Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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sorafenib 200mg film-coated tablets (Nexavar®) SMC No. (1055/15)

Bayer Plc.

05 June 2015

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 NHS Scotland. The advice is summarised as follows:

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

sorafenib (Nexavar®) is accepted for use within NHS Scotland.

Indication under review: treatment of patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine.

Treatment with sorafenib demonstrated a significant, clinically relevant five-month improvement in median progression free survival compared with placebo in patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of sorafenib. 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 the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 13 July 2015

Indication

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

Dosing Information

The recommended dose of sorafenib for differentiated thyroid carcinoma (DTC) in adults is 400mg sorafenib orally twice daily. It should be administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least one hour before or two hours after the meal. The tablets should be swallowed with a glass of water. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

If dose reduction is necessary, it should be carried out in stages as required; first to 600mg sorafenib daily in divided doses (two 200mg tablets and one 200mg tablet twelve hours apart); then to 200mg twice daily, and if necessary further reduced to one 200mg tablet once daily. After improvement of non-haematological adverse reactions, the dose may be increased.

Sorafenib treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Product availability date

June 2014. In addition to orphan status designated by the European Medicines Agency, sorafenib meets SMC ultra-orphan and end-of-life criteria.

Summary of evidence on comparative efficacy

Thyroid carcinoma is a rare disease which accounts for approximately 1% of all new cancers.[1] Sorafenib is an oral multikinase inhibitor that inhibits the activity of targets present in the tumour cell and vasculature. It is the first drug with a marketing authorisation specifically for the treatment of patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to RAI.[1,2] Recent British Thyroid Association guidelines state that the principal indication for targeted treatments is radiologically progressive, symptomatic disease, refractory to conventional treatments.[3]

The evidence is from an ongoing randomised, double-blind, placebo-controlled, phase III study, DECISION, that recruited adult patients with RAI-refractory locally advanced or metastatic DTC (papillary, follicular, Hurthle cell) and in poorly differentiated tumours, that had progressed within the previous 14 months.[4] Assessment was conducted according to Response Evaluation Criteria in Solid Tumours (RECIST) and patients had to have ≥1 measurable lesion by computed tomography or magnetic resonance imaging. RAI-refractory status was defined as ≥1 target lesion without iodine uptake; or, if the tumours had iodine uptake, disease progression after one RAI treatment within the past 16 months, or progression after two RAI treatments within 16 months of each other (with the last such treatment administered >16 months prior to randomisation), or have received cumulative RAI activity of ≥22.2GBq. Patients had to have Eastern Cooperative Oncology Group (ECOG) performance status ≤2; with adequate bone marrow, liver, and renal function, and serum thyroid stimulating hormone (TSH) concentration below 0.5mIU/L. Prior chemotherapy for thyroid cancer was not allowed.[4]

Patients were randomised in a 1:1 ratio, stratified by age (<60 or ≥60 years) and geographical location (North America or Europe or Asia), to receive treatment with sorafenib 400mg or matching placebo, twice daily at least one hour before or two hours after a meal. Study drug could be temporarily stopped or the dose could be reduced for toxicity according to pre-specified criteria. Treatment was to continue until progression, unacceptable toxicity, non-compliance, or withdrawal of consent. Upon disease progression, the treatment could be unblinded and patients (from active and placebo groups) could receive open-label sorafenib for as long as the investigator deemed appropriate.[4]

The primary outcome was progression free survival (PFS) analysed in the intention to treat (ITT) population comprising all randomised patients.[4] PFS was defined as the time from randomisation to first observed disease progression (radiological as determined by central radiological review or clinical progression due to bone lesions that required external radiation, whichever was earlier) or death (due to any cause) if it occurred before progression was documented.[1] Assessment of PFS took place every eight weeks by central independent blinded review with the use of modified RECIST guidelines.[4]

PFS events occurred in 55% (113/207) of the sorafenib group and 65% (137/210) of the placebo group.[1] Median PFS was 10.8 months in the sorafenib group and 5.8 months in the placebo group; hazard ratio (HR) 0.59 (95% confidence interval [CI]: 0.45 to 0.76); p<0.0001. The results of sub-group analyses suggest a consistent benefit in PFS for sorafenib treatment in all pre-specified subgroups, including age, sex, geographical region, histology, sites of metastases, and tumour burden.[4]

Overall survival was a secondary endpoint and an updated analysis was conducted in May 2013, nine months after the data cut-off for the primary analysis. The mortality rate was 32% (66/207) in the sorafenib group and 34% (72/210) in the placebo group. There was no statistically significant difference in overall survival between the treatment groups; HR 0.884 (95% CI: 0.633 to 1.236), one-sided p-value of 0.236. Median overall survival was not reached in the sorafenib arm and was 36.5 months in the placebo arm. The proportions of patients that received open-label sorafenib were 30% (61/207) from the original sorafenib group and 75% (157/209) from the original placebo group.[1,2]

Sorafenib did not produce any complete responses. Partial response rate was significantly higher in the sorafenib group compared with the placebo group: 12% (24/196) versus 0.5% (1/201) of patients (p<0.0001). The median duration of response to sorafenib was 10.2 months (95% CI: 7.4 to 16.6). In a post-hoc analysis, disease control rate (partial response or stable disease for ≥6 months) was 54% (106/196) with sorafenib versus 34% (68/201) with placebo (p<0.001).[4]

Health Related Quality of Life (HRQoL) was assessed as an exploratory outcome using the EuroQoL-5 Dimensions (EQ-5D) Index and visual analogue scale (VAS), and the Functional Assessment of Cancer Therapy General (FACT-G) questionnaire. The European Variation Assessment Report states that there was a stable, negative impact on HRQoL as estimated by FACT-G and EQ5D for sorafenib.[1]

Summary of evidence on comparative safety

In the double-blind phase of the DECISION study, patients were exposed to sorafenib treatment for longer than placebo. Median duration was 10.6 months versus 6.5 months, respectively. A total of 99% (204/207) of sorafenib patients and 88% (183/209) of placebo patients reported at least one adverse event, mainly grade 1 or 2 in severity. Study drug was stopped temporarily, or the dose decreased or withdrawn due to toxicity in 66% (137/207), 64% (133/207), and 19% (39/207) of patients, respectively, in the sorafenib group, and in 26% (54/209), 9.1% (19/209) and 3.8% (8/209) of patients, respectively, in the placebo group. The mean daily dose was 651mg with sorafenib and 793mg with placebo. Most adverse reactions occurred early; during the first treatment cycle approximately 70% of patients needed a dose decrease or temporary stoppage of study drug.[1,4]

The most commonly reported adverse events for sorafenib versus placebo were hand-foot skin reaction (76% versus 9.6%), diarrhoea (69% versus 15%), alopecia (67% versus 7.7%), rash or desquamation (50% versus 12%), fatigue (50% versus 25%), weight loss (47% versus 14%) and hypertension (40% versus 12%). One third (69/207) of sorafenib patients had increased serum TSH concentration >0.5mIU/L recorded as an adverse event compared with 13% (28/209) placebo patients. Hypocalcaemia was reported as an adverse event in 19% (39/207) of sorafenib patients.[4]

Serious adverse events occurred in 37% (77/207) of patients in the sorafenib group versus 26% (55/209) in the placebo group. The most common serious adverse events for sorafenib versus placebo were secondary malignancy 4.3% (n=9) versus 1.9% (n=4), dyspnoea 3.4% (n=7) versus 2.9% (n=6), and pleural effusion 2.9% (n=6) versus 1.9% (n=4).[4]

Secondary cancers occurred in nine sorafenib patients (seven had squamous cell carcinomas of the skin [one patient also had melanoma] and one each with acute myeloid leukaemia and bladder cancer) versus four placebo patients (one each of bladder cancer, colon carcinoma, pulmonary carcinoid tumours, and gastric cancer).[4]

One death in each group was considered to be related to treatment: myocardial infarction in a sorafenib patient and subdural haematoma in a placebo patient.[1,4]

Plasma concentrations of sorafenib are higher (doubled) in patients with DTC compared with renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC). The reason is not known, but this has resulted in a substantially higher frequency and higher severity of hand foot skin reaction, diarrhoea, alopecia, weight decrease, hypertension, hypocalcaemia, and keratoacanthoma/squamous cell carcinoma of skin in patients with DTC compared with patients in the RCC or HCC studies.[1,2] Close monitoring of blood calcium levels is recommended and severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes. TSH levels should also be closely monitored.[2]

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

Summary of clinical effectiveness issues

The vast majority (94%) of thyroid carcinomas are differentiated and most patients with DTC can be successfully treated with surgery (thyroidectomy), followed by RAI and thyroid hormone therapy for suppression of TSH. A small proportion of patients will develop RAI-refractory metastatic disease and should be monitored for disease progression. Most patients with widely metastatic, RAI-refractory DTC have a long indolent phase, are asymptomatic and may have a good quality of life for many years. Symptoms include difficulty in swallowing and breathing, pain, bone fracture, and spinal cord compressions.[1] There are no other treatment options specifically for patients with progressive, locally advanced or metastatic RAI-refractory DTC. Cytotoxic treatments, doxorubicin and cisplatin, have been used in the past but are generally considered to have poor efficacy and high toxicity.[3,5] In a phase II study, median overall survival for patients treated with sorafenib was 34.5 months.[6] It has been reported that once thyroid carcinoma no longer responds to RAI, survival with current treatment strategies is around three years.[7] The European Medicines Agency designated sorafenib as an orphan medicine. In addition, sorafenib meets SMC ultra-orphan and end-of-life criteria. Clinical experts consulted by SMC considered there was unmet need in this therapeutic area as there are currently no therapeutic options available.

DECISION, the first phase III study to use targeted therapy in RAI-refractory DTC, demonstrated a significant and clinically relevant five-month improvement in median PFS with sorafenib compared with placebo.[4] The response rate for sorafenib was low at 12%.[1] Efficacy in terms of overall survival has not been demonstrated: survival data reported to date are immature. Furthermore, the evidence for the effect of sorafenib on overall survival was confounded by the high level of cross over from the placebo arm when disease progression occurred. The negative effect of sorafenib on HRQoL is due to adverse events, and although statistically significant, these changes were not considered to be clinically meaningful according to minimal important differences.[7]

A limitation of the DECISION study is the inclusion of almost 10% of patients (sorafenib 12% and placebo 7.6%) with poorly differentiated thyroid cancer which is excluded from the licensed indication. Patients who had received prior chemotherapy were excluded and most (97%) patients had good ECOG performance status, ie 0 or 1. It is not known if these factors are representative of patients who would be eligible to receive sorafenib in Scotland.[4]

Clinical experts consulted by SMC considered that sorafenib offers a therapeutic advancement and would be used in patients with symptomatic RAI refractory DTC. They also noted that sorafenib has specific monitoring requirements.

Although the licensed indication does not specify the presence of symptoms, the Summary of Product Characteristics for sorafenib advises careful evaluation of prognosis in the individual patient considering maximum lesion size, symptoms related to the disease and progression rate before treatment is initiated.[2] The British Thyroid Association guidelines (July 2014) state that the principal indication for targeted treatments is radiologically progressive, symptomatic disease, refractory to conventional treatments; it advises careful consideration of the balance between potential benefits and harm.[5]

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

Summary of patient and clinical engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of sorafenib, as an ultra orphan and end of life medicine, in the context of treatments currently available in NHS Scotland for the treatment of patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI).

The key points expressed by the group were:

- DTC symptoms can be profoundly debilitating and frightening with a devastating impact on patients and their families. Locally advanced disease can cause difficulty breathing and/or swallowing, and neck pain. Metastatic disease can lead to pathological fractures due to bone metastases, chest and breathing difficulties from lung metastases, weight loss and chronic fatigue.

- There are no alternative treatment options available currently and, understandably, depression is common in patients and carers.

- Sorafenib offers the potential to relieve frightening symptoms, to markedly improve pain management and to improve both quantity and quality of life. For patients and their families the perceived psychological benefit of receiving an active treatment rather than best supportive care cannot be over-estimated.

- Clinicians suggest that patients with rapidly progressive disease and/or significant symptoms due to high disease burden are particularly likely to benefit. Sorafenib may improve symptoms to the point that patients can return to work and resume their wider societal role, which has economic and quality of life benefits for the for both the patients and their families.

- Sorafenib is an oral medication that can be given at outpatient clinic rather than requiring hospital stays, which benefits both patients and their families. In addition, it requires only short outpatient appointments (10 minutes) with a cancer specialist every 2 to 4 weeks initially to detect whether treatment is working and to monitor side effects.

- The most common adverse effect associated with sorafenib is hand and foot syndrome, but side effects can be largely managed with dose reductions and/or treatment holidays. This contrasts with the considerable toxicity, including nausea and vomiting, alopecia, and bone marrow suppression experienced with standard chemotherapy agents.

- PACE participants were extremely supportive of this medicine and described it as life changing and even life saving for this very small number of patients.

Summary of ultra orphan decision-making framework

Sorafenib has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines. Relevant factors under each of the criteria are summarised below.

Nature of the condition
Thyroid cancer is usually asymptomatic in the early stages of disease but, as the disease progresses, patients may experience difficulty swallowing and/or breathing, pain or sensitivity in the front of the neck or throat, hoarseness or other voice changes, and swelling of the lymph nodes in the neck. Metastatic disease can lead to pathological fractures due to bone metastases, chest and breathing difficulties from lung metastases, weight loss and chronic fatigue. Symptoms can become profoundly debilitating and cause patients to rely on carers.

At the Patient and Clinician Engagement (PACE) meeting, it was noted that there was a burden on families at a personal level and also at a financial level from the disease. It was also noted that psychological and mental health problems may also be experienced by patients and their carers.

Impact of the new technology
Sorafenib offers a treatment option for a group of patients who lack effective alternative therapies and thus experience high unmet need. As noted, treatment efficacy has been demonstrated in terms of a significant difference in median progression-free survival of 5 months, and a significantly greater number of patients experiencing a partial response to treatment. Overall survival data are immature and confounded by cross over; however, it is noted that in the economic model a survival gain was predicted.

At the PACE meeting, it was noted that delays in disease progression could be associated with improvements in quality of life and that symptoms such as pain can be markedly improved. Side-effects of treatment, notably hand and foot syndrome, were noted but were said to be largely manageable with dose reductions and/or treatment holidays. The side-effect profile of sorafenib was also contrasted with the distressing adverse events from standard chemotherapy such as nausea, vomiting and alopecia.

Value for money

The company submitted a lifetime cost-utility analysis comparing sorafenib plus best supportive care (BSC) with BSC alone in patients with progressive, locally advanced or metastatic DTC refractory to RAI. SMC clinical experts noted that treatment options are limited for these patients and therefore BSC is a reasonable comparator. In the analysis, BSC was assumed to include general disease management costs and palliative care costs.

A partitioned survival model was used with three health states: progression-free, progressed and dead. The model design allows for the proportion of patients in each health state to be calculated from the PFS and overall survival study data. The source of the clinical data used in the model was the DECISION study, with the placebo arm of this study assumed to represent BSC. The PFS and overall survival data from the pivotal study were extrapolated using parametric survival analysis. For PFS, goodness of fit statistics showed the log-normal curve was statistically the best fit to the data. However, the log-normal curve was judged to overestimate PFS based on clinical opinion and as a result, the company used the Weibull curve in the base case analysis on the basis that this produced more plausible estimates of survival.

A similar approach was taken to extrapolate the overall survival data that had been adjusted for crossover using the RPSFT method. Based on goodness of fit statistics, the log-normal distribution was the best statistical fit to the adjusted data, but again was judged to overestimate survival in the longer term. It was noted that the log-logistic and exponential distributions resulted in long-term survival estimates for the BSC arm which were consistent with published estimates. Due to the uncertainty over which curve was the most appropriate, the company decided to use a model averaging approach based on a weighted average which included a number of modelled survival curves (exponential, Weibull, log-normal and log-logistic). The model average results were estimated using weights derived from the goodness of fit statistics i.e. the better the statistical fit the higher the weight.

EQ-5D data were collected in the DECISION study and were used to estimate utility values for the model. The weighted average of all EQ-5D scores per cycle while patients were on treatment was assumed to represent the pre-progression utility value for each treatment arm. This resulted in utility values of 0.72 and 0.8 for the sorafenib and BSC arms respectively. Disutilities due to adverse events were not included separately in the model but the company argued these would be captured by the EQ-5D data, which may explain the lower utility value for sorafenib patients in the pre-progression phase of the model. A utility value of 0.64 was applied to all patients in the post-progression phase of the model.

The analysis included medicine acquisition costs, routine management costs and adverse event costs. Routine management costs included outpatient visits, procedures and monitoring costs, with a higher pre-progression cost per cycle estimated for the sorafenib arm due to additional monitoring while patients were on treatment. BSC included some palliative medicine costs as part of routine management but were estimated to be the same in both arms of the model. The costs of treating grade 3 or 4 adverse events observed in the DECISION study were included using rates from the study and resource use estimates based on clinical opinion.

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 given on the list price of the medicine. With the PAS, the company estimated a cost per QALY of £32,083. It is SMC policy to include the estimated quality-adjusted life-year (QALY) gain in the detailed advice document for all submissions. The PAS for sorafenib includes a discount to the NHS that is commercial in confidence and the submitting company has advised that publication of the QALY gain, when considered with other cost-

effectiveness data in the public domain, could reveal the level of discount. For this reason, SMC has agreed not to publish the estimated QALY gain for sorafenib.

The sensitivity analysis showed that the incremental cost-effectiveness ratio (ICER) was sensitive to the time horizon, with a 10-year time horizon resulting in an ICER of £46k. The results were also sensitive to the overall survival modelling approach, with the analysis using a Weibull curve increasing the ICER to £45k. Increasing the RPSFT-adjusted overall survival HR by two standard errors and increased the ICER to £38k.

In addition to the high base case cost-effectiveness ratio, the following limitations were noted:

- A key limitation with the clinical data used in the model is that the overall survival estimates are confounded by cross over. The company adjusted for this using the RPSFT method and the adjusted HR was used in the model. This approach has been used and accepted previously, but it does introduce some uncertainty into the overall survival estimates and, as noted above, the results are sensitive to the overall survival HR.
- The goodness of fit statistics showed there was little difference between the different extrapolation models. The cross over adjusted overall survival data were extrapolated over the long term using a weighted average extrapolation approach based on weights derived from goodness of fit statistics. The weighted average method included the Weibull, log-normal, loglogistic and exponential curves. This is an unusual approach to extrapolation and the results were sensitive to using alternative methods. For example, using the Weibull curve increased the ICER to £45k. The SMC statistical advisor commented that while the approach used was not inappropriate, it is not clear that it is preferable to selecting one curve and also does not solve the problem of the lack of long-term overall survival data as the basis for the extrapolation. In addition, using the model average approach makes it difficult for the model estimates to be compared with the trial data as an average curve for overall survival is not calculated.
- The model assumes patients are treated until progression resulting in a mean treatment duration of 14.8 months (16.1 cycles). SMC clinical experts noted some patients may be treated beyond progression in practice. Sensitivity analysis which increased the treatment duration by 25% to 20.1 cycles resulted in the ICER increasing to £37k. A further exploratory analysis was also provided which increased the treatment duration by 25% and reduced the time horizon to 15 years. This analysis increased the ICER to £44k. A specific question was sent to SMC clinical experts to verify the treatment duration used in the model. Responses received indicate that the mean treatment duration is probably a reasonable estimate.

Patient and clinician engagement

A Patient and Clinician Engagement (PACE) meeting was held for this submission. Participants at the PACE meeting indicated a range of potential impacts of the new technology for the patient and families/carers.

Impact beyond direct health benefits and on specialist services

At the PACE meeting, it was noted that in some cases, successful treatment could allow patients to return to normal daily activities such as caring for their children or returning to work and thus to contribute to family life. It was also emphasised that there was an important psychological benefit to patients and carers from the opportunity to receive an active treatment rather than best supportive care treatments.

Sorafenib is an oral medication that can be given at out-patient clinics rather than requiring hospital stays. This may offer benefits in terms of service provision as well as to the patient and carer.

Costs to NHS and Personal Social Services
The submitting company has estimated that between 5 and 14 patients would be treated with sorafenib per year and that this would be associated with a drug budget impact of £105k to £419k per year (without the PAS). The submitting company did not estimate any costs outside of the NHS.

The Committee also considered the benefits of sorafenib in the context of the SMC decision modifiers and agreed that the criterion regarding the absence of other treatments of proven benefit was satisfied. In addition, as sorafenib is an ultra-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 sorafenib for use in NHS Scotland.

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

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from The Butterfly Thyroid Cancer Trust and The British Thyroid Foundation. Both are registered charities.

- Both charities have received pharmaceutical company funding in the past two years but not from the submitting company.

- Patients who have advanced differentiated thyroid carcinoma (DTC) will often develop metastases in the lung, bone, and/or brain. Bone metastases can cause a lot of pain and can also lead to pathological fractures. Lung metastases can cause breathing difficulties, and swallowing difficulties can also be caused by the tumour. These are frightening symptoms and lead to a dramatic reduction in quality of life. Patients become reliant on others to carry out daily tasks and often have to give up work. There is an emotional, financial and physical burden on the entire family and relationships can suffer.

- Patients with advanced DTC have no treatment options other than palliative interventions. There are currently no medicines that offer a cure for metastatic, radioactive iodine resistant DTC. Sorafenib is the first medicine to offer benefit to these patients.

- Sorafenib may improve progression free survival and reduce tumour size resulting in less pain and other symptoms, and generally improving patients' quality of life. Sorafenib gives patients and their families hope for the future.

Additional information: guidelines and protocols

The British Thyroid Association published: "Guidelines for the management of thyroid cancer", in July 2014. 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 multidisciplinary meeting 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 experience in monitoring and managing adverse effects of targeted therapies.
iv Consideration should therefore be given to entry into clinical studies.[5]

The European Society of Medical Oncology (ESMO) published "Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up", in 2012. They state in metastatic disease chemotherapy is no longer indicated because of lack of effective results and should be replaced by enrollment of the patients in experimental trials with targeted therapy. The guidelines note that preliminary results for tyrosine kinase inhibitors, including sorafenib, for DTC in clinical studies are promising and indicate that targeted therapy might become the first line treatment of metastatic refractory thyroid cancer patients in the near future, they are not standard therapy today and should be administered only in the context of clinical trials.[6]

The ESMO guidelines predate the marketing authorisation for sorafenib in DTC.

Additional information: comparators

There are no relevant active comparators. UK and European guidelines advise that these patients participate in clinical studies.[5,6]

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Sorafenib	**400mg orally twice daily**	**38,746***

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online on 18.2.15 and do not take any patient access schemes into consideration. *Cost based on maximum dose. Cost based on 80% of maximum dose=£30,997 (approximate percentage of planned sorafenib dose in DECISION study).[1]

Additional information: budget impact

The company estimated there would be 29 patients eligible for treatment each year with an uptake rate of 13% in year 1 and 50% in year 5. This resulted in 4 patients estimated to be treated in year 1 and 15 in year 5.

Without PAS:
The gross impact on the medicines budget was £105k in year 1 and £419k in year 5. There were no displaced medicines costs.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicine Agency Committee for Medicinal Products for Human Use extension of indication variation assessment report Nexavar Procedure no.: EMEA/H/C/000690/II/0035 25 April 2014

2. Sorafenib 200mg film-coated tablets (Nexavar®) Summary of product characteristics. Bayer Plc. Electronic Medicines Compendium. Last updated 19 December 2014

3. British Thyroid Association Guidelines for the Management of Thyroid Cancer. Clinical Endocrinology Volume 81 Supplement 1 July 2014

4. Brose MS, Nutting CM, Jarzab B et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014; 384(9940):319-28

5. Pacini F, Castagna MG, Brilli L, on behalf of the ESMO Guideline Working Group. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 (suppl 7):vII110-vII119

6. Schneider TC, Abdulrahman RM, Corssmit EP. Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: final results of a phase II trial European Journal of Endocrinology 2012;167: 643-50

7. European Network for Health Technology Assessment. Sorafenib for the treatment of progressive, locally advanced or metastatic, differentiated (papillary/follicular/hürthle cell) thyroid carcinoma, refractory to radioactive iodine id: sa-[3] (Pilot rapid assessment of pharmaceuticals using the HTA Core Model® for Rapid Relative Effectiveness Assessment). Version 1.4. 17 March 2015.

This assessment is based on data submitted by the applicant company up to and including 16 April 2015.

**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.