HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 December 2009

REMOVAB 10 microgram concentrate for infusion solution
Carton containing 1 pre-filled syringe (CIP: 575 535-8)
REMOVAB 50 microgram concentrate for infusion solution
Carton containing 1 pre-filled syringe (CIP: 575 536-4)

Applicant: FRESENIUS BIOTECH GMBH

catumaxomab

ATC code: L01XC09

List I
Medicinal product reserved for hospital use. Prescription restricted to oncology or haematology specialists or doctors with cancer training.

Date of the centralised Marketing Authorisation: 20 April 2009

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

catumaxomab

1.2 Background

Catumaxomab is a rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule (EpCAM) and the CD3 antigen. The EpCAM antigen is overexpressed in most carcinomas. CD3 is expressed on mature T-cells as a component of the T-cell receptor.

1.3 Indication

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

1.4 Dosage

“REMOVAB dosing schedule comprises the following four intraperitoneal infusions:
1st dose: 10 microgram on day 0
2nd dose: 20 microgram on day 3
3rd dose: 50 microgram on day 7
4th dose: 150 microgram on day 10
An interval of at least two days must elapse between infusions. The interval between the infusion days can be prolonged in the event of relevant adverse reactions. The overall treatment period should not exceed 20 days. No dose reductions of REMOVAB were investigated during clinical trials.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XC	Monoclonal antibodies
L01XC09	Catumaxomab

2.2. Medicines in the same therapeutic category

None.

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

The dossier submitted includes 3 non-comparative phase II studies and one comparative study (IP-REM-AC-01). Only the comparative study is analysed below.

3.1. Efficacy

Randomised, open-label Phase II/III study (IP-REM-AC-01) which compared the efficacy and safety of REMOVAB plus paracentesis versus paracentesis alone in 258 patients with symptomatic malignant ascites caused by an EpCAM-positive carcinoma[1]. Patients were included only if they were not eligible for systemic chemotherapy.

REMOVAB was administered as four intraperitoneal infusions in escalating doses of 10 (day 0), 20 (day 3), 50 (day 7) and 150 (day 10) micrograms.

The primary efficacy endpoint was puncture-free survival, defined as the time to first need for therapeutic ascites puncture or death, whichever occurred first.

The secondary endpoints were overall survival, progression-free survival, tumour response and assessment of ascites signs and symptoms.

Inclusion criteria:
- Histologically confirmed cancer
- Presence of symptomatic malignant ascites
- Presence of tumour cells expressing EpCAM in the ascites fluid
- Karnofsky index ≥ 60%
- Life expectancy > 8 weeks
- Therapeutic ascites puncture within 5 weeks before inclusion in the study
- Cancer refractory/resistant to chemotherapy.

Results:
The available results are the outcome of a 4-month follow-up period. Beyond this period, the patients in the control group who had had at least one therapeutic ascites puncture were treated with REMOVAB.
The median age of the patients was almost 59. About 63% of the patients had had just one ascites puncture previously.
Because of differences in prognosis[2], the patients were stratified into 2 groups: ascites caused by ovarian cancer (n=129) and ascites associated with non-ovarian cancer (n=129). Among the patients with non-ovarian cancer, 51% had gastric cancer, 10% breast cancer, 7% pancreatic cancer, 6% colorectal cancer and 26% other types of epithelial cancer.

[1] the EpCAM antigen is overexpressed in most carcinomas
[2] the presence of ascites does not always affect the prognosis adversely in ovarian cancer and may be observed in the first stage of the disease (FIGO stage Ic)

Table 1: Efficacy results (puncture-free survival and time to first need for therapeutic ascites puncture) of study IP-REM-AC-01

	Paracentesis + REMOVAB (n = 170)	**Paracentesis alone (n = 88)**
Median puncture-free survival (days)	46	11
95% CI for median (days)	[31; 49]	[9; 16]
p value (log-rank test)	< 0.0001	
Hazard ratio (HR)	0.310	
95% CI for HR	[0.228; 0.423]	
Median time to first need for therapeutic ascites puncture (days)	77	13
95% CI for median (days)	[62; 104]	[9; 17]
p value (log-rank test)	< 0.0001	
Hazard ratio (HR)	0.169	
95% CI for HR	[0.114; 0.251]	

The average difference between the treatment groups in terms of puncture-free survival (primary endpoint) was 35 days (95% CI: [25; 45]; p <0.0001).
In all analysis groups, this time was longer in the REMOVAB group than in the control group. For the subgroup of patients with ovarian cancer, the average difference between the groups was 41 days (95% IC: [32; 50]), and for the subgroup of patients with non-ovarian cancer 23 days (95% CI: [8; 38]).

Overall survival:
The median overall survival did not differ between the two groups: 72 days in the REMOVAB group compared with 68 days in the control group.

Progression-free survival:
No pooled analysis was carried out for this efficacy parameter. For the patients with ovarian cancer, the median progression-free survival was significantly longer in the catumaxomab group than in the control group (p <0.0001). For all non-ovarian cancer patients, no statistically significant difference was observed.

Tumour response:
No pooled analysis was carried out for this efficacy parameter. For the subgroups, the results for tumour response rates according to the RECIST criteria were inconclusive owing to the small number of patients with measurable tumours and the short follow-up in the control group.

Ascites signs and symptoms:
The proportion of patients with no ascites signs or symptoms 8 days after the last injection or the last puncture was 71% in the REMOVAB group and 59% in the control group. These results must be interpreted with caution, however, because of a difference in the number of punctures performed in each of the groups; the patients in the REMOVAB group had four times as many punctures as those in the control group.

In view of the methodology of the study (open-label), the quality of life data are difficult to interpret.
About 98% of the patients in the REMOVAB group were admitted to hospital for a median period of 11 days.

3.2. Tolerance

Discontinuation of treatment because of an adverse event was observed in 7% of the patients in the REMOVAB group. The most common adverse effects were related to cytokine release. These reactions were observed commonly during and after infusion of REMOVAB. They were of grade 1 or 2 severity and were completely reversible. Grade 3 fever (5%), vomiting (3.9%), nausea (2.3%), dyspnoea (1.6%), hypotension (1.2%), hypertension (0.8%) and chills (0.8%) were reported. Cases of grade 4 dyspnoea and hypotension were also reported in one patient each.

3.3. Conclusion

The efficacy and safety of REMOVAB were assessed in a randomised open-label study in 258 patients with symptomatic malignant ascites caused by an EpCAM-positive carcinoma. The objective of the study was to compare REMOVAB plus paracentesis with paracentesis alone. Patients were included only if they were not eligible for systemic chemotherapy. About 60% of the patients had had just one ascites puncture previously.

REMOVAB was administered as four intraperitoneal infusions, each preceded by one puncture, in escalating doses of 10 (day 0), 20 (day 3), 50 (day 7) and 150 (day 10) micrograms, requiring 11 days of hospitalisation.

Puncture-free survival (primary endpoint) was significantly longer in the REMOVAB group than in the control group. In the pooled analysis, the average difference between the groups was 35 days (95% CI [25; 45]; $p < 0.0001$). In the subgroup of patients with ovarian cancer, the average difference between the groups was 41 days (95% CI [32; 50]), and in the subgroup of patients with non-ovarian cancer 23 days (95% CI: [8; 38]).

Median overall survival did not differ between the two groups: 72 days in the REMOVAB group compared with 68 days in the control group.

No pooled analysis was performed for progression-free survival and tumour response.

After a follow-up of 4 months, the patients in the control group who had had at least one therapeutic ascites puncture were treated with REMOVAB. Because of the short follow-up, it was not possible to assess the number of punctures avoided.

The most common adverse effects were related to cytokine release (fever, nausea, vomiting, hypotension). These reactions, commonly observed after infusion of REMOVAB, were of mild severity (grade 1 or 2) and transitory.

The committee notes:

- punctures numbering 4 with REMOVAB compared with 1 in the control group
- a short follow-up period for the study (4 months)
- the large number of patients included at an early stage of peritoneal involvement (around two thirds had previously had only one ascites puncture)
- the need for 11 days of hospitalisation for administration of the treatment while no evidence is available of an improvement in the quality of life for these patients
- the absence of data on repeat administration of the treatment, notably in ascites of ovarian origin, the progression of which may take several months

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Malignant ascites, a sign of advanced cancer, is often encountered at the metastatic stage. It is a serious condition, the complications of which (respiratory distress, intestinal occlusion) may be life-threatening.
These medicinal products are intended as palliative therapy.
This is a local intraperitoneal treatment for patients who are not eligible for systemic chemotherapy.
Validated alternative medicinal products do not exist.
The efficacy/adverse effects ratio is low.

Public health benefit:

The burden represented by malignant ascites at an advanced stage of epithelial cancer is difficult to quantify.

Improving the management of patients with cancer and their quality of life constitutes a public health need which comes within the scope of the established priorities (Public Health Law 2004, Cancer Plan, Plan for improving the quality of life of patients with chronic diseases).

In view of the inadequate nature of the evidence (a single Phase II/III study with an imbalance between the groups in terms of the number of punctures performed, cross-over and insufficient follow-up) and the length of the in-patient stay required for implementation of the treatment, it is not possible to presume that REMOVAB will have an impact on the quality of life of the patients treated. Furthermore, no impact has been demonstrated in terms of mortality.

In addition, the transferability of the results is not assured. The profile of the patients in daily practice will probably differ from that of the patients included in the study (notably because of the small number of previous ascites punctures).

Thus, REMOVAB is not therefore likely to meet the identified public health need.

Consequently, in the current state of knowledge, it is not expected that REMOVAB will benefit public health.

The actual benefit of these medicinal products is low.

4.2. Improvement in actual benefit (IAB)

REMOVAB does not provide an improvement in actual benefit in the management of malignant ascites in patients with EpCAM-positive carcinomas when the standard treatment is not available or when it is no longer feasible.

4.3. Therapeutic use

The treatment of malignant ascites depends on whether or not the primary tumour is sensitive to systemic chemotherapy. Where there is a response, a reduction in ascites production and relief of symptoms can be achieved. However, most patients with ascites have already had several lines of treatment and their disease has become refractory to systemic chemotherapy.

Intraperitoneal chemotherapies can be administered in peritoneal carcinosis of gastro-intestinal (gastric, intestinal, rectal) or ovarian origin: in this type of cancer, intraperitoneal chemotherapy is used as an anti-tumour treatment (bleomycin, mitoxantrone)[3] [4] [5]. Its efficacy is modest, however, and there is no medicinal product with a Marketing Authorisation. At this disease stage, the standard treatment for malignant ascites is repeated puncture for symptomatic treatment.
REMOVAB constitutes an intraperitoneal treatment for recurrent neoplastic ascites not eligible for systemic treatment.

4.4. Target population

The target population for REMOVAB corresponds to patients with recurrent neoplastic ascites which is not eligible for systemic treatment, a Karnofsky score of > 60 and a life expectancy of > 8 weeks (in conformity with the pivotal study inclusion criteria).
According to the 2007 PMSI data, the number of patients who had recourse to evacuation of ascitic fluid of neoplastic origin was 3,600 patients and the number with recurrent ascites (number of in-patient stays $\geq$ 2) was 1,633 patients.
No accurate data is available on the percentage of patients not eligible for systemic chemotherapy, with a Karnofsky score of > 60 and a life expectancy of > 8 weeks. According to experts, it can be estimated to be about half of all cases.
The target population for REMOVAB can therefore be estimated at about 800 patients per year.

4.5. Transparency Committee Recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage in the Marketing Authorisation.

[3] Maiche AG. Management of peritoneal effusion with intracavitary mitoxantrone or bleomycin. Anticancer Drugs. 1994; 5:305-308.
[4] Ostrowski MJ, Halsall GM. Intracavitary bleomycin in the management of malignant effusions: a multicenter study. Cancer Treat Rep. 1982;66:1903-7.
[5] Rosenberg S, Courtney A, Nemcek AA Jr, Omary RA. Comparison of percutaneous management techniques for recurrent malignant ascites. J Vasc Interv Radiol. 2004;15(10):1129-31.