National Institute for Health and Care Excellence

Health Technology Evaluation

Catumaxomab for intraperitoneal treatment of malignant ascites in epithelial cellular adhesion molecule-positive carcinomas when further systemic anticancer treatment is unsuitable [ID6580]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Pharmanovia	Evaluating this topic via the Single Technology Appraisal (STA) route is appropriate and aligns well with the need to provide patients with epithelial cellular adhesion molecule (EpCAM) positive malignant ascites access to an innovative and targeted treatment in a timely manner.	Thank you for your comment. No action needed.
	Breast Cancer Now	We welcome an appraisal of this treatment. Malignant ascites can have a major impact on quality of life for some people in the late stages of living with secondary breast cancer. This condition may particularly affect those with lobular breast cancer which typically metastasises to the perotineum. Additional treatment options will be valued.	Thank you for your comment. No action needed.
	METUP UK	This is an appropriate evaluation	Thank you for your comment. No action needed.
Wording	Pharmanovia	Pharmanovia suggests the following alternative wording which aligns with the anticipated marketing authorisation for catumaxomab: “To appraise the	Thank you for your comment. The scope is

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		clinical and cost-effectiveness of catumaxomab within its marketing authorisation for **intraperitoneal** treatment in **adults** with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, who are not eligible for further systemic anticancer therapy.”	intended to provide a brief overview, so, additional information has not been included. No action needed.
	Breast Cancer Now	Yes	Thank you for your comment. No action needed.
	METUP UK	No comments	Thank you for your comment. No action needed.
Additional comments on the draft remit: Timing	Pharmanovia	Current treatments for patients with malignant ascites focus on drainage of ascitic fluid providing immediate yet temporary palliation of symptoms. Patients with EpCAM+ malignant ascites do not have access to any targeted treatments which address the underlying causes of malignant ascites. Therefore, there is a high unmet need for additional treatment options in this currently underserved space.	Thank you for your comment. No action needed.
	Breast Cancer Now	Malignant ascites can have a significant impact on quality of life so the approval of new treatments is of high urgency	Thank you for your comment. No action needed.
	METUP UK	No comments	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pharmanovia	The following are suggested wording changes and corrections to be considered for accuracy. **Background, paragraph 1, lines 1 to 3, change to:** Malignant ascites is caused by cancer that originates in epithelial tissues, including those of the stomach, liver, bladder, bowel, pancreas, ovaries, endometrium and uterus. People with lung or breast cancer can also develop malignant ascites. **Background, paragraph 1, line 4, change:** (peritoneum) **to** (peritoneal cavity). **Background, paragraph 1, line 5 change to:** In patients with malignant ascites, fluid-up occurs when too much fluid enters the cavity from the surrounding blood vessels, which are 'leaky' as a result of the patient's cancer. **Background, paragraph 1, line 6, change to:** This build-up is worsened by cancer cells which have spread to the lining of peritoneal cavity (the peritoneum). Cancer cells that grow along the lining prevent fluid being drained away by nearby lymph vessels. **Background, paragraph 2, line 2 to 3, change to:** Ovarian cancer is the most common cause of malignant ascites (37% of people with malignant ascites have ovarian cancer). **Background, paragraph 2, line 3, change to:** Malignant ascites is more common in cancers that develop in females (such as ovarian and uterine cancer), therefore the majority of people with malignant ascites are women. **Background, paragraph 3, line 4:**	Thank you for your comment. The scope has been amended to state malignant ascites is caused by cancers that originate in epithelial tissues, including those of the stomach, liver, bladder, bowel, pancreas, ovaries, endometrium and uterus. People with lung and breast cancer can also develop malignant ascites. The scope has been amended to include peritoneal cavity. The scope is intended to provide a brief overview, so, additional information has not been included. The treatment pathway is kept inclusive at this stage. No action needed.

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		Remove diuretics as a standard form of management; diuretics are effective in treatment of ascites due to liver disease (e.g., cirrhosis) but considered ineffective for the treatment of ascites caused by malignancy. **Background, paragraph 3, line 5, correct spelling:** reccomends **to** recommends. **The technology, paragraph 1, line 4: Delete 'have' from this sentence:** '…….people with malignant ascites and have EpCAM positive carcinoma.'	Diuretics have now been removed from the background information. Thank you we have corrected the spelling mistake and removed 'have' from the sentence.
	Breast Cancer Now	We believe this information is complete and accurate	Thank you for your comment. No action needed.
	METUP UK	No comments	Thank you for your comment. No action needed.
	Ovarian Cancer Action	Consider adding detail as to the impact of malignant ascites in terms of symptoms, and the day-to-day impact of repeated draining on the quality of life of patient, and family.	Thank you for your comment. The scope has been amended.
	The Royal College of Pathologists	Some malignant ascites arises when the primary site of the carcinoma is unknown (carcinoma of unknown primary - CUP). Also, malignant tumours that are not carcinomas may give rise to ascites. Most of these are rare or uncommon, for example peritoneal mesothelioma.	Thank you for your comment. The background section of the scope is kept brief therefore the scope has not been amended.
Population	Pharmanovia	The population is aligned with the anticipated licensed population.	Thank you for your comment. No action needed.

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	Breast Cancer Now	Yes	Thank you for your comment. No action needed.
	METUP UK	No comments	Thank you for your comment. No action needed.
	The Royal College of Pathologists	From a pathology point of view, this is the key issue. The population is defined as “EpCAM-positive carcinomas” and one of the questions to be considered is “Are cancers in England routinely tested for EpCAM expression?” When a patient presents with ascites, the first investigation is generally to tap some fluid and examine the stained cells under the microscope (diagnostic cytopathology). Occasionally, biopsy may be the first investigation. In either case, if there is a high suspicion of malignancy, immunocytochemistry is generally carried out to type the cells. This involves applying antibodies to the cells or tissue on the slides, the antibodies having been raised against specific antigens which characterise particular cell subsets. The antibodies most commonly used to infer epithelial differentiation of atypical cells in a serous effusion (and therefore a diagnosis of carcinoma, rather than mesothelioma or a benign mesothelial proliferation) are MOC31 and BerEp4. Both of these are antibodies to EpCAM alt So, to summarise: Carcinomas in ascitic fluids are commonly tested with anti-EpCAM antibodies but this is to make the diagnosis of carcinoma in the first place, not to further characterise it after diagnosis There are a number of anti-EpCAM antibodies available, reactivity will vary with different tumours and not all tumours from a particular site will necessary have the same reactivity. The challenge will be to define what constitutes “positivity” Tumours other than carcinomas may uncommonly show positivity with anti-EpCAM antibodies	Thank you for your comment. No action needed.

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Subgroups	Pharmanovia	Pharmanovia does not foresee there being subgroups for separate consideration. This is because catumaxomab targets EpCAM-positive tumour cells that have metastasised to the peritoneum irrespective of primary tumour type or other clinical parameters.	Thank you for your comment. The subgroup section is kept inclusive at this stage. No action needed.
	Breast Cancer Now	The original clinical trial considered those with ovarian cancer as a separate sub-group	Thank you for your comment. No action needed.
	METUP UK	No comments	Thank you for your comment. No action needed.
Comparators	Pharmanovia	Paracentesis (also referred to as large volume paracentesis, or 'LVP') is the established clinical management for patients with malignant ascites in the UK and is the only relevant comparator for catumaxomab. Conversely, the following are mentioned as treatments in the background section but are not comparators: • Diuretics are not effective in the treatment of malignant ascites and hence are not standard management for the condition. Rather, diuretics are used to treat non-malignant ascites, which have a different pathophysiology and are more likely to respond to diuretics compared with malignant ascites. • The proposed indication for catumaxomab is in people who are no longer eligible for further systemic treatments. Systemic anti-cancer therapy is therefore not a comparator.	Thank you for your comment. The treatment pathway in the background section is kept inclusive at this stage. No action needed.

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		• PeritX is recommended for people with malignant ascites who have received at least two prior LVPs within a short period of time (typically within one month). It is proposed that catumaxomab is used earlier in the treatment pathway.	
	Breast Cancer Now	Yes	Thank you for your comment. No action needed.
	METUP UK	None listed because depends on cancer type.	Thank you for your comment. No action needed.
Outcomes	Pharmanovia	Yes, the outcomes are appropriate.	Thank you for your comment. No action needed.
	Breast Cancer Now	Yes	Thank you for your comment. No action needed.
Equality	Pharmanovia	Based on evidence gathered from clinical experts in the UK, there is inequality in access to current standards of care for people with recurrent malignant ascites. Under the NHS, paracentesis can be offered as a day-case service. However, sporadic availability to day-case paracentesis clinics across the UK means some people with recurrent malignant ascites receive paracentesis as a hospital inpatient. People with recurrent malignant ascites are nearing the end-of life, with only months or weeks left to live, a time when medical appointments should be minimised in an effort to preserve quality of life (NG142). Treatment with catumaxomab significantly increases the time to	Thank you for your comment. Any equality issues will be considered by the committee. Treatment availability based on geographical location is outside of the remit of a NICE technology

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		next symptomatic recurrence and so extends the amount of time spent out of hospital for the purpose of paracentesis. Catumaxomab can therefore address the unmet clinical needs of people with recurrent malignant ascites who have inadequate access to current standards of care.	appraisal. No action needed.
	Breast Cancer Now	None that we are aware of	Thank you for your comment. No action needed.
	METUP UK	No comments	Thank you for your comment. No action needed.
Other considerations	Breast Cancer Now	The logistics of administering this drug may be challenging as it requires a 3-6 hour infusion on days 0, 3, 7 and 10.	Thank you for your comment. No action needed.
	METUP UK	No comments	Thank you for your comment.
Questions for consultation	Pharmanovia	**Where do you consider catumaxomab will fit into the existing care pathway for malignant ascites caused by epithelial cellular adhesion molecule-positive carcinoma?** Current treatment pathway: In alignment with current guidance, and validated by key opinion leaders, the following sequence represents the current treatment pathway for people with malignant ascites in the UK: First occurrence of malignant ascites: treatment with an appropriate systemic therapy for the type of primary cancer First recurrence: LVP Second recurrence: LVP	Thank you for your comment. No action needed.

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		Further recurrences: LVP. In some cases, and if locally available, an indwelling intraperitoneal catheter (IPC) may be offered to patients who have required at least two LVPs and in rapid succession (within a month) and who express a preference for the indwelling IPC device over LVP. Patients must also have adequate support for safe and effective use of an indwelling IPC at home. Positioning: It is anticipated EpCAM status would be determined at step 2 of the pathway (LVP for first recurrence). Catumaxomab would then be positioned at step 3 (at the time of second recurrence for patients with confirmed EpCAMpositivity). **Would the effectiveness of catumaxomab be affected by primary tumour site?** In the pivotal Phase II/III trial and a subsequent Phase III study, catumaxomab was used to treat malignant ascites in patients with different types of primary epithelial tumour. Primary and secondary efficacy endpoints (puncture-free survival [PuFS] and time-to-next puncture [TTPu] were significantly longer among patients in the catumaxomab treatment arm irrespective of primary tumour site. Based on these data, it is not expected that the effectiveness of catumaxomab will vary with primary tumour type. **Would catumaxomab be used alongside established clinical management or would be catumaxomab be used with paracentesis only?** Catumaxomab is administered by intraperitoneal infusion via a temporary IPC. The same IPC is used to drain the ascitic fluid at the time of each administration and is removed after the final administration. Any subsequent drainage following the final administration of catumaxomab (should it be required) is performed using LVP, which is established clinical management for this patient population. **Are cancers in England routinely tested for EpCAM expression?**	

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		Although EpCAM is highly expressed across a range of epithelial cancers, there is no routine testing in place in the UK. EpCAM testing of ascitic fluid samples to determine patient eligibility for catumaxomab will be carried out through a validated assay and will be fully funded by Pharmanovia. Pharmanovia will also manage logistical aspects of transferring specimens in a timely manner to facilities authorised to perform the validated test, therefore the addition of the EpCAM testing for catumaxomab would not incur any additional costs to the NHS. Please select from the following, will catumaxomab be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. **Would catumaxomab be a candidate for managed access?** It is not currently anticipated that catumaxomab will be a candidate for managed access. **Do you consider that the use of catumaxomab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Most health-related benefits will be captured in the QALY calculation. Korjuny prolongs the time to next paracentesis, which reflects the delay in ascitic fluid reaccumulation. Since fluid reaccumulation is directly linked to debilitating symptoms that significantly impair patients' ability to carry out everyday tasks, engage socially, and participate in activities they enjoy, this delay may lead to meaningful improvements not fully captured in utility scores. As there is a lack of targeted treatments for EpCAM+ malignant ascites, the introduction of catumaxomab would provide patients and clinicians with a	

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		treatment alternative that addresses the underlying disease, thereby covering a significant unmet clinical need.	
	Breast Cancer Now	**Where do you consider catumaxomab will fit into the existing care pathway for malignant ascites caused by epithelial cellular adhesion molecule-positive carcinoma?** We understand that catumaxomab would be used in patients with advanced disease who are no longer receiving SACT. **Would the effectiveness of catumaxomab be affected by primary tumour site?** We are not aware of any data testing this. **Would catumaxomab be used alongside established clinical management or would catumaxomab be used with paracentesis only?** We understand that catumaxomab would be used only after other SACT options have been exhausted. We are not clear whether it would be used alongside or in place of other aspects of clinical management. **Are cancers in England routinely tested for EpCAM expression?** We are not aware of breast cancers currently being tested for EpCAM expression Please select from the following, will catumaxomab be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Standard clinical management for advanced cancers for those requiring paracentesis will usually take place in secondary care. Those no longer	Thank you for your comment. No action needed.

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		receiving active treatment for their cancer may be treated by primary care and hospice. **Would catumaxomab be a candidate for managed access?** No comments **Do you consider that the use of catumaxomab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** No comments Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. No comments	
	METUP UK	EpCAM expression is not routinely tested within the NHS. I would like more information about testing and the capacity of the NHS to test for EpCAM overexpression in a wide variety of cancer types.	Thank you for your comment. No action needed.
Additional comments on the draft scope	Pharmanovia	We do not believe that Haemochromatosis UK is a relevant patient organisation for this appraisal	Thank you for your comment. The stakeholder list has been amended.
	METUP UK	As a lay commentator, the scope does not explicitly mention that the treatment is given by intraperitoneal infusion, which could be relevant to patients.	Thank you for your comment. No action needed.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope