NCPE Assessment

Technical Summary

Ibrutinib (Imbruvica®)

22054

09/02/2024

Applicant: Janssen

Ibrutinib in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ibrutinib (Imbruvica®) (given in combination with venetoclax) for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia. Following assessment of the Applicant's submission, the NCPE recommends that ibrutinib (Imbruvica®) 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 (Janssen) Health Technology Assessment of ibrutinib (Imbruvica®). 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 February 2023, Janssen submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of ibrutinib (Imbruvica®) in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). Janssen is seeking reimbursement of ibrutinib on the High Tech Drug Arrangement for three subpopulations with previously untreated CLL; fit, unfit and high-risk. These three subpopulations combined reflect the licensed population. Fit patients were defined, by the Applicant, as having a cumulative illness risk score (CIRS) ≤ 6 and/or creatinine clearance (CrCl) ≥ 70mL/min. Unfit patients were defined as having a CIRS > 6 and/or CrCl < 70mL/min, or who are ≥ 65 years old. High-risk patients were defined as having del(17p) or TP53 mutations.

Ibrutinib is an oral targeted Bruton's tyrosine kinase inhibitor (BTKi). Venetoclax is an oral inhibitor of B-cell lymphoma-2. For the treatment of untreated CLL, ibrutinib in combination with venetoclax (I+V) are given for a fixed duration of up to 15 cycles (each cycle is 28-days length) or until disease progression or unacceptable toxicity. Ibrutinib is given at 420mg once daily (cycles 1 to 15 inclusive). Venetoclax is given from cycles 4 to 15 inclusive; the starting dose is 20mg once daily for seven days and the dose is gradually increased over five weeks up to 400mg once daily. The current standard of care treatment of CLL, in Ireland, are fixed duration venetoclax in combination with obinutuzumab (VenO) in the fit, unfit and high-risk subpopulations; fixed duration chlorambucil in combination with obinutuzumab (O-Clb) in the unfit subpopulation; and continuous acalabrutinib or ibrutinib monotherapy in the high-risk subpopulation. The Applicant included fludarabine, cyclophosphamide and rituximab (FCR) chemotherapy as a comparator in this submission, however clinical opinion indicates that FCR is no longer part of standard of care treatment in CLL in Ireland.

1. Comparative effectiveness of ibrutinib

Key direct evidence, in the fit subpopulation, came from the fixed-duration (FD) cohort of the CAPTIVATE trial, an on-going, non-comparative, open label phase II trial of I+V in a fit population with previously untreated CLL. Participants with del(17p) or TP53 mutations were eligible for this study. In the CAPTIVATE (FD cohort), of the 159 patients enrolled and treated ('all-treated participants'), 136 were without del(17p) ('participants without del(17p)'). Data

from participants without del(17p) informed most of the comparative and cost-effectiveness analyses in the submission. The primary endpoint was complete response (CR) rate per investigator (INV) assessment. At the primary analysis (median follow up 27.9 months), CR rates were 55.3%, (95% CI 47.6% to 63.1%) in the all-treated participants and 55.9% (95% CI 47.5% to 64.2%) in participants without del(17p), which exceeded the pre-specified minimum CR rate of 37%. CR rates, consistent with the primary analysis, were observed with longer follow up (up to median 55.7 month). Median INV-assessed progression free survival (PFS) and overall survival (OS) were not reached at primary analysis or subsequent analyses. The trial is considered at high risk of bias due to its open-label design and non-blinded INV assessments of all primary and secondary outcomes. The interpretation of efficacy and safety data are also limited by a lack of a control group; all efficacy and safety results are descriptive only.

Key direct evidence, in the unfit subpopulation, comes from GLOW, an on-going, randomised, open-label, phase III trial comparing I+V to O-Clb in an unfit population with previously untreated CLL. The GLOW trial included a small number of high-risk participants with TP53 mutation (4.3%); patients with del(17p) mutation were excluded. At primary analysis the median follow up was 27.7 months. The primary endpoint was independent review committee (IRC)-assessed PFS; hazard ratio (HR; I+V versus O-Clb) was 0.22 (95% CI 0.13 to 0.36; p<0.0001). Primary and extended-follow up analyses of IRC- and INV-assessed PFS were consistent. At primary analysis, the IRC-assessed objective response rate (ORR), a key secondary endpoint, was comparable across arms; I+V and O-Clb. The hierarchical statistical testing strategy ended at IRC-assessed ORR (at primary analysis); the remaining secondary endpoints, including OS, were exploratory. OS data are still immature and median OS is not reached in either arm at 52-months median follow up.

CAPTIVATE (FD cohort) is single-arm evidence; no comparative evidence is available for I+V in the fit subpopulation. The GLOW trial provided direct-comparative evidence for I+V versus O-Clb in the unfit subpopulation. However, O-Clb is not routinely used in the first-line setting in unfit patients in Ireland. Clinical opinion obtained by the Review Group report that VenO (for fit, unfit and high risk patients) and continuous treatment with acalabrutinib or ibrutinib monotherapies (for high-risk patients) are standard of care in the first-line setting. However,

there are no head-to-head data for I+V versus these comparators. Indirect treatment comparisons (ITC) using matching-adjusted indirect treatment comparison (MAIC) and inverse probability of treatment weighting were submitted to inform the comparisons between I+V and VenO and ibrutinib in the unfit subpopulation only. An ITC, in the high risk subpopulation, was not undertaken. The Applicant stated that is was not feasible. However, we note that the Applicant did not present a feasibility assessment of an ITC of I+V with alcabrutinib, despite identifying relevant evidence (e.g. ELEVATE-TN phase III trial).

There are key limitations in the comparative-effectiveness data. ITC outputs are not robust. The ITCs indicate a potential benefit of I+V over FCR, however the effect estimates are likely biased as adjustment for all relevant prognostic factors was not possible. It is not clear that the anchored MAIC ITC of I+V versus VenO adequately adjusted for treatment effect modifiers. As the proportional hazards assumption does not hold the hazard ratios presented for PFS in the I+V versus VenO ITC are unlikely to provide a meaningful estimate of relative treatment effect. There is substantial uncertainty regarding the comparative effectiveness of I+V versus VenO in the unfit subpopulation. Evidence of comparative effectiveness for I+V versus VenO is not available in the fit or high risk subpopulations. The Applicant assumed that the relative-treatment effects and baseline risks between the unfit and high-risk subpopulations are comparable. There is no evidence to support the assumption that the ITC outputs, for I+V versus ibrutinib monotherapy, in the unfit subpopulation are generalisable to high-risk patients. A number of relevant prognostic factors could not be adjusted for in the I+V versus ibrutinib ITC due to lack of available data, therefore the comparison is potentially biased. The Applicant assumed that the efficacy of continuous acalabrutinib or ibrutinib monotherapy was equivalent to that of I+V.

2. Safety of ibrutinib

The EMA concluded that the safety profiles of I+V, that were seen in GLOW and CAPTIVATE, were consistent with the known safety profiles of single agents ibrutinib and venetoclax in other CLL regimens. No cases of tumour lysis syndrome were reported in GLOW or the CAPTIVATE (FD cohort). At the primary analysis, the median duration of I+V treatment, in the CAPTIVATE (FD cohort) was 13.8 months. The most common grade ≥3 treatment emergent adverse events (TEAEs) occurring in ≥5% of participants were neutropenia, hypertension and neutrophil count decreased. Adverse events (AEs) of special interest included treatment

emergent haemorrhage events (TEHE) including cerebral haemorrhage, haemorrhagic cerebral infarction, and retinal haemorrhage which occurred in three (1.9%) of participants (none were fatal). At the primary analysis of the GLOW trial, the median duration of treatment in the I+V and O-Clb arms were 13.8 months and 5.1 months respectively. TEAEs that were more frequently reported in the I+V arm; those occurring ≥10% difference (I+V versus O-Clb) were diarrhoea, rash, urinary tract infection, peripheral oedema, atrial fibrillation and hyperphosphatemia. The most common serious TEAEs occurring in ≥2% of participants in the I+V arm were atrial fibrillation, pneumonia, anaemia, cardiac failure and diarrhoea and in the O-Clb arm were pneumonia, febrile neutropenia and infusion-related reaction. The incidence of TEHE was higher in the I+V arm (3.8% versus 1%).

3. Cost effectiveness of ibrutinib

A semi-Markov cohort state transition model comprised four mutually exclusive health states: progression free in first-line treatment (PF1L), second-line treatment (PF2L), post-progression (PPS), and death. Each subpopulation (fit, unfit, or high-risk) was modelled separately. The treatment effects captured were the delay of disease progression and death. The key efficacy input was PFS. Utilities were informed by health-related quality of life data from GLOW and the literature. The Review Group identified a number of concerns:

- There is uncertainty regarding the Applicant's assumption of comparable relative-treatment effects and baseline risks between the unfit and high-risk subpopulations.
- The key limitations in the synthesised and assumed comparative-effectiveness data.
- The use of PFS, to model time on treatment, will likely overestimate treatment duration and associated costs, particularly for continuous treatments. This will bias the model in favour of I+V.

Due to limitations in the comparative-effectiveness data, the Applicant's incremental cost-effectiveness ratios (ICERs) are not considered reliable by the Review Group.

Results

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Fit subpopulation					
I+V	345,061	9.39	-	-	-

VenO	420,677	8.14	-75,616	1.25	I+V Dominant
FCR	363,000	7.42	-17,939	1.97	I+V Dominant
Unfit subpopulation					
I+V	273,735	6.69	-	-	-
VenO	375,380	6.14	-101,645	0.55	I+V Dominant
O-Clb	412,427	4.93	-138,692	1.76	I+V Dominant
High risk subpopulation					
I+V	273,735	6.69			
VenO	375,380	6.14	-101,645	0.55	I+V Dominant
Ibrutinib monotherapy	606,788	6.94	-333,053	-0.25	I+V is less costly, less effective
Acalabrutinib monotherapy	633,553	6.94	-359,817	-0.25	I+V is less costly, less effective

Abbreviations: FCR = fludarabine + cyclophosphamide + rituximab; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab

[a] Corresponding probabilistic ICERs, using 1,000 iterations, are in line with deterministic ICERs. Figures in the table are rounded, and so calculations may not be directly replicable

Given the limitations in the comparative-effectiveness evidence, the Review Group are unable to undertake a NCPE-adjusted base case analysis. A key scenario analysis, undertaken by the Review Group, indicates that if equal efficacy (I+V and VenO) is assumed, then I+V is dominated by VenO in the unfit and high risk subpopulations, and the ICER (I+V versus VenO) is €262,777 per QALY in the fit subpopulation.

4. Budget impact of ibrutinib

The price to wholesaler per pack of ibrutinib (28 x 420mg tablets) is €5,019.22. The total cost per pack, to the HSE, on the High Tech Drug Arrangement, inclusive of rebate, is €4,994.12. The Applicant assumes that 180 patients are eligible for treatment in the first year, rising to 187 patients in the fifth year. The NCPE-adjusted base case assumes that there will be 211 eligible patients in the first year and 220 eligible patients by the fifth year. The Applicant excluded a proportion of incident patients, as it was assumed that these patients would receive treatment in clinical trials. The NCPE-adjusted base case removes this assumption. Based on these revised assumptions, the Review Group estimates the cumulative five-year gross budget impact of I+V is €41,702,183 (VAT not applicable). The estimated cumulative five-year net budget impact of I+V is €20,665,653 excluding VAT (€18,758,904 including VAT).

5. Patient Organisation Submission

A patient organisation submission was received from CLL Ireland.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that ibrutinib (given in combination with venetoclax) for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia, 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