HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 July 2011

HALAVEN 0.44 mg/ml, solution for injection
B/1 vial of 5 ml containing 2 ml of solution (CIP code: 418 352-3)
B/6 vials of 5 ml containing 2 ml of solution (CIP code: 418 354-6)

Applicant: EISAI SAS

eribulin

ATC Code: L01XX41 (other antineoplastic agents)

List I
Medicine for hospital prescription only. Prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

Date of the Marketing Authorisation (centralised European procedure): 17 March 2011

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

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Eribulin

1.2. Background

Eribulin mesylate is a halichondrin type antineoplastic agent.

1.3. Indication

"HALAVEN is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease (see section 5.1 of the SPC).
Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments."

1.4. Dosage

"The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 of eribulin mesylate) which should be administered intravenously over two to five minutes on Days 1 and 8 of every 21-day cycle."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

L	:	antineoplastic and immunomodulating agents
L01	:	antineoplastic agents
L01X	:	other antineoplastic agents
L01XX	:	other antineoplastic agents
L01XX41	:	eribulin

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines:

None: there are no comparator medicines in the same therapeutic category

2.3. Medicines with a similar therapeutic aim

a) Cytotoxic medicinal products with the same indication:

- XELODA (capecitabine): "XELODA is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxane and anthracycline chemotherapy or when anthracycline chemotherapy is not indicated.
- NAVELBINE (vinorelbine) and its generics: Marketing Authorisation "Metastatic breast cancer"
- GEMZAR (gemcitabine) and its generics: “Gemcitabine, in combination with paclitaxel, indicated for the treatment of patients with locally advanced or metastatic breast cancer, in remission after adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated."

b) Other cytotoxic medicinal products used as monotherapy or for combination use for breast cancer.

- ADRIBLASTINA (doxorubicin) and its generics
- CAELYX (liposomal doxorubicin)
- FARMORUBICIN (epirubicin) and its generics
- NOVANTRONE (mitoxantrone) and its generics
- AMETYCINE (mitomycin C)
- AVASTIN (bevacizumab)
- HERCEPTIN (trastuzumab)
- TYVERB (lapatinib)
- FLUOROURACIL ICN (fluorouracil) and its generics
- METHOTREXATE BELLON (methotrexate) and its generics
- TAXOTERE (docetaxel)
- TAXOL (paclitaxel) and its generics
- ABRAXANE (paclitaxel)
- VELBE (vinblastine)

b) Hormone therapy: aromatase inhibitors, anti-oestrogen agents and progestins.

3 ANALYSIS OF AVAILABLE DATA

The file submitted includes two phase II studies (201 and 211) and a pivotal phase III study (EMBRACE – 305).

3.1. Efficacy

Study 201
The non-comparative phase II study assessed the efficacy and the tolerance of eribulin mesylate in patients with metastatic breast cancer previously treated with anthracyclines and taxanes. The patients had a measurable illness (according to the RECIST criteria), were in good general health (ECOG score ≤ 1) and had no neuropathy or a grade ≤ 2 neuropathy. The eligible population had seen a progression in their disease in the six months following the start of their last chemotherapy regimen.

The primary efficacy endpoint of the study was the percentage of overall response (full response + partial response).

The patients received eribulin mesylate (1.4 mg/m^2) intravenously over two to five minutes on Days 1, 8 and 15, every 28 days.
Due to neutropenia occurring at Day 15, the protocol was amended during the study: eribulin mesylate was administered at Day 1 and Day 8, every 21 days.

Results:
In the PP population (n=87), the percentage of overall response was 11.5%. The median duration of response was 5.6 months.
The median progression-free survival was 2.6 months and the median overall survival was nine months.
Grade 3-4 reactions linked to treatment, regardless of the treatment regimen, were neutropenia (64%), leucopoenia (18%), fatigue (5%), peripheral neuropathy (grade 3: 5% - grade 4: 0) and febrile neutropenia (4%).

Study 211
The non-comparative phase II study assessed the efficacy and the tolerance of eribulin mesylate in patients with metastatic breast cancer, previously treated with anthracyclines, taxanes and capecitabine. The patients had a measurable illness (according to the RECIST criteria), were in good general health (ECOG score ≤ 1) and had no neuropathy or a grade ≤ 2 neuropathy.
The eligible population received between two and five chemotherapy regimens and progressed in the six months following.

The patients received eribulin mesylate (1.4 mg/m^2) intravenously over two to five minutes on Days 1, and 8 every, 21 days.

Results:
The efficacy analysis was based on 269 of the 291 patients included. The percentage of overall response was 9.3% according to independent inspection and 14.1% according to the clinical investigator. The median duration of response was 4.1 months.
The median progression-free survival was 2.6 months and the median overall survival was 10.4 months.
Grade 3-4 reactions linked to treatment were neutropenia (54%), febrile neutropenia (5.5%), leucopoenia (14%) and asthenia/fatigue (10%; no grade 4).
Grade 3 peripheral neuropathy was observed in 6.9% of patients (no grade 4).

EMBRACE STUDY (305)

An open-label, randomised phase III study compared eribulin mesylate (HALAVEN) with an active treatment, left to the choice of the clinical investigator (Treatment of Physician's Choice or "TPC") with locally advanced or metastatic breast cancer who have had at least two failed chemotherapeutic regimens including anthracycline and taxane.
The patients were randomised 2:1 to receive one of the treatments:

- eribulin mesylate: 1.4 mg/m^2 in 2-5 min via IV at Day 1 and Day 8 every 21 days.
- TPC could be an active treatment (chemotherapy, hormone therapy and radiotherapy) or supportive care alone.

The patients were divided into strata based on:
- their HER2 status: positive, negative, unknown.
- a previous treatment with capecitabine: yes, no.
- their geographical region[1]:

The primary efficacy endpoint was overall survival, defined as the time between randomisation and the patients' death from any cause

The secondary endpoints were:

- progression-free survival, defined as the time between randomisation and the date of tumour progression or death from any cause.
- the objective response rate (complete and partial response)2
- the duration of response, defined as the time between the first documented evidence of a complete and/or partial response and the first documented sign of disease progression or death from any cause.
- tolerance

Inclusion criteria:

- patients at least 18 years old, in good general health (ECOG ≤ 2) with localised or metastatic breast cancer, confirmed by histology or cytology;
- have received between two and five chemotherapy regimens including one anthracycline and one taxane (except if contraindicated), and at least two regimens for advanced disease;
- refractory tumour at previous chemotherapy regimen, with progression under chemotherapy or in the six months following the last regimen;
- previous treatment with chemotherapy, radiotherapy, trastuzumab or hormone therapy must have been stopped three weeks before the administration of eribulin mesylate or TPC;
- life expectancy of at least three months;
- correct renal function with serum creatinine ≤ 2.0 mg/dl or creatinine clearance ≥ 40 ml/min according to the Cockroft and Gault formula;
- correct liver function with bilirubin ≤ 1.5 times the ULN (Upper Limit of Normal), alkaline phosphatase, ALT and AST ≤ 3 times ULN and ≤ 5 times the ULN in cases of liver metastases;
- normal haematopoietic function with an absolute neutrophil count ≥ 1.5x10^9/l, haemoglobin ≥ 10 g/dl and a platelet count ≥ 100 x10^9/l;

[1] - Region 1: North America, Western Europe, (i.e. Australia, Belgium, Canada, France, Germany, Italy, Spain, Switzerland, United Kingdom and the United States);
- Region 2: Eastern Europe (i.e. Croatia, Czech Republic, Hungary, Poland, Russia and Turkey) ;
- Region 3: Latin America, South Africa.

[2] RECIST criteria: evaluation of tumour response in solid tumours: full response (disappearance of target lesions), partial response (reduction by 30% of target lesions to their largest diameter), progression of the disease (increase by 20% of target lesions to their largest diameter) and stabilisation.

Results:

A total of 762 patients were included (508 eribulin mesylate, 254 TPC).
The median age of patients was 55 years and 75.9% were menopausal. Patients were in a good state of general health: ECOG score 0: 42% and ECOG 1: 48.6%.
Close to 82% of patients had a HER2 negative tumour. A HER2 positive tumour status was present for around 18% of patients. Patients with three tumour receptors (HER2, oestrogen and progesterone) were absent, "triple negatives" represented 19.8% of cases.

The TPC group consisted of chemotherapy in 97% of cases (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy agents) or hormone therapy in 3% of cases.

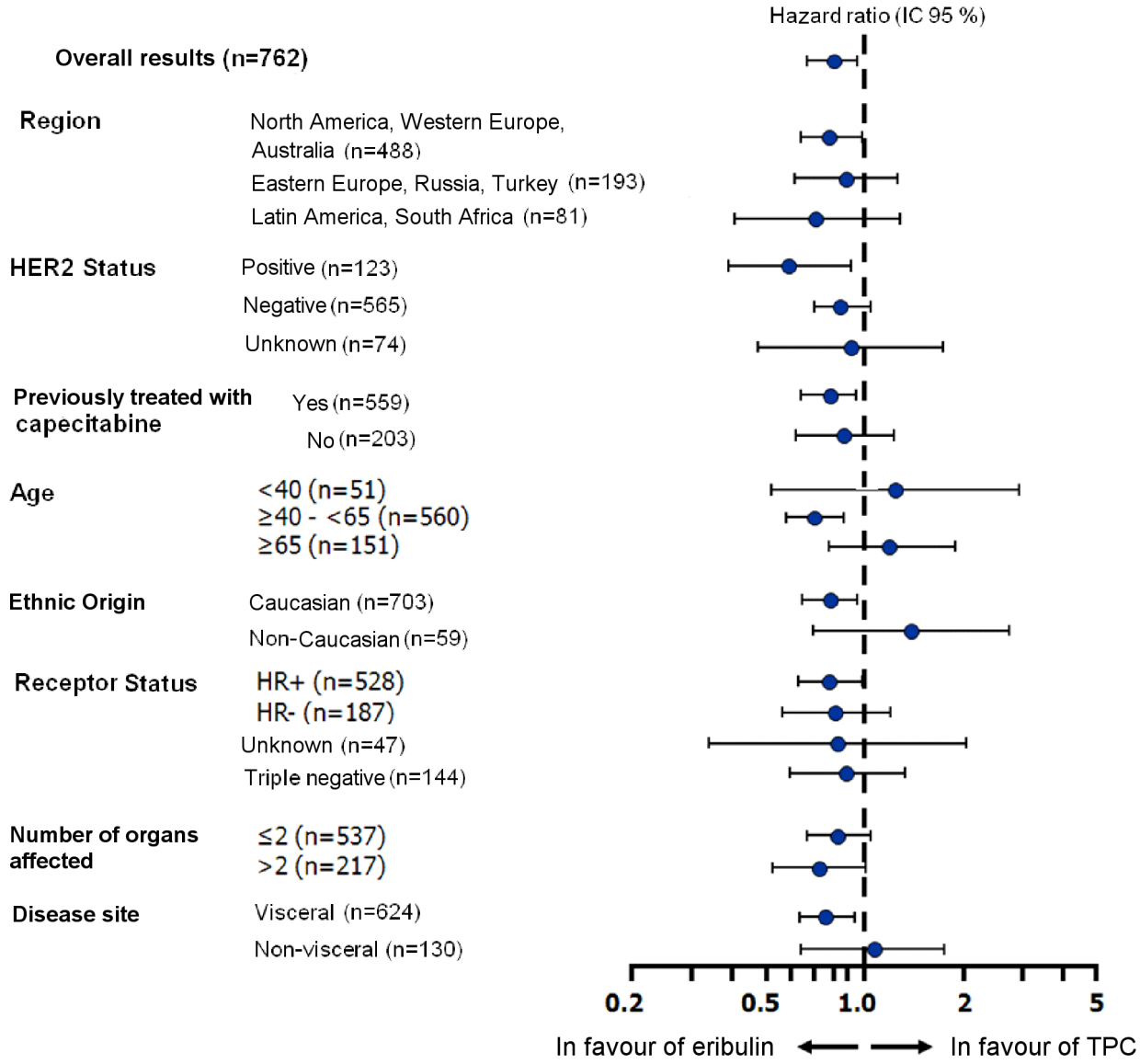
The results from an ad-hoc analysis were based on an analysis carried out on 422 events (deaths).
The median overall survival (primary endpoint) was 13.1 months in the eribulin mesylate group versus 10.6 months in the TPC group, with an absolute difference of 2.5 months in favour of the eribulin mesylate group(HR = 0.809 [IC 95% 0.66 - 0.991]).

Due to this being an open-label study, the results for the secondary endpoints presented were those assessed by an independent committee:
- the median progression-free survival, as assessed by an independent committee, was 3.7 months in the eribulin mesylate group versus 2.2 months in the TPC group, with an absolute difference of 1.5 months in favour of the eribulin mesylate group.
- the objective response rate was 12.2% in the eribulin mesylate group versus 4.7% in the TPC group (p=0.002).

There was no quality of life data available.
Analysis of updated survival data (77% of events (deaths) as opposed to 55% in the initial analysis) shows a superiority for eribulin mesylate over TPC in terms of overall survival time; this difference is of the same order as was observed in the initial analysis (13.2 months versus 10.5 months for the TPC group).

Sub-group analysis (figure 1) gave the following results:
- in the sub-group of capecitabine refractory patients, the result for the median overall survival was in favour of eribulin mesylate versus TPC (HR = 0.68; [IC 95% 0.53 - 0.88]). However, in non-refractory capecitabine patients no advantage for eribulin mesylate versus TPC was observed HR = 1.13; [IC 95% 0.80 - 1.60].
- in the sub-group of HER 2+ patients, the results for the overall survival endpoint were in favour of the group treated with eribulin mesylate compared with the TPC group: HR = 0.594; [IC 95% 0.389 - 0.907]. No difference was observed between the two groups for HER2- cases (HR = 0.849; [IC 95%: 0.695-1.036]).

Figure 1: Representation of the Hazard ratio (IC 95%) as a function of the different sub-groups of patients from a follow-up analysis (not proven by the protocol)



3.2. Adverse effects

Treatment was stopped due to adverse events in 13.3% of the eribulin mesylate group versus 15.4% in the TPC group.

The most commonly occurring adverse events linked to treatment reported (eribulin mesylate vs. TPC) were asthenia/fatigue (45.5% vs. 29.6%), neutropenia (50.7% vs. 27.5%), alopecia (44.1% vs. 9.3%), peripheral neuropathy (31.6% vs. 13.8%), and nausea (29.8% vs. 23.1%).

The incidence of grade 3-4 adverse events was higher in the eribulin mesylate group (grade 3: 36.2% and grade 4: 27.2%) than those treated with TPC (grade 3: 34.0% and grade 4: 10.5%).

3.3. Conclusion

An open-label, randomised phase III study compared eribulin mesylate (HALAVEN) with an active treatment left to the choice of the clinical investigator (Treatment of Physician's Choice or "TPC") with locally advanced or metastatic breast cancer who have had at least two failed chemotherapeutic regimens including anthracycline and taxane.
The median age of patients was 55 years and 75.9% of them were menopausal.
Close to 82% of patients had a HER2 negative tumour. A HER2 positive tumour status was present for around 18% of patients. Patients with three tumour receptors (HER2, oestrogen and progesterone) were absent, "triple negatives" represented 19.8% of cases.
The TPC group consisted of chemotherapy in 97% of cases (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy agents) or hormone therapy in 3% of cases.
Analysis results of overall survival from a final analysis of the study were obtained from 422 events (deaths).

The median overall survival (primary endpoint) was 13.1 months in the eribulin mesylate group versus 10.6 months in the TPC group, with an absolute difference of 2.5 months in favour of the eribulin mesylate group(HR = 0.809 [IC 95% 0.66 -0.991]).
The median progression-free survival, as assessed by an independent committee, was 3.7 months in the eribulin mesylate group versus 2.2 months in the TPC group, with an absolute difference of 1.5 months in favour of the eribulin mesylate group.
The objective response rate was 12.2% in the eribulin mesylate group versus 4.7% in the TPC group.
There was no quality of life data available.
The main reactions observed in the eribulin mesylate group were haematological (neutropenia) and neurological (peripheral neuropathy).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Breast cancer is a condition that has a life-threatening prognosis;
This medicinal product is intended as curative therapy;
The efficacy/adverse effects ratio is moderate;
This medicinal product is a third-line treatment and more for use after failed anthracycline and taxane chemotherapy;
There are few medicinal product alternatives for this stage of the disease;

Public health benefit

The public health burden which metastatic breast cancer represents is considerable. The sub-population of women having had a failed second-line treatment and likely to benefit from eribulin is small.

The availability of new therapeutic options for the treatment of metastatic breast cancer is a public health need.

The data available does not allow the impact of HALAVEN on the morbidity-mortality linked to metastatic breast cancer after failure of a second line treatment to be estimated, compared with current treatment. Indeed, the transferability of experimental data is not possible due to the small percentage of patients recruited treated with a capecitabine chemotherapy agent (18%) in the comparator group, a chemotherapy agent normally used to treat patients in France at this stage of the disease. The impact of the treatment on the quality of life is not documented.

Therefore, based on current knowledge, it is not possible to determine the capacity HALAVEN has to meet an identified public health need.

As a result, HALAVEN is not expected to be of benefit to public health.

The actual benefit of HALAVEN is substantial.

4.2. Improvement in actual benefit

HALAVEN provides a minor improvement in actual benefit (level IV) in the treatment of patients with metastatic or locally advanced breast cancer and who have seen disease progression after previous treatment with anthracycline and taxane, except for patients not able to receive these treatments.

4.3. Therapeutic use

First-line treatment of metastatic breast cancer is governed by:
- the length of time between adjuvant and first-line metastatic treatment (in particular an interval of over one year),
- the presence, or not, of hormone receptors and/or HER2 amplification,
- the type of metastases: number of sites, size and location (particularly visceral),
- the general state of health of the patient,
- the type of adjuvant therapy.

In the absence of bad prognosis factors combined with the presence of hormonal receptors, first-line treatment is hormone therapy.
With bad prognosis factors, the first-line treatment is chemotherapy.
If, alongside bad prognosis factors, hormone receptors are present, chemotherapy and hormone therapy can be used sequentially.

In cases of HER2 tumour amplification, the recommended first-line treatment is trastuzumab (monoclonal antibody), in combination with paclitaxel or docetaxel and is independent of hormonal status[3,4]. The combination of trastuzumab with taxane chemotherapy gives an advantage in overall survival compared with chemotherapy alone.
There are no current guidelines on treating patients that have received at least two chemotherapy regimens with anthracycline and taxane for advanced breast cancer. However, capecitabine is indicated as a second-line treatment of metastatic breast cancer amplifying the HER2 receptor. For amplification of HER2 receptors in patients previously treated with trastuzumab, capecitabine is combined with lapatinib; this combination showed an advantage in terms of progression-free survival over capecitabine monotherapy.
In the absence of a comparison with a capecitabine based chemotherapy agent (only for HER2- and in particular combined with lapatinib in cases of HER2+), the therapeutic use of eribulin (HALAVEN) is yet to be clarified. However, American guidelines from NCCN[5] state it as a treatment option for this stage of the disease.

4.4. Target population

The target population for HALAVEN is represented by patients with metastatic breast cancer with one failed second-line treatment or more.

In 2010, the projected incidence of breast cancer in France was evaluated at 52,500 patients per year[6].
The population of patients with metastatic breast cancer can be subdivided into two sub-populations:

- immediately metastatic (5%[7] to 15%[8] diagnosed cases);
- localised which develops into metastatic (28%[9] of cases);

85%8 of metastatic patients are likely to receive chemotherapy, or 16,850 patients as a first line treatment.

<u>Population of patients likely to receive second and third line chemotherapy for metastatic cancer:</u>
The probability of survival for advanced breast cancer is 70.5% at six months and 55.0% at one year[10].
It should be noted that only women under 70 with advanced breast cancer and a survival time of more than six months will receive second-line chemotherapy, or approximately 56%.
Likewise, only women under 70 with advanced breast cancer, surviving after one year of progression will receive third-line chemotherapy, or approximately 44%.
For a total of 52,500 new cases per year, 16,850 patients have metastatic cancer. Less than half of them (44%) are likely to receive third line treatment, which is 7,400 patients. No specific data is available on the proportion of surviving patients which are able to receive chemotherapy beyond third line for metastatic cancer.

The target population for HALAVEN can therefore be estimated as 7,400 patients per year.

4.5. Transparency Committee recommendations

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

[3] Recommandations pour la Pratique Clinique [Recommendations for clinical practice]: Saint Paul de Vence 2007 "cancers du sein" [breast cancer]
[4] National Cancer Institut Recommandations. Breast Cancer (WWW.cancer.gov/ updated on: 01/05/2011)
[5] NCCN Guidelines™ for Breast Cancer V.2.2011. ©2011 National Comprehensive Cancer Network, Inc. (http://www.nccn.org/ordertemplates/default.asp?did=26)
[6] InVS, HCL, Francim, INCa : Projections of the incidence and mortality of cancer in France in 2010. Technical report April 2010.
[7] FRANCIM
[8] FLNCC investigation
[9] Louis Harris 2003 investigation
[10] Thierry Delozier Report: Evolution of the natural developments and prognosis of breast cancer metastases over four decades. Study of 4,110 metastasised breast cancer cases. T. Delozier, O. Switsers, J.M. Ollivier, C. Lévy, A. Rivière, D. Allouache, C. Delcambre, P. Berthet et K. Gunzer. Le cancer du sein avancé. Springer 2007