20 July 2018
EMA/625772/2017
Committee for Orphan Medicinal Products

Withdrawal Assessment Report - Orphan Maintenance

Lenvima (Lenvatinib)
Treatment of hepatocellular carcinoma
EU/3/15/1460 (EMA/OD/287/14)
Sponsor: Eisai Europe Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Product and administrative information

Product	
Active substance	Lenvatinib
International Non-Proprietary Name	Lenvatinib
Orphan indication	Treatment of hepatocellular carcinoma
Pharmaceutical form	Capsule, hard
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L01XE05
Sponsor's details:	Eisai Europe Limited European Knowledge Centre Mosquito Way Hatfield Herts AL10 9SN United Kingdom
Orphan medicinal product designation procedural history	
Sponsor/applicant	Eisai Europe Limited
COMP opinion date	12 February 2015
EC decision date	19 March 2015
EC registration number	EU/3/15/1460
Type II variation procedural history	
Rapporteur / co-Rapporteur	Bart Van der Schueren, Robert James Hemmings
Applicant	Eisai Europe Limited
Application submission date	24 July 2017
Procedure start date	12 August 2017
Procedure number	EMA/H/C/003727
Invented name	Lenvatinib
Therapeutic indication	Extension of indication to include treatment of hepatocellular carcinoma Further information on Lenvima can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/ European public assessment reports
CHMP opinion date	28 June 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	D. O'Connor – K. Westermark
Sponsor's report submission date	23/08/2017 and 29/09/2017
COMP discussion and adoption of list of questions	30-31 October 2017
Oral explanation	17 July 2018
Sponsor's removal request	18 July 2018

Following communication of the outcome of the discussion, the sponsor formally requested the withdrawal of the orphan designation on 18 July 2018, prior to final opinion.

2. Grounds for the COMP opinion

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing lenvatinib was considered justified based on pre-clinical in vivo models of the condition and preliminary clinical data in patients with the condition;
- the condition is life-threatening because it is often discovered in advanced phase, and survival following diagnosis is approximately 6 to 20 months. The main chronically debilitating manifestations include abdominal pain, weight loss, ascites, encephalopathy, jaundice and variceal bleeding;
- the condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide. Chronic liver disease and cirrhosis remain the most important risk factors for the development of HCC of which viral hepatitis and excessive alcohol intake are the leading risk factors worldwide. Chronic viral hepatitis can lead to cirrhosis and/or HCC. Diabetes is an independent risk factor for HCC. HCC is an adenocarcinoma and the composing tumor cells resemble normal hepatocytes. Stromal invasion, or tumor cell invasion into the portal tracts or fibrous septa, defines HCC and is not present in dysplastic lesions [III, A]. Other histological features of HCC, however, may also be seen in dysplastic lesions: (i) increased cell density more than two times that of the surrounding tissue, with an increased nuclear/cytoplasm ratio and irregular thin-trabecular pattern; (ii) intratumoral portal tracts); (iii) pseudoglandular pattern; (iv) diffuse fatty change (up to 40% in early well-differentiated tumors, uncommon in tumors >3 cm; and (v) varying numbers of unpaired arteries.

To obtain the best treatment result for HCC, early diagnosis is the key. Chronic hepatitis leads to the development of cirrhosis. Cirrhotic livers exhibit regenerative nodules, which result from increased proliferation of hepatocytes. Differentiation between these regenerative nodules and HCC can vary based on the size of the nodules. Percutaneous biopsy should be limited to those nodules that are radiologically nontypical on CT or MRI for HCC.

HCC is an aggressive cancer that occurs in the setting of chronic liver disease and cirrhosis that frequently presents in advanced stages. Concomitant liver dysfunction with advanced tumor stages further impedes curative therapies.

HCC as well as other cancers, can be prevented if appropriate measures, including HBV vaccination, universal screening of blood products, use of safe injection practices, treatment and education of alcoholics and intravenous drug users, and initiation of antiviral therapy, have shown to be effective.

The proposed therapeutic indication "Treatment of adult patients with hepatocellular carcinoma" falls within the scope of the designated orphan indication "treatment of hepatocellular carcinoma".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified. Please see EPAR – scientific document.

Chronically debilitating and life-threatening nature

The prognosis of patients with HCC and the choice among the available therapeutic options, largely depends on tumor extension and underlying liver function. The condition now ranks sixth in the world among all malignancies, contributing to the third leading cause of mortality attributed to cancer *(World J Hepatol. 2015 Nov 18; 7(26): 2648–2663.*). Patients detected at an early stage can achieve 5-year survival rates of 70% with transplant or resection, whereas those with advanced HCC are only eligible for palliative treatments and have a median survival of less than one year (*World J Hepatol 2015 November 18; 7(26): 2648-2663*). HCC remains a complex and heterogeneous disease with wide prognosis (*Future Oncol. (2017) 13(15), 1297–1300*). Mortality outcomes depends on the degree of hepatocellular cancer diagnosed. For example post-embolization syndrome can affect up to 50% of patients that may induce acute liver failure, with an associated risk of post-procedure mortality. (*World J Hepatol 2015 November 18; 7(26): 2648-2663*). Patients who are eligible for liver transplant can have four-year rate of survival was 75% (*N Engl J Med 1996; 334:693-699*). It is reported that the three- and five-year survivals are 64.7% and 56.2% respectively, and what had been seen was 71.3% and 57.8%, respectively using the Metroticket methodology. However, the predicted five year rate of survival was 43.5% (*World J Gastroenterol 2013; 19: 8093-8098*). With the establishment of the MELD system, five-year survival without HCC therapy, with local tumor ablation, surgical resection and liver transplantation was 15.2%, 37.6%, 55.5% and 77.2% respectively. Current management of HCC includes surgical resection/hepatectomy, liver transplantation (deceased and living), thermal or chemical ablation, chemoembolization, and medical treatment.

Number of people affected or at risk

The incidence of HCC is reported by the sponsor to be increasing in Europe and worldwide. In the EU-28, the sponsor highlights that the incidence of primary liver and intrahepatic bile duct cancers (all cancer types) is estimated at 7.6/100,000 for men and 2.4/100,000 for women (Global Cancer Observatory, IARC, https://gco.iarc.fr, 2016). The sponsor offers a variety of sources from the literature regarding the reported incidence of the condition. The publications range from 2008 to 2017. There is variability in the reporting of the incidence of the condition across Europe. The sponsor has used sources from National registries and Rarecare. The sponsor highlights that whilst German, UK, and Dutch data do report annual figures, the changes in incidence have slowed in recent years and averages are hard to estimate across all nation states. They propose to correct this incidence calculation with data from SEER. However, this correction could skew the prevalence calculation as the epidemiology for hepatocellular carcinoma could be different in the US to that in Europe. The incidence in SEER is proposed as 1.05 in 10,000 and is associated with an increase of 3% in HCC year on year. It is not clear how this could compare with what appears to be slower increases in Europe.

The sponsor indicates that the GLOBOCAN data for 2012 reported a 5-year prevalence of primary liver cancers in men and women as 46,988 cases. Primary liver cancers include hepatocellular carcinoma and biliary tract cancers. The sponsor has not indicated the ratio between the two so it is difficult to establish the relevance of the proposed numbers in the prevalence for hepatocellular carcinoma. The sponsor does not indicate which of the primary liver cancers are being included in the prevalence

calculation. In addition they are mixing in the 3% increase reported in SEER which may not reflect the situation in Europe.

The sponsor provides a final calculation based on 5 year survival. As the average survival appears to be below 5 years as reported in the recent literature (*the predicted five year rate of survival was 43.5% World J Gastroenterol 2013; 19: 8093-8098*), it would appear that a partial prevalence calculation, using a 5 years duration, is acceptable. The sponsor concludes on 1.05 in 10,000 in Europe which based on assumptions associated with what is reported in SEER for 2016. As reporting of the incidence and prevalence maybe different in the United States due to factors which maybe different to those in Europe the final number potentially may not reflect current epidemiological considerations in Europe.

It has been recently reported that HCC is more common among males with a male:female ratio of 2.4 in its worldwide distribution and that the most common age at presentation is usually between 30 and 50. Europe is generally considered to have a low incidence with certain regions having a mid-range incidence when compared with Asia and the US (J Carcinog. 2017; 16: 1.). Therefore the assumption made by the sponsor regarding the findings in SEER and their inclusion in the calculation does not seem to be needed considering what is reported in In the US, SEER reports that HCC accounts for 65% of all cases of liver cancers. It would be of interest to understand if the same percentage for HCC is applicable to Europe and this is not addressed by the sponsor. The remainder of the primary liver cancers involve biliary tract cancers for which the COMP has recently accepted a prevalence calculation of 1.46 in 10,000. This should be considered in the prevalence calculation as the sponsor has provided a prevalence calculation which includes all primary liver cancers. It is also noted in a recent publication from 2017 in *J Hepatol. 2017 Aug;67(2):302-309* that: *In European men, mortality rates were stable during the last decade (3.5/100,000). HCC mortality increased in Northern and Central Europe, and decreased in Southern Europe. In the USA, HCC mortality increased by 35% between 2002 and 2012, reaching 3.1/100,000 men in 2012; it is predicted to remain stable to 2020*.

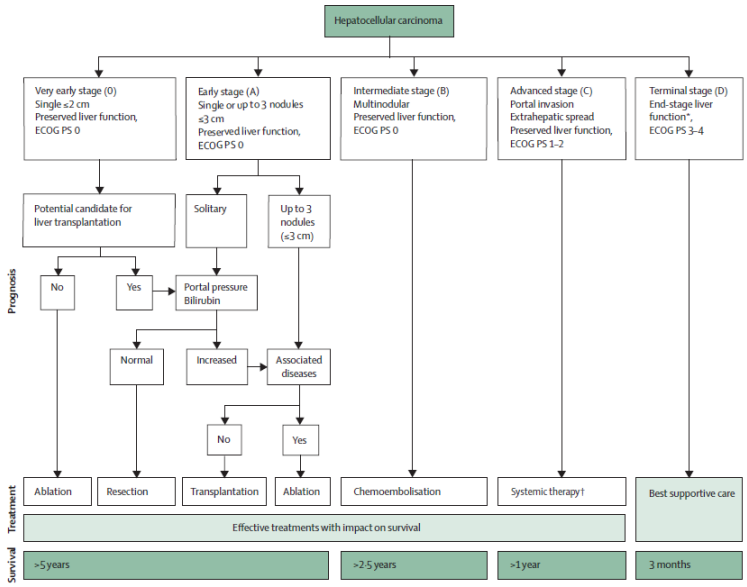
The sponsor was invited to recalculate the prevalence using assumptions which reflect the current situation in Europe. Although the revised prevalence calculation was accepted by the COMP the sponsor withdrew the application following the oral explanation due to other considerations.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Currently sorafenib is considered standard of care for patients with advanced HCC in the first line setting. The indication for sorafenib is: "*Treatment of hepatocellular carcinoma".* It is recommended for use in advanced metastatic stage (C) forms of hepatocellular carcinoma. Treatment is based on the Barcelona-Clinic Liver Cancer (BCLC) staging system came about from data obtained in multiple studies done by the Barcelona-Clinic Liver Cancer Group. The BCLC became a standardized measure of identifying prognosis for patients with HCC. The treatment algorithm has been adopted in the ESMO and the EASL-EORTC clinical practice guidelines: Management of Hepatocellular Carcinoma and the same is used in the US.



Current management of HCC includes surgical resection/hepatectomy, liver transplantation (deceased and living), thermal or chemical ablation, chemoembolization, and medical treatment. (*Forner, Reig and Bruix, The Lancet January 2018*). For intermediate stage (B) forms the preferred treatment is the application of intra-arterial administration of chemotherapy (e.g. doxorubicin, cisplatin), embolizing material (e.g. coils, gelatin sponge particles) or radioactive particles. Transarterial chemoembolization (TACE) involves the combination of selective injection through the hepatic artery of antineoplastic agents and selective obstruction of tumoral feeding vessels. TACE may induce partial responses in 15%– 55% of patients, which are associated with a benefit in overall and progression-free survival. Doxorubicin and cisplatin are used in the treatment of this condition off-label. Regorafenib is approved centrally for patients who have been previously treated with sorafenib. Lenvatinib has been shown to be noninferior to sorafenib, but no second-line option after lenvatinib has been explored. Mitoxantrone is approved nationally in some member states for non-resectable primary hepatocellular carcinoma.

Significant benefit

The sponsor is proposing that: *As the first new therapy for first-line HCC submitted for approval in a decade, lenvatinib would provide a significant benefit as both a major contribution to the care of patients with HCC and clinically relevant advantage over sorafenib, the standard of care in subjects with advanced or unresectable HCC.*

The sponsor obtained for Scientific Advice on 15 November 2012 before they obtained their orphan designation which was on the 19 Mar 2015. The sponsor has not therefore raised a question on significant benefit.

The sponsor's product is an oral formulation comprised of 4 mg tablets.

For the purpose of significant benefit assessment only sorafenib will be considered as it is the one product used for the targeted patient population. Sorafenib is an oral formulation of 200mg. The indication for sorafenib is: *Treatment of adult patients with hepatocellular carcinoma*. According to current ESMO Guidelines for the treatment of HCC, sorafenib is to be used in the management of locally advanced/metastatic disease with palliative treatments such as transarterial chemoembolization (TACE).

The sponsor has conducted two studies which are summarised below:

Study ID (Status)	Indication	No. Study Centers (Location)	Dates - Study Start[a]/ Clinical Cutoff[b]	Study Design	Study Treatment: Dose, Route & Regimen	No. Subjects Enrolled/ Treated/ Ongoing[c]
Pivotal Phase 3 Trial						
E7080-G000-304 (Extension phase ongoing)	First-line treatment of unresectable or advanced HCC in pts with CP class A (score 5-6)	183 sites: Asia, (China, Japan, Republic of Korea, Singapore, Taiwan, Hong Kong, Thailand, Philippines, Malaysia), the EU, North America, Russia, Israel	01 Mar 2013 / 13 Nov 2016	Randomized (1:1), open-label, noninferiority of lenvatinib vs sorafenib	Lenvatinib QD: 8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) oral capsules Sorafenib 400 mg BID oral tablets	Lenvatinib: 478/476/27 Sorafenib: 476/475/25
Supportive Phase 1/2 Study						
E7080-J081-202 (Completed)	Unresectable or advanced HCC in pts with CP class A (score 5-6) or CP class B (score 7-8)	Phase 1: Japan (2 sites) Phase 2: Japan (12 sites), Korea (2 sites)	24 Jul 2009 (1st subject signed informed consent) 15 Jun 2014 (clinical cutoff for primary analysis) 13 Aug 2015 (cutoff date for final analysis)	Phase 1/2, nonrandomized, multicenter, multidose, open-label study with a dose-escalation component (Phase 1) and an expansion component at the RP2 dose (Phase 2)	Lenvatinib QD: Phase 1: 8, 12, or 16 mg Phase 2: 12 mg (RP2 dose) oral tablets	Phase 1: Group 1 (CP score 5-6): Actual: n=9 Group 2 (CP score 7-8): Actual: n=11 Ongoing: 0 (Groups 1+2) Phase 2: (CP score 5-6) 46 / 1[e] / 0[d]

BID = twice daily; BW = body weight; CP = Child-Pugh; EU = European Union; HCC = hepatocellular cancer; pts = patients; QD = once daily; RP2 = recommended Phase 2 (dose).
a: Clinical start date is date that the first subject signed informed consent.
b: Cutoff date is the planned clinical cutoff date for primary analysis in the study.
c: Ongoing subjects are those still receiving study drug as of the planned clinical cutoff date for primary analysis.
d: No subjects were ongoing as of the cutoff date for the final analysis.

Although sorafenib doesn't seem to be used extensively within the context of intermediate forms of hepatocellular carcinoma it is currently accepted that it is indicated for this form of this malignancy as well as the more advanced metastatic forms and all other forms covering the milder and more severe forms. The sponsor of lenvatinib has indicated they have studied in their pivotal phase III study (A multicentre, randomised, open-label, Phase III trail to compare the efficacy an safety of lenvatinib versus sorafenib in First-line treatment of subjects with unresectable hepatocellular carcinoma) patients who had unresectable hepatocellular carcinoma. This study was a direct comparison to sorafenib and the primary outcome measure was overall survival for which non-inferiority was shown.

The sponsor claims that their product offers a clinically relevant advantage to sorafenib due to better outcomes as measured through their secondary end-points: "*lenvatinib demonstrated highly statistically significant, clinically meaningful improvement for all secondary efficacy endpoints (PFS, TTP, and ORR) compared with sorafenib, which reflects the direct antitumor effect of lenvatinib without the confounding effects of postprogression therapies. Results were consistent across all subgroups. Furthermore, lenvatinib showed significantly more tumour shrinkage compared with sorafenib".*

The COMP in their discussions noted the following points. Lenvatinib was non-inferior compared to sorafenib in the first line setting against sorafenib for OS. In the secondary endpoints, lenvatinib appears superior for PFS, TTP and ORR compared with sorafenib.

- OS: 13.6 months for lenvatinib vs. 12.3 months for sorafenib. HR = 0.92 [95% CI of (0.79, 1.06)].
- PFS: 7.4 vs 3.7 months; HR = 0.66; 95% CI (0.57, 0.77); P<0.00001
- TTP: 8.9 vs 3.7 months; HR = 0.63; 95% CI (0.53, 0.73); P<0.00001
- ORR (CR + PR): 24.1% versus 9.2% (P<0.00001)

With regards to QoL measurements, the sponsor states that "*The health-related QoL results suggest that any comparative survival benefit observed among subjects in either treatment group would not be at the cost of QoL relative to the alternative treatment*". However, globally there was no evidence of an improvement in QoL shown for patients on Lenvima versus sorafenib.

In conclusion, lenvatinib has been shown to be non-inferior for the primary endpoint of survival, but superior in terms of secondary endpoints. The argument for significant benefit based on improved efficacy remains unsubstantiated as overall survival is considered to be the most clinically relevant endpoint for these patients. The safety data presented do not appear to favour the lenvatinib arm e.g. SAEs including fatal events were 43.1% for lenvatinib and 30.3% for sorafenib and the data on the QoL do not conclusively favour lenvatinib. Currently the justification for significant benefit cannot be accepted and the sponsor should be asked to demonstrate robust improvement in QoL or other meaningful patient outcome measures.

The sponsor decided to withdraw the request for Maintenance of the Orphan Designation following the oral explanation.

4. COMP list of issues

Prevalence:

The assumptions the sponsor has made in the proposed methodology to establish the prevalence of hepatocellular carcinoma appear to be insufficient in that SEER data are used which would not reflect the current situation in Europe which could be different. The sponsor should recalculate the prevalence focusing primarily on recent European sources to establish the prevalence of the condition.

Significant Benefit

The sponsor is claiming a clinically relevant advantage of their product within the context of how sorafenib is used in advanced metastatic forms of the condition. The main study 304 only demonstrated non-inferiority in the primary endpoint to sorafenib and the data submitted by the sponsor does not clearly establish either a clinically relevant advantage or major contribution to patient care. The sponsor is invited to further elaborate on the data to support a claim of significant benefit.