**Cost-effectiveness of cabozantinib (Cabometyx®) for the treatment of advanced renal cell carcinoma in adults following prior vascular endothelial growth factor targeted therapy.**

The NCPE has issued a recommendation regarding the cost-effectiveness of cabozantinib (Cabometyx®). Following assessment of the Applicant's submission, the NCPE recommends that cabozantinib (Cabometyx®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Ispen Pharmaceuticals Ltd.) economic dossier on the cost effectiveness of cabozantinib (Cabometyx®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

**About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

**National Centre for Pharmacoeconomics** **July** **2018**

## Summary

In November 2017, Ispen Pharmaceuticals Ltd. submitted a dossier examining the clinical, safety and economic evidence in support of an appraisal of the cost-effectiveness and budget impact of cabozantinib (Cabometyx®) for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor targeted therapy. Final data submitted by the Applicant was received on 29th June 2018. Ispen Pharmaceuticals Ltd. are seeking reimbursement for cabozantinib (Cabometyx®) on the High Tech Drug Scheme (HTDS).

**Cabozantinib (Cabometyx®)**

Cabozantinib is a tyrosine kinase inhibitor (TKI) that exhibits inhibitory activity against a variety of kinases including vascular endothelial growth factor (VEGF) and hepatocyte growth factor receptor protein (MET) receptors. Inhibition of such receptors disrupts tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer.

The recommended dose of cabozantinib for this indication is 60 mg orally once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity. Cabozantinib is formulated as a film coated tablet in three different strengths: 20 mg, 40 mg and 60 mg.

Everolimus, axitinib and nivolumab were identified as the main comparators of interest by the Applicant. The NCPE Review Group considers this to be appropriate and in line with the current standard of care in Ireland. It is anticipated that cabozantinib will be used in the second-line setting in line with its marketing authorisation.

1. **Comparative effectiveness of cabozantinib**

Relative efficacy outcomes for the comparison of cabozantinib versus everolimus were derived from the METEOR trial. This study was an open-label, multi-national, Phase III, randomised controlled trial of 658 patients with advanced clear-cell RCC, whose disease had progressed after previous VEGF-receptor tyrosine kinase inhibitor treatment. Patients were

assigned (1:1) to either oral cabozantinib at a dose of 60 mg once daily (n=330) or oral everolimus at a dose of 10 mg once daily (n=328). Patients were allowed to continue study treatment beyond progression at the discretion of the investigator if they were considered to be experiencing clinical benefit and the potential benefit of continuing treatment outweighed potential risks. Data was presented for numerous data cuts. The Review Group note that the trial population had clear-cell advanced RCC. This is a subgroup of the entire licensed population.

In the trial, cabozantinib was associated with an increase in overall survival (OS) compared to everolimus. The median OS with cabozantinib was 21.4 months (95% CI 18.7, not estimable) compared to 16.5 months (95% CI 14.7, 18.8) with everolimus. Progression free survival (PFS) was significantly improved with cabozantinib compared to everolimus treatment, with a median PFS of 7.4 months and 3.8 months, respectively (HR 0.58; 95% CI 0.45, 0.75; p<0.001). The objective response rate (ORR) was statistically significantly improved with cabozantinib treatment, with an ORR of 17% (95% CI 13, 22) seen in the cabozantinib arm compared to 3% (95% CI 2, 6) in the everolimus arm (p<0.001). There were no clinically meaningful differences in quality of life between the two treatment arms.

A network meta-analysis (NMA) based on fractional polynomial modelling was conducted to provide estimates of relative treatment efficacy for axitinib versus cabozantinib, everolimus versus cabozantinib, and nivolumab versus cabozantinib. Data from the METEOR trial was used to inform the comparison with everolimus in the NMA. To compare to nivolumab, the network linked CheckMate 025 (nivolumab vs. everolimus) with METEOR. In order to generate a comparison with axitinib, it was assumed that axitinib had equal efficacy to everolimus. This assumption was made as a previous NMA containing a larger network of treatments predicted axitinib to have better clinical outcomes than everolimus. According to clinical experts consulted by the Applicant, this is not realistic. The NCPE Review Group have concerns over the Applicant's preference of this assumption over the use of randomised controlled data to inform the axitinib arm of the model. Furthermore, concerns exist regarding the heterogeneity of the trials included in the final network.

## 2. Safety of cabozantinib

Safety and tolerability was a secondary endpoint of the METEOR trial. The overall incidence of adverse events (AEs) irrespective of causality was 100% for both groups. The most common AEs in the cabozantinib group compared with the everolimus treatment group were diarrhoea (75% vs. 28%), fatigue (59% vs. 47%), nausea (53% vs. 30%), decreased appetite (47% vs. 36%) and palmar-plantar erythrodysaesthesia syndrome (PPES) (42% vs. 6%). AEs of Grade 3 or 4 were recorded in 71% of patients treated with cabozantinib and 60% of patients treated with everolimus. The most common Grade 3 or 4 AEs (cabozantinib vs. everolimus) were hypertension (15% vs. 4%), diarrhoea (13% vs. 2%), fatigue (11% vs. 7%), and PPES (8% vs. 1%). The incidence of serious AEs of Grade 3 or higher was comparable between both treatment arms: 39% for cabozantinib versus 40% for everolimus. The most common serious AEs (cabozantinib vs. everolimus) were abdominal pain (3% vs. 1%), pleural effusion (2% vs. 2%), pneumonia (2% vs. 4%), pulmonary embolism (2% vs. <1%), and anaemia (2% vs. 3%). One death was assessed as treatment related in the cabozantinib group (not otherwise specified) and two were assessed as treatment-related in the everolimus group (one aspergillus infection and one pneumonia aspiration).

## 3. Cost effectiveness of cabozantinib

For the cost-effectiveness analysis, the effectiveness inputs in the model were PFS and OS. Clinical efficacy inputs were derived from METEOR and the NMA. The intention to treat (ITT) population of the METEOR trial pertains to patients with advanced or metastatic RCC with a clear-cell histology. The Review Group note that this is a subgroup of the entire licensed population. Therefore, the economic evaluation does not support the use of cabozantinib in the entire licensed population.

Cost-effectiveness was investigated using a three health state model with a 30 year time horizon. The model simulates patients through three health states: 'Progression-free', 'Progressive disease' and 'Death'. All health states are mutually exclusive, and death is an absorbing state. All patients start in the progression-free state; transitions to the death state could occur from either the progression-free or progressive disease states. Patient characteristics, dose intensity, utility measurement, and adverse event frequency used in the model are derived from METEOR. Resource use in the model was based on studies

identified by literature review and previous health technology assessments, and captured costs for drug acquisition and administration, hospital resource use, monitoring and follow up, management of Grade 3 and 4 AEs and terminal care costs. Future costs and health-related outcomes are discounted at 5% per annum.

Survival outcomes based on the NMA were extrapolated to the full time horizon of the model using fractional polynomial modelling extrapolation. An analysis was also presented employing only the data from the METEOR trial. In this instance, survival outcomes for METEOR were extrapolated to the full time horizon of the model using parametric extrapolation. The Review Group have concerns over the survival estimates generated from the fractional polynomial approach, particularly regarding the nivolumab estimates. The Review Group consider the nivolumab survival estimates to be an underestimation of the true outcomes expected in clinical practice. The subsequent incremental cost-effectiveness estimate may not be a true reflection of the cabozantinib vs. nivolumab comparison (i.e. it may be an over-estimation of the cost-effectiveness of cabozantinib relative to nivolumab).

Analyses presented in this summary document are based on the list prices of all interventions.

In the Applicant base case analysis (i.e. the fractional polynomial modelling NMA informed analysis) the ICER for cabozantinib versus axitinib was €131,310/QALY (incremental costs €48,960, incremental QALYs 0.37) and for cabozantinib versus everolimus was €184,266/QALY (incremental costs €68,454, incremental QALYs 0.37). Cabozantinib was associated with lower costs and higher QALYs than nivolumab and so dominated this comparator (incremental costs -€37,718, incremental QALYs 0.13).

The NCPE implemented a number of changes to the model including employing alternative utility values, assuming a relative dose intensity of 100% for nivolumab, and inclusion of a GP visit in the PFS state. These alternative assumptions resulted in a final ICER of €163,626/QALY (incremental costs €48,859, incremental QALYs 0.30) versus axitinib and €229,950/QALY (incremental costs €68,350, incremental QALYs 0.30) versus everolimus. Cabozantinib was associated with lower costs and higher QALYs than nivolumab and so

dominated this comparator (incremental costs -€14,383, incremental QALYs 0.10).

In the trial based analysis (i.e. analysis informed only by the METEOR trial data) presented by the Applicant, the ICER for cabozantinib versus everolimus was €172,210/QALY (incremental costs €69,218, incremental QALYs 0.40). The NCPE implemented a number of changes to this trial-based model, generating an ICER of €208,156/QALY (incremental costs €68,960, incremental QALYs 0.33) versus everolimus.

A probabilistic sensitivity analysis was presented by the Applicant. The probability of cost-effectiveness at a willingness to pay (WTP) threshold of €45,000 was 0% for both axitinib and everolimus when both the Applicant and NCPE base-case assumptions are considered. The probability of cost-effectiveness at a WTP threshold of €45,000 versus nivolumab was 97.7% based on the Applicant's base-case assumptions and 88.7% based on the NCPE preferred base-case. The Applicant also presented a variety of scenario analyses and sensitivity analyses. The NCPE preformed a number of additional sensitivity analyses to test assumptions made in the model.

4. **Budget impact of cabozantinib**

The price to wholesaler (PTW) of cabozantinib is €6,100 per 30 tablets. This price is further subject to mark-up, rebate and a High-Tech Patient Care Fee. A flat-pricing model has been adopted for all strengths of cabozantinib. The estimated annual cost of treatment per patient is €57,651.40, assuming patients receive 9 treatment cycles.

Based on the Applicant's estimate of the current eligible population, the projected gross budget impact over the first five years is approximately €11.6 million, plausibly increasing to over €21 million if treatment duration is increased to 14 cycles based on the economic model predictions. The estimated net budget impact is estimated to be €191,933, plausibly increasing to €9.3 million if treatment durations are longer.

**5. Patient submissions**

No patient organisation submissions were received during the course of this appraisal.

## 6. Conclusion

The efficacy and cost-effectiveness of cabozantinib according to the entire license (i.e. for the treatment of advanced RCC in adults following prior VEGF-targeted therapy) has not been investigated. Therefore it is not recommended for reimbursement in this setting.

Further, following assessment of the Applicant's submission, the NCPE recommends that cabozantinib (Cabometyx®) for the treatment of advanced or metastatic *clear-cell* RCC not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.