NCPE Assessment

Technical Summary

Cemiplimab (Libtayo®)

HTA ID: 21007

23 October 2023

Applicant: Sanofi

Cemiplimab as monotherapy for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of cemiplimab (Libtayo®).

Following assessment of the Applicant's submission, the NCPE recommends that cemiplimab (Libtayo®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Sanofi) Health Technology Assessment of cemiplimab (Libtayo®). 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 January 2023, Sanofi submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of cemiplimab (Libtayo®) for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or curative radiation. Cemiplimab is a PD-1 pathway inhibitor. Sanofi is seeking reimbursement of cemiplimab on the Oncology Drug Management System. Cemiplimab is administered as an intravenous (IV) infusion at a dose of 350mg once every three weeks until disease progression or unacceptable toxicity. Standard of care in Ireland comprises platinum-based chemotherapy (PBC). Patients ineligible for PBC receive best supportive care (BSC). PBC is the most relevant comparator for decision-making.

1. Comparative effectiveness of cemiplimab

There is no direct comparative evidence for cemiplimab against PBC or BSC.
The pivotal trial evaluating the efficacy and safety of cemiplimab in the licenced population is EMPOWER-CSCC 1, an ongoing, phase two, open-label, single-arm trial. There were multiple groups with various dosing regimens recruited. Efficacy data from groups One (n=59) and Three (n=56), comprising patients with metastatic CSCC, and group Two (n=78), comprising patients with locally advanced CSCC, were used to inform the regulatory approval assessment. Patients in groups One and Two received cemiplimab IV at a dose of 3mg/kg once every two weeks for up to 96 weeks, while patients in group Three received cemiplimab at a dose of 350mg once every three weeks for up to 54 weeks. The primary endpoint of the trial was overall response rate (ORR) as assessed by independent review committee; progression-free survival (PFS) and overall survival (OS) were key secondary endpoints.

At the final analysis (March 2022) (for the pooled analysis of groups One, Two and Three), the ORR was 47% (95% confidence interval (CI) 39.9 to 54.4). Median PFS was 22.1 months (95% CI 10.4 to 32.3) while median OS had not been reached. An additional cohort of patients with both metastatic and locally advanced CSCC, group Six (n=167), were recruited

in order to satisfy the requirements of conditional regulatory approval. Cemiplimab was administered at a dose of 350mg once every three weeks in this cohort. A similar ORR (45.1%) was observed to the pooled analysis (of groups One, Two and Three). The Applicant also presented data from patients with metastatic or locally advanced CSCC (n=26) who received cemiplimab at a dose of 3mg/kg once every three weeks for up to 48 weeks in a phase one study, Study 1423. Results from the latest data-cut (April 2019) indicated a median PFS of 22 months. OS data were still immature with 34.6% experiencing an OS event by data cut-off.

The Applicant pooled data from groups One, Two, Three and Six in the EMPOWER-CSCC 1 trial and Study 1423 (total n=386). This informed the clinical efficacy for cemiplimab in an indirect treatment comparison (ITC) with the main comparator of relevance, platinum-based chemotherapy (PBC). Efficacy inputs for PBC (assumed to be cisplatin in combination with 5-fluorouracil), were informed by a retrospective chart review study of patients with non-head or neck, metastatic or locally advanced CSCC (n=18). The Applicant presented results from a naïve ITC, as well as a population-adjusted ITC (using simulated treatment comparison methodology). For both models, an OS benefit was suggested for cemiplimab compared with PBC.

The Review Group noted many limitations of the clinical evidence for cemiplimab including a lack of direct comparative evidence with PBC, exclusion of key patient groups from the pivotal trial, variability in the dosing regimen, uncertainty regarding the optimal treatment duration of cemiplimab and heterogeneity of studies included in the ITC.

2. Safety of cemiplimab

Safety data for cemiplimab are derived from 591 patients with advanced solid tumours across cemiplimab trials: EMPOWER-CSCC 1 (n=193) and Study 1423 (N=398 of whom n=26 had CSCC). Of the 219 patients with CSCC included in the safety analysis set, 48.3% experienced a grade three or higher treatment-emergent adverse event (TEAE). Commonly reported TEAEs included fatigue, diarrhoea, nausea, pruritis and maculo-papular rash. Severe cutaneous adverse reactions have been associated with cemiplimab treatment. The safety profile of cemiplimab is similar to that of other PD-1 inhibitors. Conditional EMA approval for cemiplimab is dependent on the collection of further safety data.

3. Cost effectiveness of cemiplimab

Methods

A cost-utility analysis was conducted using a three health-state partitioned survival model, constructed in Microsoft Excel®.

Cemiplimab efficacy inputs were informed by the pooled analysis of data from EMPOWER-CSCC-1 (groups One, Two, Three and Six) and Study 1423 (total n=386). The relative treatment effects in the model, for cemiplimab versus PBC, are based on the naïve ITC. A scenario analysis comparing cemiplimab with BSC, informed by data from a retrospective chart review study (n=20), was also presented. Treatment waning is implemented in the model; the Applicant assumed that the hazard for PFS and OS of cemiplimab will switch to that of PBC at 60 months. In the model, it is assumed that cemiplimab is administered at a dose of 350mg IV once every three weeks, and treatment duration is based on time-on-treatment data from the pooled analysis. The Applicant assumed a maximum treatment duration of 24 months. The Review Group did not agree with this assumption as a stopping rule is not stipulated in the licence. Treatment can continue until disease progression in the NCPE adjusted base case. The Review Group highlight that there are a number of limitations with the clinical evidence and comparative-effectiveness analysis, in the submission, that cannot be overcome. The Review Group did not consider results from the population-adjusted ITC or the scenario analysis with BSC to be informative for decision-making.

Results

The results of the Applicant base case deterministic analysis are reported in Table 1. Results of the NCPE adjusted base case analysis are reported in Table 2.

Table 1 Results of Applicant base case deterministic cost-effectiveness analysis

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Cemiplimab [a]	207,567	4.65	133,889	2.13	62,767
Platinum-based chemotherapy (PBC)	73,678	2.51	-	-	-

ICER: incremental cost-effectiveness ratio; **PBC:** platinum-based chemotherapy; **QALY:** quality-adjusted life year. Costs and outcomes are discounted at 4%. Figures in the table are rounded, and so calculations may not be directly replicable

[a] Corresponding probabilistic ICER using 1,000 iterations =€65,970/QALY.

Table 2 Results of the NCPE adjusted base case deterministic cost-effectiveness analysis

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Cemiplimab	297,832	4.65	224,154	2.13	105,083

Platinum-based chemotherapy (PBC)	73,678	2.51	-	-	-

ICER: incremental cost-effectiveness ratio; **PBC**: Platinum-based chemotherapy; **QALY**: Quality-adjusted life year. Costs and outcomes are discounted at 4%. Figures in the table are rounded, and so calculations may not be directly replicable

[a] Corresponding probabilistic ICER using 1,000 iterations =€115,591/QALY.

Scenario analyses were conducted comparing cemiplimab to BSC. Using the Applicant's assumptions, the ICER for the comparison between cemiplimab and BSC is €43,404/QALY. Using the Review Group's preferred assumptions, the ICER for the comparison between cemiplimab and BSC is €67,611/QALY.

Sensitivity analysis

The probability of cemiplimab being cost-effective at the willingness-to-pay thresholds of €20,000/QALY and €45,000/QALY, respectively, is 0% in both the NCPE adjusted base case analysis and the Applicant base case analysis. Deterministic sensitivity analyses indicate that the ICER is sensitive to treatment duration assumptions and extrapolation distributions for the OS curve for PBC. A price-ICER analysis was conducted to estimate the reductions in the price-to-wholesaler (PtW) of cemiplimab (expressed as a total rebate on the PtW) which would be required for cemiplimab to meet the €45,000/QALY and €20,000/QALY thresholds. An additional rebate of 66.39%, in addition to the Framework Agreement rebate of 8.5%, is required in order to reduce the ICER below €45,000/QALY.

4. Budget impact of cemiplimab

The price-to-wholesaler of cemiplimab is €5,485.25 (one x 7mL vial containing 350mg cemiplimab). The Applicant assumes that the mean treatment duration with cemiplimab will be 9.87 months, resulting in an estimated per-patient, treatment course cost of €89,848 (€71,800 excluding VAT). The NCPE estimated the mean treatment duration based on the extrapolated time-to-treatment discontinuation curve in the cost-effectiveness model, with the stopping rule removed (27.77 months). The per-patient, treatment course cost is estimated to be €252,795 (€202,015 excluding VAT). The Applicant estimates that eight patients will be treated in year one, rising to 23 in year five. The Review Group estimated the eligible patient population based on more recent epidemiological estimates and clinical opinion to the Review Group. The Review Group estimate that 17 patients will be treated in year one, rising to 51 patients in year five.

The Applicant estimates the five-year cumulative gross drug budget impact of cemiplimab to be €7.97 million (including VAT) and the net drug budget impact over five years to be €7.95 million (including VAT). The Review Group estimate the five-year cumulative gross drug budget impact to be €39.56 million (including VAT) and the five-year net drug budget impact to be €39.49 million (including VAT). The Review Group highlight there is considerable uncertainty associated with budget impact estimates due to uncertainty regarding the number of patients eligible to receive cemiplimab and the likely treatment duration in Irish clinical practice.

5. Patient Organisation Submission

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

6. Conclusion

Following the assessment of the Applicant's submission, the NCPE recommends that cemiplimab 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.*