# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# GUIDANCE EXECUTIVE (GE)

## Review of TA215; Pazopanib for the first line treatment of advanced and/or metastatic renal cell carcinoma

This guidance was issued in February 2011 (and re-issued in August 2013).

The review date for this guidance is December 2013.

### 1. Recommendation

The re-issued August 2013 TA215 guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

### 2. Original remit(s)

To appraise the clinical and cost effectiveness of pazopanib within its licensed indication for the first-line treatment of advanced and/or metastatic renal cell carcinoma.

### 3. Current guidance (as re-issued TA215 August 2013)

1.1 Pazopanib is recommended as a first-line treatment option for people with advanced renal cell carcinoma

- who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 **and**
- if the manufacturer provides pazopanib with a 12.5% discount on the list price, as agreed in the patient access scheme.

1.2 When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

1.3 People who are currently being treated with pazopanib for advanced metastatic renal cell carcinoma but who do not meet the criteria in 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

## 4. Rationale[1]

Current NICE guidance recommends sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (TA169) and does not recommend bevacizumab, sorafenib or temsirolimus as first-line treatments, or sorafenib or sunitinib as second-line treatments for people with advanced and/or metastatic RCC (TA 178). As a result of review decisions in 2012, both TA178 and TA169 were transferred to the 'static guidance list'. New pazopanib evidence from the VEG105192 and COMPARZ trials is consistent with the Committee's conclusions about the clinical and cost-effectiveness of pazopanib. TA 215 has been re-issued August 2013 after a change to the patient access scheme. There is no change to the licensed indication of pazopanib, and no new drugs for the same indication have been referred by the Department of Health for appraisal. A review of TA215 pazopanib guidance is therefore not needed and it should be transferred to the 'static guidance list'

## 5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

## 6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2010 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

## *7.* Summary of evidence and implications for review

Current NICE guidance recommends sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (TA169) and does not recommend bevacizumab, sorafenib or temsirolimus as first-line treatments, or sorafenib or sunitinib as second-line treatments for people with advanced and/or metastatic RCC (TA 178). As a result of review decisions in 2012, both TA178 and TA169 are on the 'static guidance list'

In TA 215 guidance issued February 2011, for the comparison of pazopanib with sunitinib, the Committee considered evidence from an indirect comparison between the 2 treatments, noting that the results of a direct comparison would be available when the COMPARZ trial was complete, but that until then it was reasonable to consider that pazopanib was as clinically effective as sunitinib. COMPARZ was a phase III randomised controlled trial, evaluating the efficacy, safety and quality of life of pazopanib, versus sunitinib, in 1100 patients. The primary end point was to establish non-inferiority of progression-free survival; the predefined criterion for non-

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

inferiority was an upper bound of a two-sided 95% confidence interval of 1.25. In COMPARZ, the hazard ratio for progression-free survival was 1.05 (95% CI 0.90 to 1.22), and the difference in median progression-free survival was 1.1 months in favour of sunitinib (pazopanib 8.4 months, sunitinib 9.5 months). The analysis of overall survival, which was a secondary end point, gave a hazard ratio of 0.91 (95% CI 0.76 to 1.08, p=0.275), with a 0.9 month difference in survival for sunitinib.

The Committee heard from the clinical specialists that the evidence from the indirect comparison suggested that pazopanib has a more favourable toxicity profile than sunitinib, especially in relation to hand-foot syndrome. In the COMPARZ trial, the most common adverse events (incidence of 30% or more, all grades) were comparable for pazopanib and sunitinib, with hand-foot syndrome occurring in 29% of patients who received pazopanib and 50% of those who received sunitinib. Serious adverse events and fatal adverse events were also similar in both treatment groups. The Committee considered evidence from indirect comparisons between pazopanib and interferon-α, concluding that pazopanib was likely to be more clinically effective than interferon-α.

TA 215 guidance has been re-issued after a change to the patient access scheme (August 2013). The literature search for this review did not identify any new or ongoing head-to-head trials comparing pazopanib with interferon-α. The literature search for this review identified a 'patient preference' study in patients with locally advanced or metastatic renal cell carcinoma who did not receive prior systemic (PISCES). The objective of this study was to evaluate whether pazopanib or sunitinib was preferred by patients based on the tolerability and safety of each drug. Patients were initially randomised to either pazopanib followed by sunitinib or vice versa, and their preference was measured using a questionnaire. The study reported that 70% of patients preferred treatment with pazopanib, 22% preferred sunitinib, and 8% had no preference (the difference between the 2 drugs was 49.3% [p<0.001]); the most common reasons given for preferring pazopanib treatment were a better quality of life and less fatigue.

In summary, the new evidence about pazopanib, either from the VEG105192 or the COMPARZ trial, is consistent with the Committee's conclusions about the effectiveness of pazopanib. There is no change to the licensed indication of pazopanib, and no new drugs for the same indication have been referred by the Department of Health for appraisal. In view of that, a review of the guidance is not needed.

## 8. Implementation

A submission from Implementation is included in Appendix 3.

There was an increasing trend in pazopanib prescribing before NICE technology appraisal guidance 215 was published, and this trend continued post publication. However, because pazopanib is also licensed for soft tissue sarcoma, and the data do not link to the indication for which pazopanib was prescribed, it is difficult to establish the impact of NICE guidance on prescribing pazopanib for advanced renal cell carcinoma.

## 9. Equality issues

The Committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

**GE paper sign off:** Frances Sutcliffe, Associate Director, 19 August 2013

**Contributors to this paper:**

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# Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

| **Options** | **Consequence** | **Selected – 'Yes/No'** |
|---|---|---|
| A review of the guidance should be planned into the appraisal work programme. | A review of the appraisal will be planned into the NICE's work programme. | No |
| The decision to review the guidance should be deferred to [specify date or trial]. | NICE will reconsider whether a review is necessary at the specified date. | No |
| A review of the guidance should be combined with a review of a related technology appraisal. | A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology. | No |
| A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. | A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology. | No |
| The guidance should be incorporated into an on-going clinical guideline. | The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.<br>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal. | No |
| The guidance should be updated in an on-going clinical guideline. | Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.<br>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation). | No |

| Options | Consequence | Selected – 'Yes/No' |
|---|---|---|
| The guidance should be transferred to the 'static guidance list'. | The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review. | **Yes** |

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

# Appendix 2 – supporting information

## Relevant Institute work

*Published*

Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. Technology Appraisal TA178. Issued August 2009. Review decision date: May 2012. Review decision: guidance to be transferred to the static guidance list.

Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. Technology Appraisal TA169. Issued March 2009. Review decision date: May 2012. Review decision date: May 2012. Review decision: guidance to be transferred to the static guidance list.

## Details of changes to the indications of the technology

| Indication considered in original appraisal | Proposed indication (for this appraisal) |
|---|---|
| The first-line treatment of advanced renal cell carcinoma and for patients who have received prior cytokine therapy for advanced disease. | Unchanged |

## Details of new products

| Drug (manufacturer) | Details (phase of development, expected launch date, ) |
|---|---|
| IMA 901 (Immatics) | Cancer vaccine for renal cell carcinoma<br>Phase 3 Trials, [redacted] |
| Naptumomab Estafenatox (Active Biotech) | Tumour targeting superantigen (TTS) for advanced renal cell carcinoma.<br>Phase 3 Trials, [redacted] |
| Temsirolimus (Pfizer) | 1st-line + bevacizumab, 2nd line sunitinib failure.<br>Phase 3 Trials, [redacted] |
| Tivozanib (Astellas) | For renal cell carcinoma (advanced or metastatic) |
| Axitinib (Pfizer) | For the first line treatment of advanced and/or metastatic renal cell carcinoma |

## Registered and unpublished trials

| Trial name and registration number | Details |
|---|---|
| Phase III Sequential Open-label Study to Evaluate the Efficacy and Safety of Sorafenib Followed by Pazopanib Versus Pazopanib Followed by Sorafenib in the Treatment of Advanced / Metastatic Renal Cell Carcinoma (SWITCH-II)<br>NCT01613846<br>Phase 3 | Phase III Randomized Sequential Open-label Study to Evaluate the Efficacy and Safety of Sorafenib Followed by Pazopanib Versus Pazopanib Followed by Sorafenib in the Treatment of Advanced / Metastatic Renal Cell Carcinoma<br>Status: Currently recruiting<br>Estimated Enrollment: 544<br>Estimated Completion date: June 2016 |
| Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma<br>NCT00720941<br>Phase 3 | COMPARZ Trial<br>Study VEG108844, A Study of Pazopanib Versus Sunitinib in the Treatment of Subjects With Locally Advanced and/or Metastatic Renal Cell Carcinoma<br>Status: Ongoing<br>Estimated Enrollment: 927<br>Primary completion date: May 2012<br>Estimated Completion date: December 2014 |
| Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer<br>NCT01064310<br>Phase 3 | PISCES Trial<br>A Randomised Double-blind Cross-over Patient Preference Study of Pazopanib Versus Sunitinib in Treatment naïve Locally Advanced or Metastatic Renal Cell Carcinoma.<br>Status: Ongoing<br>Estimated Enrollment: 160<br>Primary completion date: October 2011<br>Estimated Completion date: November 2013 |

| Trial name and registration number | Details |
|---|---|
| Safety and Efficacy of GW786034 (Pazopanib) In Metastatic Renal Cell Carcinoma<br>NCT00334282<br>Phase 3 | A Randomised, Double-blind, Placebo Controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib (GW786034) Compared to Placebo in Patients With Locally Advanced and/or Metastatic Renal Cell Carcinoma.<br>Status: Ongoing<br>Estimated Enrollment: 435<br>Estimated Completion date: December 2013 |
| Standard vs Modified Drug Therapy in Renal Cancer<br>ISRCTN06473203<br>Phase 2/3 | STAR Trial<br>A randomised multi stage, phase II/III trial of Standard first-line therapy (sunitinib or pazopanib) comparing temporary cessation with allowing continuation, at the time of maximal radiological response, in the treatment of locally advanced and/or metastatic renal cancer<br>Status: Ongoing<br>Estimated Enrollment: 210 (Phase 2), continuing to 1000 for Phase 3.<br>Estimated Completion date: April 2018 |

## Additional information

Pazopanib is included in the 'Drugs under intensive surveillance (Black triangle list)' (MHRA).

## References

Sternberg, C. N., Hawkins, R. E., Wagstaff, J., Salman, P., Mardiak, J., Barrios, C. H., Zarba, J. J., Gladkov, O. A., Lee, E., Szczylik, C., McCann, L., Rubin, S. D., Chen, M., and Davis, I. D. (2013). A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. *European Journal of Cancer* 49 (6) 1287-1296.

## Appendix 3 – Implementation submission

# Implementation feedback: review of NICE technology appraisal guidance 215

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|---|
| NICE Technology Appraisal 215 Pazopanib for the first line treatment of advanced and/or metastatic renal cell carcinoma |
| Implementation input required by 11/03/2013 |
| Please contact Rebecca Braithwaite regarding any queries<br>rebecca.braithwaite@nice.org.uk |

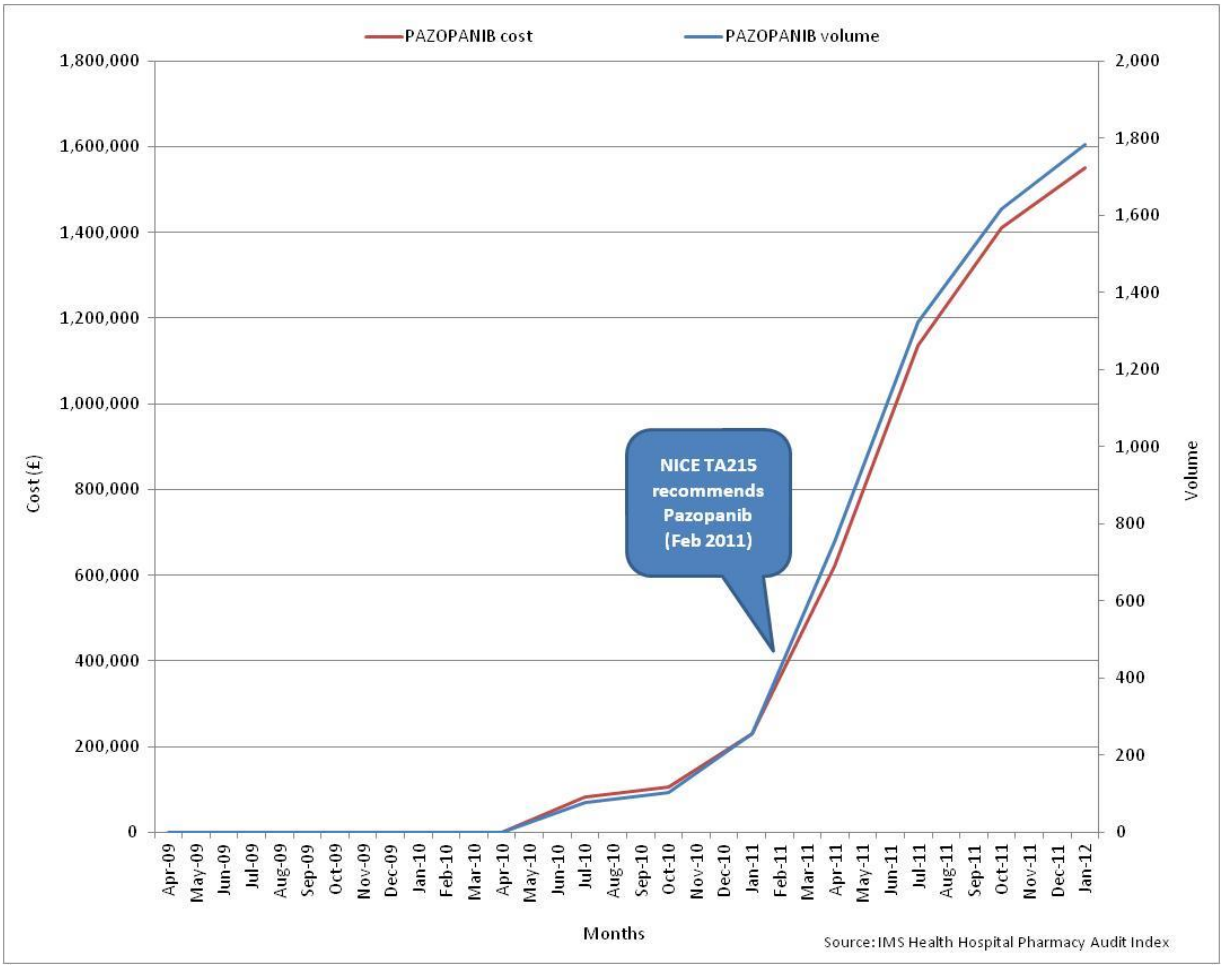
## Contents

# 1 Routine healthcare activity data

## 1.1 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of Pazopanib prescribed and dispensed in hospitals in England between April 2009 and January 2012.

**Figure 1 Cost and volume of Pazopanib prescribed in hospitals in England**



# 2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

***Nothing to add at this time.***

# 3 Qualitative input from the field team

***The implementation field team have recorded the following feedback in relation to this guidance:***

Nothing to add at this time.