Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2138

lenvatinib 4mg hard capsules (Lenvima®)

Eisai Limited

8 March 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

lenvatinib (Lenvima®) is accepted for use within NHSScotland.

Indication under review: As monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy.

In a phase III study in patients with unresectable hepatocellular carcinoma who had not received treatment for advanced disease, lenvatinib was non-inferior to another multikinase inhibitor for overall survival.

SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of lenvatinib and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.[1]

Dosing Information

The recommended daily dose of lenvatinib is 8mg (two 4mg capsules) once daily for patients with a body weight of <60kg and 12mg (three 4mg capsules) once daily for patients with a body weight of ≥60 kg. Dose adjustments are based only on toxicities observed and not on body weight changes during treatment. The daily dose is to be modified, as needed, according to the dose/toxicity management plan. If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Optimal medical management (ie treatment or therapy) for nausea, vomiting, and diarrhoea should be initiated prior to any lenvatinib therapy interruption or dose reduction; gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or failure.

Treatment should be initiated and supervised by a health care professional experienced in the use of anti-cancer therapies.

Further details are included in the Summary of Product Characteristics (SPC).[1]

Product availability date

20 August 2018

Lenvatinib meets SMC end of life criteria and orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor which selectively inhibits kinases involved in tumour angiogenesis and oncogenesis.[1, 2] It is the second multikinase inhibitor to be licensed for this indication after sorafenib.

Key evidence comes from the open-label, multi-centre, non-inferiority phase III REFLECT study. REFLECT recruited adult patients with unresectable hepatocellular carcinoma (HCC), confirmed histologically or cytologically, or confirmed clinically in accordance with American Association for the Study of Liver Diseases criteria, who had not received treatment for advanced disease.[3] Patients with cirrhosis of any aetiology, or with chronic hepatitis B or C infection were eligible. Eligible patients were required to have one or more measurable target lesions based on modified Response Evaluation Criteria in Solid Tumours (mRECIST). Lesions previously treated with radiotherapy or locoregional therapy had to show radiographic evidence of disease progression to

be deemed target lesions. Patients were required to be classified as Barcelona Clinic Liver Cancer (BCLC) stage B (intermediate stage) or stage C (advanced stage) , Child-Pugh class A, and have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1[2, 3] The BCLC staging system uses criteria, including the Child-Pugh classification, to stage and guide the management of patients with hepatocellular carcinoma.[4] The Child-Pugh classification scores five variables (ascites, encephalopathy, prothrombin time, serum bilirubin and albumin) and the total score gives Child-Pugh A, B or C classifications (Child-Pugh A indicating best liver function).[5] All eligible patients had controlled blood pressure (up to three anti-hypertensive agents were allowed), and adequate liver, bone marrow, blood (INR ≤2.3), renal, and pancreatic function.[2, 3]

Patients were randomised equally to receive either lenvatinib (n=478) or sorafenib (n=476) stratified by region (Asia-Pacific or Western), macroscopic portal vein invasion, extrahepatic spread, or both (yes or no), ECOG performance status (0 or 1), and bodyweight (<60kg or ≥60kg). Patients received oral lenvatinib 12mg/day (bodyweight ≥60kg) or 8mg/day (bodyweight <60kg) or sorafenib 400 mg twice daily in 28-day cycles until disease progression. Dose interruptions/reductions for toxicities related to lenvatinib were allowed. Sorafenib dose modifications were implemented according to prescribing information in each region.[2, 3]

The primary endpoint was overall survival, measured from the date of randomisation until the date of death from any cause. This was first tested for non-inferiority of lenvatinib compared with sorafenib, then for superiority. The intention-to-treat population was used for all efficacy outcomes. Patients who were lost to follow-up were censored at the last date they were known to be alive, and patients who remained alive were censored at the time of data cut-off.[2, 3] Duration of median overall survival was 13.6 months in the lenvatinib group, compared with 12.3 months in the sorafenib group (hazard ratio [HR] 0.92, 95% confidence interval [CI]: 0.79 to 1.06).[3] Lenvatinib was demonstrated to be non-inferior for overall survival compared with sorafenib. Superiority was not demonstrated.[3]

Hazard ratios for subgroups analysed generally supported the primary outcome of non-inferiority of lenvatinib compared with sorafenib however the hazard ratio in the Western population was higher (HR 1.08 [95% CI: 0.82–1.42]) than in the full population. Median overall survival was similar in patients who received lenvatinib in both the Western and Asia-Pacific subgroups (13.6 months and 13.5 months) but was longer in the Western subgroup compared with the Asia-Pacific subgroup of the patients who received sorafenib (14.2 months and 11.0 months).[3]

Superiority of lenvatinib compared with sorafenib was demonstrated for the secondary outcomes, progression-free survival (PFS), time to progression (TTP) and objective response rate (ORR) as shown in table 1.[3]

Table 1: Primary outcome and selected secondary outcomes from the REFLECT study. [3]

	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	P value
Median overall survival (months)	13.6	12.3	HR 0.92 (0.79 to 1.06)	-
Median progression-free survival (months)	7.4	3.7	HR 0.66 (0.57 to 0.77)	<0.0001
Median time to progression (months)	8.9	3.7	HR 0.63 (0.53 to 0.73)	<0.0001
Objective response rate (%)	24%	9.2%	OR 3.13 (2.15 to 4.56)	<0.0001

HR: hazard ratio, OR: odds ratio, CI: confidence interval

The median duration of study treatment for patients in the lenvatinib group was 5.7 months (Interquartile range [IQR] 2.9 to 11.1 months), compared with 3.7 months (IQR 1.8 to 7.4 months) in the sorafenib group. [3]

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), the hepatocellular carcinoma specific EORTC QLQ-HCC18 and EuroQol-5 Dimensions 3 level version (EQ-5D-3L) health questionnaires. Baseline scores were similar in the lenvatinib and sorafenib treatment groups. Following treatment, scores declined in both groups. There were no significant differences between the lenvatinib and sorafenib groups for most domains.[2, 3]

Summary of evidence on comparative safety

Treatment emergent adverse events were reported in 99% of patients in both groups. These were grade three or above in 75% of patients in the lenvatinib group and 67% of patients in the sorafenib group. Serious treatment-emergent adverse events were reported in 43% and 30% of the respective groups. Treatment-related treatment-emergent adverse events led to drug interruption in 40% and 32%, dose reduction in 37% and 38%, and drug withdrawal in 8.8% and 7.2% of patients in the lenvatinib and sorafenib groups respectively.[3]

The most common adverse events were hypertension (which occurred in 42% of patients in the lenvatinib group compared with 30% in the sorafenib group), diarrhoea (39% and 46%), decreased appetite (34% and 27%), decreased weight (31% and 22%), fatigue (30% and 25%), palmar-plantar erythrodysaesthesia (27% and 52%), proteinuria (25% and 11%) and dysphonia (24% and 12%).

Other notable adverse events that occurred more commonly in the lenvatinib group included hypothyroidism (16% versus 1.7%) and vomiting (16% versus 7.6%).[3] Concomitant anti-hypertensive medication was taken by 73% and 68% of patients in the lenvatinib and sorafenib groups respectively. Levothyroxine was given to more patients in the lenvatinib group, 14% compared with 4.6% in the sorafenib group.[2]

The European Medicines Agency (EMA) noted that the incidence of hepatic-related serious adverse events and hepatic-related deaths was higher in the lenvatinib group (n=21) than in the sorafenib group (n=2). Hepatic encephalopathy was four times more frequent in the lenvatinib group and remained higher after adjustment by duration of exposure.[2]

Summary of clinical effectiveness issues

HCC usually occurs in the setting of liver cirrhosis, chronic hepatitis B or C infections, alcohol consumption, non-alcoholic steatohepatitis, or diabetes and the global incidence is increasing. In most HCC patients, the disease is diagnosed at advanced stages, when curative treatments, including resection, liver transplantation, and ablation, are no longer suitable. Prognosis is poor and treatment options are very limited for these patients.[2] Sorafenib, another oral multikinase inhibitor, is accepted by SMC for use in patients with advanced HCC, restricted to those who have failed or are unsuitable for surgical or loco-regional therapies (SMC no. 482/08). Regorafenib is available for second-line use in patients with HCC previously treated with sorafenib (SMC no. 1316/18). Median overall survival in the REFLECT study was 12.3 months in the sorafenib group which represents current treatment in Scotland for patients with unresectable advanced HCC.[3] Lenvatinib meets SMC end of life criteria and orphan equivalent criteria for this indication.

Non-inferiority of lenvatinib compared with sorafenib was demonstrated for overall survival in the key phase III REFLECT study however superiority was not demonstrated. The overall survival data are sufficiently mature. Superiority of lenvatinib was demonstrated for key secondary outcomes including PFS, TTP and ORR.[3] The REFLECT study was open-label and key secondary outcomes were assessed by investigators which could have introduced bias in assessment of disease progression. A retrospective blinded independent review using mRECIST or RECIST version 1.1 criteria supported the results of the investigator-led assessments.

During survival follow-up, 43% of lenvatinib patients and 51% of sorafenib patients had received subsequent anti-cancer treatment (medications and procedures) after stopping study treatment[2] and this could have confounded survival results. Of the patients who received further anti-cancer medication, more patients in the lenvatinib group than in the sorafenib group (25% versus 12%) received sorafenib during survival follow-up[2, 3] which could also have confounded the results. More patients in the sorafenib group (9.5% versus 3.1%) received anti-cancer therapy with investigational medications post-study treatment. Imbalances between groups in baseline serum alpha fetoprotein (AFP) levels and the proportion of patients with underlying hepatitis C may have favoured the sorafenib arm.[3]

A high proportion of patients recruited to the REFLECT study were Asian (69%). [3] Around a third of patients were recruited from Western regions. In the Western population, imbalances between the lenvatinib and sorafenib groups in the proportion of patients receiving anti-cancer medication after study treatment and baseline AFP levels may have favoured sorafenib for overall survival and resulted in the higher hazard ratio in the Western region, although the median overall survival difference between groups was only 0.6 months. The EMA also noted that this may be due to different aetiologies for HCC in the West where there is less hepatitis C induced cirrhosis and more alcohol induced, leading to an increased likelihood of developing hepatic encephalopathy.[2]

Patients recruited to REFLECT were required to be categorised as Child-Pugh class A and have an ECOG performance status score of 0 or 1.[2, 3] This is not specified in the licensed indication. The efficacy and safety profile of lenvatinib in patients with liver impairment or worse performance status are uncertain. Since lenvatinib is mainly eliminated by hepatic metabolism, an increase in exposure in patients with moderate to severe hepatic impairment is expected. Close monitoring of the overall safety including liver function tests are recommended in patients with mild or moderate hepatic impairment.[1] The EMA states that *'a non-interventional post-marketing Phase IV safety study will be performed in the EU (or Western population) to better characterise safety, primarily hepatotoxicity, in real-life conditions and to inform further on contributing factors'*.[2]

The introduction of lenvatinib would provide another treatment option for patients with advanced or unresectable HCC who have received no prior systemic therapy. Prognosis is poor in this patient group and treatment options are very limited. Clinical experts consulted by SMC considered that the place in therapy of lenvatinib is as an alternative to sorafenib. Lenvatinib is administered orally, as is the relevant comparator, sorafenib, and clinical experts considered that it would have similar service implications.

Summary of comparative health economic evidence

The submitting company presented a lifetime cost-utility analysis comparing lenvatinib to sorafenib in the full licensed population. Sorafenib was confirmed by SMC clinical experts as being an appropriate comparator.

A 3-state partitioned survival model was used and the key source of clinical data was the REFLECT trial described above. Extrapolation of overall survival (OS) and PFS was carried out. Multivariate adjustments to the OS and PFS data were made for baseline imbalances between the two arms of the trial population and the adjusted results were used as the base case figures in the economic analysis. OS for lenvatinib and sorafenib was extrapolated using the log-logistic distribution and PFS extrapolation used the log-normal distribution. The time horizon of the model was 20 years.

Quality of life was assessed within the pivotal study using EQ-5D-3L and this provided the source of the utility values in the model. The resultant values for progression-free and progressed disease were 0.745 and 0.678 respectively. No adjustment was made for disutilities related to adverse events.

Costs in the model related to medicines acquisition costs, treatment of adverse events, subsequent treatment costs (as per the REFLECT study) and costs associated with background disease management. Dosing for lenvatinib was based on the mean dosing in the REFLECT study (9.4mg). Monitoring was assumed to be equivalent between the arms of the model.

A Patient Access Scheme (PAS) was proposed by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. The base case results without the PAS and key sensitivity analyses are presented below. A PAS discount is in place for sorafenib and this was included in the results used for decision-making by the SMC by using estimates of the comparator PAS prices.

Without the PAS for either medicine, the incremental cost-effectiveness ratio (ICER) was £46,145 per QALY based on an incremental cost of £8,127 and a QALY gain of 0.18. Sensitivity analysis around this ICER is shown in table 2.

Table 2: key sensitivity analyses

	Scenario	ICERs using list price for both medicines
1	1 year time horizon	£125,127
2	Resource use halved in all health states	£48,606
3	Adjustment for AFP and stratification factors only	£47,826
4	Removal of survival gains for lenvatinib (sorafenib OS used for both arms of the model)	£30,044
5	Use of corrected group method for adjustment of baseline characteristics	£47,454
6	Assuming all patients receive a dose of lenvatinib of 12mg per day	£65,468

AFP= alpha fetoprotein, OS=overall survival, ICER=incremental cost-effectiveness ratio, PAS=patient access scheme.

The results presented do not take account of the PAS for sorafenib or the PAS for lenvatinib but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for sorafenib due to commercial confidentiality and competition law issues.

There were a number of weaknesses with the analysis:

- The economic model predicted a survival gain with lenvatinib compared to sorafenib. While it is noted there may have been some biases in the analysis towards sorafenib given differences in post-progression treatment use, the trial showed non-significant differences in overall survival. As such, the company was asked to provide analysis where the predicted QALY gain is on the basis of PFS benefits only. Analysis removing any OS gain was provided by the company and showed that when this change was implemented in the model (OS for sorafenib applied in both arms of the model) the lenvatinib ICER reduced (Table 2, analysis 4). This occurs because removing survival benefit in the lenvatinib arm of the model leads to reduced post-progression costs alongside the reduced QALY gain.

- The base case analysis used PFS and OS adjusted for imbalances in baseline characteristics between arms of the trial using multivariable adjustments. The SMC statisticians have indicated that there are weaknesses with this method of adjustment and suggested that the corrected group prognosis method may be more appropriate. The company provided additional sensitivity analysis using this method and this resulted in only a small increase in the base case ICER (sensitivity analysis 5 in the table above).
- Lenvatinib is dosed according to patient weight and in the model uses the mean dosing in the clinical study. Given the predominance of Asian patients in the study and thus potentially lower weights compared to the population in NHSScotland, the company was asked to provide a worst case analysis assuming all patients would require the 12mg per day dosing. This increased the ICER as shown in sensitivity analysis 6.

The Committee considered the benefits of lenvatinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as lenvatinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the Committee accepted lenvatinib for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified patient groups

- We received submissions from the British Liver Trust and Hepatitis Scotland. Both organisations are registered charities.

- The British Liver Trust has received 11.3% pharmaceutical company funding in the past two years, with none from the submitting company. Hepatitis Scotland has not received any pharmaceutical company funding in the past two years.

- Patients with advanced HCC have a very poor prognosis and if surgery or liver transplant are not appropriate then there are few treatment options. There are often no symptoms in the early stages so people are usually diagnosed very late.

- When patients are diagnosed with HCC, they often experience depression from the poor prognosis and a range of symptoms including severe pain that cannot be treated without worsening their liver condition. Patients and their families live with uncertainty, hopelessness and often stigma and isolation due to the image of liver disease.

- Patients with HCC are often younger than those with other cancers and as the prognosis for those with advanced HCC is particularly poor, the opportunity to gain extra time with

lenvatinib is of significant importance to patients and their families to make financial and other arrangements.

- Some patients may have improved health-related quality of life using one drug rather than another so it is important that clinicians have more than one treatment option when treating patients.

Additional information: guidelines and protocols

The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of hepatocellular carcinoma (2018) notes that for patients with advanced HCC sorafenib is recommended as the standard first-line systemic therapy. It is indicated for patients with well-preserved liver function (Child-Pugh A) and with advanced tumours (BCLC–C) or earlier stage tumours progressing upon or unsuitable for loco-regional therapies. Lenvatinib has recently been shown to be non-inferior to sorafenib and is also recommended in the first-line setting. Regorafenib is recommended as second-line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A) and good performance status (evidence high; recommendation strong). Recently, cabozantinib has shown survival benefits versus placebo in this setting. Based on uncontrolled but promising data, immune therapy with nivolumab has received FDA approval in second-line treatment, pending phase III data for conventional approval, however the EASL guideline notes that the data are not mature enough to give a clear recommendation.[6]

The European Society for Medical Oncology (ESMO) guideline (The Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [2018]), states that sorafenib is the standard of care for patients with advanced HCC. It is recommended in patients with well-preserved liver function and Eastern Cooperative Oncology Group (ECOG) PS 0–2. Lenvatinib, which was pending European Medicines Agency (EMA) approval at the time this guideline was published, showed non-inferiority efficacy compared with sorafenib and can be considered in patients with advanced HCC without main portal vein invasion and with ECOG PS 0–1 as a first-line systemic treatment option. Regorafenib is the standard of care for patients with advanced HCC who have tolerated sorafenib but progressed. The guideline also notes that cabozantinib and ramucirumab can be considered as second-line treatment options. Lastly, this guideline advises that immunotherapy with nivolumab and pembrolizumab can be considered in patients who are intolerant to, or have progressed under, approved tyrosine kinase inhibitors (pending EMA approval). They note that for a definitive recommendation, it is necessary to wait for the results of randomised trials.[7]

In Scotland, the Scottish HepatoPancreatoBiliary Cancers Managed Clinical Network published an updated guideline for the management of hepatocellular carcinoma in 2016.[8] This guideline predates the availability of lenvatinib for the indication under review and in relation to systemic anti-cancer therapy it recommends sorafenib in patients with HCC who are not suitable for curative treatment, as long as patients have Child-Pugh class A or possibly B, performance status

0-2, blood pressure well controlled (including with anti-hypertensive medication) and limited cardiovascular and other comorbidity.[8]

Additional information: comparators

Sorafenib

Cost of relevant comparators

Medicine	Dose Regimen	Cost per 28 days (£)
Lenvatinib	<60kg: 8mg orally once daily ≥60 kg: 12mg orally once daily	**2,682 to 4,024**
Sorafenib	400mg orally twice daily	3,577

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 06.01.18. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 123 patients eligible for treatment with lenvatinib in year 1, rising to 144 in year 5. The estimated uptake rate was 16% in year 1 and 57% in year 5, resulting in 20 patients estimated to receive treatment in year 1, rising to 82 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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7. Vogel A CA, Chau I, Daniele B, Llovet J, Meyer T, Nault J-C, Neumann U,, Ricke J SB, Schirmacher P, Verslype C, Zech CJ, Arnold D & Martinelli E. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.
8. North, South East and West of Scotland Cancer Networks HepatoPancreatoBiliary Cancers National Managed Clinical Network. Scottish Clinical Management Guideline for Hepatocellular Carcinoma (HCC). 2016.

This assessment is based on data submitted by the applicant company up to and including 15 February 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.