EU Risk Management Plan for Korjuny (catumaxomab)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

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Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission.

Summary of significant changes in this RMP: Not applicable.

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP: Not applicable.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Catumaxomab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies (L01FX03)
Marketing Authorisation Applicant	Lindis Biotech GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Korjuny
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: monoclonal bispecific trifunctional antibody
	Summary of mode 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.
	Important information about its composition: catumaxomab is a rat-mouse hybrid IgG2 monoclonal antibody produced in a rat-mouse hybrid-hybridoma cell line
Hyperlink to the Product Information	Korjuny Product Information

Indication(s) in the EEA	Current: 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.
	Proposed (if applicable): not applicable
Dosage in the EEA	Current: Korjuny dosing schedule comprises the following four i.p. infusions: 1st dose 10 micrograms on day 0 2nd dose 20 micrograms on day 3 3rd dose 50 micrograms on day 7 4th dose 150 micrograms on day 10 Korjuny has to be administered as constant rate i.p. infusion with an infusion time of at least 3 hours. In clinical trials, 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. The interval between the infusion days can be prolonged at the discretion of the treating physician in order to minimise the risk of adverse reactions. The overall treatment period should not exceed 21 days.
	Proposed (if applicable): not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): 10 micrograms concentrate for solution for infusion; 50 micrograms concentrate for solution for infusion
	Proposed (if applicable): not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

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.

Incidence and prevalence: Ascites is the pathological accumulation of fluid in the peritoneal cavity. Often, malignant ascites is a sign of peritoneal carcinomatosis, i.e. of the presence of malignant cells in the peritoneal cavity (Sangisetty 2012). Peritoneal carcinomatoses can be primary tumours of the peritoneum or disseminate secondarily as peritoneal metastasis from tumours of other organs, which include those of intraperitoneal (i.p.) origin (tumours of the digestive and female reproductive tract; sarcoma) and those of extraperitoneal origin (lung, prostate, breast, kidney). The incidence of peritoneal carcinomatosis varies by underlying malignancy. Reported relative incidence of peritoneal metastases from ovarian cancer is 60–70%, vs <10% for other gynaecological malignancies. Among gastrointestinal (GI) malignancies, the relative incidence is highest for gastric cancer (15–43%) (Cortés-Guiral 2021).

Demographics of the population in the proposed indication and risk factors for the disease: Malignant ascites is a complication of advanced cancer. The demographics depend on the underlying malignancy.

The main existing treatment options: In patients presenting with malignant ascites, treatment is based on systemic therapy approaches directed towards the primary tumour. In tumours still responsive to anticancer therapy, which is rare in advanced cancer, prevention of further ascites build-up can likely be achieved (RCOG 2014). Use of systemic chemotherapy, endocrine therapy, biologics, and immunotherapy depends on the primary tumour origin, extent of peritoneal spread, the option of cytoreductive surgery, and the patient's performance status and organ function (Cortés-Guiral 2021). In ovarian cancer in particular, ascites is essentially treated by treating the underlying cancer disease (Kipps 2013), which may include both systemic therapy and abdominal surgery. In patients with gastrointestinal (GI) malignancies, chemotherapy and debulking surgery may be attempted (Saif 2009). Clinical trial data show that the overall survival (OS) of patients with peritoneal metastases from various primary tumours has gradually improved. This is due to increasing use of cytoreductive surgery (to resect tumour implants on the peritoneal surfaces); in some tumour types also hyperthermic i.p. chemotherapy (HIPEC); earlier diagnosis due to improved imaging; and more effective systemic therapies for metastatic disease including peritoneal carcinomatosis (Cortés-Guiral 2021). However, despite this medical progress, once treatment-resistant cancer disease has developed, the malignant ascites may become intractable (Kipps 2013).

While treatment options for primary cancers have evolved over time, potentially moving the occurrence of malignant ascites to later-line (and thus, prognostically worse) patient populations, there has been little progress for the treatment of malignant ascites itself. There is no approved treatment, and there are no generally accepted, evidence-based treatment guidelines for malignant ascites or peritoneal carcinomatosis, except for guidelines of individual institutions or organisations, such as the Royal College of Obstetricians and Gynaecologists in the United Kingdom (UK) (RCOG 2014). Clinical practice guidelines of the European Society for Medical Oncology (ESMO) for relevant cancer types fail to make specific management recommendations for ascites. Thus, treatment is typically based on physician experience and often adapted from the treatment of cirrhosis-associated ascites.

The mainstay of palliative treatment is the removal of the ascitic fluid (RCOG 2014). Paracentesis via percutaneous drainage provides immediate short-term palliation of symptoms in about 90% of patients (Saif 2009). Possible complications include continuous leakage from the drainage site (Kipps 2013), secondary peritonitis, pulmonary emboli, and hypotension (Saif 2009). Paracentesis often requires hospitalisation and may have to be frequently repeated (Kipps 2013). Overall, patient acceptability of drainage is good due to the symptomatic relief achieved with only temporary inconvenience (RCOG 2014). Once drainage is complete, the catheter is typically removed to avoid infection, although it may be left in the peritoneal cavity for longer time periods (Smith 2003). The effect of paracentesis is of limited duration; it may be as short as 72 h in very bad cases (Sangisetty 2012), although most authors report persistence of the effects for 7-14 days (Ross 1989; Mackey 1996; Mackey 2000; Smith 2003; Bar-Sela 2006).

Alternative means to remove ascites fluid have been developed. Permanent drains may prevent the need for repeated paracentesis (Smith 2003). Indwelling i.p. catheters allow patient self-drainage and achieve a high technical success rate of insertion with a low complication rate (Kipps 2013). They are suited in particular for patients with rapid or excessive built-up of ascites, as they allow more frequent drainage of smaller quantities (Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust 2013: www.dbth.nhs.uk; RCOG 2014). Peritoneovenous shunts (PVSs) direct ascitic fluid through a one-way valve into the vena cava. Not only do they reduce the need for repeated paracentesis and relieve ascites symptoms but they also reduce protein and fluid depletion secondary to ascites drainage (Sangisetty 2012). Primary shunt patency reaches about 3 months. Frequent complications include pulmonary oedema, pulmonary embolus, and infection (Kipps 2013). PVSs are contraindicated in GI cancers due to a lower response rate relative to other cancers, in haemorrhagic ascites or ascites with high protein content (Saif 2009), and loculated ascites (Sangisetty 2012). Due to the risks of the procedure, PVSs should only be used when other treatment options have failed and patient life expectancy is long enough to derive benefit (Saif 2009). Other alternatives include e.g. the ALFApump®, an implantable, wirelessly-charged, CE-marked system that automatically and continuously pumps ascites from the abdominal cavity into the bladder for urinary elimination. Originally developed for ascites due to liver cirrhosis, first data indicate that the pump may also be effective in malignant ascites (Fotopoulou 2019).

Use of diuretics for the management of malignant ascites is common clinical practice, but there is limited evidence to support this approach (RCOG 2014). Diuretics are unlikely to mobilise ascitic fluid. If weight loss is achieved it may be from loss of extra-peritoneal fluid, potentially leading to dehydration if patients are not carefully supervised (Pockros 1992).

Multiple groups have aimed to target the ascites-generating tumour environment in the peritoneal cavity in order to reduce the ascites. Jordan (2016) performed a placebo-controlled phase II study of the anti-VEGF antibody bevacizumab i.p. in patients with advanced GI cancers and malignant ascites, due to the role that VEGF plays in ascites build-up. Bevacizumab did not result in better symptom control (median puncture-free survival [PuFS] 14 days with bevacizumab vs 10.5 days with placebo), although survival was numerically prolonged with bevacizumab (median OS 64 vs 31.5 days); neither result was statistically significant (Jordan 2016).

Other groups tried to address the underlying peritoneal carcinomatosis. Intraperitoneal use of anticancer agents allows to increase dose intensity at the intracavitary tumour site while reducing systemic toxicity. Response rates of 50% or higher have been reported with different chemotherapy agents or radioisotopes i.p. in smaller clinical trials and case series, where response was defined in terms of ascites control and survival time, and ascites control was achieved for up to several months (Smith 2003). However, this approach is limited to tumour types with general sensitivity to the

respective therapy. Newer modalities, such as HIPEC or PIPAC (pressurised i.p. aerosol chemotherapy) can be used after cytoreductive surgery, but also as palliative treatment to control ascites in patients still sensitive to chemotherapy (Cortés-Guiral 2021). However, until today, no such i.p. treatment approach has become standard of care or been included in clinical practice guidelines.

Overall, given the burden to and poor prognosis of patients with malignant ascites, there remains a need to develop safe and effective therapies for patients suffering from malignant ascites.

Natural history of the indicated condition in the population, including mortality and morbidity: Symptoms of malignant ascites include pain, respiratory compromise, abdominal bloating, feeling of fullness, early satiety, nausea, anorexia, insomnia, and fatigue (Preston 1995; Parsons 1996; Hostetter 1997). The urinary system may be affected (Kipps 2013). Complications include spontaneous bacterial pneumonitis and hepatorenal syndrome (Saif 2009). Ascites is associated with an extreme discomfort, leading to a poor quality of life and affecting the patient's physiological and sociological functioning (Becker 2006).

Secondary peritoneal carcinomatosis arises when the primary tumour is at an advanced stage (Cortés-Guiral 2021), and malignant ascites as a key symptom of peritoneal carcinomatosis is a manifestation of end-stage cancer disease (Saif 2009). Malignant ascites overall has a poor prognosis, with only 11% of patients surviving >6 months (Kipps 2013). A relatively better prognosis is by most authors reported for epithelial ovarian cancer; and patients with stage III/IV ovarian cancer with ascites may still achieve median progression-free survival (PFS) of 16-22 months and a 5-year survival rate of 27% after surgery and combination chemotherapy (Kipps 2013). Even better results are now being reported with improvements in anticancer therapy (Stukan 2017).

Important co-morbidities: Malignant ascites is a sign of advanced cancer with poor prognosis and associated morbidity (Sangisetty 2012).

Part II: Module SII - Nonclinical part of the safety specification

Catumaxomab is a trifunctional bispecific antibody that binds specifically to the human EpCAM antigen and the human CD3 antigen on T lymphocytes. As a result of the trifunctional mechanism of action, its pharmacological activity is dependent on the interaction of human immune effector cells (CD3-positive T-cells and FcγR I, IIa, and/or III-positive accessory cells like e.g. monocytes and natural killer [NK] cells) and EpCAM-positive target cells.

The nonclinical development of biologics requires testing in a species in which the therapeutic product is pharmacologically active. This requires binding of the therapeutic product to the targeted receptor or epitope. The full pharmacological activity of catumaxomab will only be achieved if all of its binding partners are present.

Since catumaxomab does not bind to EpCAM and CD3 of standard animal species including non-human primates (although catumaxomab is able to bind to monkey FcγR-positive blood cells), standard animal models such as rodents or even non-human primates are not appropriate for nonclinical testing. The species-specificity of catumaxomab for its human target antigens thus limits the ability to investigate functional effects on the major physiological systems and thus restricts the relevance of the nonclinical findings in non-relevant species for the human situation.

A targeted nonclinical testing strategy was developed to obtain relevant information from scientifically justified pharmacological, pharmacokinetic, and toxicological model systems.

- *In vitro* effects of catumaxomab were assessed in models using human cells where catumaxomab is able to exert its full pharmacological activity.
- A surrogate antibody (BiLu), which is of equivalent structure to catumaxomab and has the same principal target specificity but binds to mouse CD3 instead of human CD3, was used for pharmacology, pharmacokinetic, and toxicology studies in mouse models.

An overview of key safety findings from nonclinical studies along with their relevance to human usage is provided in Table SII.1.

Table SII.1 Key safety findings from nonclinical studies and relevance to human usage

Key safety findings	**Relevance to human usage**
Secondary pharmacodynamics	
Effects on cytokine release The potential of catumaxomab to induce the release of cytokines was investigated *in vitro*. Whole blood samples from three healthy human donors were incubated with catumaxomab (2.5, 25 and 250 ng/mL) in the presence or absence of HCT-8 human colon tumour cells. The amount of tumour necrosis factor alpha (TNF-α), interleukin (IL)-1ß, IL-6, IL-2 and IL-12 secreted was assayed to determine a stimulatory effect. The stimulatory effect was more pronounced when the antibody was incubated together with blood cells and tumour cells than when it was incubated with blood cells alone. Predominantly, TNF-α, IL-6, and IL-2 were found, whereas IL-12 and IL-1ß were produced only in small amounts. However, this does not exclude biological effects of these potent mediators.	Cytokine release syndrome (CRS)/systemic inflammatory response syndrome (SIRS) is included as an important identified risk.
Neutralizing potential of anti-antibodies The influence of human anti-mouse antibodies (HAMA) on binding of catumaxomab was investigated *in vitro*. HAMA-positive sera from patients who had been treated with catumaxomab were analysed for their ability to inhibit binding of catumaxomab to its target antigens *in vitro*. Anti-antibodies from catumaxomab-treated patients inhibited catumaxomab binding to its target antigens. In addition, the influence of HAMA and human anti-rat antibodies (HARA) on the functional activity of catumaxomab was investigated. A potential neutralizing activity of HAMA/HARA was assessed by evaluation of the anti-tumoural activity of catumaxomab in the presence of HAMA/HARA positive serum samples. It was found that therapy-induced HAMA/HARA from patient samples collected after catumaxomab therapy exhibit neutralizing activity.	The development of HAMA and HARA is a well-known consequence of the administration of rat and mouse antibodies. From clinical data with catumaxomab, virtually all patients are expected to develop anti-drug antibodies (ADAs) upon catumaxomab treatment. Based on available data, there is currently no indication of a negative impact of ADAs on efficacy or safety in patients. This observation is based on the fact that catumaxomab treatment is routinely completed after 11 days when ADA has developed only in single cases. Moreover, a clinical study called SECIMAS investigated and confirmed the possibility of treating patients with comparable success, who received catumaxomab, developed an ADA response, and were then treated with a second cycle of catumaxomab. Taken together, the study demonstrated that the presence of ADAs did not affect catumaxomab's

	safety and efficacy (Pietzner 2014).
Effects on lymphocytes in vivo (influence of BiLu on lymphocytes in mice) The effects of antibody binding to CD3 on lymphocytes were investigated in a nonclinical model using BiLu (anti-human EpCAM x anti-mouse CD3) as a surrogate antibody. Treatment of BALB/c mice with BiLu resulted in dose-dependent, transient decreases in T-cells. There was a dose-dependent transient decrease in total CD3+ T-cells that was apparent 4 h after application of BiLu and persisted up to 24 h post-application, after which CD3+ cell levels returned to baseline values.	Treatment of BALB/c mice with BiLu resulted in a dose-dependent transient decrease in CD3+ T-cells that returned to normal levels after 48 h post-application. These results are consistent with observations in clinical studies where peripheral lymphocyte count was seen to drop after the catumaxomab infusion and return to baseline before the subsequent infusion. The very short recovery interval argues against an antibody-mediated destruction (depletion) of lymphocytes; it is more likely an antibody-induced adhesion and/or migration of T-cells out of the blood stream into the tissues and possibly into the tumour due to cytokine interactions with lymphocytes and the endothelium, an effect that is well known (Schoentag 1993). Indeed, it was shown that catumaxomab dose-dependently enhanced transient adhesion of T-cell to endothelial cells by TNFα-mediated upregulation of adhesion molecules CD54 and CD62E (Dettmar 2012). Transient lymphopenia is an adverse drug reaction for Korjuny.
Safety pharmacology	
The species-specificity of catumaxomab limits the ability to investigate functional effects on the major physiological systems and thus restricts the relevance of the nonclinical findings for the human situation. Therefore, no specific *in vivo* safety pharmacology studies have been conducted. <u>Tissue binding on normal human tissues</u> Specific aspects were deduced from tissue cross-reactivity studies *in vitro*. The list of stained human tissues reflects the specificity of the antibody and may help to understand possible side effects in the clinical setting. The cross-reactivity of catumaxomab with 35 human	In these studies, binding of catumaxomab was assessed under "best-case" conditions (free availability of the binding epitopes for the bispecific antibody). Under

tissues, with each tissue sourced from 3 unrelated donors was tested. Catumaxomab showed specific staining in tissue regions that contained epithelium and lymphocyte cells. In addition, staining indicative of cross-reactivity (primarily at cell membranes) was seen in parenchymatous tissues such as adrenals, lung, pancreas, parathyroid, parotid, pituitary, spinal cord, testes, tonsils and spleen. Staining may represent EpCAM-positive, CD3-positive or Fc-gamma receptor-positive cells.	physiological conditions, catumaxomab must cross the blood vessels in order to bind to EpCAM in healthy tissues. In contrast to tumour tissue, blood vessels in healthy tissues are not leaky which impedes the penetration of makromolecules. Also, the expression of EpCAM on normal tissue epithelium is restricted basolateral and not overexpressed. Thus, although catumaxomab can bind to a number of human tissues, it is unlikely that significant amounts of catumaxomab can reach normal tissues. It is therefore very difficult to predict any side effects in humans on the basis of the binding patterns of catumaxomab with human tissues and to relate such cross-reactivity findings to the clinical situation. Since intact antibodies have a lower tissue penetration than small single-chain antibodies and antibody fragments, EpCAM is expected to be accessible for binding with intact antibodies only in the mosaic vessels of solid tumours or in body fluids such as ascites or pleural effusions and at inflamed and injured sites.
<u>Effects on human hepatocytes *in vitro*</u> Binding studies with human hepatocytes *in vitro* showed no significant binding of catumaxomab or its parental anti-EpCAM antibody HO-3 to hepatocytes in purified cell samples or in liver tissue samples. However, there was significant binding of catumaxomab to bile duct cells in liver tissue samples. These results are supported by literature data showing that EpCAM is expressed on bile ducts but not on hepatocytes (Balzar 1999). Additional studies evaluated whether or not the bispecific antibody catumaxomab (anti-EpCAM x anti-CD3) or its parental monospecific antibody HO-3 (anti-EpCAM) has any effect on metabolic functions of human hepatocytes *in vitro*. Freshly harvested hepatocytes were used in co-culture experiments: In several *in vitro* settings the effects of different concentrations of catumaxomab or HO-3 were	In clinical studies, increases in liver values have been observed, which were infrequently associated with clinical consequences. This may be due to the contact of systemic catumaxomab with EpCAM+ bile duct cells, which may cause antibody-mediated cytotoxicity, local inflammation with intrahepatic cholestasis, and with resultant increases in liver values. Patients treated with Korjuny should be closely monitored for signs of clinically significant elevated liver parameters.

assessed. An increase in aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and lactate levels in transfer cultures (transfer of culture supernatants from effector cells) with purified hepatocytes was found. However, no functional impairment was observed as no impact on urea synthesis, albumin levels ammonia clearance, and uridine diphosphate clearance was detected *in vitro*.	
Toxicity	
Key issues identified from acute or repeated-dose toxicity studies <u>Toxicity of intravenous and intraperitoneal catumaxomab</u> The administration of 100 µg / 200 µg or 500 µg / 1000 µg catumaxomab into the peritoneal cavity of mice or guinea pigs respectively did not cause any symptoms of disease. I.v. single dose administration of up to 1.5 mg/kg body weight (b.w.) into NMRI mice[1] and up to 5.0 mg/kg b.w. into Wistar rats did not reveal any signs of substance-related acute toxicity. Even after repeated i.v. infusion of escalating doses of catumaxomab up to 300 µg/kg b.w. into a cynomolgus monkey, no effect on clinical signs, body weight, hematologic and biochemical parameters, cytokine or complement levels was observed. Repeated-dose toxicity studies have not been conducted with catumaxomab due to the lack of an appropriate animal species. <u>Toxicity of intravenous and intraperitoneal BiLu (anti-human EpCAM x anti-mouse CD3) in the mouse</u> BiLu was administered twice weekly i.p. into BALB/c mice using a low (0.2 to 3.0 µg/kg b.w.), mid (2 to 30 µg/kg b.w.) and high (20 to 300 µg/kg b.w.) dosing group (5 male and 5 female mice per group). Additionally, BiLu was injected twice weekly i.v. (20 to 300 µg/kg b.w.) into another group. The mid-dose group corresponds to the human equivalent dose of catumaxomab administered i.p. in patients, applying the appropriate dose-conversion factor for mice. In the high i.p. dosing group centrilobular necrosis was detected in the liver of two male animals. In the mid i.p. dosing group mild focal necrosis was found in the liver of one treated and one control animal. In one male animal of	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. BiLu is specific for mouse CD3 but specific for human EpCAM which is significantly different from murine EpCAM (Schnell 2013). The toxicity findings obtained with the surrogate antibody BiLu are of limited value. Due to the lack of relevant animal model, safety assessment of catumaxomab should therefore mainly depend on the clinical safety assessment.

[1] Outbred strain of mouse (Naval Medical Research Institute)

the mid i.p. dosing group mild hydropic cell degeneration was seen. These liver findings were not detected in female mice. Ductular ectasia was observed in 1/5, 2/5 and 1/5 animals in the i.p. mid-dosing, i.p. high dosing, and i.v. high dosing groups, respectively. The finding "ductular ectasia" describes a non-neoplastic change. It is recognized as a dilation of mammary ducts. The lumen of the ducts may contain proteinaceous material and occasionally lipid and may be associated with macrophage infiltration. In the high dosing i.p. and i.v. groups a decrease in lymphocytes, predominantly CD4+ cells and an increase in reticulocytes was found. From mid i.p. dose upwards an increasing erythroid hyperplasia and myeloid depression was observed. In i.v. treated mice an increase in reticulocytes and in i.v. treated male mice an increasing erythroid hyperplasia and myeloid depression was detected. The tissue tolerability of BiLu was good. The high dosing group was at the border of toxicity for male mice. The mid-dosing regime was in the tolerable range for male and female mice. The low dosing group marks the No Observed Adverse Effect Load (NOAEL) of this study.	
Genotoxicity The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed [CPMP/ICH/302/95]. It is not expected that catumaxomab would interact directly with DNA or other chromosomal material. Moreover, the administration of large quantities of an antibody may yield uninterpretable results.	None
Carcinogenicity Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals [CPMP/ICH/302/95]. Catumaxomab does not have the potential to induce proliferation of EpCAM-positive or CD3-positive tumour cells. There is no potential concern about accumulation of spontaneously mutated cells with catumaxomab.	None
Reproductive/developmental toxicity	Animal studies are insufficient with

Studies to investigate reproductive and developmental toxicity have not been performed due to the lack of an appropriate animal species, the intended patient population and the late stage of the malignant disease.	respect to reproductive toxicity. It is unknown whether catumaxomab/metabolites are excreted in milk. A risk to the newborns/infants cannot be excluded.

Part II: Module SIII - Clinical trial exposure

Key studies for characterisation of the safety profile of catumaxomab in malignant ascites are the 4 studies performed in this indication: IP-REM-AC-01; STP-REM-01; IP-REM-PK-01-EU; and IP-REM-AC-02-US. Three studies were uncontrolled; the only controlled study was IP-REM-AC-01, comparing catumaxomab plus paracentesis vs paracentesis alone. In addition, a further 9 studies in further indications contribute to the assessment of safety of catumaxomab, in 7 of which catumaxomab was administered i.p. The design of these studies is summarised in Table SIII.1. In these studies, 517 patients received catumaxomab i.p. (ISS2). The number of patients exposed to catumaxomab is presented by age group and gender in Table SIII.2, by dose per infusion and total dose in Table SIII.3, and by race in Table SIII.4.

Table SIII.1: Clinical studies contributing to the evaluation of safety of catumaxomab

Study ID	Indication	Phase	Study design	Dose	Patients, (n)[1]	Route	Infusion duration (hours)	Included in ISS2 (2010 cut-off)
	Malignant ascites							
IP-REM-AC-01	Malignant ascites due to epithelial cancers	II/III	R, C, OL	10-20-50-150 µg	Total: 245 Cat: 157 CatCr: 46	i.p.	6	yes
STP-REM-01	Malignant ascites due to ovarian cancer	I/II	OL, UC, DE	5-10-10-10 µg 10-50-50-50 µg 10-20-50-50 µg 10-20-50-100 µg 10-20-50-200 µg 10-20-50-200-200 µg	23	i.p.	6	yes
IP-REM-PK-01-EU	Malignant ascites due to epithelial tumours	II	OL, UC	10-20-50-150 µg	13	i.p.	6	yes
IP-REM-AC-02-US	Malignant ascites due to ovarian cancer	II	OL, UC	10-20-50-150 µg	32	i.p.	3	yes
	Other indications – i.p.							
AGO-OVAR-2.10	Ovarian cancer	IIa	R, OL, UC	10-10-10-10 µg 10-20-50-100 µg	41	i.p.	6	yes
IP-REM-PC-01-DE	Peritoneal carcinomatosis due to epithelial GI malignancies	I	OL, UC, DE	10-10-30-50 µg; 6-h 10-20-50-100 µg; 6-h 10-20-50-200 µg; 6-h 10-20-100-200 µg; 6-h 10-20-50-200 µg; 3-h 20-50-100-400 µg; 3-h +dexamethaso	24	i.p.	3/6	yes

				ne 40-100-200-800 µg; 3-h +dexamethasone				
IP-REM-GC-01	Intraabdominal epithelial tumours	I	OL, UC, DE	5-20-50-150 µg 10-20-50-150 µg 20-10-20-50-150 µg	12	i.p.	3	yes
IP-CAT-OC-01	Advanced epithelial ovarian cancer; after complete response to chemotherapy	II	OL, UC	10-20-50-150 µg	47	i.p.	3	yes
IP-CAT-OC-02	Epithelial ovarian cancer	II	OL, UC	10-10-20-50-150 µg	41	i.p.	3	yes
IP-REM-GC-02	Gastric adenocarcinoma after curative resection	II	OL, R, C	10-10-20-50-150 µg	Total: 55 Cat: 28	i.p.	3	yes
IP-CAT-GC-03	Gastric adenocarcinoma; after neoadjuvant chemotherapy, intended curative resection	II	OL, UC	10-10-20-50-150 µg	54	i.p.	3	yes
Other indications – other methods of administration (i.pl. and i.v.)								
IPL-REM-PL-01-DE	Pleural effusion	II	OL, R, UC	5-10-20 µg 10-20-50 µg 20-50-100 µg	24	i.pl.	3	no[2]
IV-REM-01-DE	NSCLC	II	OL, UC	Single doses of 2, 5, 10, 15, 20 µg	24	i.v.	8	no[2]

Abbreviations: C = controlled, Cat = catumaxomab, CatCr = catumaxomab crossover, CSR = clinical study report, DE = dose escalation, i.p. = intraperitoneal, i.pl. = intrapleural, i.v. = intravenous, NSCLC = non-small cell lung cancer, OL = open-label, R = randomised, UC = uncontrolled.

1 Number of treated patients

2 These studies are not included in ISS2, however CSRs for these studies are included in the marketing authorisation application

Table SIII.2: Age and Gender (ISS2 – safety set)

	Patients
N	517
Age (years)	
Mean (SD)	59.1 (11.2)
Median (min, max)	59.0 (23-86)
Gender N (%)	
Female	409 (79.1%)
Male	108 (20.9%)

Source: Tables 2.1.2 and 2.2.2, ISS2 (2010)

Abbreviations: max = maximum, min = minimum, SD = standard deviation.

Table SIII.3: Dose per infusion and total dose (ISS2 – safety set)

	Patients (N=517)
Actual dose [µg] at 1st infusion	
N	517
Mean (SD)	10.1 (1.4)
Median (min, max)	10.0 (5, 20)
Actual dose [µg] at 2nd infusion	
N	468
Mean (SD)	17.6 (5.8)
Median (min, max)	20.0 (10,50)
Actual dose [µg] at 3rd infusion	
N	424
Mean (SD)	42.3 (15.4)
Median (min, max)	50.0 (10, 100)
Actual dose [µg] at 4th infusion	
N	390
Mean (SD)	121.4 (54.7)
Median (min, max)	150.0 (10, 400)
Actual dose [µg] at 5th infusion	
N	86
Mean (SD)	152.3 (10.6)
Median (min, max)	150.0 (150, 200)
Total dose [µg] received	
N	517
Mean (SD)	177.7 (97.8)
Median (min, max)	230.0 (10, 570)

Source: Table 3.2.2, ISS2 (2010)

Abbreviations: max = maximum, min = minimum, SD = standard deviation.

Table SIII.4: Race (ISS2 – safety set)

	Patients
N	517
Asian	3 (0.6%)
Black or African American	3 (0.6%)
White	505 (97.7%)
Other	6 (1.2%)

Source: Derived from Table 2.2.2, ISS2 (2010)

Clinical studies and other investigations of catumaxomab in addition to those presented in Table SIII.1 have been performed; however, the Applicant has no rights to the respective data and reports, and, therefore, the data are presented in the marketing authorisation application (MAA) as supportive information based on published literature. In particular, safety data are available from 2 further studies, i.e. a Phase IIIb open-label, randomised, parallel-group study (IP-CAT-AC-03; CASIMAS) in patients with malignant ascites (Sehouli 2014) and a Phase II study (IP-CAT-AC-04; SECIMAS) investigating repeated treatment with catumaxomab in patients who completed study IP-CAT-AC-03 (Pietzner 2014). Also, results for study IV-CAT-ST-01 of catumaxomab i.v. were reported by Mau-Sorensen (2015) and Borlak (2016).

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria in IP-REM-AC-01, the pivotal clinical study with i.p. application of catumaxomab, are discussed below.

1 Acute or chronic infections,

Reason for exclusion: Patients with acute or chronic infections were excluded due to a potentially imbalanced benefit/risk ratio.

Is it considered to be included as missing information?: No

Rationale: As stated in the summary of product characteristics (SmPC), Section 4.4, in presence of factors interfering with the immune system, in particular acute infections, the administration of catumaxomab is not recommended. This is considered sufficient.

2 Exposure to investigational product, cancer chemo- or radiotherapy within the last 28 days (6 weeks for nitrosoureas or mitomycin C) before first infusion,

Reason for exclusion: Patients with recent anticancer treatment are routinely excluded from clinical trials in order to avoid confounding factors affecting efficacy and safety.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with Korjuny is made by the healthcare professional after consideration of the product information.

3 Previous treatment with mouse or rat monoclonal antibodies,

Reason for exclusion: Patients with previous exposure to mouse or rat monoclonal antibodies may have been at greater risk of adverse effects or diminished efficacy.

Is it considered to be included as missing information?: No

Rationale: In an *in vitro* assessment of the neutralizing potential of ADAs, pre-existing antibodies against rat or mouse proteins but unrelated to catumaxomab did not influence catumaxomab-mediated cytotoxicity *in vitro* (Module 2.4, Section 2.2.1.2).

4 Known or suspected hypersensitivity to catumaxomab or similar antibodies,

Reason for exclusion: Patients with known or suspected hypersensitivity to catumaxomab or similar antibodies are at greater risk of hypersensitivity reactions to catumaxomab.

Is it considered to be included as missing information?: No

Rationale: As stated in the SmPC, Section 4.3, hypersensitivity to the active substance or hypersensitivity to murine (rat and/or mouse) proteins are contraindications for use. This is considered sufficient.

5 Inadequate renal function (creatinine > 1.5 x upper limit of normal [ULN]),

Reason for exclusion: Patients with relevant co-morbidity were excluded from studies due to a potentially imbalanced benefit/risk ratio.

Is it considered to be included as missing information?: No

Rationale: Patients with inadequate renal function are not included as missing information, as catumaxomab is not eliminated via the renal pathway. This information is included in the SmPC Section 4.4. In addition, Section 4.4 states that patients with moderate to severe renal impairment have not been investigated and that treatment of these patients with Korjuny should only be considered after a thorough evaluation of benefit/risk. This is considered sufficient.

6 Inadequate hepatic function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltransferase [GGT] ≥ 5 x ULN; bilirubin > 1.5 x ULN),

Reason for exclusion: Patients with inadequate hepatic function were excluded from studies due to a potentially imbalanced benefit/risk ratio.

Is it considered to be included as missing information?: Yes

Rationale: Not applicable. Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases are included as missing information.

7 Platelets< 80000 cells/mm^3; absolute neutrophil count (ANC) < 1500 cells/mm^3,

Reason for exclusion: Patients at greater risk of bleeding or at greater risk of infection were excluded from studies due to a potentially imbalanced benefit/risk ratio.

Is it considered to be included as missing information?: No

Rationale: The administration of catumaxomab is not recommended in the presence of factors interfering with the immune system (Section 4.4 SmPC). Thrombocytopenia or neutropenia were not identified as adverse reactions to catumaxomab in malignant ascites patients (Section 4.8 SmPC).

8 Body-mass index (BMI) <17,

Reason for exclusion: Patients with a BMI of <17 were excluded due to a potentially imbalanced benefit/risk ratio.

Is it considered to be included as missing information?: No

Rationale: Information on the nature and frequency of adverse reactions for catumaxomab, including decreased appetite and weight decreased, is provided in Section 4.8 of the SmPC. .

9 Patients with a reduced nutritional status requiring predominantly parenteral nutrition (> 50% of energy intake),

Reason for exclusion: Patients requiring predominantly parenteral nutrition were excluded due to a potentially imbalanced benefit/risk ratio.

Is it considered to be included as missing information?: No

Rationale: Gastrointestinal adverse reactions as well as decreased appetite and weight decreased are identified as adverse reactions for catumaxomab in the Section 4.8 of the SmPC.

10 Patients with gastric or small bowel feeding tube at study entry,

Reason for exclusion: Patients with gastric or small bowel feeding tube were excluded due to a potentially imbalanced benefit/risk ratio as effects on the gastrointestinal system are recognized adverse reactions for catumaxomab.

Is it considered to be included as missing information?: No

Rationale: Information on the nature and frequency of adverse reactions to catumaxomab, including gastrointestinal adverse reactions, is included in Section 4.8 of the SmPC.

11 Patients with ileus within the last 30 days,

Reason for exclusion: Patients with a recent history of ileus were excluded due to a potentially imbalanced benefit/risk ratio as effects on the gastrointestinal system are recognized adverse reactions for catumaxomab.

Is it considered to be included as missing information?: No

Rationale: Information on gastrointestinal adverse reactions to catumaxomab, including sub-ileus and ileus paralytic, is included in Section 4.8 of the SmPC.

12 Patients with any other severe disease that would have rendered a participation in the study an undue risk,

Reason for exclusion: Patients with other severe diseases are routinely excluded from clinical trials to avoid confounding factors affecting efficacy and safety.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with Korjuny is made by the healthcare professional after consideration of the product information.

13 Known brain metastases in cancer history,

Reason for exclusion: Patients with known brain metastases in cancer history are routinely excluded from clinical trials to avoid confounding facts affecting efficacy and safety.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with Korjuny is made by the healthcare professional after consideration of the product information.

14 Pregnant or nursing women, or women with childbearing potential and males who were not using an effective contraceptive method during the study and for at least 3 months after the last infusion,

Reason for exclusion: Pregnant and nursing women and women of childbearing potential or their partners not using effective contraception are routinely excluded from clinical trials to protect the health of the unborn or nursing child.

Is it considered to be included as missing information?: No

Rationale: As stated in the SmPC Section 4.6, Korjuny is not recommended during pregnancy and in women of childbearing potential not using contraception. A risk to newborns/infants through excretion in human milk cannot be excluded and 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. This is considered sufficient.

15 History of myocardial infarction,

Reason for exclusion: Patients with a history of myocardial infarction were excluded to avoid confounding factors affecting safety and efficacy assessments and to protect the health of the subject.

Is it considered to be included as missing information?: No

Rationale: No cardiac safety concerns were identified in catumaxomab studies, including in two malignant ascites studies with on-treatment electrocardiography (ECG) assessments (STP-REM-01 and IP-REM-AC-02-US) (Module 2.7.4, Section 4.2).

16 Signs or symptoms of relevant cardiovascular disease, congestive heart failure or cardiac arrhythmias (New York Heart Association [NYHA] class > II),

Reason for exclusion: These patients were excluded to avoid confounding factors affecting safety and efficacy assessments and to protect the health of the subject.

Is it considered to be included as missing information?: No

Rationale: No cardiac safety concerns were identified in catumaxomab studies, including in two malignant ascites studies with on-treatment ECG assessments (STP-REM-01 and IP-REM-AC-02-US) (Module 2.7.4, Section 4.2). Cardiac adverse reactions, including sinus tachycardia and tachycardia, are identified as adverse reactions for catumaxomab in the SmPC Section 4.8.

17 History of cerebrovascular accident,

Reason for exclusion: Patients with a history of cerebrovascular accident were excluded to avoid confounding factors affecting safety and efficacy assessments and to protect the health of the subject.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with Korjuny is made by the healthcare professional after consideration of the product information.

18 Patients with portal vein obstruction or portal vein thrombosis diagnosed by computed tomography (CT) scan at screening,

Reason for exclusion: Patients with portal vein thrombosis/obstruction were excluded from studies due to a potentially imbalanced benefit/risk ratio.

Is it considered to be included as missing information?: No

Rationale: As stated in Section 4 of the SmPC, patients with 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.

The decision to treat with Korjuny is made by the healthcare professional after consideration of the product information.

19 Patients with extensive liver metastases (> 70% of the liver was metastasized),

Reason for exclusion: Patients with extensive liver metastases were excluded from studies due to a potentially imbalanced benefit/risk ratio.

Is it considered to be included as missing information?: Yes

Rationale: Not applicable. Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases are included under missing information.

20 Inadequate respiratory function in the opinion of the investigator,

Reason for exclusion: Patients with inadequate respiratory function are routinely excluded from clinical studies in order to avoid confounding factors for efficacy and safety assessments and protect the health of the subject.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with Korjuny is made by the healthcare professional after consideration of the product information.

21 Any further condition, which according to the investigator resulted in an undue risk of the patient by participating in the present study.

Reason for exclusion: This broad exclusion criterion is routinely included in clinical studies in order to avoid confounding factors for efficacy and safety assessments.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with Korjuny is made by the healthcare professional after consideration of the product information.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**.
Pregnant women	Not included in the clinical development program.
Breast-feeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with at least severe hepatic dysfunction, with at least 70% of the liver affected by metastases, at least moderate renal dysfunction, and/or portal vein thrombosis/obstruction were not included in the clinical development program. Patients with cardiac impairment (defined as a history of myocardial infarction, signs, or symptoms of relevant cardiovascular disease, congestive heart failure or cardiac arrhythmias [NYHA class > II] in the pivotal study) were not included in the clinical development program. Immunocompromised patients (defined as ANC <1500 cells/mm^3 in the pivotal study) were not included in the clinical development program. The clinical development of catumaxomab in malignant ascites focused mainly on patients in the end stage of their fatal disease.
Population with relevant different ethnic origin	The majority of patients were white (see Table SIII.4).
Subpopulations carrying relevant genetic polymorphisms	No data available.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

The first marketing authorisation for catumaxomab in the i.p. application (tradename: Removab) was received on 20 April 2009 in the European Union (EU). Catumaxomab was additionally authorised in Israel on 17 August 2011, in Canada on 11 May 2012, and in Russia on 08 October 2012. Due to the lack of a distributor in Canada and Russia, catumaxomab was marketed in the EU and Israel only.

Removab has not been marketed in the EU since 2014 and it was withdrawn for commercial reasons on 02 June 2017. Registration was not renewed in Israel, and the registration status in Israel expired on 17 August 2016.

SV.1.1 Method used to calculate exposure

Patient exposure to commercial catumaxomab was approximated based on the number of Removab packages delivered in the market as described in the Removab periodic safety update reports (PSURs) 1 to 10.

One course of catumaxomab treatment as per the approved product information (during the approved period) consisted of 10-20-50-150 µg catumaxomab, or 230 µg catumaxomab in total. Based on experience from clinical studies and market experience, compliance with the schedule prescribed by the product information was considered to be 80%, so that a patient would receive 184 µg rather than 230 µg catumaxomab in total. The approximate number of patients was derived from the total amount of delivered catumaxomab and administration of 184 µg catumaxomab per patient and treatment course.

SV.1.2 Exposure

A total number of 2082 exposed patients was determined (Table SV.1). Note that this is in line with the sum of exposed patients as detailed in each of the 10 PSURs. However, PSUR 9 and 10 both indicate that in the period from marketing authorisation through the data lock point of the respective PSUR, a total of 7003 packages of catumaxomab 10 µg and 6170 packages of catumaxomab 50 µg were sold, for a cumulated exposure of 2121 patients. The reason for the difference of 39 patients is not specified in the PSURs.

Additionally, catumaxomab exposure of 101 patients in investigator-initiated trials (IITs) was reported i.e. 12 patients in PSUR 4 Section 6; 26 patients in PSUR 5 Section 6; 41 patients in PSUR 6 Section 5.2; 17 patients in PSUR 7 Section 5.2; and 5 patients in PSUR 8 Section 5.2.1.

Several PSURs highlighted that the number of delivered Removab 10 µg packages was higher than the number of 50 µg packages, while a full catumaxomab treatment course (i.e. 10-20-50-150 µg) would require 3 x 10 µg packages and 4 x 50 µg packages per patient. The sponsor assumed that hospitals might have ordered Removab 10 µg and put them on stock, which was unlikely to be done for the more expensive 50 µg syringes. Also, Removab 10 µg packages counted in Table SV.1 included samples provided to health care professionals (which also were more likely the less expensive 10 µg packages). In order to not overestimate the number of exposed patients, exposure was corrected by assuming only 80% compliance for each patient; the 80% compliance rate was based on clinical studies and market experience.

Table SV.1: Approximated exposure of patients to commercial catumaxomab (Removab PSURs 1 to 10)

PSUR	Period	Removab 10 µg packages, n	Removab 50 µg packages, n	Patients exposed, n
1	20 Apr 2009-20 Oct 2009	456	391	131
2	21 Oct 2009-20 Apr 2010	631	416	147
3	21 Apr 2010-20 Oct 2010	799	406	154
4[1]	21 Oct 2010-20 Apr 2011	717	711	232
5[1]	21 Apr 2011-20 Apr 2012	1744	1698	556
6[1]	21 Apr 2012-20 Apr 2013	1544	1371	456
7	21 Apr 2013-20 Apr 2014	1456	1159	394
8[2]	21 Apr 2014-20 Apr 2015	37	34	12
9[3]	21 Apr 2015-20 Apr 2016	0	0	0
10[3]	21 Apr 2016-20 Apr 2017	0	0	0
Total		7384	6186	2082

[1] Including patients treated in noninterventional studies performed by the marketing authorisation holder (MAH) at that time (CARMA, ACT)

[2] Removab was not marketed anymore after end of March 2014. However, 37 packages Removab 10 µg and 34 packages Removab 50 µg had been delivered to hospitals where patients had started treatment or were prepared to be treated with Removab. Assuming that all patients received at least the first 2 doses of the treatment schedule as described in the SmPC, i.e. 3 x 10 µg packages, exposure was estimated as 12 patients treated with marketed Removab.

[3] Removab was not marketed anymore after end of March 2014.

Source data: Removab PSURs 1 to 10

No breakdown of post-marketing exposure data is available by gender, age group, or region.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is a limited potential for the illegal use of catumaxomab. Catumaxomab has neither psycho-stimulating effects nor any other effect that may lead to dependency. Additionally, catumaxomab is handled within a highly controlled hospital environment or experienced oncologic practices.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised) are provided in Table SVII.1.

Table SVII.1 Adverse reactions reported from patients receiving catumaxomab treatment not considered important for inclusion in the list of safety concerns

System Organ Class Frequency	**Adverse reaction**
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	
Common	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*
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 complications	
Uncommon	Anastomotic complication*, Procedural pain*, Wound dehiscence*

* 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=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.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Cytokine release syndrome (CRS)/systemic inflammatory response syndrome (SIRS)

CRS/SIRS is a systemic inflammatory response that can present with a variety of signs and symptoms ranging from mild, flu-like symptoms to severe life-threatening manifestations. Cytokine release related clinical symptoms reported during and after catumaxomab administration include events of fever, hypotension, gastrointestinal symptoms, headache, myalgia, arthralgia, tachycardia, chills, respiratory symptoms, skin symptoms, and fatigue. Isolated incidence of SIRS (with concurrent fever, increased heart rate and respiratory rate, and abnormal leukocyte count) have been reported in association with catumaxomab administration.

Risk-benefit impact: Cytokine release related clinical symptoms can be expected in patients receiving catumaxomab and the adverse event profile seems to be predictable. In some cases, serious manifestations were observed. The information provided in the label, including recommendations on medication for the prophylactic treatment of cytokine release symptoms, haemodynamic status before treatment, post-administration observation, and patient counselling, and the patient card are considered to be adequate to mitigate the risk of CRS/SIRS, and therefore, the risk-benefit balance remains favourable.

Important Potential Risk 1: More severe adverse reactions due to accidental i.v. infusions instead of i.p.

Two spontaneous reports of accidental i.v. infusion instead of i.p. were received during post-marketing of Removab. Consequently accidental i.v. infusion instead of i.p. was included first as an important potential (in Removab PSUR 1) and then as an important identified risk (in Removab PSUR 4). In the first of the two reported cases, the patient's third infusion of Removab was erroneously administered i.v. which was noticed after 3 hours infusion time after the patient had received about 25 ug catumaxomab (Removab PSUR 1, Section 10.12). Serious adverse reactions (SARs) of cardiovascular insufficiency and poor peripheral circulation and an adverse reaction of systemic inflammatory response syndrome (SIRS) were attributed to the erroneous i.v. administration (Removab PSUR 1). No adverse reactions were reported in association with the erroneous i.v. administration for the second patient who received 5 µg i.v. before the error was detected (Removab PSUR4, Section 10.13).

It is possible that more severe adverse reactions may occur due to accidental i.v. infusions instead of i.p. Therefore, "more severe adverse reactions due to accidental i.v. infusions instead of i.p." has been included as an important potential risk.

Risk-benefit impact: The prominent display of the route of administration in the primary and secondary packaging and warning sticker are considered adequate to mitigate the risk of accidental i.v. infusion, and therefore, the risk-benefit balance remains favourable.

Missing information 1: Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases

Patients with severe hepatic impairment and/or with more than 70% of the liver metastasized were excluded from clinical trial due to a potentially imbalanced benefit/risk ratio.

Risk-benefit impact: As stated in Section 4.4 of the SmPC, use in these patients should only be considered after a thorough evaluation of benefit/risk for the individual patient.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Cytokine release syndrome (CRS)/Systemic Inflammatory Response Syndrome (SIRS)

Potential mechanisms:

Due to catumaxomab's mechanism of action, induction of cytokines is not only expected but desired, as cytokines are involved in the immunological activation and resultant anticancer activity. Side effects in line with the cytokine release induced by catumaxomab may be expected. CRS is a systemic inflammatory response that can be triggered by a variety of factors, including infections as well as certain drugs, and that presents with a variety of symptoms ranging from mild, flu-like symptoms to severe life-threatening manifestations of overshooting inflammatory response (Shimabukuro-Vornhagen 2018). 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, including events of fever, hypotension, gastrointestinal symptoms, headache, myalgia, arthralgia, tachycardia, chills, respiratory symptoms, skin symptoms, and fatigue, have been reported during and after the catumaxomab administration.

Evidence source(s) and strength of evidence:

Due to catumaxomab's mechanism of action, side effects in line with the cytokine release induced by catumaxomab may be expected. 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. Isolated incidence of SIRS (with concurrent fever, increased heart rate and respiratory rate, and abnormal leukocyte count) have been reported in association with catumaxomab administration.

Characterisation of the risk:

In the original MAA (ISS1) and for the renewal in 2010 (ISS2; N = 517), cytokine release related symptoms were summarized based on individual preferred terms that were considered to be typical for CRS and by scrutinising tables and listings for these events. This method is unspecific, as it is based on individual adverse event terms whose occurrence may not necessarily indicate a true CRS episode.

Thus, an additional post hoc analysis is presented aiming to better characterise clinically relevant suspected CRS episodes in the pivotal study IP-REM-AC-01. For completeness, both analyses are presented below.

Note, the analyses described below captured cases with cytokine release related symptoms, including events with the preferred term systemic inflammatory response syndrome, and therefore include cases of reported SIRS.

'Historical' analysis of CRS based on individual Medical Dictionary for Regulatory Activities (MedDRA) preferred terms – ISS2

Overall, 72% of all catumaxomab exposed patients experienced CRS according to the definition used in the ISS2 (Module 2.7.4, Section 2.1.6.1.1). It is interesting to note that in this analysis only < 1% of patients had CRS reported as a preferred term, suggesting that investigators did not identify signs and symptoms of CRS as a medical concept. This can be understood, because the term CRS became more widely known only with the rather recent introduction of CAR-T cells and checkpoint inhibitor antibodies as well as one further approved bispecific T-cell directed antibody (Blincyto, Amgen). The most frequent preferred term contributing to CRS was pyrexia (44%); additionally, 2% and < 1% reporting body temperature increased and hyperthermia, respectively. Chills were reported by 13% of the patients. Next most frequent were nausea (36%) and vomiting (32%). Preferred terms indicative of blood pressure changes were reported in a total of 64 patients (12%). Dyspnoea was reported in 6% of patients. Duration of CRS was typically short, with a duration of 1 day in 46% of patients and 2-3 days in 42% of patients. It is notable that CRS was ongoing in 6% (i.e. ongoing at the time of death, loss to follow-up, or data cut-off date, so that no resolution date was recorded).

Suspected CRS episodes as per post-hoc analysis – Study IP-REM-AC-01

As detailed above, according to the original CRS analysis presented for ISS2, 72% of catumaxomab exposed patients (ISS2) experienced CRS. However, this assessment based on individual preferred terms is regarded as highly unspecific as their occurrence may not necessarily indicate a true CRS episode. Therefore, an algorithm-based analysis of CRS, including cases of SIRS, was retrospectively performed for pivotal study IP-REM-AC-01, using an algorithm to identify patients with symptoms suggestive of CRS according to current standards (Breslin 2007; Parsons 2010; Lee 2014).

In the main study period of IP-REM-AC-01, 23% of all exposed patients had episodes of suspected CRS according to this algorithm, which was comparable to 22% in the crossover period, in which patients who were previously in the control arm received catumaxomab treatment. Patients with ovarian and nonovarian cancer had comparable incidences (26% vs 20% in the main study period, 25% vs 18% in the crossover period) (Module 2.7.4 Section 2.1.6.1.2). No patient in the control group was identified with a suspected CRS episode.

A total of 53 suspected CRS episodes were identified in the main study period and crossover period together. Most of these episodes (66%) were of low grade (Grade 1 or 2), 30% were of Grade 3, and 4% included a symptom of Grade 4. Most episodes resolved completely (68%) and thus, were reversible, 9% resolved with sequelae, and in 23%, at least one symptom was ongoing (mostly fatigue, nausea, tachycardia) at the patient's death or last visit. Most episodes started on the day of or the day after the first catumaxomab infusion. Later onsets most likely represent episodes related to a later infusion rather than a delayed reaction related to the first infusion.

SIRS cases - Study IP-REM-AC-01

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 IP-REM-AC-01 (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.

Additional data from PSURs for Removab (catumaxomab)

Post-marketing data for catumaxomab are available from 10 PSURs, available as text parts in redacted form, without the appendices including line listings. Cumulatively to 20 Apr 2017 (data lock point [DLP] of last Removab PSUR), itemization of cytokine related release syndrome related SARs from all post-marketing sources: pyrexia (27 SARs), vomiting (10 SARs), nausea (9 SARs), chills (6 SARs), hypotension (5 SARs), dyspnoea (2 SAR), hypertension (2 SARs), and no SAR reports on cytokine storm or CRS. There were 10 SARs of the preferred term systemic inflammatory response syndrome. Overall, a total of 271 SARs were cumulatively reported for Removab from marketing authorisation until withdrawal (according to PSUR10, 2,121 patients were treated with marketed product in the cumulative period from marketing authorisation until DLP of the last PSUR) (Removab PSUR 10).

Risk factors and risk groups:

None identified.

Preventability:

The use of medication for the prophylactic treatment of cytokine release symptoms as recommended in the SmPC (SmPC, Section 4.2).

Dosing in accordance with the dosing schedule and adequate supervision of the patient after the end of infusion (SmPC, Section 4.2).

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 (SmPC, Section 4.2).

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 (SmPC, Section 4.4).

Patients should be counselled to seek immediate medical attention if signs or symptoms of CRS/SIRS occur at any time (SmPC, Section 4.4).

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 (SmPC, Section 4.4).

The prescriber must discuss the risks of Korjuny therapy with the patient. Patients should carry a patient card to remind them of the key signs and symptoms of CRS/SIRS and when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS/SIRS present themselves.

Impact on the risk-benefit balance of the product:

Use of catumaxomab is associated with potential CRS/SIRS. The recommendations in the label and the patient card are considered adequate to mitigate the risk of CRS/SIRS, and therefore, the risk-benefit balance remains favourable.

Public health impact:

No impact on public health.

Important Potential Risk: More severe adverse reactions due to accidental i.v. infusions instead of i.p. .

Potential mechanisms:

Erroneous connection of catumaxomab administration syringe with the patient's i.v. line.

Evidence source(s) and strength of evidence:

Spontaneous reports of accidental i.v. infusion instead of i.p. have been reported from marketed use of catumaxomab.

Characterisation of the risk:

No reports of accidental i.v. infusion instead of i.p. infusion were reported for the i.p. studies in ISS2 (N = 517).

Two cases of accidental i.v. infusion instead of i.p. are known from spontaneous sources from marketed use of Removab. In PSUR 1, a PPD erroneously received approximately 25 µg catumaxomab i.v. before the error was noticed. The patient had 2 SARs, cardiovascular insufficiency and poor peripheral circulation, and an adverse reaction of SIRS, which were attributed to an accidental systemic overdose following erroneous i.v. administration of catumaxomab (Removab PSUR 1, Section 10.12). A further report was received in PSUR 4 of a patient who erroneously received catumaxomab i.v. instead of i.p. After approximately 5 µg were given i.v., the error was detected and the infusion was discontinued. It was reported that the patient did not develop any adverse event (Removab PSUR 4, Section 10.13).

Risk factors and risk groups:

Cancer patients in the end stage of their malignant disease are often subject to multiple medicinal therapies with different ways of drug administration.

Preventability:

The potential risk of medication error through administration via the i.v. use is minimised by displaying the route of administration in a prominent way on all components of the primary and secondary packaging material. In addition, peelable warning stickers are provided displaying the text "Diluted Korjuny. Intraperitoneal use only." that must be attached to the 50 mL administration syringe containing the diluted Korjuny solution for i.p. infusion.

Impact on the risk-benefit balance of the product:

Spontaneous reports of accidental i.v. infusion instead of i.p. have been received post-marketing. The prominent display of the route of administration in the primary and secondary packaging and warning sticker are considered adequate to mitigate the risk of accidental i.v. infusion, and therefore, the risk-benefit balance remains favourable.

Public health impact:

No impact on public health.

SVII.3.2. Presentation of the missing information

Missing information: Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases

Evidence source:

Patients with at least severe hepatic dysfunction or with at least 70% of the liver metastasized were not included in the clinical development program.

Population in need of further characterisation:

Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases.

Part II: Module SVIII - Summary of the safety concerns

A summary of safety concerns for Korjuny is provided in Table SVIII.1.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Cytokine release syndrome (CRS)/Systemic inflammatory response syndrome (SIRS)
Important potential risks	More severe adverse reactions due to accidental i.v. infusions instead of i.p.
Missing information	Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

- **Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases;**

Specific questionnaires will be used to collect data to help further characterise and/or closely monitor each of the respective safety concerns specified above.

This form is provided in Annex 4.

Other forms of routine pharmacovigilance activities for <safety concerns>: none

III.2 Additional pharmacovigilance activities

None.

III.3 Summary table of additional pharmacovigilance activities

Not applicable. There are no additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

Not applicable. There are no planned post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Cytokine release syndrome (CRS)/Systemic inflammatory response syndrome (SIRS)	Routine risk communication: SmPC Sections 4.2, 4.4, 4.8 PIL Sections 2, 3, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for patient supervision after end of Korjuny infusion are included in SmPC Section 4.2 Recommendations on the use of medication for the prophylactic treatment of cytokine release symptoms are included in SmPC Section 4.2 Recommendations to ensure circulatory stability before treatment are included in SmPC Section 4.4 Recommendation to counsel patients to seek immediate medical attention if signs or symptoms of CRS/SIRS occur at any time are included in SmPC, Section 4.4 Recommendations to monitoring of patient after end of Korjuny infusion are included in SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: restricted prescription
More severe adverse reactions due to	Routine risk communication:

accidental i.v. infusions instead of i.p.	SmPC Sections 4.2, 4.4, 6.6 PIL Section 3 Warning sticker for the syringe containing the diluted Korjuny solution indicating the name (Korjuny) and route of application (i.p.) Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted prescription
Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases	Routine risk communication: SmPC Sections 4.2, 4.4 PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: restricted prescription

V.2. Additional risk minimisation measures

Additional risk minimisation 1: Patient card

Objectives:

To remind patients of the risk of CRS/SIRS and to alert healthcare professionals, and in particular, those who have not prescribed the product, that the patient has received Korjuny and to provide the contact details of the prescribing physician.

Rationale for the additional risk minimisation activity:

The patient card is intended to remind patients of the key signs and symptoms of CRS/SIRS and when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or SIRS present themselves. In addition, patients are instructed to present the card to inform healthcare professionals, and in particular those who have not prescribed the product, on the risk of CRS/SIRS with Korjuny and provide the contact details of the prescribing physician.

Target audience and planned distribution path:

The target audience is the patient. The patient card will be distributed to all relevant prescribers. The prescriber will complete the prescriber's contact details and the patient card will be handed to the patients by the prescriber.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be measured by the number and outcome of reports of CRS/SIRS notified to the marketing authorisation holder (MAH). Proposed review period: PSURs.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cytokine release syndrome (CRS)/Systemic inflammatory response syndrome (SIRS)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8 SmPC Section 4.2, where recommendations are given on patient supervision and advice on use of medication for the prophylactic treatment of cytokine release symptoms SmPC Section 4.4 where recommendations are given to ensure circulatory stability before treatment, on patient counselling, and on post-treatment monitoring PIL Sections 2, 3, 4 Additional risk minimisation measures: Patient card	None
More severe adverse reactions due to accidental i.v. infusions instead of i.p.	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 6.6 PIL Section 3 Warning sticker for the syringe containing the diluted Korjuny solution indicating the name (Korjuny) and route of application (i.p.)	None
Patients with at least severe hepatic dysfunction and/or with at least 70% of the	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal

Safety concern	Risk minimisation measures	Pharmacovigilance activities
liver affected by metastases	PIL Section 2	detection: Specific follow-up questionnaire

Part VI: Summary of the risk management plan

Summary of risk management plan for Korjuny (catumaxomab)

This is a summary of the risk management plan (RMP) for Korjuny. The RMP details important risks of Korjuny, how these risks can be minimised, and how more information will be obtained about Korjuny's risks and uncertainties (missing information).

Korjuny's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Korjuny should be used.

This summary of the RMP for Korjuny should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Korjuny's RMP.

I. The medicine and what it is used for

Korjuny is authorised for the intraperitoneal (i.p.) treatment of malignant ascites in adults with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, who are not eligible for further systemic anticancer therapy (see SmPC for the full indication). It contains catumaxomab as the active substance and it is given by the i.p. route of administration.

Further information about the evaluation of Korjuny's benefits can be found in Korjuny's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Korjuny, together with measures to minimise such risks and the proposed studies for learning more about Korjuny's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Korjuny, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Korjuny is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Korjuny are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Korjuny. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Cytokine release syndrome (CRS)/Systemic inflammatory response syndrome (SIRS)
Important potential risks	More severe adverse reactions due to accidental i.v. infusions instead of i.p.
Missing information	Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases

II.B Summary of important risks

Important identified risk: Cytokine release syndrome (CRS)/Systemic inflammatory response syndrome (SIRS)	
Evidence for linking the risk to the medicine	Due to catumaxomab's mechanism of action, side effects in line with the cytokine release induced by catumaxomab may be expected. Cytokine release related clinical symptoms have been reported during and after catumaxomab's administration, including events of fever, hypotension, gastrointestinal symptoms, headache, myalgia, arthralgia, tachycardia, chills, respiratory symptoms, skin symptoms, and fatigue. Isolated incidence of SIRS (with concurrent fever, increased heart rate and respiratory rate, and abnormal leukocyte count) have been reported in association with catumaxomab administration.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures:

	SmPC Sections 4.2, 4.4, and 4.8 SmPC Section 4.2, where recommendations are given on patient supervision and advice on use of medication for the prophylactic treatment of cytokine release symptoms SmPC Section 4.4 where recommendations are given to ensure circulatory stability before treatment, on patient counselling, and on post-treatment monitoring PIL Sections 2, 3, 4 Additional risk minimisation measures: Patient card

Important potential risk: More severe adverse reactions due to accidental i.v. infusions instead of i.p.	
Evidence for linking the risk to the medicine	Spontaneous reports of accidental i.v. infusion instead of i.p. have been reported from marketed use of catumaxomab.
Risk factors and risk groups	Cancer patients in the end stage of their malignant disease are often subject to multiple medicinal therapies with different ways of drug administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 6.6 PIL Section 3 Warning sticker for the syringe containing the diluted Korjuny solution indicating the name (Korjuny) and route of application (i.p.)

Missing information: Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4 PIL Section 2

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Korjuny.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Korjuny.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Annex 7 - Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Annex 4 - Specific adverse drug reaction follow-up forms

Table of contents

Follow-up forms

Catumaxomab – QUESTIONNAIRE
Severe hepatic dysfunction and/or at least 70% liver metastases

There is only limited information available for patients treated with Catumaxomab who have severe hepatic dysfunction and/ or at least 70% liver metastases. With this questionnaire, we are therefore requesting additional information which will help us to better understand the use of Catumaxomab in patients with these conditions.

Reporter

Name of Reporter completing this form: ……..

Health Care Provider? ☐ Yes, specify speciality: ……

☐ No Specify: ……

Phone Number: …… Fax Number: ……..…

Address: …… Email Address: ……..…

……

……

Patient and Treatment Information

Gender	Age (years)	Indication for Catumaxomab/ Description of underlying disease
☐ Female ☐ Male ☐ Diverse		☐ Malignant Ascites ☐ Other, please specify: _____ Date of diagnosis (malignant ascites): _____ (dd-mmm-yyyy) Tumor type: _____ Date of tumor diagnosis: _____ (dd-mmm-yyyy)

Trade name/ INN	Mode of application	Therapy dates (from – to) & dosage
KORJUNY/ Catumaxomab	☐ **intraperitoneal (as per SmPC)** ☐ Other, please specify: _____	Date (dd-mmm-yyyy) / Dosage (µg) / Comment(s) 1st dose: _____ 2nd dose: _____ 3rd dose: _____ 4th dose: _____

Was pre-medication administered prior to Catumaxomab i.p. infusion?

Prior to:	Date (dd-mmm-yyyy)	Pre-medication (indicate medicinal product or INN)	Dosage
1st dose:			
2nd dose:			
3rd dose:			
4th dose:			

Was any of the following medication administered in addition to the pre-medication regimen during Catumaxomab therapy:

☐ Analgesics, please specify: ……..

☐ Antipyretics, please specify: ……

☐ Non-steroidal antiphlogistics, please specify: ……

Catumaxomab – QUESTIONNAIRE
Severe hepatic dysfunction and/or at least 70% liver metastases

General Information on the Severe Hepatic Dysfunction

Please describe the underlying hepatic dysfunction and its (suspected) cause:

☐ Pre-existing non-malignant hepatic impairment, please specify: ……..
……
……

☐ Hepatic impairment due to underlying malignancy, please specify: ……..
……
……

Risk Factors

Did the patient have any risk factors in addition to the malignancy contributing to the hepatic dysfunction?

☐ Liver cirrhosis
☐ Other hepatobiliary disorder(s), please specify: ……
……
……
……
……
……
……
……

Hepatic Status of Patient

Extent of liver metastases:

☐ 0-25% ☐ 26-50% ☐ 51-70% ☐ ≥71% ☐ unknown:

Prior to Catumaxomab Therapy	**Shortly after last Catumaxomab Therapy**
Encephalopathy	**Encephalopathy**
☐ None	☐ None
☐ Grade 1: Altered mood/ confusion	☐ Grade 1: Altered mood/ confusion
☐ Grade 2: Inappropriate behavior, impending stupor, somnolence	☐ Grade 2: Inappropriate behavior, impending stupor, somnolence
☐ Grade 3: Markedly confused, stuporous but arousable	☐ Grade 3: Markedly confused, stuporous but arousable
☐ Grade 4: Comatose/ unresponive	☐ Grade 4: Comatose/ unresponive
☐ unknown	☐ unknown
Ascites	**Ascites**
☐ Absent	☐ Absent
☐ Slight	☐ Slight
☐ Moderate	☐ Moderate
☐ unknown	☐ unknown
Bilirubin	**Bilirubin**
☐ <2mg/dL	☐ <2mg/dL
☐ 2-3mg/dL	☐ 2-3mg/dL
☐ >3mg/ dL	☐ >3mg/ dL
☐ unknown	☐ unknown

Catumaxomab – QUESTIONNAIRE
Severe hepatic dysfunction and/or at least 70% liver metastases

Prior to Catumaxomab Therapy	Shortly after last Catumaxomab Therapy
Albumin ☐ >3.5g/dL ☐ 2.8-3.5g/dL ☐ <2.8g/dL ☐ unknown **Prothrombin time prolongation** ☐ Less than 4 seconds above control/ INR <1.7 ☐ 4-6 seconds above control/ INR 1.7-2.3 ☐ More than 6 seconds above control/ INR >2.3 ☐ unknown	**Albumin** ☐ >3.5g/dL ☐ 2.8-3.5g/dL ☐ <2.8g/dL ☐ unknown **Prothrombin time prolongation** ☐ Less than 4 seconds above control/ INR <1.7 ☐ 4-6 seconds above control/ INR 1.7-2.3 ☐ More than 6 seconds above control/ INR >2.3 ☐ unknown

	Prior to Catumaxomab Therapy	Shortly after Catumaxomab Therapy	>2 Weeks after Catumaxomab Therapy
ALT (GPT)	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……
AST (GOT)	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……
AP	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……
GGT	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……
LDH	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……	Date (dd-mmm-yyyy): …… Value (with unit): ……

Further comments:

……

……

……

Please return the completed form to:

safety@fgk-pv.com

Thank you very much for your cooperation!

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Approved key messages of the additional risk minimisation measures

Patient card:

The patient card contains 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.