special populations

Hepatic impairment
No dose adjustment is needed for patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment 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 Korjuny should only be considered after a thorough evaluation of benefit/risk (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is needed for patients with mild renal impairment. Patients with moderate to severe renal impairment have not been studied. Treatment of these patients with Korjuny should only be considered after a thorough evaluation of benefit/risk (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Korjuny in children aged less than 18 years have not been established. No data are available.

Method of administration

Korjuny must be administered as an intraperitoneal infusion only.
Korjuny 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 6.5.

Korjuny 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 4 doses, an infusion time of 6 hours may be considered depending on the patient's health condition.

Precautions to be taken before administering the medicinal product
Before administration of Korjuny, the concentrate for solution for infusion is diluted in sodium chloride 9 mg/mL (0.9%) solution for injection. The diluted KORJUNY 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

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

Cytokine release related symptoms (CRS)

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 have been reported during and after catumaxomab administration, including events of fever, hypotension, gastrointestinal symptoms, headache, myalgia, arthralgia, tachycardia, chills, respiratory symptoms, skin symptoms, and fatigue.

Despite pre-medication (see sections 4.2 and 5.1), patients may experience CRS as described above with an intensity of up to grade 4, (see section 4.8). Patients should be counselled to seek immediate medical attention if signs or symptoms of CRS occur at any time. CRS should be treated as medically indicated and according to the current standard of care.

Systemic inflammatory response syndrome (SIRS)

Isolated incidence of SIRS (with concurrent fever, increased heart rate and respiratory rate, and abnormal leukocyte count) have been reported during and after treatment with catumaxomab. Patients should be counselled to seek immediate medical attention if signs or symptoms of SIRS occur at any time. SIRS should be treated as medically indicated and according to the current standard of care.

Acute infections

In presence of factors interfering with the immune system, in particular acute infections, the administration of catumaxomab is not recommended. Patients should be monitored for signs and symptoms of infection, before and after Korjuny administration and treated appropriately.

Conditions affecting haemodynamic status of patients

Appropriate medical management of ascites drainage is a prerequisite for Korjuny 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.

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

Hepatic function

No dose adjustment is needed for patients with mild to moderate hepatic impairment. Transient

elevations of liver parameters after catumaxomab infusions were observed in clinical studies which subsequently improved in the majority of patients shortly after completion of the last catumaxomab infusion. In rare cases, catumaxomab -drug induced liver injury (DILI) or hepatitis may occur, potentially leading to hepatic failure including fatal outcome. Patients treated with Korjuny should be closely monitored for signs of clinically significant elevated liver parameters.

Patients with severe hepatic impairment and/or with more than 70% of the liver volume involved by metastatic disease and/or portal vein thrombosis/obstruction have not been investigated. Treatment of these patients with catumaxomab should only be considered after a thorough evaluation of benefit/risk (see section 5.2).

Renal impairment

Catumaxomab is not eliminated via the renal pathway. Patients with moderate to severe renal impairment have not been investigated. Treatment of these patients with Korjuny should only be considered after a thorough evaluation of benefit/risk (see section 5.2).

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.

Monitoring

Adequate monitoring of the patient after end of Korjuny infusion is recommended with close medical supervision for at least 24 hours after the first infusion of Korjuny and for at least 6 hours after subsequent infusions.

Performance status and Body Mass Index (BMI)

In the pivotal study IP-REM-AC-01, patients with a Karnofsky performance score of < 60 and with a BMI of < 17 or > 40 kg/m^2 have not been investigated. Treating these patients with Korjuny is at the discretion of the treating physician.

Patient card

The prescriber must discuss the risks of Korjuny therapy with the patient. The patient should be provided with the patient card and instructed to carry it at all times. The patient card describes the common signs and symptoms of CRS and SIRS and provides instructions on when a patient should seek medical attention.

Excipient

This medicine contains 21.6 micrograms polysorbate 80 in each pre-filled syringe Korjuny 10 micrograms and 108 micrograms of polysorbate 80 in each pre-filled syringe Korjuny 50 micrograms. Polysorbates may cause allergic reactions.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose unit, that is to say essentially ‘sodium-free’. The amount of sodium administered per infusion is higher than that contained in the medicinal product due to the dilution of the concentrate with sodium chloride 9 mg/mL (0.9%) solution for injection. An additional 500 mL of sodium chloride 9 mg/mL (0.9%) solution for injection is given before each Korjuny administration and 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection is given in parallel with each Korjuny administration. See section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Korjuny is not recommended in women of childbearing potential not using contraception.

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). Korjuny is not recommended during pregnancy.

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 Korjuny 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

Korjuny has minor 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

The most commonly reported adverse reactions were pyrexia (62%), abdominal pain (42%), nausea (41%), and vomiting (38%). The most serious adverse reactions are systemic inflammatory response syndrome and hepatic failure.

Tabulated list of adverse reactions

Adverse reactions are derived from an integrated safety analysis of 11 studies including 4 studies in patients with malignant ascites and 7 studies in patients with various other cancers. This includes data from the randomised, controlled main study period from pivotal study IP-REM-AC-01. Of 517 patients included in the analysis, 293 patients received catumaxomab intraperitoneally as 6-hour infusion and 224 patients received catumaxomab intraperitoneally as 3-hour infusion.

In Table 2, adverse reactions are listed by MedDRA system organ class. Frequency groupings are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping the adverse reactions are presented in the order of decreasing seriousness.

Table 2 Adverse reactions reported from patients receiving catumaxomab treatment

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Common	Infection
	Uncommon	Oral candidiasis, Skin infection, Erythema induratum*, Herpes simplex*, Localised infection*, Pneumonia*, Urinary tract infection*
Blood and lymphatic system disorders	Common	Anaemia, Leukocytosis, Lymphopenia
	Uncommon	Coagulopathy*, Leukopenia*, Neutropenia*, Thrombocytopenia*, Thrombocythaemia
Immune system disorders	Very common	Cytokine release syndrome**
	Common	Systemic inflammatory response syndrome, Hypersensitivity*
Metabolism and nutrition disorders	Common	Decreased appetite, Dehydration, Hypokalaemia, Hyponatraemia, Hypoalbuminaemia, Hyperglycaemia*, Hypocalcaemia*, Hypoproteinaemia*
	Uncommon	Fluid retention*, Hypoglycaemia, Polydipsia, Hypomagnesaemia*
Psychiatric disorders	Common	Anxiety*
	Uncommon	Agitation, Depression*
Nervous system disorders	Common	Dizziness
	Uncommon	Syncope, Tremor, Paraesthesia, Convulsion*, Lethargy, Peripheral sensory neuropathy*, Polyneuropathy*, Dysgeusia*
Eye disorders	Uncommon	Vision blurred*
Ear and labyrinth disorders	Uncommon	Vertigo*
Cardiac disorders	Common	Tachycardia
	Uncommon	Sinus tachycardia, Palpitations*, Arrhythmia*, Cardiac failure*
Vascular disorders	Common	Hypertension, Hypotension, Flushing, Hot flush*
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Hypoxia, Pleural effusion*
	Uncommon	Pulmonary embolism, Acute respiratory distress syndrome*, Bronchospasm*, Cough*, Hiccups*, Lung infiltration*, Pharyngolaryngeal pain, Respiratory distress*, Respiratory failure*, Tachypnoea*, Wheezing*
Gastrointestinal disorders	Very common	Abdominal pain, Nausea, Vomiting, Diarrhoea
	Common	Abdominal discomfort, Abdominal distension, Upper abdominal pain, Gastrooesophageal reflux disease, Sub-ileus, Flatulence*
	Uncommon	Abdominal cramps, Dry mouth, Ileus paralytic, Impaired gastric emptying, Abdominal rigidity*, Ascites*, Duodenogastric reflux*, Gastric disorder*, Gastrointestinal hypomotility*, Heartburn*, Peritonitis*, Retching*, Small intestinal obstruction*, Stomach discomfort*, Lower abdominal pain, Haematemesis*, Stomatitis*

System Organ Class	Frequency	Adverse reactions
Hepatobiliary disorders	Common	Hyperbilirubinaemia, Cholangitis*
	Uncommon	Cytolytic hepatitis***, Hepatic failure****, Cholestasis*, Hepatic function abnormal*, Hepatitis toxic*, Jaundice*
Skin and subcutaneous tissue disorders	Common	Dermatitis allergic, Rash, Erythema, Hyperhidrosis, Pruritis
	Uncommon	Night sweats, Urticaria, Palmar erythema*, Rash pruritic*, Skin reaction
Musculoskeletal and connective tissue disorders	Common	Back pain, Myalgia, Arthralgia*
	Uncommon	Bone pain, Flank pain*, Musculoskeletal pain*, Pain in extremity*
Renal and urinary disorders	Common	Haematuria, Proteinuria*
	Uncommon	Dysuria*, Leukocyturia, Oliguria*, Renal failure*, Renal failure acute*, Renal pain*
Reproductive system and breast disorders	Uncommon	Pelvic pain
General disorders and administration site conditions	Very common	Pyrexia, Chills, Fatigue, Pain
	Common	Asthenia*, Inflammation, Oedema, Chest pain, Influenza-like illness*, Malaise*, Oedema peripheral*
	Uncommon	Application site inflammation, Catheter site pain, Early satiety*, Extravasation, Feeling cold*, Feeling hot*, Injection site reaction*, Mucosal inflammation*, Thirst, Catheter site erythema*, General physical health deterioration*
Investigations	Very common	C-reactive protein increased
	Common	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Body temperature increased, Gamma-glutamyltransferase increased, Haemoglobin decreased, Neutrophil count increased, Protein total decreased, Weight decreased, White blood cell count increased, Blood creatinine increased*, Blood potassium decreased*, Hepatic enzyme increased*, Procalcitonin increased*, Blood urea increased, Blood amylase increased*, Blood creatinine phosphokinase increased*, Platelet count increased*
	Uncommon	Bilirubin conjugated increased, Body temperature decreased, Oxygen saturation decreased, Transaminases increased, Blood fibrinogen increased*, Blood iron decreased*, Blood lactate dehydrogenase increased*, Blood pressure increased*, Cells in urine*, Elevated liver enzymes, Haematocrit decreased, Lipase increased*, Liver function test abnormal*, Red blood cell count decreased*, Urobilin urine present, White blood cells urine positive*, Activated thromboplastin time prolonged*, Blood chloride decreased*, Blood sodium decreased*, Blood uric acid increased*, International normalised ratio increased*
Injury, poisoning and procedural	Uncommon	Anastomotic complication*, Procedural pain*, Wound dehiscence*

System Organ Class	Frequency	Adverse reactions
complications		

* Adverse reaction terms indicated by asterisk are included due to the inclusion of n=7 studies in indications other than malignant ascites (e.g. in cancer subjects undergoing curative surgery and intraoperative administration of catumaxomab)

** n=7 events of cytokine release syndrome (CRS) were specifically reported as event terms in 6 of 517 subjects each treated with catumaxomab in the 11 studies included in the analysis (frequency category "common"). However, the frequency of CRS displayed in the above table is based on the retrospective, algorithm-based analysis of CRS that was used in the pivotal study IP-REM-AC-01 where the algorithm took into consideration diagnoses of CRS as well as a combination of symptoms such as fever, hypotension, gastrointestinal symptoms, headache, myalgia, arthralgia, tachycardia, chills, respiratory symptoms, skin symptoms and fatigue.

*** n=3 events of cytolytic hepatitis were reported in 3 subjects; however, 2 events were of mild intensity and one was of moderate intensity, and all 3 events were assessed as non-serious.

**** n=5 events of hepatic failure were reported in 3 subjects; all events were of moderate intensity and assessed as non-serious. Most of these events consisted of increased hepatic/hepatobiliary laboratory values.

Description of selected adverse reactions

Cytokine release syndrome

Cytokine release syndrome (CRS), identified based on occurrence of hallmark symptoms for CRS (fever, hypotension, gastrointestinal symptoms, headache, myalgia, arthralgia, tachycardia, chills, respiratory symptoms, skin symptoms, and fatigue) in close temporal relationship (fever and at least 2 additional adverse reactions within a 4 day time window). At the time of the conduct of the pivotal study, 72% of catumaxomab exposed patients (ISS2) experienced at least one adverse event counted as hallmark symptoms of CRS during or within 1 day after a catumaxomab infusion. As the analysis was highly unspecific, data from the pivotal study were reanalysed according to an algorithm based on current CRS definitions and guidelines. Based on this re-analysis, 23% of patients treated with catumaxomab experienced CRS in the main study period or the crossover period of the pivotal clinical phase II/III study.

In the majority of cases, CRS was of CTCAE grade 1 or 2. Of 41 suspected CRS episodes, 3 were of grade 1, 27 were of grade 2, 10 were of grade 3, and 1 was of grade 4. Symptoms of cytokine release can be ameliorated or avoided by pre-medication (see sections 4.2 and 4.4).

Systemic inflammatory response syndrome (SIRS)

SIRS (with concurrent fever, increased heart rate and respiratory rate, and abnormal leukocyte count) was reported in 2 patients out of 203 patients exposed to catumaxomab in the pivotal study (157 in the main study period, 46 after crossover from control to catumaxomab). In both patients, SIRS was of Grade 4, required hospitalisation/prolongation of hospitalisation, and led to discontinuation of the treatment.

Abdominal pain

In 38.9% of patients in the main study period of the pivotal study, abdominal pain was reported as an adverse reaction, reaching grade 3 or higher in 8.9% of patients, but it resolved under symptomatic treatment.

Hepatic laboratory values

Transient increases in hepatic enzymes (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]) and total bilirubin were commonly observed after the administration of catumaxomab. In general, the changes in laboratory parameters were not clinically relevant and mostly returned to baseline after end of treatment. In the pivotal clinical phase II/III study, 12 patients (5.6%) treated with catumaxomab experienced elevations of ALT of > 3 × upper limit of normal (ULN) in conjunction with bilirubin > 2 × ULN. In 2 of 12 patients, values continued to increase after end of infusion whereas in 10 of 12 patients, the increased values were reversible and showed a trend to improve shortly after the last catumaxomab infusion. Only in case of clinically relevant or persisting increase further diagnostics or therapy should be considered.

Duration of infusion
Data on a 3-hour infusion duration of catumaxomab are available from studies in malignant ascites and studies in other oncological indications, mainly ovarian cancer and gastric cancer. The safety profile of catumaxomab using a 3 hour versus a 6-hour infusion time is in general comparable with regards to nature, frequency and severity of adverse reactions. An increased frequency of some adverse reactions was seen in relation to 3-hour administration including chills and hypotension (grades 1 or 2), diarrhoea (all grades) fatigue (grade 1 or 2), anaemia (all grades), and pleural effusion (grades 1 or 2).

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

Symptoms

Higher planned doses of catumaxomab were investigated in dose escalation studies, up to single treatment courses of catumaxomab 10-20-50-200-200 micrograms. Overall, effects observed with catumaxomab doses higher than the proposed dose were in line with known adverse reactions associated with catumaxomab administration and its mechanism of action. Laboratory values, notably changes in liver parameters, showed transient increases that were dose-dependent and showed tendency to accumulate.

Treatment

No antidote for catumaxomab is available. In case of overdose, symptomatic treatment should be initiated at the physician's discretion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX03

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 expressed on most cancers especially 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 Fc-gamma 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, T-cell mediated killing via the granzyme / perforin system, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and phagocytosis. This results in destruction of tumour cells in the peritoneal cavity, thereby eliminating a major cause of malignant ascites.

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 evaluated in one phase II/III clinical study. Patients of non-Caucasian origin have not been included in this clinical study.

IP-REM-AC-01
A pivotal, two-arm, randomised, open-label, phase II/III clinical study in 258 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas of whom 170 were randomised to catumaxomab treatment. Presence of EpCAM-positive cells in ascites fluid was determined using an immunohistochemistry (IHC) assay. Patients were eligible for enrolment if ascites fluid contained ≥ 400 EpCAM- positive cells/10^6 analysed ascites cells. 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. On infusion days (Days 0, 3, 7, 10), patients remained hospitalised for at least 24 h (see section 4.2).

Among patients randomised (n=258), 79% of patients were female (100% in the ovarian cancer stratum, 59% in the non-ovarian cancer stratum). Mean age was 58.5 years in the ovarian cancer stratum and 58.8 years in the non-ovarian cancer stratum. Caucasians accounted for 99% of patients overall. The most frequent cancer types in the non-ovarian cancer stratum was gastric cancer (51%), followed by breast cancer (10%); other cancer types (colon, pancreas, lung, endometrium, others) were individually present in < 10% of patients in the non-ovarian cancer stratum.

In this study, the primary efficacy endpoint was puncture-free survival in the randomised, controlled main study period, 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 are presented in Table 3. Kaplan Meier estimates for puncture-free survival are given in Figure 1.

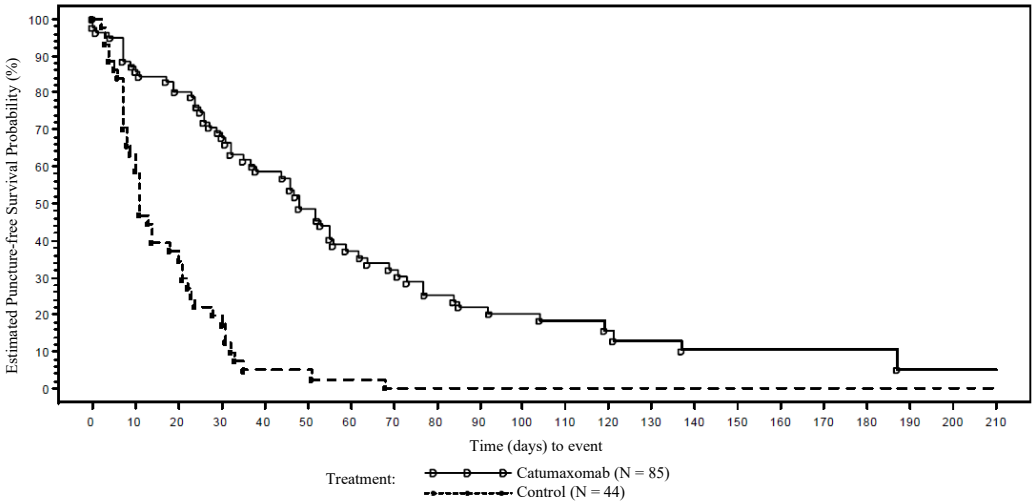
Table 3 Efficacy results (puncture-free survival) of study IP-REM-AC-01

	Ovarian cancer		**Non-ovarian cancer**	
	Catumaxomab	**Control**	**Catumaxomab**	**Control**
Patients, n	85	44	85	44
Patients with event, n (%)	58 (68.2)	42 (95.5)	73 (85.9)	40 (90.9)
PuFS [days], median	48	11	30	14
95% CI	37, 59	9, 20	20, 45	8, 17
p-value (log rank test)	< 0.0001		< 0.0001	
HR (95% CI)	Not calculated		Not calculated	

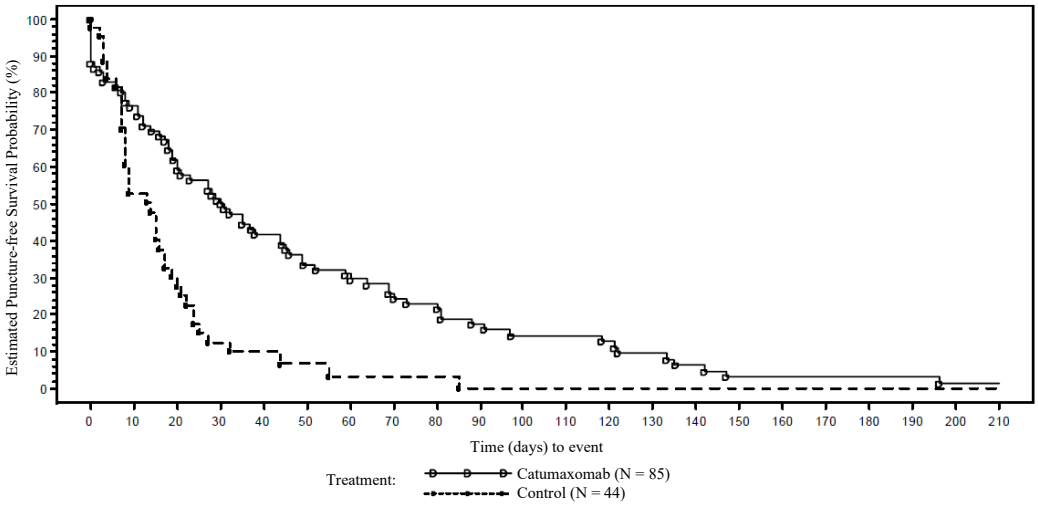
Patients who completed the study at the scheduled study end without therapeutic puncture were censored at the date of the scheduled study end. Patients who discontinued the study after randomisation but before the endpoint of puncture or death were censored at the date of premature discontinuation.
HR: Hazard ratio, PuFS: puncture-free survival

Figure 1 Kaplan-Meier estimates of puncture-free survival in study IP-REM-AC-01

Ovarian cancer



Non-ovarian cancer



Compared with paracentesis alone (control), treatment with paracentesis and catumaxomab in patients with malignant ascites due to EpCAM-positive carcinomas prolonged puncture-free survival from 11 to 48 days in ovarian cancer patients and from 14 to 30 days in non-ovarian cancer patients.

After completion of the main study period, patients were further observed until the end of their lifetime to assess overall survival. Patients receiving paracentesis (control) could cross over to paracentesis and catumaxomab after completion of the main study period; nevertheless, these patients were counted as control patients despite the crossover. There was no worsening in overall survival in patients receiving paracentesis and catumaxomab relative to patients receiving paracentesis (Table 4).

Table 4 Overall survival of study IP-REM-AC-01

	Paracentesis + catumaxomab (N=170)	**Paracentesis (control)[1] (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

[1] Crossover patients were counted as control patients despite crossing over to paracentesis and catumaxomab treatment; this were 45 of 88 (51%) patients in the control arm.

Immunogenicity

The induction of anti-catumaxomab antibodies is an intrinsic effect of murine monoclonal antibodies. Data on catumaxomab derived from the pivotal study show that < 10% of patients were anti-catumaxomab antibodies positive before the 4th infusion.
Anti-catumaxomab antibodies were present in 95% of patients one month after the last catumaxomab infusion.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Korjuny in all subsets of the paediatric population in the treatment of malignant ascites (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics of catumaxomab during and after four intraperitoneal infusions of 10, 20, 50 and 150 micrograms catumaxomab as 6-hour infusion were investigated in a dedicated study in 13 patients with symptomatic malignant ascites due to EpCAM-positive carcinomas.

Catumaxomab was detectable in 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.

Absorption
Catumaxomab is administered via the intraperitoneal route and therefore is immediately available at the targeted site of malignant cells in the peritoneal cavity.

Distribution
Upon intraperitoneal infusion, catumaxomab distributes in ascites fluid as the site of action. Mean and median C_{max} for ascites fluid were 7122 and 3270 pg/mL, respectively.
After intraperitoneal administration and binding to target cells in the peritoneal cavity, residual catumaxomab reaches systemic circulation in intact form. The geometric mean plasma C_{max} was 0.5 ng/ml (range 0 to 2.3), and the geometric mean plasma AUC was 1.7 day* ng/ml (range < LLOQ (lower limit of quantification) to 13.5).
The variability between subjects in ascites and plasma catumaxomab levels was high, due to varying ascites volume and malignant cell burden in the peritoneal cavity.

Metabolism and elimination
The metabolism and elimination of catumaxomab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body; it does not rely primarily on elimination through the kidneys and liver.
For systemic catumaxomab, i.e. residual (not target-bound) catumaxomab that reached the circulation from the peritoneal cavity, geometric mean apparent terminal plasma elimination half-life ($t_{1/2}$) was 2.5 days (range 0.7 to 17.5).

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 product 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 (E331)
Citric acid monohydrate (E330)
Polysorbate 80 (E433)
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

3 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

Pre-filled syringe (type I glass, siliconised) with plunger stopper (bromobutyl rubber) and luer lock system (polypropylene siliconised and polycarbonate), with tip cap (bromobutyl rubber). A cannula is enclosed.

Korjuny 10 micrograms concentrate for solution for infusion

The pre-filled syringe contains 0.1 mL concentrate for solution and is packed in a carton with a blue colour code.
Pack size: 3 pre-filled syringes and 5 cannulas

Korjuny 50 micrograms concentrate for solution for infusion

The pre-filled syringe contains 0.5 mL concentrate for solution and is packed in a carton with a red colour code.
Pack size: 4 pre-filled syringes and 5 cannulas

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The pre-filled syringe is for single use only.

Material and equipment required for dilution and administration of Korjuny:
- sodium chloride 9 mg/mL (0.9%) solution for injection
- 50 mL polypropylene syringes
- cap for 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 silicon-coated catheters
- precision perfusion pump

Dilution prior to administration

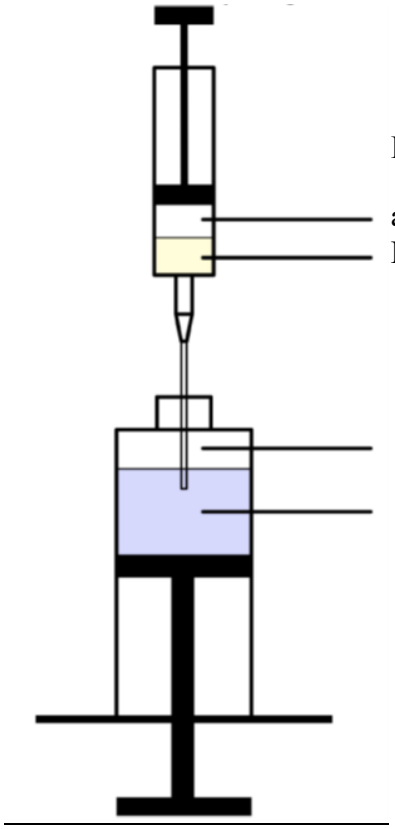
Korjuny should be prepared by a healthcare professional using appropriate aseptic technique.
The outer surface of the pre-filled syringe is not sterile.

- The volume of sodium chloride 9 mg/mL (0.9%) solution for injection listed in Table 5 is extracted with a 50 mL syringe.
- An additional air buffer of at least 3 mL is included in the 50 mL syringe.
- The Korjuny pre-filled syringe(s) of the required strength listed in Table 5 below are visually inspected for any foreign particulates or discolouration.
- With the pre-filled syringe tip pointing up, the tip cap is gently removed. **Do not** twist off or rotate the cap.
- The enclosed cannula is attached to the pre-filled syringe and the cannula shield removed. A new cannula must be used for each syringe.
- The 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).
  Do not administer the Korjuny pre-filled syringe directly to a patient.
- The entire content of the pre-filled syringe is injected 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, to avoid contamination and to ensure that the correct volume is ejected.
- Based on Table 5, the previous steps are repeated to inject the required number of pre-filled syringes into the 50 mL syringe.
- The 50 mL syringe is closed with a cap and shaken gently to mix the solution.
- After removing the cap, any air bubbles are eliminated from the 50 mL syringe.
- The red peelable sticker, which is provided inside the carton lid, displaying the text “Diluted Korjuny. Intraperitoneal use only.” must be attached to the 50 mL syringe. This is a precautionary measure to ensure Korjuny is intraperitoneally infused only.
- The 50 mL syringe is inserted in the infusion pump.

Table 5 Number of pre-filled syringes and volumes required for preparation of Korjuny solution for intraperitoneal infusion

Infusion / Dose	Number of **10** micrograms pre-filled syringes	Number of **50** micrograms pre-filled syringes	**Total** volume of Korjuny concentrate for solution for infusion	Sodium chloride 9 mg/mL (0.9%) solution for injection	Final volume for administration
1st infusion / 10 micrograms	1	---	0.1 mL	10 mL	10.1 mL
2nd infusion / 20 micrograms	2	---	0.2 mL	20 mL	20.2 mL
3rd infusion / 50 micrograms	---	1	0.5 mL	49.5 mL	50 mL

4th infusion / 150 micrograms	---	3	1.5 mL	48.5 mL	50 mL



Korjuny pre-filled syringe

air buffer

Korjuny concentrate for solution for infusion

50 mL syringe

air buffer

sodium chloride 9 mg/mL (0.9%) solution for injection

Method of administration

The catheter for intraperitoneal administration is placed under ultrasound guidance by a doctor experienced in intraperitoneal administration. The catheter is used for ascites drainage, and administration of diluted Korjuny solution for infusion 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 based on the judgement of the treating physician on the day after the last infusion.

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

Diluted Korjuny solution for infusion is intraperitoneally administered over an infusion time of at least 3 hours via a constant infusion pump system, as follows:

- The connected perfusion tubing equipment of the infusion pump is prefilled with the diluted Korjuny solution for infusion.
- The perfusion tubing is connected to the Y connection.
- Parallel to each Korjuny administration, 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection is 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 of at least 3 hours.
- When the 50 mL syringe containing the diluted Korjuny 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, 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 is performed until cessation of spontaneous flow. Subsequently, the catheter can be removed.

Disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Atnahs Pharma Netherlands B. V.
Copenhagen Towers
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1826/001
EU/1/24/1826/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 February 2025

10. DATE OF REVISION OF THE TEXT

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

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
Celonic Deutschland GmbH & Co. KG
Czernyring 22
Weststadt, Heidelberg
69115 Baden-Wuerttemberg
Germany

Name and address of the manufacturer responsible for batch release
Celonic Deutschland GmbH & Co. KG
Czernyring 22
Weststadt, Heidelberg
69115 Baden-Wuerttemberg
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 requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and subsequent updates published on the European Medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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.

- **Additional risk minimisation measure**

The MAH shall ensure that in each Member State where Korjuny is marketed, all patients/carers who are expected to use catumaxomab have access to/are provided with the Patient Card which will inform and explain to patients the risks of cytokine release syndrome (CRS) and systemic inflammatory

response syndrome (SIRS). The Patient Card also includes a warning message for healthcare professionals treating the patient that the patient is receiving catumaxomab.
The **Patient Card** shall contain the following key messages:

- A description of the key signs and symptoms of cytokine release syndrome/systemic inflammatory response syndrome.
- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of cytokine release syndrome/systemic inflammatory response syndrome present themselves.
- The prescribing physician's contact details.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Korjuny 10 micrograms concentrate for solution for infusion
catumaxomab

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid monohydrate, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
3 pre-filled syringes
5 sterile cannulas

5. METHOD AND ROUTE 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

Atnahs Pharma Netherlands B. V.
Copenhagen Towers
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/24/1826/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Korjuny 10 micrograms sterile concentrate
catumaxomab
Intraperitoneal use only, after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Korjuny 50 micrograms concentrate for solution for infusion
catumaxomab

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Excipients: sodium citrate, citric acid monohydrate, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
4 pre-filled syringes
5 sterile cannulas

5. METHOD AND ROUTE 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

Atnahs Pharma Netherlands B. V.
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12. MARKETING AUTHORISATION NUMBER

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14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Korjuny 50 micrograms sterile concentrate
catumaxomab
Intraperitoneal use only, after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

WARNING TEXT FOR PEELABLE STICKER TO BE ATTACHED TO 50 ML SYRINGE CONTAINING THE DILUTED KORJUNY SOLUTION FOR INFUSION

(Part of the Outer Carton)

Diluted Korjuny.
Intraperitoneal use only.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Korjuny 10 micrograms concentrate for solution for infusion
Korjuny 50 micrograms concentrate for solution for infusion
catumaxomab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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.
- 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 Korjuny is and what it is used for

Korjuny contains the active substance catumaxomab. Catumaxomab is a monoclonal antibody, a type of protein that binds to a target on the surface of cancer cells. This target is called epithelial cell adhesion molecule (EpCAM), and it is found on the surface of different types of cancer cells. It is also present on cancer cells in ascites fluid. Malignant ascites is the build-up of fluid containing cancer cells in the abdomen of cancer patients.

Catumaxomab activates cells of the immune system (part of the body's natural defences) to destroy the cancer cells.

Korjuny is used to treat malignant ascites in adults, when standard treatment of the cancer is no longer feasible.

2. What you need to know before you are given Korjuny

Do not use Korjuny if you are
- allergic to catumaxomab or any of the other ingredients of this medicine (listed in section 6)
- allergic to rat and/or mouse proteins

Warnings and precautions
Talk to your doctor or nurse before you are given Korjuny or during treatment if you have:
- signs of a condition known as cytokine release syndrome. This is a serious immune reaction with symptoms such as fever, low blood pressure, chills, difficulty breathing, fatigue, headache, fast heartbeat and increased level of liver enzymes in the blood. Please consider the instructions provided in your patient card, such as when you should seek medical attention. Before each infusion of Korjuny, you may be given medicines, which help reduce possible side effects of cytokine release syndrome.
- signs of the so-called systemic inflammatory response syndrome. Possible signs are fever,

increased heartbeat, faster breathing and abnormal white blood cell counts. Contact your doctor immediately if you have any of these signs and consider the instructions provided in your patient card.
- an infection or signs of an infection such as feeling warm, fever, chills or shivering, sore throat or mouth ulcers. The infection will be treated before you are given Korjuny.
- low blood volume with symptoms such as cold hands and feet, light headedness, difficulty passing urine, increased heart rate or weakness
- symptoms of low levels of blood proteins such as weakness, shortness of breath or fluid retention
- low blood pressure with symptoms such as feeling dizzy, faint or weakness
- liver problems, including a blood clot or obstruction in the portal vein (a blood vessel that carries blood to the liver from the intestines, spleen, pancreas and gallbladder)
- kidney problems

Tests and checks
- Before you are given Korjuny, your doctor will check conditions that may affect your blood flow. This will include tests of your blood volume, level of blood proteins, blood pressure, pulse and kidney function.
- You may experience infusion-related reactions during or after the infusion of Korjuny. These can sometimes be severe with symptoms such as fever, low blood pressure, chills, headache, nausea, vomiting, muscle and joint pain, very fast heartbeat and shortness of breath. It is recommended that your doctor keep you under observation for at least 24 hours after the first infusion and at least 6 hours after each subsequent infusion.
- Your doctor may also conduct tests to check your liver function during treatment with Korjuny.

Children and adolescents
Korjuny is not recommended in children and adolescents under 18 years, as it has not been studied in this age group.

Other medicines and Korjuny
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
Korjuny is not recommended during pregnancy, breast-feeding and in women of childbearing potential not using contraception.

The effects of Korjuny on the developing foetus are unknown and a risk to a newborn/infant cannot be excluded.

If you could become pregnant, you must use effective contraception during treatment with Korjuny. Inform your doctor immediately if you become pregnant while being treated with this medicine.

It is not known if catumaxomab passes into breast milk. There may be a risk to breastfed newborns/infants. Ask your doctor for advice if you are breast-feeding.

Driving and using machines
Do not drive or use machines if you have side effects such as dizziness or infusion-related side effects during or after administration.

Korjuny contains polysorbate 80 and sodium
This medicine contains 21.6 micrograms polysorbate 80 in each pre-filled syringe Korjuny 10 micrograms and 108 micrograms of polysorbate 80 in each pre-filled syringe Korjuny 50 micrograms. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’. The amount of sodium administered per infusion is higher than that contained in the medicinal product due to the dilution of the concentrate with sodium chloride 9 mg/mL (0.9%) solution. An

additional 500 mL of sodium chloride 9 mg/mL (0.9%) solution for injection is given before each Korjuny administration and 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection is given in parallel with each Korjuny administration.

3. How to use Korjuny

You will be given Korjuny under supervision of a doctor experienced in the treatment of cancer.

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

Korjuny is given as an infusion into the abdominal cavity over a period of at least 3 and a maximum of 6 hours.
You will be given 4 infusions that follow an increasing dose schedule: 10, 20, 50 and 150 micrograms. The infusions are separated by at least 2 infusion-free calendar days. For example, you will receive an infusion on day 0, 3, 7 and 10. However, your doctor may decide to extend the time between infusions in order to reduce the risk of side effects. The overall treatment period should not exceed a total of 21 days.

A catheter is placed in your abdominal cavity for the whole treatment period, until the day after your last infusion.

After the first Korjuny infusion your doctor will observe you for at least 24 hours for infusion-related reactions and at least 6 hours after each subsequent infusion.

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

4. Possible side effects

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

Inform your doctor immediately if you have any of the following **serious side effects**:
Very common (may affect more than 1 in 10 people)
- **infusion-related side effects**
  During and after infusion with Korjuny patients may experience infusion-related side effects. These include symptoms such as fever, low blood pressure, chills, headache, nausea, vomiting, muscle and joint pain. It can also cause rapid heartbeat, shortness of breath, skin symptoms and fatigue. These symptoms occur mainly within 24 hours after infusion and can become life-threatening. These side effects require immediate treatment.

Your doctor may consider reducing the infusion rate of Korjuny or giving you additional treatment to reduce serious symptoms.

Other side effects may occur with the following frequencies:
Very common (may affect more than 1 in 10 people)
- inflammatory response syndrome called cytokine release syndrome – see section 2, “Warnings and precautions”
- nausea, vomiting, diarrhoea
- abdominal pain
- fever, chills, fatigue, pain
- increased blood levels of C-reactive protein (a marker of inflammation)

Common (may affect up to 1 in 10 people)
- infection
- reduced number of red blood cells

- increased number of white blood cells, or specific white blood cells called neutrophils
- lack of certain white blood cells called lymphocytes
- systemic inflammatory response syndrome – see section 2, “Warnings and precautions”
- hypersensitivity
- decreased appetite
- dehydration
- low blood level of sodium, potassium or calcium
- increased blood sugar level
- decrease blood level of protein, like albumin
- anxiety
- dizziness
- accelerated heartbeat
- low or high blood pressure
- flushing, hot flush
- abdominal discomfort, wind
- heartburn
- upper abdominal pain
- partial bowel obstruction
- increased blood level of bilirubin, a yellow breakdown substance of the blood pigment
- inflammation of the bile duct
- allergic skin inflammation
- rash, skin reddening, itching
- excessive sweating
- back pain, muscle pain, joint pain
- blood in the urine, excess of protein in the urine
- weakness
- chest pain
- inflammation
- tissue swelling caused by excess fluid
- influenza-like illness
- feeling unwell
- accumulation of fluid in arms and/or legs
- insufficient oxygen supply of the whole body or a region of the body
- breathing difficulties, fluid in the thorax
- increased levels of liver enzymes, such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase
- increased body temperature
- increased blood levels of urea, procalcitonin, amylase, creatinine phosphatase, the breakdown product from muscle tissue called creatinine
- decreased red blood cell pigment level
- increased number of blood platelets
- decreased total protein
- decreased weight

Uncommon (may affect up to 1 in 100 people)
- thrush
- skin infection
- inflammation of the fatty tissue under the skin with skin nodules on the calves
- herpes simplex infection, localised infection, urinary tract infection
- lung inflammation
- reduced number of blood platelets, reduced blood clotting
- lack of white blood cells, such as neutrophils
- low blood sugar level
- low blood level of magnesium

- fluid retention
- restlessness, depression
- abnormal sensation such as prickling, tingling and itchiness
- sensory disorders in hands or feet caused by nerve damage
- nerve disorder effecting many nerves in the arms and/or legs simultaneously
- fainting, lethargy
- uncontrollable shaking, fit
- taste disturbance
- blurred vision
- feeling of increased heartbeat, irregular heartbeat
- heart weakness
- blockage of a lung artery
- breathing distress, cramp of bronchial muscles
- cough, hiccup
- migration of inflammatory cells or tumour cells in the lung tissue, lung failure
- pain in the throat and larynx
- faster breathing, wheezing
- abnormal cramps
- dry mouth
- loss of bowel movement
- reduced stomach emptying
- lower abdominal pain
- abdominal stiffness
- accumulation of fluid in the abdominal cavity
- backflow of bile from the first section of the small bowel into the stomach
- stomach disorder
- reduced stomach and bowel movement
- inflammation of the membrane which lines the abdomen cavity and covers the abdominal organs
- retching
- small bowel obstruction
- stomach discomfort
- vomiting blood
- inflammation of the inner lining of the mouth
- liver inflammation with destruction of cells, medicine-induced liver inflammation
- liver failure
- reduced bile flow
- abnormal liver function
- yellowing of the skin or whites of the eyes caused by liver problems
- night sweats
- redness of the palm, nettle-rash and other skin reactions
- bone pain, flank pain
- pain affecting muscles and skeleton, pain in arms and legs
- painful and difficult urination, decreased output of urine
- increased number of white blood cells in the urine
- kidney failure, kidney pain
- inflammation at application site
- pain at the catheter site, leakage of a fluid
- feeling full after eating very little food
- feeling cold or hot
- injection site reaction
- inflammation of mucous-secreting lining
- thirst
- skin reddening at the catheter site

- general health deterioration
- pelvic pain
- abnormal liver function tests, elevated liver enzymes
- increased level of the liver enzymes transaminases
- decreased oxygen saturation in the blood
- increased blood levels of conjugated bilirubin, uric acid, fibrinogen, lactate dehydrogenase, lipase
- decreased blood levels of iron, chloride
- decreased body temperature
- decreased percentage of blood cells on the blood volume
- urobilin in urine
- cells in urine, including white blood cells
- prolonged activated thromboblastin time – a test to control blood coagulation
- increased international normalised ratio, which shows that the blood is clotting too slowly
- problems during administration: pain, divergence of adjacent wound edges, anastomotic complication (e.g. bleeding or leakage at connections between vessels or hollow organs)

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 Korjuny

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 and syringe 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 Korjuny contains
- The active substance is catumaxomab.
  One pre-filled syringe Korjuny 10 micrograms contains 10 micrograms of catumaxomab in 0.1 mL concentrate, corresponding to 0.1 mg/mL.
  One pre-filled syringe Korjuny 50 micrograms contains 50 micrograms of catumaxomab in 0.5 mL concentrate, corresponding to 0.1 mg/mL.
- The other ingredients are sodium citrate (E331), citric acid monohydrate (E330), polysorbate 80 (E433) and water for injections. See section 2, ”Korjuny contains polysorbate 80 and sodium”.

What Korjuny looks like and contents of the pack
Korjuny is a clear and colourless concentrate for solution for infusion (sterile concentrate) in pre-filled glass syringes with tip caps.

Pack sizes:
- Korjuny 10 micrograms: 3 pre-filled syringes and 5 cannulas in a carton with a blue colour code
- Korjuny 50 micrograms: 4 pre-filled syringes and 5 cannulas in a carton with a red colour code

Marketing Authorisation Holder
Atnahs Pharma Netherlands B. V.
Copenhagen Towers
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

Manufacturer
Celonic Deutschland GmbH & Co. KG
Czernyring 22
Weststadt, Heidelberg
69115 Baden-Wuerttemberg
Germany

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

This leaflet was last revised in

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

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The following information is intended for healthcare professionals only:

Material and equipment required for dilution and administration of Korjuny
- sodium chloride 9 mg/mL (0.9%) solution for injection
- 50 mL polypropylene syringes
- cap for 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 silicon-coated catheters
- precision perfusion pump

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

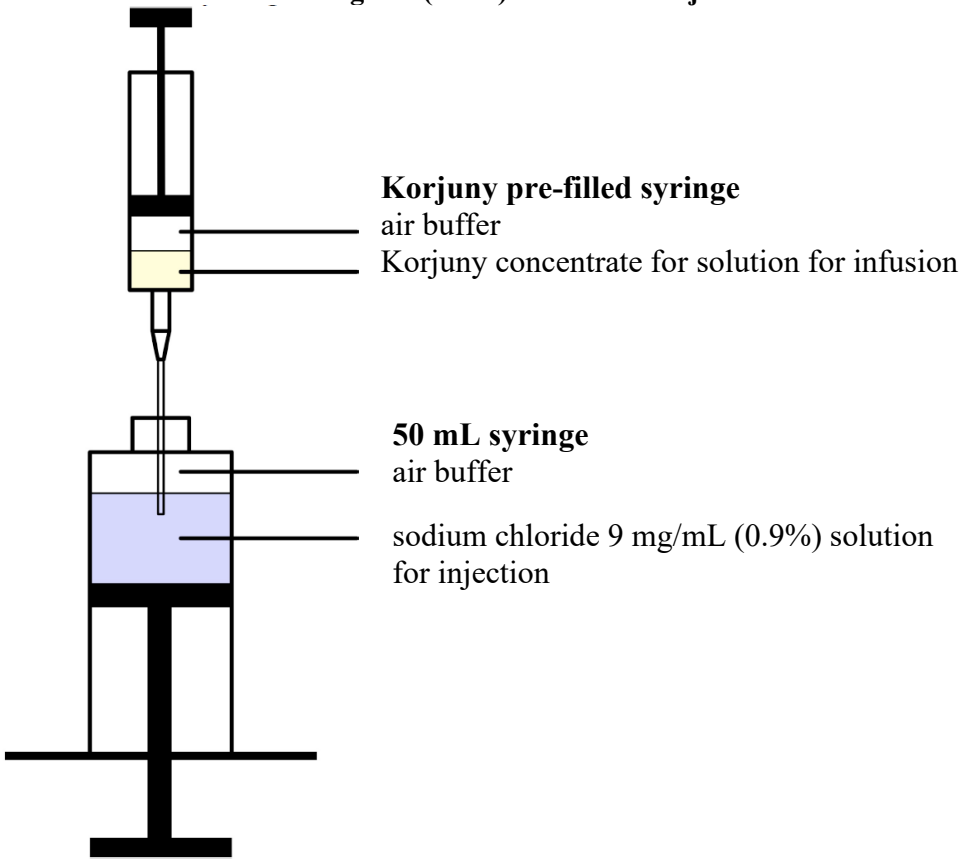
- The volume of sodium chloride 9 mg/mL (0.9%) solution for injection listed in the table is extracted with a 50 mL syringe.
- An additional air buffer of at least 3 mL is included in the 50 mL syringe.
- The Korjuny pre-filled syringe(s) of the required strength listed in the table are visually inspected for any foreign particulates or discolouration.
- With the pre-filled syringe tip pointing up, the tip cap is gently removed. **Do not** twist off or rotate the cap.
- The enclosed cannula is attached to the pre-filled syringe and the cannula shield removed. A new cannula must be used for each syringe.
- The 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).
  Do not administer the Korjuny pre-filled syringe directly to a patient.
- The entire content of the pre-filled syringe is injected 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, to avoid contamination and to ensure that the correct volume is ejected.
- Based on the table, the previous steps are repeated to inject the required number of pre-filled syringes into the 50 mL syringe.
- The 50 mL syringe is closed with a cap and shaken gently to mix the solution.

- After removing the cap, any air bubbles are eliminated from the 50 mL syringe.
- The red peelable sticker, which is provided inside the carton lid, displaying the text “Diluted Korjuny. Intraperitoneal use only.” must be attached to the 50 mL syringe. This is a precautionary measure to ensure Korjuny is intraperitoneally infused only.
- The 50 mL syringe is inserted in the infusion pump.

Table Number of pre-filled syringes and volumes required for preparation of Korjuny solution for intraperitoneal infusion

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

Figure Transfer of Korjuny from the pre-filled syringe to the 50 mL syringe containing sodium chloride 9 mg/mL (0.9%) solution for injection



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.

Method of administration
The catheter for intraperitoneal administration is placed under ultrasound guidance by a doctor experienced in intraperitoneal administration. The catheter is used for ascites drainage, and administration of diluted Korjuny solution for infusion 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 based on the judgement of the treating doctor on the day after the last infusion.

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

Diluted Korjuny solution for infusion is intraperitoneally administered over an infusion time of at least 3 hours via a constant infusion pump system, as follows:

- The connected perfusion tubing equipment of the infusion pump is prefilled with the diluted Korjuny solution for infusion.
- The perfusion tubing is connected to the Y connection.
- Parallel to each Korjuny administration, 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection is 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 of at least 3 hours.
- When the 50 mL syringe containing the diluted Korjuny 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, 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 is performed until cessation of spontaneous flow. Subsequently, the catheter can be removed.

Disposal
No special requirements.