NCPE Assessment

Technical Summary

Cabozantinib (Cabometyx®)

HTA ID: 22018

18 September 2025

Applicant: Ipsen Pharmaceuticals Ltd

Cabozantinib in combination with nivolumab for the first-line treatment of advanced renal cell carcinoma in adults

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (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.

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 Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Ipsen Pharmaceuticals Ltd) Health Technology Assessment of cabozantinib (Cabometyx®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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.

Summary

In November 2024, Ipsen Pharmaceuticals Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness, and budget impact of cabozantinib (Cabometyx®) in combination with nivolumab (Opdivo®) [cabo+nivo] for the first-line treatment of advanced renal cell carcinoma (aRCC) in adults. Ipsen Pharmaceuticals Ltd is seeking reimbursement of cabozantinib on the Oncology Drugs Management Scheme.

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases implicated in tumour growth and metastatic progression of cancer. Nivolumab is a human immunoglobulin G4 monoclonal antibody, which binds to the programmed death-1 receptor and blocks its interaction with PD-ligand 1 and 2. The recommended dose of cabo+nivo is cabozantinib 40mg (taken orally) once daily, and nivolumab (via intravenous infusion) 240mg once every two weeks or 480mg once every four weeks, continued until disease progression or unacceptable toxicity. Nivolumab is continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression as per the SmPC.

The current standard of care in the first-line treatment of patients with aRCC in Ireland, includes monotherapy tyrosine kinase inhibitors (TKI), pazopanib or sunitinib. For patients with intermediate or poor risk disease (as per the International Metastatic RCC Database Consortium (IMDC)), ipilimumab in combination with nivolumab (ipi+nivo) is used. Several other immunotherapy (IO)-TKI combinations recommended by clinical guidelines in the first-line treatment setting are licensed but are not currently reimbursed in Ireland. These include: pembrolizumab in combination with lenvatinib; pembrolizumab in combination with axitinib; and avelumab in combination with axitinib. The Review Group highlights that these therapies may become relevant comparators in the future if reimbursed.

1. Comparative effectiveness of cabozantinib in combination with nivolumab

The efficacy and safety of cabo+nivo was assessed in the CheckMate 9ER trial (n=651). CheckMate 9ER is a randomised, open-label, active-controlled, phase III trial comparing the efficacy and safety of cabo+nivo versus sunitinib for the first-line treatment of aRCC. Cabozantinib was administered as per the SmPC dosing. Nivolumab was administered at a

dose of 240mg once every two weeks, until disease progression or unacceptable toxicity, or the maximum duration of 24 months as per the SmPC. Sunitinib was administered at a dose of 50mg once daily (orally). The primary endpoint of CheckMate 9ER was progression-free survival (PFS) as assessed by blinded, independent, central review (BICR), and key secondary endpoints included overall survival (OS), objective response rate, and duration of response.

In the most recent datacut (67.6 months follow-up), in the intention to treat [ITT] population (all IMDC risk), median PFS was 16.4 months (95% confidence interval [CI] 12.5, 19.3) in the cabo+nivo arm and 8.3 months (95% CI 7.0, 9.7) in the sunitinib arm. The hazard ratio [HR] was 0.58 (95% CI 0.49, 0.70). Median OS was 46.5 months (95% CI 40.6, 53.8) in the cabo+nivo arm and 35.5 months in the sunitinib arm (95% CI 29.2, 42.8). The HR was 0.79 (95% CI 0.65, 0.96).

In the intermediate or poor IMDC risk group, median PFS was 15.4 months (95% CI 11.1, 18.6) in the cabo+nivo arm and 7.1 months (95% CI 5.7, 8.9) in the sunitinib arm. The HR was 0.56 (95% CI 0.46, 0.69). Median OS was 43.9 months (95% CI 34.9, 53.0) in the cabo+nivo arm and 29.2 months in the sunitinib arm (95% CI 23.7, 36.0). The HR was 0.74 (95% CI 0.60, 0.92). The Review Group note that a statistically significant improvement in PFS, but not OS, was observed in the favourable IMDC risk group for cabo+nivo versus sunitinib, consistent with the earlier datacuts. Limitations of the CheckMate 9ER trial include the open label design; the efficacy in participants with non-clear cell RCC is unknown (as only participants with clear-cell RCC were eligible for CheckMate 9ER); nivolumab 480mg once every four weeks dosing was not investigated (as this dose was not approved at the time of the trial); the contribution of each component in the cabo+nivo regimen has not been investigated; and the impact of adjuvant treatment was not assessed in CheckMate 9ER: adjuvant pembrolizumab for the treatment of adults with RCC at increased risk of recurrence following nephrectomy is licensed and reimbursed in Ireland. Therefore, the relative effectiveness, in the real-world setting, is likely to be different than that observed from the trial, and the magnitude of this difference is unknown.

CheckMate 9ER provided head-to-head comparative efficacy data for cabo+nivo versus sunitinib. Head-to-head evidence for cabo+nivo versus ipi+nivo and versus pazopanib was not available and a network meta-analysis (NMA) was required. The Applicant's NMA

compared PFS and OS between cabo+nivo (from CheckMate 9ER), and ipi+nivo (from CheckMate 214) and pazopanib (from COMPARZ), using a fractional polynomial (FP) approach, which assumes that the HR between the treatments changes over time. In the NMA, a PFS benefit in terms of median PFS for cabo+nivo was observed versus ipi+nivo and versus pazopanib. For OS, a benefit was observed for cabo+nivo versus pazopanib, but a similar median OS was observed for ipi+nivo and cabo+nivo. Limitations of the NMA include that not all studies reported results according to IMDC patient risk group: therefore, the network of studies differed according to subgroup and outcome.

IMDC risk group is an important consideration when determining treatment choice. The Applicant declined to implement a NMA in the setting of favourable IMDC risk. The Review Group consider this to be a limitation of the evidence submitted here. We note that cabo+nivo was not associated with an OS benefit, versus sunitinib, in this subgroup in CheckMate 9ER.

2. Safety of cabozantinib in combination with nivolumab

In the cabo+nivo arm of CheckMate 9ER (n=320), the most frequent adverse events (AEs) (≥25%) reported at 67.6 months follow-up were diarrhoea, palmar-plantar erythrodysaesthesia syndrome, hypertension, fatigue, hypothyroidism, and nausea. The most frequently reported immune-mediated adverse events (IMAEs) in the cabo+nivo arm were hypothyroidism (28%), hyperthyroidism (10%), and rash (8%). The toxicity profile for cabo+nivo appears manageable with dose delays, dose reductions and, in case of immune-related AEs, immune modulating therapies as per the EPAR. However, the high frequency of dose modifications indicates poor tolerability of the combination therapy. The tolerability profile and benefit/risk balance may be improved with lower initial cabozantinib doses. As lower doses have not been prospectively investigated for efficacy, and the dose-response relationship is not characterised, it is unknown whether lower initial doses would maintain similar clinical benefit. The SmPC cautions that physician monitoring during the first eight weeks of treatment with cabozantinib is required to determine if dose modifications are warranted. In the CheckMate 9ER trial, at 67.6 months follow-up, dose reductions of cabozantinib due to an AE were needed in 62% of participants in the cabo+nivo arm, versus 55% of participants receiving sunitinib.

3. Cost effectiveness of cabozantinib in combination with nivolumab

The Applicant has compared the cost-effectiveness of cabo+nivo to sunitinib, pazopanib and ipi+nivo (intermediate or poor IMDC risk group) in the base case.

Methods

The cost-effectiveness model (CEM) for cabo+nivo is a partitioned survival model with three health states: Progression Free [PF], Progressed Disease [PD], and Death. These health states capture PFS and OS. The population was modelled based on the CheckMate 9ER trial. All patients enter the model in the PF health state and receive treatment with either cabo+nivo, ipi+nivo, pazopanib or sunitinib. During each model cycle, patients can transition from the PF health state to the PD health state or Death health state or remain in the PF health state. Following disease progression, patients cannot transition back to improved health states and can either remain in the PD health state or transition to the Death health state. In each cycle, patients accrue quality adjusted life years (QALYs) and incur costs based on their health state, treatment arm, and time on treatment (ToT). The Applicant assumed ToT for cabo+nivo and all comparators is equal to PFS in the model. A lifetime horizon with a one-week cycle length was used.

Results

An incremental analysis of the costs and benefits of cabo+nivo versus sunitinib or pazopanib (all IMDC risk population) and versus ipi+nivo or sunitinib (intermediate or poor IMDC risk population) was presented by the Applicant. Results of the analysis are presented in Table 1. The probabilistic results, which were estimated for 1,000 simulations, are stable and similar to the deterministic results. The Review Group note in the below table that in the intermediate or poor IMDC risk group, the costs and QALYs between the joint-fit model (which is used for the comparison for sunitinib and assumes a constant HR over time) and the FP NMA (which is used for the comparison for ipi+nivo and assumes a variable HR over time) shows a large discrepancy. For cabo+nivo both the costs and QALYs were higher in the joint-fit NMA. This discrepancy notes a high potential bias between the two methods and is deemed a limitation by the Review Group.

Table 1: Applicant base case incremental cost-effectiveness results[a, b, c,]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full licensed population (all IMDC risk groups)					

Sunitinib	67,827	3.169	161,202	0.791	203,893
Pazopanib	86,759	3.169	142,270	0.791	179,947
Cabozantinib + nivolumab	229,029	3.960	-	-.--	-
Intermediate or poor IMDC risk group					
Sunitinib	63,673	2.859	159,812	0.998	160,102
Ipilimumab + nivolumab	180,782	3.420	11,546	-0.155	Ipilimumab +nivolumab dominates
Cabozantinib + nivolumab (JF model log-logistic)	223,485	3.857	-	-.--	-
Cabozantinib + nivolumab (FP NMA)[d]	192,328	3.265	-	-.--	-

IMDC: International Metastatic RCC Database Consortium; **QALY**: Quality adjusted life year; **ICER**: Incremental cost-effectiveness ratio; **JF**: Jointly-fit; **OS**: Overall survival; **FP NMA**: Fractional polynomial network meta-analysis

[a] Corresponding probabilistic ICER using 1,000 iterations Vs Sunitinib (all IMDC risk groups) =€210,126/QALY, Vs Pazopanib (all IMDC risk groups) = €189,008/QALY, Vs Ipi+nivo (intermediate or poor IMDC risk group) = dominates. Figures in the table are rounded, and so calculations may not be directly replicable

[b] A CIC PAS has been proposed for cabozantinib, and is in place for nivolumab and ipilimumab, not included here

[c] Sunitinib and pazopanib results calculated using a joint fitted model (log-logistic) while ipi+nivo results are calculated via a FP NMA

[d] FP NMA cabo+nivo is not the Applicant base case. Only included here for comparison to ipi+nivo (which is modelled using the same FP NMA)

The Review Group assessment identified a number of limitations in the Applicant's base case which were explored in the NCPE adjusted base case. These included: choice of OS extrapolation curve, and the incorporation of every two weeks and every four weeks dosing for nivolumab. The NCPE adjusted base case is presented in Table 2. As mentioned, the Applicant declined to submit an evaluation in the population with a favourable IMDC risk profile.

Table 2: NCPE adjusted base case incremental cost-effectiveness results[a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full licensed population (all IMDC risk groups)					
Sunitinib	65,135	2.767	165,532	0.597	277,143
Pazopanib	84,065	2.767	146,602	0.597	245,450
Cabozantinib + nivolumab	230,667	3.365	-	-.--	-
Intermediate or poor IMDC risk group [c]					
Sunitinib	61,518	2.512	163,727	0.796	205,634
Ipilimumab + nivolumab	180,782	3.420	17,311	-0.155	Ipilimumab+nivolumab dominates
Cabozantinib + nivolumab (JF model Weibull)	225,245	3.309	-	-.--	-
Cabozantinib + nivolumab (FP NMA)	198,092	3.265	-	-.--	-

IMDC: International Metastatic RCC Database Consortium; **QALY**: Quality adjusted life year; **ICER**: Incremental cost-effectiveness ratio; **FP NMA:** Fractional polynomial network meta-analysis; **JF:** Joint fit

[a] Corresponding probabilistic ICER using 1,000 iterations Vs Sunitinib =€281,629/QALY, Vs Pazopanib = €249,463/QALY, Vs Ipi+nivo (in intermediate or poor IMDC risk group) = dominates. Figures in the table are rounded, and so calculations may not be directly replicable

[b] A CIC PAS has been proposed for cabozantinib, and is in place for nivolumab and ipilimumab, not included here

[c] Sunitinib and pazopanib results below calculated using a joint fitted model Weibull while ipi+nivo results are calculated via a FP NMA

Sensitivity analysis

An analysis of the price-ICER relationship was conducted (where the price to wholesaler [PtW] for cabozantinib was reduced) which indicated that cabo+nivo could not achieve cost-effectiveness at any discount. This is due to the very high incremental cost of this combination treatment and small incremental benefit relative to comparators.

4. Budget impact of cabozantinib in combination with nivolumab

The PtW of cabozantinib is €5,377.36 per pack (30 x 20mg or 30 x 40mg or 30 x 60mg tablets). The PtW for nivolumab is €2,943.87 per pack (1 x 240mg vial). The estimated cost of cabo+nivo per-patient, per-treatment course is €376,408 (including VAT), assuming a mean treatment duration of 29.5 months for cabo+nivo. The Applicant's estimated gross and net drug budget impact estimates were considered very uncertain, and a NCPE adjusted budget impact model is presented with the following changes: an up to date incidence rate applied; the correct application of the age-standardised incidence rate to the whole population; and the inclusion of patients diagnosed with early stage RCC (70%) who progress to advanced disease (23%). These changes result in an eligible patient population of 287 in Year one, increasing to 299 by Year five, and a cumulative total of 1,464 patients.

The NCPE adjusted five-year gross drug budget impact estimate for cabo+nivo is €469 million (including VAT) and the cumulative five-year net drug-budget impact estimate is €164 million (including VAT). The Review Group considers the budget impact estimates highly uncertain, in particular the eligible patient population and market shares. The Applicant applied a relative dose intensity (RDI) of 100% for all treatments in the BIM but applied lower RDIs (derived from CheckMate 9ER) in the CEM. The Review Group considers that the RDI for these drugs are very uncertain. The Review Group anticipate the launch of a biosimilar for nivolumab in 2030. Assuming this in year five of the BIM (with a 60% rebate on the PtW) for nivolumab used in the cabo+nivo regimen and in the ipi+nivo regimen, the cumulative gross drug budget impact estimate is €375 million (including VAT), and the five-year cumulative net drug budget impact estimate is €128 million (including VAT).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that cabo+nivo not be considered for reimbursement*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.