Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

lenvatinib 4mg and 10mg hard capsules (Lenvima®) SMC No. (1179/16)

Eisai Ltd.

09 September 2016

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and ultra-orphan medicine processes

lenvatinib (Lenvima®) is accepted for use within NHS Scotland.

Indication under review: treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

Lenvatinib, compared with placebo, significantly improved progression free survival in adults with RAI-refractory DTC.

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

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 10 October 2016

Indication

Treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

Dosing Information

24mg orally once daily, at about the same time each day, with or without food. The capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

The daily dose can be modified as needed according to the toxicity management plan detailed in the summary of product characteristics (SPC). Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

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

Product availability date

June 2015
Lenvatinib has been designated as an orphan medicine by the European Medicines Agency (EMA). It also meets SMC ultra-orphan and end-of-life criteria.

Background

Lenvatinibis a multikinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3, fibroblast growth factor receptors (FGFR)-1, -2, -3, and -4, and platelet derived growth factor receptor alpha (PDGFRα). It has anti-angiogenic properties and inhibits tumour growth.Lenvatinib is licensed for treatment of radioactive iodine (RAI)-refractory differentiated thyroid carcinoma (DTC) and has been designated by the EMA as an orphan medicinal product for this indication.[1,2]

Lenvatinib is the second therapy, after sorafenib, licensed for treatment of RAI-refractory DTC. Both drugs are multikinase inhibitors, including inhibition of tyrosine kinase, and decrease tumour cell proliferation and inhibit tumour growth. They have both been designated as orphan medicinal products for treatment of thyroid cancer by the European Commission.[1-3,7,8] Sorafenib has been accepted by SMC for use within NHS Scotland for progressive, locally advanced or metastatic, RAI-refractory DTC.Lenvatinib meets SMC ultra-orphan and end-of-life criteria.

Lenvatinibis eligible for consideration by SMC under its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

DTC is the most common thyroid cancer, accounting for 90% to 95% of cases. Initial treatment is surgery (thyroidectomy) then RAI ablation followed by thyroxine therapy. Tumour recurrence may occur in up to 25% of patients as local recurrence or distant metastasis. Approximately one third of distant metastatic DTC become refractory to RAI, at which point they assume a more aggressive course with 10-year survival of approximately 10%.[3] Symptoms include swallowing and breathing

difficulties related to cervical and lung metastasis. Recurrent neck lesions cause a third of the cancer-related deaths, with the remainder due to distant metastasis mainly within the lung and bones.[8] Chemotherapy for RAI-refractory DTC has been used in the past, but offered little benefit and significant toxicity.

Prior to licensing of sorafenib, treatment of RAI-refractory DTC, which comprised chemotherapy or best supportive care, was associated with median survival rates of typically less than three years. Sorafenib may now be considered standard of care. Currently, it is difficult to estimate median OS with sorafenib. In a small phase II study median OS with sorafenib was around three years,[8,11] but it is not yet known within the sorafenib group in the pivotal placebo-controlled phase III (DECISION) study. A significant proportion (75%) of patients in the placebo group of the latter study received open-label sorafenib after disease progression and median OS from randomisation in the placebo group was 36.5 months (median time to progression in the placebo group was around 5.8 months).[8,12,13]

A patient and clinician engagement (PACE) meeting was held to consider the added value of lenvatinib in the context of treatment currently available in NHS Scotland. At the PACE meeting, attention was drawn to the lack of therapeutic options, and therefore unmet need, for patients who are unsuitable for, or intolerant of, sorafenib, or who progress on sorafenib. Metastatic disease can be significantly symptomatic. In addition, patients may suffer a poor quality of life and the psychological impact of RAI-refractory DTC can be substantial with low mood and fatigue.

Impact of new technology

Summary of evidence on comparative efficacy

A double-blind phase III study (SELECT) recruited 392 adults who had RAI-refractory DTC with radiographic evidence of progression, defined by Response Evaluation Criteria in Solid Tumour (RECIST) version 1.1,within the preceding 12 months and Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2. Randomisation was stratified by region (Europe, North America or other), age (≤65 or >65 years), prior VEGF or VEGFR-targeted therapy (none or one). Patients were assigned in a 2:1 ratio to lenvatinib 24mg orally once daily or placebo. Treatment continued until disease progression or unacceptable toxicity. After confirmed disease progression patients in the placebo group could receive open-label lenvatinib in an extension study. The primary outcome was progression free survival (PFS), defined as time from randomisation to death or confirmed disease progression assessed using RECIST version 1.1 by a blinded independent radiologic review at a core imaging laboratory. This was assessed in the intention-to-treat (ITT) population, which comprised all randomised patients, using a stratified log-rank test.[3,4]

At the cut off (15 November 2013) for analysis of the primary outcome within the lenvatinib and placebo groups, 41% (107/261) and 86% (113/131) of patients had a PFS event, with 36% (93/261) and 83% (109/131) having confirmed disease progression, and 5.4% (14/261) and 3.1% (4/131) having died before confirmed disease progression. Lenvatinib, compared with placebo, significantly increased PFS, with hazard ratio (HR) of 0.21 (99% confidence interval [CI]: 0.14 to 0.31), p<0.0001. Median PFS was 18.3 months (95% CI: 15.1 to not estimable) and 3.6 months (2.2 to 3.7) in the respective groups. Objective response rate (ORR), defined as complete response (CR) or partial response (PR) on RECISTversion 1.1 by independent radiologic review, was significantly greater in the lenvatinib group compared with placebo: 65% (169/261) versus 1.5% (2/131). All responses were PR, except for four patients in the lenvatinib group who had CR.[3,4]

In an updated analysis at data cut off 31 August 2015, median PFS was 19.4 and 3.7 months in the lenvatinib and placebo groups, respectively, with a HR of 0.24 (95% CI: 0.17 to 0.35), p<0.0001.[14]

In an analysis at data cut off 15 June 2014, overall survival (OS) data were immature. There had been crossover of 88% (115/131) of patients in the placebo group to open-label lenvatinib. In the lenvatinib and placebo groups, median follow-up for OS was 23.6 versus 24.1 months, and 36% (93/261) versus 42% (55/131) of patients had died, respectively. In analysis that did not adjust for crossover of placebo patients to lenvatinib at disease progression, the HR was 0.80 (95% CI: 0.57 to 1.12), p=0.1993, and median OS had not been reached in either group. After adjustment for crossover using the rank preserving structural failure time (RPSFT) model, the HR was 0.53 (95% CI: 0.34 to 0.82), p=0.0051. Median OS could not be estimated in the lenvatinib group and was estimated at 19.1 months in the placebo group.[5]

Subgroup analysis of PFS by age, sex, race, region, tumour size, histology, and presence of BRAF or RAS mutations were consistent with the primary analysis. Within the lenvatinib and placebo groups, 25% (66/261) and 21% (27/131) had received previous treatment with VEGFR-targeted therapies, respectively. The PFS HR in this subgroup, 0.22 (95% CI: 0.12 to 0.41), was similar to that in VEGFR-targeted therapy-naive patients, 0.20 (95% CI: 0.14 to 0.27). The majority of patients were randomised within three months of their most recent assessment of progressive disease, 83% (215/261) and 76% (100/131) in the lenvatinib and placebo groups, respectively. In this subgroup, the HR for PFS was 0.19 (95% CI: 0.14 to 0.27). In patients who were randomised at least three months after their last assessment of progressive disease the HR was 0.35 (95% CI: 0.17 to 0.74).[3,4]

An open-label phase II study recruited 117 adults with RAI-refractory DTC or medullary thyroid cancer. In the cohort of 58 patients with DTC,two patients received lenvatinib 10mg twice daily and 56 patients received lenvatinib24mg once daily. The primary outcome, ORR assessed by independent radiologic review, was 50% (95% CI: 36.3 to 63.4) and all were PR. Median duration of response was 12.7 months. Median PFS was 12.6 months and OS data were immature.[3,6]

Summary of evidence on comparative safety

The overall safety profile of lenvatinib was in line with the safety profile of other multiple kinase inhibitors targeting VEGFRs and other tyrosine kinase inhibitors.It is characterised by adverse events of hypertension and proteinuria, which tend to occur at the beginning of treatment. Other common adverse events include diarrhoea, decreased appetite and weight, fatigue, nausea and vomiting, stomatitis, dysphonia, headache and palmer-plantar erythrodysaesthesia syndrome. These appear consistent with lenvatinib's pharmacology based on published reports of other VEGF and VEGFR-targeted therapies.[3]

There were no direct safety data relative to an active direct comparator. In the pivotal phase III study (SELECT) at the cut off on 15 March 2014, within the lenvatinib and placebo groups, 99.6% (260/261) and 90% (118/131) of patients had experienced an adverse event, which was related to treatment in 97% (254/261) and 61% (80/131), respectively. Lenvatinib, compared with placebo, was associated with higher rates of adverse events leading to dose reduction or interruption in 90% (234/261) and 19% (25/131) and discontinuation from treatment in 18% (46/261) versus 4.6% (6/131), respectively.[3]

Serious adverse events were reported in the lenvatinib and placebo groups by 53% (139/261) and 24% (31/131) patients, respectively.The available safety data indicate that the serious adverse events with lenvatinib include renal failure and impairment, cardiac failure, intracranial haemorrhage, posterior reversible encephalopathy, hepatic failure and arterial thromboembolism (cerebrovascular accident, transient ischaemic attack and myocardial infarction).[3]

Based on indirect comparison, the EPAR notes that lenvatinib is associated with a similar overall safety profile to sorafenib, although lenvatinib seems to be associated with higher rates of hypertension, proteinuria and gastrointestinal events such as nausea and vomiting while sorafenib is associated with higher rates of palmer-plantar erythrodysaesthesia (PPE), rash, alopecia and increased thyroid-stimulating hormone (TSH).

Summary of clinical effectiveness issues

In the lenvatinibpivotal phase III study (SELECT), the primary outcome of PFS was significantly improved by about 15 months with lenvatinib compared with placebo, which was considered by the European Medicines Agency (EMA) to be clinically meaningful. Lenvatinibwas also associated with an ORR of 65%.OS data were immature and there was significant crossover of patients from the placebo group to open-label lenvatinib at disease progression: 83% and 88% at November 2013 and June 2014 cut offs, respectively. At the latter cut-off, a RPSFT analysis to adjust for crossover suggested an improvement in OS with lenvatinib compared with placebo. The EMA noted that the RPSFT model has serious limitations, including an assumption that treatment effect is constant irrespective of when it is initiated in the course of the disease. However, this was considered to be untestable and, as prognosis changes after disease progression, likely to be untrue. The adjustment was considered likely to result in over-estimation of treatment effect. It was noted that results were sensitive to other statistical criteria (i.e. method for determining acceleration factor F and re-censoring applied to all censored patients irrespective of switch). In summary, the EMA noted that results from the RPSFT model could only be considered as supportive.[3]

In the SELECT study,90% of lenvatinib-treated patients had an adverse event that resulted in a dose reduction or interruption. In practice, monitoring may be required for prompt detection and effective management of these to prevent dose reductions or interruptions, which may impact efficacy.[3]

In the SELECT study,96% of patients had an ECOG performance status of 0 or 1 and this may limit the application of results to patients with poorer performance status.[3]Quality of life was not assessed in this study.

There are no direct comparative data versus sorafenib, the key comparator. The EMA requested a naïve indirect comparison of key efficacy data of the lenvatinib (SELECT) study and sorafenib (DECISION) study, and noted that the difference in median PFS between the active treatment and placebo arms was 14.7 months in the SELECT and 5.0 months in the DECISION study. The HR and CIs for lenvatinib versus placebo in SELECT (0.21; 95% CI: 0.14 to 0.31) were lower than and did not overlap with those of sorafenib versus placebo in the DECISION trial (0.59; 95% CI: 0.45 to 0.76). However, it was noted that differences in populations might have contributed to the differences observed between the two studies.

The company conducted a matched adjusted indirect comparison (MAIC) of lenvatinib versus sorafenib in adults with RAI-refractory DTC for the outcomes PFS and OS, which included data from the pivotal phase III studies supporting the licences, SELECT and DECISION. This suggested a statistically significant PFS advantage for lenvatinib compared with sorafenib within RAI-refractory DTC patients who have not received prior VEGFR-targeted therapy. OS data from both studies were immature and possibly confounded, with no significant differencebetween lenvatinib and sorafenib for these. The validity of the results may be limited by weaknesses in the MAIC, including heterogeneity across the studies in inclusion criteria, assessment of disease progression and analysis of PFS. There was insufficient detail to compare all possible confounding baseline characteristics and itfailedto adjust for unobserved confounding factors or for factors not observed in both studies. The indirect comparison did not include comparisons of quality-of-life or safety data. However, the results of the MAIC were not applied to the base case economic analysis which, following RPSFT adjustment, predicted a mean survival gain of0.79 life years or 9.5 months.

Clinical expert opinion indicates that lenvatinib is viewed as a therapeutic advancement and is likely to replace sorafenib as first-line treatment for progressing RAI-refractory DTC.

At the PACE meeting, it was noted that shrinkage of lesions would be expected to reduce symptoms of shortness of breath and pain, thus improving quality of life and general well-being. Clinicians

described personal experience of rapid response and reduction in tumour size following use of lenvatinib. Lenvatinib was considered to offer superior PFS compared to sorafenib, along with a more manageable side-effect profile.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of lenvatinib, as an end of life and ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.
The key points expressed by the group were:

- RAI refractory DTC is a rare cancer associated with a significantly reduced life expectancy. Patients have metastatic disease, which is progressive, unresponsive to standard treatments and associated with significant symptoms such as breathlessness and cough in relation to lung metastases and difficult pain syndromes from bony disease.

- Current treatment options are limited. Conventional chemotherapy is considered as ineffective. Sorafenib is the only effective treatment available at present and there are no therapeutic options available for patients who are unsuitable for, or unable to tolerate, sorafenib or for those who progress on sorafenib.

- Lenvatinib appears to offer superior PFS compared with sorafenib and its side effect profile may be more manageable. Stabilisation and/or shrinkage of the disease can potentially improve both quality and duration of life for this small group of patients. Clinicians described personal experience of rapid response (within 6-8 weeks) and considerable reduction in tumour size.

- The burden of this oral treatment is relatively limited for the majority of patients and their families. Side effects (e.g. hypertension, proteinuria) can be well managed via outpatient clinics.

- PACE participants considered lenvatinib to be the first choice TKI for RAI-refractory DTC. In addition, patients currently receiving sorafenib would be expected to move to lenvatinib on development of intolerance or disease progression.

Additional Patient and Carer Involvement
We received patient group submissions from British Thyroid Foundation, Butterfly Thyroid Cancer Trust and Thyroid Cancer Alliance. British Thyroid Foundation has received 13% pharmaceutical company funding in the past two years, including from the submitting company. Butterfly Thyroid Cancer Trust has received approximately 10% pharmaceutical company funding in the past two years, but none from the submitting company. Thyroid Cancer Alliance has received 95% pharmaceutical company funding in the past two years, but none from the submitting company. Representatives from each patient group also participated in the PACE meeting. The keys points of their submissions have been included in the full PACE statement.

Value for money

The submitting company presented a cost-utility analysis of lenvatinib compared with sorafenib in adult patients with progressive, locally advanced or metastatic DTC refractory to RAI. Based on SMC clinical expert feedback the comparator is appropriate, having been accepted for use by SMC in the same patient population. The economic model was a partitioned area under the curve survival model, with the following health states: starting state of stable disease/no response, with possible transitions to response to treatment, progressive disease and death. The time horizon was initially set at 10 years; however, a lifetime horizon represents the appropriate base case and the company was asked to provide updated base case results using a lifetime horizon.

Progression free and overall survival data used in the model were derived from an indirect comparison of lenvatinib versus sorafenib using the pivotal phase III clinical study data for each medicine (SELECT and DECISION studies respectively), with adjustment for the crossover of placebo patients to active drug in each study using the RPSFT modelling approach (87.8% and 74.8% of lenvatinib and sorafenib patients respectively). In the base case, PFS data from the first data-cut from the SELECT study (the primary analysis) for lenvatinib was felt to be sufficiently mature not to require extrapolation, whereas for OS based on the second data cut (34 months follow-up) there were around 50% of patients still alive so OS extrapolation was performed by fitting an exponential function to the end of the Kaplan-Meier plot using a piecewise model. The piecewise model was stated to represent the optimal approach of several approaches tested, and the exponential the best fitting function based on several criteria, including statistical fit, level of uncertainty and face validity of results. Alternative models and parametric functions were tested in scenario analysis. The HRs from the indirect comparison of lenvatinib versus sorafenib for PFS (HR=0.36, 95%CI: 0.2-0.6) and OS (HR=0.77, 95%CI: 0.5-1.3) were then applied to estimate relative life years gained. Adverse events of grade ≥3 and alopecia were included in the model for estimation of disutilities and management costs.

Utility estimates for the model health states were derived from a published vignette-based time trade-off study using health state descriptions for thyroid cancer conducted in 100 members of the UK general public. This provided estimates of 0.80 for the base stable disease state, 0.86 for response, 0.5 for progressive disease, and estimated utility decrements of -0.042 for lenvatinib and -0.117 for sorafenib applied in the stable or response states for several adverse events impacting on health-related quality of life (diarrhoea, fatigue, hand and foot syndrome, alopecia).

The model included drug acquisition and oral administration costs for lenvatinib and sorafenib, taking into account dose reductions to manage toxicity, based on data from the SELECT and DECISION studies. An estimated daily dose of 15.3mg for lenvatinib based on the last dose received derived from the open-label extension phase of the SELECT study, and an average daily dose of 651mg for sorafenib derived from the DECISION study (which equated to 1.93 lenvatinib capsules and 3.25 sorafenib tablets per patient per day), were used to estimate monthly drug acquisition costs in the economic analysis. Duration of treatment was until disease progression and based on relative PFS estimates of an average of 21.55 and 8.15 months for lenvatinib and sorefenib respectively. Post progression (secondary) treatment consisted of the same therapies (doxorubicin and cisplatin) and duration for each treatment arm. Costs of adverse event management were included, which consisted only of the costs associated with hospital stay. Disease management costs included use of outpatient visits and hospital stay based on a thyroid cancer chart audit conducted in Europe and verified by UK clinicians. The costs of end of life care were also included.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

Under the PAS, a simple discount was offered on the list price of the medicine. With the PAS, the base case result (for a lifetime horizon) was an incremental cost-effectiveness ratio (ICER) of £49,525 per quality-adjusted life-year (QALY) gained for lenvatinib versus sorafenib. This ICER includes an estimate of the PAS that is in place for sorafenib and is based on discounted incremental life years gained of 0.79 or 9.5 months. The key cost driver is the difference in drug acquisition costs. Incremental life year gains were estimated for lenvatinib over sorafenib pre-progression, with an incremental PFS gain of 1.04 years, partly offset by higher post-progression life years for sorafenib.

Scenario and sensitivity analysis demonstrated sensitivity to using standard deviations to vary the HR for overall survival for lenvatinib, with an ICER range of £29k/QALY to £96k/QALY with PAS. The results were also reasonably sensitive to varying all health state utilities by ±20%, with an ICER range of £41k to £62k/QALY with PAS. Applying the Weibull and Gompertz parametric functions for extrapolation of the OS data (the next best fitting functions) resulted in ICERs of £53k/QALY and £59k/QALY respectively with PAS. There was not high sensitivity to removing the additional utility increment associated with treatment response, or to varying relative adverse event disutilities.

In addition to the high ICER estimates, there were a number of issues and limitations in the economic analysis:

- OS data for lenvatinib used in the economic model were immature with median OS not having been reached, which limits the robustness of the economic analysis.
- The base case estimate of relative PFS and OS was from a naive indirect comparison of the SELECT and DECISION studies, with uncertainties over the comparability of the studies, additional uncertainty generated by the high crossover of placebo patients in both lenvatinib and sorafenib studies, and the need to adjust the OS HR using the RPSFT method. Also, there was no statistically significant difference in OS from the indirect comparison, and applying a HR of one is associated with an ICER of £92k/QALY with PAS, though this was considered to be a particularly conservative analysis. The company also provided an analysis using the HRs from the MAIC which resulted in an ICER of £47k/QALY with PAS. However, there are also limitations with the MAIC as described above.
- Whilst the OS analysis was based on the second data cut, the less mature primary analysis PFS data were used in the base case on the assumption that this is more robust as it represented the primary endpoint analysis in the SELECT study. However, it could also be considered appropriate to use the second data cut given it is more mature and aligns with the data used for the OS analysis. With this data-cut used for PFS and OS the ICER increased to £54k/QALY with PAS.
- There is uncertainty over the dose estimates used in the economic analysis. The estimate used for lenvatinib is based on the last mean dose in the SELECT study open-label phase and was justified by the company on the grounds that it represents the optimal and stable dose of lenvatinib. However, the sorafenib dose is based on the overall mean from the DECISION study so, unlike the lenvatinib estimate, would take into account the time patients spent on higher doses prior to dose reduction. Using the main study-based mean estimates seems more appropriate for a like-for-like dose reduction comparison. The company provided a scenario analysis applying the mean dose for lenvatinib of 17.2mg per day from the SELECT study after taking dose reduction and interruptions into account, producing an ICER estimate of £58k/QALY with PAS. Even with this comparison there is uncertainty over the relative dose reduction estimates for lenvatinib and sorafenib.
- There is some uncertainty about how lenvatinib may be used in clinical practice, with a possibility that it could be used in some patients after treatment with sorafenib. The company provided an exploratory analysis based on data from the SELECT study in which lenvatinib was compared to best supportive care. This was also intended to provide a benchmark ICER to assess cost-effectiveness of lenvatinib using direct study evidence rather than the indirect

comparison. In this analysis, the ICER was estimated at £49k/QALY or £55k/QALY with PAS, depending on the mean dose assumed for lenvatinib. It should be noted that this is based on the whole SELECT patient population and not just those who have received a prior therapy (the latter was 25% of the study population), so has some data limitations and was considered as supportive evidence only.

Impact beyond direct health benefits and on specialist services

At the PACE meeting, attention was drawn to the importance of delaying disease progression which can allow patients to retain their independence, experience a good quality of life and continue to work or maintain an active non-work life. This, in turn, reduces the carer burden and financial impact of a family member having to give up work. The physiological benefit of providing hope to patients and their families was emphasised.

The service impact associated with lenvatinib is likely to be minimal.

Costs to NHS and Personal Social Services

The submitting company estimated there would be would be 22 patients eligible for treatment with lenvatinib in year 1 and 62 patients in year 5. A mortality rate of 11% has been applied in year 2 and incrementally to year 5 (44%).

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 commercially confidential.**

Conclusion

The Committee also 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 medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted lenvatinib for use in NHS Scotland.

Additional information: guidelines and protocols

In July 2014 the British Thyroid Association published: “Guidelines for the management of thyroid cancer”. In the section on palliative care in recurrent/persistent DTC, it notes that palliative chemotherapy has largely been superseded by targeted therapies although chemotherapy can be considered in good performance status patients with rapidly progressive, symptomatic, RAI-refractory, locally advanced or metastatic disease when targeted therapies are unavailable or have proved unsuccessful. The agents used are doxorubicin and cisplatin, but durable responses are uncommon. The guidelines discuss targeted therapies for DTC including sorafenib. They state that the use of targeted therapies is a rapidly evolving area and clear guidance cannot be given at present and note the following points:

i The use of targeted therapies outside clinical trials should be endorsed by the multidisciplinarymeeting after careful consideration of the balance between potential benefits and harm .
ii The principal indication for targeted treatments is radiologically progressive, symptomatic disease,refractory to conventional treatments.
iii Targeted therapies should only be administered in the setting of cancer units that have experiencein monitoring and managing adverse effects of targeted therapies.
iv Consideration should therefore be given to entry into clinical studies.[9]

In 2012 the European Society of Medical Oncology (ESMO) published "Thyroid cancer: ESMO ClinicalPractice Guidelines for diagnosis, treatment and follow-up". They state in metastatic diseasechemotherapy is no longer indicated because of lack of effective results and should be replaced byenrollment of the patients in experimental trials with targeted therapy. The guidelines note thatpreliminary results for tyrosine kinase inhibitors, including sorafenib, for DTC in clinical studies arepromising and indicate that targeted therapy might become the first line treatment of metastaticrefractory thyroid cancer patients in the near future, they are not standard therapy today and should be administered only in the context of clinical trials.[10]

These guidelines pre-date the licensing of TKI for this indication.

Additional information: comparators

The comparator is the other multikinase inhibitor licensed for treatment of RAI-refractory DTC, sorafenib.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Lenvatinib	**24mg orally once daily**	**52,307**
Sorafenib	400mg orally twice daily	38,746

Doses are for general comparison and do not imply therapeutic equivalence. Cost of sorafenib is from eVadis03 May 2016 and for lenvatinib is from eMC dictionary of medicines and devices on 02 June 2016. Costs do not take account of any patient access schemes.

References

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This assessment is based on data submitted by the applicant company up to and including 15 July 2016.

*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_statements/Policy_Statements

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.