

The European Medicines Agency Review of Eribulin for the Treatment of Patients with Locally Advanced or Metastatic Breast Cancer: Summary of the Scientific Assessment of the Committee for Medicinal Products for Human Use

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Abstract

The European Commission issued on March 17, 2011, a marketing authorization valid throughout the European Union (EU) for eribulin (Halaven; Eisai Limited). The decision was based on the favorable opinion of the Committee for Medicinal Products for Human Use recommending a marketing authorization for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least 2 chemotherapeutic regimens for advanced disease. Eribulin mesylate is a structurally simplified synthetic analogue of halichondrin B, which is a natural product isolated from the marine sponge *Halichondria okadai* (ATC code L01XX41). Eribulin is a nontaxane, microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates leading to G₂-M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage. The recommended dose of eribulin is 1.23 mg/m² (equivalent to 1.4 mg/m² eribulin mesylate) to be administered intravenously over 2 to 5 min on days 1 and 8 of a 3-week cycle. In the pivotal trial, eribulin was associated with increased overall survival in patients with locally advanced or metastatic breast cancer who received at least 2 prior chemotherapy lines for advanced disease (median overall survival was 13.2 months in the eribulin arm vs. 10.6 months in the control arm; HR = 0.805; 95% confidence interval, 0.677–0.958; *P* = 0.014). The most common side effects are asthenia or fatigue and neutropenia. The objective of this article is to summarize the scientific review of the application leading to approval in the EU. The detailed scientific assessment report and product information, including the summary report and product information, including product characteristics, are available on the European Medicines Agency website. *Clin Cancer Res*; 18(17); 4491–7. ©2012 AACR.

Introduction

Despite notable progress in the treatment of metastatic breast cancer, it is generally not considered curable and the realistic aims are the prolongation of survival and the improvement of quality of life. Unlike other cancer types, patients with breast cancer frequently receive multiple sequential lines of treatment for their metastatic disease even though the impact of every single line on overall sur-

vival is difficult to quantify and often debated. For patients who need further palliative chemotherapy beyond anthracyclines and taxanes, there is no gold standard option, even though capecitabine has been approved in the European Union (EU) and the United States and has gained wide acceptance among physicians and patients. Targeted therapy, including trastuzumab for HER2-positive breast cancer, and various endocrine therapies are also commonly used.

In April 2010, Eisai Limited applied for a marketing authorization via the European Medicines Agency (EMA) centralized procedure for eribulin under the trade name Halaven. A review was conducted by the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the EMA responsible for providing a scientific opinion on the granting of a marketing authorization. The review started on May 26, 2010, and a positive opinion was issued in January 2011. The approved indication in the EU is "Halaven monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer

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who have progressed after at least 2 chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments."

This article summarizes the assessment of the scientific data submitted for the initial marketing authorization application in the EU. The detailed scientific assessment report and product information such as the summary of product characteristics, including any updated information on the marketing authorization, are available on the EMA website (1).

Nonclinical Aspects

Pharmacology

Eribulin is a structurally simplified synthetic analogue of halichondrin B, which is a natural product isolated from the marine sponge *Halichondria okadai* (Fig. 1). Eribulin inhibits the growth phase of microtubule dynamics and sequesters tubulin into nonproductive aggregates. This pattern is distinct from that of members of tubulin-targeting classes currently in clinical use, including taxanes, vinca alkaloids, and epothilones. Eribulin has shown *in vitro* activity against drug-resistant cells that harbor β -tubulin mutations associated with taxane resistance.

The antiproliferative effects of eribulin were studied *in vitro* and were compared with the microtubule destabilizer vinblastine and the microtubule stabilizer paclitaxel in 6 cultured human cancer cell lines. In these studies, eribulin inhibited growth of a wide range of established human cancer cell lines at IC_{50} values in the nanomolar range via a tubulin-based antimetabolic mechanism, leading to the block of G_2 -M cell-cycle phase.

The antiproliferative effects of eribulin were also studied on both nonpermeability glycoprotein (P-gp)-expressing

and P-gp-overexpressing human cancer cells. Eribulin was shown to be a substrate for the P-gp drug efflux pump and thus showed reduced *in vitro* potency against human cancer cells expressing high levels of P-gp.

In vitro eribulin showed activity against 1A9PTX10 and 1A9PTX22 cancer cells that are both taxane (paclitaxel)-resistant based on distinct mutations in β -tubulin. Eribulin showed activity comparable with that of vinblastine with no significant resistance (resistance ratios approximately 1.3 in both cell lines).

In toxicology studies, eribulin caused hematologic toxicity at the lowest doses tested in the rat and dog. Irreversible testicular toxicity has been observed in both rats (hypocellularity of seminiferous epithelium with hypospermia/aspermia) and dogs. Thus, male fertility may be compromised by treatment with eribulin mesylate. Histopathologic changes (degeneration) of the skeletal muscle and sciatic nerve were also noted in rats. All toxicity, except for the changes in the testes and rat sciatic nerve, were reversible. At higher doses, the liver has been identified as a target organ for toxicity. Gastrointestinal toxicity such as emesis and diarrhea was shown in dogs. In addition, an effect of eribulin mesylate on female fertility cannot be excluded because of a trend toward dose-dependent reduction in the numbers of implantation sites shown when pregnant rats were exposed to the drug.

There is no information on the use of eribulin in pregnant women. Eribulin is embryotoxic, fetotoxic, and teratogenic in rats. Eribulin should not be used during pregnancy unless clearly necessary and after discussion of risks and benefits for both mother and fetus.

Women of childbearing age must be advised to avoid becoming pregnant while they or their male partner are receiving eribulin and should use effective contraception during and up to 3 months after treatment.

There is no information on the excretion of eribulin or its metabolites in human or animal breast milk. A risk to newborns or infants cannot be excluded and therefore eribulin must not be used during breastfeeding.

Clinical Aspects

Pharmacokinetics

Eribulin administered by i.v. infusion had a rapid distribution phase followed by a prolonged elimination phase with a mean terminal half-life of approximately 40 hours. It had a relatively large volume of distribution (range of means 43–114 L/m²). Eribulin had a low protein binding. Based on a mass-balance study, no or very little metabolism of eribulin took place and no metabolites have been identified in plasma *in vivo*. Eribulin was mainly eliminated through biliary excretion of unchanged drug. This route contributed to 70% of total clearance. Clearance was low with average estimates varying from 1.2 to 2.4 L/h/m² following a dose of 1.23 mg/m². The results from a population pharmacokinetics (PK) analysis supported the body surface area–based dosing regimen.

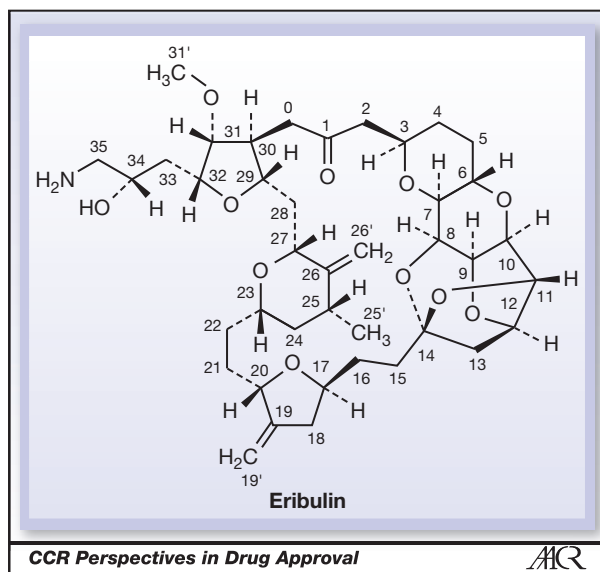


Figure 1. Chemical structure and numbering system of eribulin. Image courtesy of EMA European public assessment report for Halaven. Structural formula of eribulin mesylate (E7389).

Eribulin exposure was increased in patients with creatinine clearance below 30 to 40 mL/min, which could be caused by reduced biliary secretion, and markedly increased in hepatic impairment (2- and 3-fold in mild and moderate impairment respectively, see text under the heading "Clinical safety").

No relevant drug–drug interactions have been identified based on PK data so far but the transport protein involved in the biliary excretion of eribulin, which is the main elimination pathway, has not been identified (see Clinical safety for further drug–drug interaction studies). Complete inhibition of the transport could give rise to a 3-fold increase in plasma concentrations. It is not recommended to use substances that are inhibitors of hepatic transport proteins, such as organic anion-transporting proteins, P-glycoprotein (P-gp), and multidrug resistant proteins concomitantly with eribulin. Known inhibitors of such transporters include cyclosporine, ritonavir, saquinavir, lopinavir and other protease inhibitors, efavirenz, emtricitabine, verapamil, clarithromycin, quinine, quinidine, and disopyramide.

Concomitant treatment with enzyme-inducing substances, such as rifampicin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*), is not recommended as these drugs are likely to give rise to markedly reduced plasma concentrations of eribulin.

No drug–drug interactions are expected with CYP3A4 inhibitors unless they are potent inhibitors of P-gp. Eribulin exposure [area under the curve (AUC) and peak plasma concentration, C_{max}] was unaffected by ketoconazole, a CYP3A4 inhibitor.

Eribulin may inhibit the drug metabolizing enzyme CYP3A4, as indicated by *in vitro* data, whereas no *in vivo* data are available. Concomitant use with substances that are mainly metabolized by CYP3A4 should be made with caution, and it is recommended that the patient be closely monitored for adverse effects because of increased plasma concentrations of the concomitantly used substance. If the substance has a narrow therapeutic range, concomitant use should be avoided.

Clinical efficacy

Three studies were submitted as the basis for establishing clinical efficacy of eribulin in the proposed indication: the 305 pivotal phase III open-label multicenter trial (NCT00388726, EMBRACE; ref. 2); the 201 study, a phase II trial carried out in 104 patients with advanced or metastatic breast cancer treated according to 2 different schedules of eribulin, on days 1, 8, and 15 every 28 days (cohort 1) or on days 1 and 8 every 21 days (the schedule selected for further development, cohort 2; ref. 3); and the 211 phase II study, which investigated the activity of the drug in 291 patients with advanced or metastatic breast cancer (4).

The 305 phase III study enrolled 762 patients with locally advanced or metastatic breast cancer, who received at least 2 prior chemotherapy regimens for their advanced disease, including anthracyclines and taxanes. Moreover, 73% of patients had also received capecitabine (a stratification factor at randomization).

The study was designed to detect a 3-month increase in overall survival in the experimental arm over the control arm. Secondary endpoints were progression-free survival (PFS), objective response rate, and duration of response.

Patients were randomized 2:1 to receive eribulin ($n = 508$) or treatment of physician's choice (TPC, $n = 254$). The medicinal products used in the TPC arm included but were not limited to vinorelbine, gemcitabine, capecitabine, taxanes, and anthracyclines. The baseline patient characteristics were overall well balanced, although with small differences in the number of liver and lymph node metastasis, number of metastatic sites involved, amount of triple-negative tumors, performance status, cancer stage, and prior therapies, which were in favor of the experimental arm (Table 1). Most patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 (42% and 43%, respectively). The median total number of prior chemotherapy regimens was 4 in both groups, reflecting the late stage of disease, and indicating that patients had received available standard therapy prior to the study. In both groups, 84% of HER2-positive patients had received trastuzumab. Most patients had thus received optimal evidence-based therapy before inclusion.

The study met its primary endpoint: The median survival of the eribulin group (median, 399 days/13.1 months) compared with the TPC group (median, 324 days/10.6 months) improved by 75 days/2.5 months [HR = 0.809; 95% confidence interval (CI), 0.660–0.991; $P = 0.041$]. This result was confirmed with an updated overall survival analysis carried out at 77% of events with the median survival of the eribulin group (median, 403 days/13.2 months) compared with the TPC group (median, 321 days/10.5 months) improved by 82 days/2.7 months (HR = 0.805; 95% CI, 0.677–0.958; nominal $P = 0.014$; Fig. 2). The median PFS durations (local evaluation) were 3.6 months in the experimental arm and 2.2 months in the control arm, respectively (HR = 0.76; 95% CI, 0.64–0.90; $P = 0.002$). In evaluable patients who received eribulin, the objective response rate (according to Response Evaluation Criteria in Solid Tumors, version 1.0) was 12.2% (95% CI, 9.4%–15.5%) with median response duration by independent review of 4.2 months compared with respectively 4.7% (95% CI, 2.3%–8.4%) and 6.7 months in patients receiving TPC.

The improvement in overall survival and PFS was seen in both taxane-refractory and nonrefractory patients. In the updated analysis of overall survival (March 3, 2010), the HR was 0.90 (95% CI, 0.71–1.14) in taxane-refractory patients and 0.73 (95% CI, 0.56–0.96) in taxane-nonrefractory patients, respectively. In the PFS analysis based on the local evaluation (original data cutoff), the HR was 0.77 (95% CI, 0.61–0.97) for taxane-refractory and 0.76 (95% CI, 0.58–0.99) for taxane-nonrefractory patients. The almost identical HRs for PFS suggest the absence of any important cross-resistance.

The positive effect on OS was not dependent on previous capecitabine exposure. A survival benefit in favor of the experimental arm was detected in capecitabine-pretreated

Table 1. Summary of selected baseline characteristics (ITT population: study 305)

Parameter	Treatment group		Total N = 762, n (%)
	Eribulin N = 508, n (%)	TPC N = 254, n (%)	
Time since original diagnosis, y			
Median	5.4	5.1	5.2
Tumor sites in >10% patients overall, n (%)			
Bone	306 (60.2)	158 (62.2)	464 (60.9)
Liver	296 (58.3)	159 (62.6)	455 (59.7)
Lymph nodes	220 (43.3)	118 (46.5)	338 (44.4)
Lung	197 (38.8)	95 (37.4)	292 (38.3)
Pleura	87 (17.1)	42 (16.5)	129 (16.9)
Breast	54 (10.6)	24 (9.4)	78 (10.2)
Number of organs involved, n (%) ^a			
1	85 (16.7)	35 (13.8)	120 (15.7)
2	172 (33.9)	82 (32.3)	254 (33.3)
3	145 (28.5)	77 (30.3)	222 (29.1)
4	71 (14.0)	37 (14.6)	108 (14.2)
5	24 (4.7)	16 (6.3)	40 (5.2)
≥6	9 (1.8)	7 (2.8)	16 (2.1)
HER2/ <i>neu</i> status (combined FISH and IHC tests), n (%) ^b			
Positive	83 (16.3)	40 (15.7)	123 (16.1)
Negative	373 (73.4)	192 (75.6)	565 (74.1)
Unknown	4 (0.8)	0 (0)	4 (0.5)
Not done	48 (9.4)	22 (8.7)	70 (9.2)
ER status, n (%)			
Positive	336 (66.1)	171 (67.3)	507 (66.5)
Negative	143 (28.1)	72 (28.3)	215 (28.2)
Unknown	1 (0.2)	0 (0)	1 (0.1)
Not done	28 (5.5)	11 (4.3)	39 (5.1)
PgR status, n (%)			
Positive	254 (50.0)	123 (48.4)	377 (49.5)
Negative	197 (38.8)	102 (40.2)	299 (39.2)
Unknown	1 (0.2)	0 (0)	1 (0.1)
Not done	56 (11.0)	29 (11.4)	85 (11.2)
Negative for ER, PgR, and HER2/ <i>neu</i> , n (%)			
Yes	93 (18.3)	51 (20.1)	144 (18.9)
No	380 (74.8)	192 (75.6)	572 (75.1)
Unknown ^c	35 (6.9)	11 (4.3)	46 (6.0)
Cancer stage at diagnosis			
0	2 (0.4)	0 (0)	2 (0.3)
I	62 (12.2)	30 (11.8)	92 (12.1)
II	213 (41.9)	89 (35.0)	302 (39.6)
III	142 (28.0)	71 (28.0)	213 (28.0)
IV	81 (15.9)	59 (23.2)	140 (18.4)
Not available	8 (1.6)	5 (2.0)	13 (1.7)

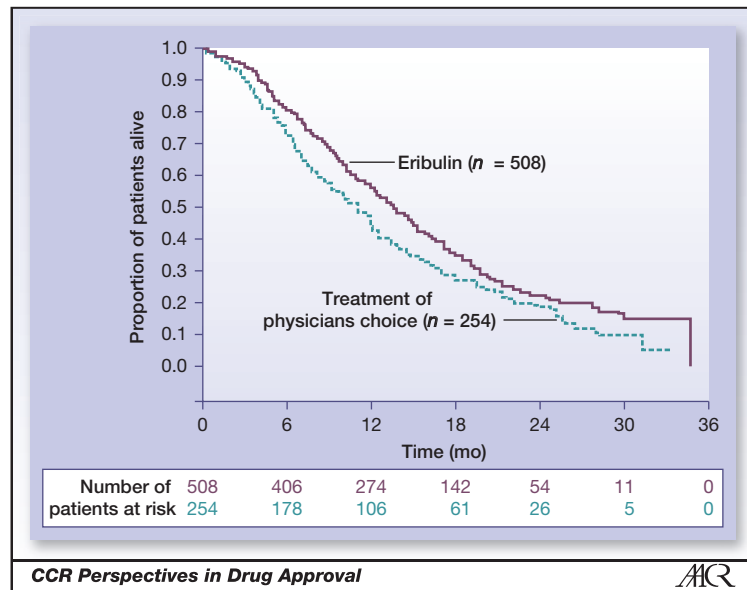
Abbreviations: ER, estrogen receptor; HER2/*neu*, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ITT, intent to treat; PgR, progesterone receptor.

^aThe number of organs involved is based on the local evaluation.

^bFor patients who were tested with FISH their status is derived from the FISH test irrespective of IHC results even if the FISH test yielded a result of unknown. Results from the IHC tests are used only when the FISH test was not conducted. For these patients, a result of 3+ indicates that the patient was Her2/*neu* positive.

^cIncludes patients whose results were ER and PgR negative and who were never tested for their Her2 status ($n = 26$ and 10 for eribulin and TPC, respectively).

Figure 2. Overall survival: Kaplan–Meier estimates of the survival function by treatment group for the data from the updated analysis (intent-to-treat population). Image courtesy of EMA European public assessment report for Halaven.



(HR = 0.787; 95% CI, 0.645–0.961), as well as in capecitabine-naïve patients (HR = 0.865; 95% CI, 0.606–1.233). In the analysis based on local evaluation, an improved PFS was detected in the capecitabine-pretreated subgroup (HR = 0.68; 95% CI, 0.56–0.83), whereas no advantage was found in the capecitabine-naïve subgroup (HR = 1.03; 95% CI, 0.73–1.45).

The overall response rates in the phase II studies by independent review were 11.5 and 9.3 in the 201 and 211 studies, respectively, supporting the activity of eribulin as a single agent in heavily pretreated patients with advanced disease.

Clinical safety

The safety of eribulin has been evaluated in 12 completed clinical studies in different cancer types. In the pivotal trial, the toxicity profile of eribulin was as expected from a tubulin-active chemotherapeutic agent. The most common adverse events in the eribulin arm were asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), nausea (34.6%), peripheral neuropathy (34.6%), constipation (24.7%), and leukopenia (23.1%). Neutropenia, leukopenia, peripheral neuropathy, and asthenia/fatigue were the most common adverse events reported at Common Terminology Criteria for Adverse Events (CTCAE) grades 3 and 4. Neutropenia was the most common adverse events reported at CTCAE grade 4 in the eribulin group (24.1%).

Serious adverse events were reported for 27% of the subjects treated with eribulin in the breast cancer populations (BCP, $n = 827$), which included patients who received the recommended dose of eribulin in the 2 phase II and the pivotal phase 3 breast cancer studies. The 5 most commonly reported serious adverse events were febrile neutropenia (3.9%), pyrexia (2.2%), dyspnea (1.9%), neutropenia (1.9%), and pleural effusion (1.7%). Neutropenia was dose-dependent, reversible, and not cumulative. The mean

time to nadir was 13 days, and the mean time to recovery from severe neutropenia ($<0.5 \times 10^9/L$) was 8 days. Grade 4 neutropenia lasting more than 7 days occurred in 13% of BCP treated with eribulin. Febrile neutropenia occurred in $<5\%$ of BCP treated with eribulin. Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>3 \times$ the upper limit of normal (ULN) experienced a higher incidence of grade 4 neutropenia and febrile neutropenia. Although data were limited, patients with bilirubin $>1.5 \times$ ULN also had a higher incidence of grade 4 neutropenia and febrile neutropenia.

In the pivotal trial, 20% of patients with metastatic breast cancer required treatment with granulocyte colony-stimulating factor or other granulopoiesis-stimulating agent. Severe neutropenia may be managed by the use of granulopoiesis-stimulating agents in accordance with relevant guidelines. Because of its hematologic safety profile, treatment with eribulin should only be initiated in patients with absolute neutrophil count values $\geq 1.5 \times 10^9/L$ and platelets $>100 \times 10^9/L$. Also complete blood counts should be conducted on all patients before each dose of eribulin. Dose modifications and treatment delays related to hematologic and nonhematologic adverse reactions are recommended.

Of the 827 patients in the BCP, 35% experienced peripheral neuropathy. The median time to grade 2 peripheral neuropathy was 85 days (after 4 cycles). Development of grade 3 or 4 peripheral neuropathy occurred in 7% of BCP. Patients with preexisting neuropathy were as likely to develop new or worsening symptoms as those entering the study without the condition. Peripheral motor neuropathy was experienced by 5% of the patients. Time to resolution of neuropathy has not been fully characterized. Patients should be closely monitored for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of dose.

The incidence of treatment-related nausea and vomiting (36% and 14%, respectively, in the BCP) would support antiemetic premedication, according to relevant guidelines.

In the pivotal trial and in the BCP safety population treatment-related deaths occurred with a frequency of less than 1%, most frequently because of infections.

In an uncontrolled open-label electrocardiography (ECG) study in 26 patients, QT prolongation was observed on day 8, independent of eribulin concentration, with no QT prolongation observed on day 1. ECG monitoring is recommended if therapy is initiated in patients with bradyarrhythmia, electrolyte abnormalities, or concomitantly to drugs that prolong the QT interval. Hypokalemia or hypomagnesemia should be corrected before initiating eribulin therapy, and these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long-QT syndrome.

Eribulin is minimally excreted via the kidney. Subgroup analysis of the pooled safety populations showed trends of increased toxicity in patients with serum-creatinine clearance levels below normal, but the groups were small and may be confounded by other factors. Patients with severely impaired renal function (creatinine clearance <40 mL/min) may need a reduction of the dose, although the optimal dose for this patient groups remains to be established. In patients with mild-to-moderate renal impairment, no specific dose adjustments are recommended.

The effect of hepatic impairment on eribulin exposure has been studied in 17 subjects. Hepatic impairment increased the mean dose-normalized eribulin C_{max} and increased exposure to eribulin. Patients in the all eribulin-treated population [all eribulin-treated patients (AETP), $n = 1,222$ patients] and BCP with abnormal serum liver function values (bilirubin, ALT, and AST) had more grade ≥ 3 treatment-related adverse events and serious adverse events. Specifically, all types and grades of neutropenia events increased consistently with increasing levels of all 3 parameters, and peripheral neuropathy increased with ALT/AST, whereas asthenia/fatigue appeared not to be affected.

In the AETP, 244 patients (20.0%) were >65 to 75 years of age and 66 patients (5.4%) were >75 years of age. Among the 827 of these patients who received the recommended dose of eribulin in the BCP, 121 patients (14.6%) were > 65 to 75 years of age and 17 patients (2.1%) were >75 years of age. The safety profile of eribulin in elderly patients (>65 years of age) was similar to that of patients ≤ 65 years of age. No dose adjustments are recommended for the elderly population.

The applicant submitted a risk management plan identifying relevant identified/potential risks and important missing information. Safety concerns that will be further addressed using additional studies or analyses include myelosuppression and associated infections, peripheral neuropathy, hepatic impairment, and renal impairment. Further drug-drug interactions studies will elucidate inhibitors of hepatic uptake and efflux transporter inhibitors

which could be involved in eribulin biliary excretion, *in vitro* studies aimed at identifying the transporter involved in the marked biliary excretion of eribulin, ketoconazole as a P-gp inhibitor, and investigations of the concomitant use of CYP3A4 inhibitors will be conducted.

Benefit-Risk Assessment

Acceptable primary endpoints for confirmatory trials include overall survival, and PFS. Indeed, convincing favorable effects on overall survival are, from both a clinical and methodologic perspective, the most persuasive outcome of a clinical trial. Prolonged PFS as such, however, is also considered to be of benefit to the patient. The choice of primary endpoint should be guided by the relative toxicity of the experimental therapy, but, for example, expected survival after progression, available next-line therapies, and the prevalence of the condition must also be taken into account (5).

The CHMP regarded as clinically meaningful, the observed effect in terms of overall survival taking into account the pragmatic design of the 305 pivotal trial that allowed the investigator to choose the best available standard treatment as comparator. The pivotal trial submitted included TPC as control. This pragmatic choice was considered appropriate because there was no generally agreed treatment option in the target indication, although a number of active treatments have been used. Such treatments would generally be acceptable in a confirmatory trial and should be chosen based on best available, evidence-based therapeutic options that are widely used (but not necessarily licensed regimens). This control arm does not constitute a problem normally for superiority studies in this situation, as long as the reference is evidence-based (5).

When overall survival is reported as primary endpoint, consistency is expected as regards effects on PFS. No statistically significant difference was observed for the prespecified PFS analysis based on blinded independent review (HR = 0.865; 95% CI, 0.71–1.05). It was noted, however, that blinded independent review led to a large proportion of censored patients (30% and 35% for eribulin and TPC arms, respectively) compared with local evaluation (16% and 19%), potentially introducing informative censoring. The too early adjudication of progression by local evaluation leading to censoring in the blinded independent review occurred similarly between treatment arms and bias in the treatment comparison in the local evaluation of progression was considered unlikely. Thus, more weight was given to PFS according to local evaluation, which indeed did support the primary endpoint, with HR = 0.76 (95% CI, 0.64–0.90; $P = 0.002$).

Because eribulin is a tubulin-targeting drug, the issue of cross-resistance between eribulin and other tubulin-active drugs was investigated. The positive effect on OS and PFS was seen in both taxane-refractory and nonrefractory groups of patients.

The incidence of neutropenia and febrile neutropenia was high and associated with cases of deaths. However, these were not considered to outweigh the benefits of

treatment in terms of overall survival. The nausea and vomiting observed were considered acceptable when balanced against the beneficial effects. Peripheral neuropathy is an inherent problem with tubulin-targeting drugs, which can be acceptable in light of the benefits. Robust data regarding time to resolution of peripheral neuropathy were not available, but other studies are ongoing that will address this issue. Overall, the toxicity profile of eribulin was considered reasonably well characterized and as expected for cytotoxic drugs with this mechanism of action.

The pharmacokinetics of eribulin are currently not fully characterized. The main pathway of elimination is biliary excretion, but there is no information on which transporters are involved in the process. If the biliary secretion is completely inhibited, the exposure (AUC) could increase by 250%. CYP3A4 is an important drug-metabolizing enzyme. *In vitro* data indicate that eribulin may inhibit CYP3A4 in the liver. No *in vivo* data are available. If eribulin inhibits the enzyme significantly *in vivo*, this may lead to interactions with a number of drugs. Drug-drug interaction studies are being conducted to further address this issue.

The CHMP concluded that there was a clear benefit in terms of overall survival associated with eribulin in the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least 2 chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments. Subsequently, on March 17, 2011, the European Commission granted a

marketing authorization valid throughout the European Union for eribulin. The EMA will review new information about eribulin on a regular basis. Up-to-date information on this medicinal product is available on the website of the EMA (<http://www.ema.europa.eu>).

Disclosure of Potential Conflicts of Interest

S. Klaar is employed as a co-investigator in clinical trials at Uppsala Akademiska University Hospital. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

This publication is a summary of the European Public Assessment Report (EPAR) available in the public domain, together with the summary of product characteristics (SmPC), and other product information on the EMA website (www.ema.europa.eu). The authors remain solely responsible for the opinions expressed therein.

Authors' Contributions

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Writing, review, and/or revision of the manuscript: E. Pean, S. Klaar, E. G. Berglund, T. Salmonsén, J. Borregaard, K. F. Hofland, J. Erbsøll, E. Abadie, R. Giuliani, F. Pignatti

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