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SUBMISSION TO THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

BEVACIZUMAB, SORAFENIB, SUNITINIB AND TEMSIROLIMUS FOR RENAL CELL CARCINOMA[1]

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[1] Throughout this document the term 'metastatic Renal Cell Carcinoma (mRCC)', should be taken as referring to 'metastatic and/or advanced Renal Cell Carcinoma', the population identified within the final scoping document as relevant to this submission.

EXECUTIVE SUMMARY

Background

- Cancer of the kidney is the thirteenth most common cancer in the UK with an annual incidence of 2% and is increasing at a rate of 2% per annum.
- Renal Cell Carcinoma occurs predominantly in those aged in the sixth and seventh decade, is more common in men than women, and rare under the age of forty years.
- Traditionally therapy has involved nephrectomy and, depending on patient's frailty and ability to tolerate, immunotherapy with IFN-α or IL-2. This approach has yielded limited success in the form of either an increase in Progression Free Survival (PFS) or Overall Survival (OS).
- Immunotherapy use carries a high symptom burden and has a significant impact on quality of life for those patients able to tolerate initiation of therapy. This, added to the limited success of the agents, has led to IFN-a now only being recommended as a control in clinical studies (Ljungberg et al, 2007) since the availability of systemic alternatives.
- The new agents that have recently become available are; the tyrosine kinase inhibitor sunitinib, temsirolimus an mTOR inhibitor, bevacizumab (for use only with IFN-α) an anti-VEGF MAb, and one other tyrosine kinase inhibitor, sorafenib.
- Sunitinib is a small molecule with anti-tumour properties pharmacologically mediated through inhibition of multiple RTKs that are important in regulation of tumour cell growth, angiogenesis, and metastatic progression.
- Sunitinib was given the first ever positive opinion on the granting of a conditional marketing authorisation (designed to facilitate early access to medicines) by the CHMP effective July 2006 for second line use in mRCC and GIST. This decision is strongly aligned with the proposals in the Cooksey Report subsequently, adopted by the UK Government, for Conditional Licensing to be granted to medicines which demonstrate evidence of appropriate efficacy and safety, especially in patient populations with significant unmet clinical need.
- Based on the interim data made available to them, in October 2006 the EMEA extended the licence for mRCC to cover first line use as well, at which point the full licence was granted.
- The tyrosine kinase inhibitors are now recommended for use as first line (sunitinib) and second line (sunitinib, sorafenib) therapy for patients with mRCC by the European Association of Urology.
- Whilst sunitinib has shown benefit, and is licensed for use, across a broad range of patients, a predictive model and a nomogram specific to sunitinib have been developed that allow more effective targeting of sunitinib treatment based on predicted PFS.

Clinical Effectiveness of sunitinib in metastatic Renal Cell Carcinoma

- The efficacy, safety and tolerability of sunitinib have been studied in three pivotal trials involving 919 patients and within an Expanded Access Programme that has made the drug available to nearly 4,000 more patients.
- Sunitinib, unlike other targeted therapies, has demonstrated efficacy and safety in first line and second line treatment for patients with mRCC as a monotherapy in all patient types.
- Progression Free Survival was selected as the primary endpoint in the clinical trials based on its importance and relevance to both patients and physicians alike.
- Two analyses of PFS from the pivotal trial of sunitinib in first line therapy are available (an interim pre-specified planned analysis and an updated analysis

conducted outwith the analysis plan). Both are reported in this submission and used in the cost-effectiveness analyses. A number of patients crossed over from IFN-α to sunitinib between these two analyses. The effect of this on the updated analysis is hard to quantify although it moves the analysis from one of sunitinib versus IFN-α towards one of sunitinib therapy versus delayed sunitinib therapy.

- In first line therapy versus IFN-α (Trial A6181034) Progression Free Survival from the interim pre-specified analysis was 11 months versus 4 months: Hazard Ratio 0.42 (95% CI 0.33-0.52) based on investigator assessment and 11 months versus 5 months: Hazard Ratio 0.42 (95% CI 0.32-0.54) based on independent radiographic assessment.
- In first line therapy versus IFN-α (Trial A6181034) Progression Free Survival from the unplanned updated analysis was 10.8 months versus 4.1 months: Hazard Ratio 0.519 (95% CI 0.435-0.618) based on investigator assessment and 11 months versus 5.1 months: Hazard Ratio 0.538 (95% CI 0.439-0.658) based on independent radiographic assessment.
- For all quality of life measures evaluated in trial A6181034, patients treated with sunitinib reported statistically significant better outcomes (FKSI-DRS, FACT-G, PWB, SWB, EWB, FWB and FKSI).
- Compared to IFN-α, patients treated with sunitinib reported statistically significant better outcomes in their weighted health state (as measured by EQ-5D Index).
- In second line use, Progression Free Survival with sunitinib was 8.7 months (95% CI, 5.5-10.7) in Trial RTKC-0511-014, and 8.3 months (95% CI, 7.8-14.5) in Trial A6181006.
- Progression Free Survival from a pooled analysis of trials RTKC-0511-014 and A6181006 was 8.2 months (95% CI, 7.8-10.4).
- An Expanded Access Programme continues to demonstrate the efficacy, tolerability and safety of sunitinib in nearly 4,000 patients with mRCC in both first and second line use.
- An indirect comparison of sunitinib versus bevacizumab + IFN-α for first line treatment of mRCC demonstrated a statistically significant difference in favour of sunitinib in one of the two analyses for PFS as evaluated by investigator. An analysis of independently assessed PFS was not possible because of the absence of such an evaluation for bevacizumab + IFN-α.
- An indirect comparison of sunitinib versus sorafenib for first line treatment of mRCC demonstrates a statistically significant difference in favour of sunitinib in both analyses for PFS as evaluated independently.

Cost Effectiveness of sunitinib in the management of mRCC

- In order to understand the cost efficacy of sunitinib in treating mRCC, two cost utility analyses are presented, one for first line treatment and one for second line treatment. The first line treatment base case has been undertaken using two different analyses from the A6181034 study and the results from each are presented separately.
- The pricing assumptions within the analyses incorporate the sunitinib drug cost for the first cycle as being free to the NHS, as previously agreed between the Department of Health and Pfizer.
- Pfizer agreed to make the drug costs for the first cycle free to enable greater access to this innovative treatment to more effectively treat patients with mRCC who have so few effective options available to them.
- The base case analysis of sunitinib vs IFN-α in the first line treatment of mRCC, utilising the pre-planned interim analysis data shows that sunitinib increased overall survival by an additional 0.82 years, increased progression free survival by 0.38 years and resulted in an additional 0.60 quality adjusted life years when compared to IFN-α. The incremental cost effectiveness ratio for sunitinib compared to IFN-α in this base

case is: £21,280 per life year gained; £45,736 per progression free year gained; and £28,546 per quality adjusted life year gained.

- Based on these results, the PSA demonstrates that at a willingness to pay threshold of £30,000 per QALY sunitinib has a 54% probability of being cost-effective compared to IFN-α.
- The base case analysis of sunitinib vs IFN-α in the first line treatment of mRCC, utilising the unplanned updated analysis data shows that sunitinib increased overall survival by an additional 0.82 years, increased progression free survival by 0.43 years and resulted in an additional 0.60 quality adjusted life years when compared to IFN-α. The incremental cost effectiveness ratio for sunitinib compared to IFN-α in base case 2 is: £24,410 per life year gained; £46,940 per progression free year gained; and £33,241 per quality adjusted life year gained
- Based on these results the PSA demonstrates that at a willingness to pay threshold of £30,000 per QALY sunitinib has a 36% probability of being cost-effective compared to IFN-α.
- The second analysis explores the cost-effectiveness of sunitinib vs BSC in second line treatment of mRCC. The second line refers to patients who have failed previous first line treatment with cytokine therapy. Best supportive care is defined as the monitoring of progression, symptom control, palliative care, but no active treatment.
- In the second line model, the base case analysis estimated that sunitinib increased overall survival by an additional 0.77 years, progression free survival by 0.54 year and resulted in an additional 0.60 quality adjusted life years when compared to BSC. The incremental cost effectiveness ratio for sunitinib compared to BSC is £29,061 per life year gained; £41,817 per progression free year gained; £37,519 per quality adjusted life year gained.
- Based on these results the PSA demonstrates that at a willingness to pay threshold of £30,000 per QALY sunitinib has a 36% probability of being cost-effective compared to IFN-α.

Wider Implications to the NHS with sunitinib in mRCC

- The budget impact implications associated with the use of sunitinib are calculated for a five-year period up to 2012 on the assumption that sunitinib receives positive recommendation for use in both first and second line setting.
- Across the two treatment settings, the number of patients to be treated with sunitinib in England and Wales is estimated to be 505 in 2008 rising to 962 in 2012 within the first line setting; and 101 in 2008 rising to 425 in 2012 in the second line setting.
- The introduction of sunitinib in England and Wales is associated with an estimated net direct cost of approximately £6 million in 2008 increasing to £13 million in 2010 in the first line setting; and £1.9 million increasing to £8 million in the second line setting.
- Sunitinib represents a valuable treatment option for mRCC patients, a group with few effective treatment options, across the first and second line treatment settings in England and Wales.

Conclusion

- Sunitinib has demonstrated clinical efficacy in first and second line use in metastatic Renal Cell Carcinoma.
- For patients who will benefit from treatment with sunitinib it is a cost-effective intervention.