

NCPE Assessment

Technical Summary

Selumetinib/Koselugo®

HTA ID: 22032

13 December 2024

Applicant: Alexion Pharmaceuticals

Selumetinib (Koselugo®) for the treatment of symptomatic inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

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

Following assessment of the Applicant's submission, the NCPE recommends that selumetinib (Koselugo®) not be considered for reimbursement*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Alexion Pharmaceuticals) Health Technology Assessment of selumetinib (Koselugo®). 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 Committee.

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, Alexion Pharmaceuticals submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of selumetinib (Koselugo®) for the treatment of symptomatic inoperable plexiform neurofibromas (PNs) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above. Alexion Pharmaceuticals withdrew this dossier in June 2023. Alexion Pharmaceuticals subsequently re-submitted the dossier in January 2024. Selumetinib is a selective inhibitor of mitogen activated protein kinases 1 and 2 (MEK 1/2), which acts by blocking the proliferation and survival of tumour cells. Selumetinib is available in 10mg and 25mg oral capsules. The licensed dose of selumetinib is 25mg/m² twice daily. The current standard of care for the licensed population is best supportive care (BSC) comprising mainly of symptom and pain management. Selumetinib is given in addition to BSC.

Alexion Pharmaceuticals is seeking reimbursement of selumetinib on the High Tech Drug Arrangement.

1. Comparative effectiveness of selumetinib

The efficacy and safety of selumetinib was investigated in the SPRINT study. The licensed population relates to participants from stratum one of the phase II stage of the open-label, single arm SPRINT study only, which included 50 participants aged 2 years to 18 years with NF1 and symptomatic, inoperable PNs. The primary endpoint for SPRINT phase II, stratum one was objective response rate (ORR), defined as the rate of confirmed partial response (PR) and complete response (CR). Response was assessed using centrally read volumetric magnetic resonance imaging (MRI) performed by a single reader in an unblinded investigator review. At the most recently available data cut off (31 March 2021), the median duration of follow-up for participants in SPRINT phase II, stratum one was four years and seven months. The ORR (unblinded review) was 68% (i.e. 68% had a PR (defined as $\geq 20\%$ decrease in PN volume); 0% had a CR (defined as complete disappearance of the PN)). Progressive disease was defined in SPRINT as an increase in the target PN volume by 20% or more compared with baseline or the time of best response after documenting a PR. Progression-free survival (PFS) was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of objective disease progression on treatment or death (by any cause

in the absence of progression). A sensitivity analysis (MRI analysed by independent central review (ICR) committee) was presented. At the June 2018 data cut, the ORR (ICR) was 44%, while the ORR (unblinded investigator review) was 66%. The ORR in both assessments was comprised entirely of PRs. ICR sensitivity analysis was not conducted for the latest data cut available (31 March 2021). The Review Group consider that there is considerable uncertainty around the true benefit of treatment with selumetinib.

Direct comparative trials of selumetinib, for this indication, were not conducted. As such, indirect treatment comparisons (ITCs) were required to estimate the relative effectiveness of selumetinib versus BSC. ITCs were conducted comparing outcomes from SPRINT phase II, stratum one, using unblinded outcome data, with an age-matched subgroup of the NCI Natural History (NH) study of patients with NF1 (NCT00924196) and with the placebo arm of the 01-C-0222 study. 01-C-0222 study is a randomised controlled trial (RCT) comparing tipifarnib with placebo in paediatric patients with NF1 and progressive PNs. Both comparisons were prespecified as part of the SPRINT I clinical study report. NCT00924196 and 01-C-0222 were not identified as part of the systematic literature review conducted by the Applicant, which the Review Group consider to be a potential source of bias. Naïve ITCs were conducted for the outcomes of ORR, PN growth rate, and PFS. These analyses were descriptive in nature and no treatment effect estimates were computed. Propensity score-based methods were also used to compare PFS between SPRINT phase II, stratum one and the age-matched NH cohort. Four different analysis methods were presented, with similar results favouring selumetinib obtained from all analyses. The Review Group highlight results from the ITCs were not used to inform treatment effectiveness estimates in the cost-effectiveness model.

Limitations of the clinical trial evidence include the single-arm nature of the SPRINT study, unblinded assessment of outcomes in SPRINT and the short duration of follow-up in SPRINT. Comparative effectiveness analyses are at risk of bias due to heterogeneity between study populations, the potential for residual confounding in both naïve and propensity score-adjusted ITCs, the absence of a common definition of 'time zero' of the follow-up period across studies, and unblinded MRI assessment carried out by a single reviewer. Therefore, while the comparative effectiveness analyses suggest improvements in ORR, PFS and PN growth rate

with selumetinib compared to BSC, the results are highly uncertain and there is a considerable risk that the true effects could differ substantially from what has been estimated. Furthermore, the comparative effectiveness analysis included outcomes defined in terms of PN-volume only. The Applicant has not demonstrated that selumetinib is more effective than BSC with regards to patient-relevant outcomes such as PN-associated mortality, morbidity, and health-related quality of life.

2. Safety of selumetinib

There are no comparative safety data; the safety of selumetinib versus BSC is unclear.

The safety data for selumetinib was sourced from the phase I and phase II cohorts of the SPRINT study (N=74), and included all participants who received at least one dose of selumetinib. Most participants (99%) experienced at least one adverse event (AE). Dose interruptions and reductions due to AEs were reported in 78% and 32% of participants, respectively. Serious AEs were reported in 17 participants (23%). The most commonly reported serious AEs included diarrhoea (3%), anaemia (3%), pyrexia (3%), elevated blood creatinine phosphokinase (3%), and elevated blood creatinine (1%). Special warnings and precautions associated with use of selumetinib include reduction in left ventricular ejection fraction, ocular toxicity, liver laboratory abnormalities, skin and subcutaneous disorders, and risk of choking. Left ventricular ejection fraction should be evaluated by echocardiogram before initiation of treatment to establish baseline values. The Summary of Product Characteristics (SmPC) recommends that it should be re-evaluated approximately every three months, or more frequently as clinically indicated, during treatment.

Selumetinib is formulated as a hard capsule that must be swallowed whole. The SmPC states that patients should be assessed for their ability to swallow a capsule before starting treatment.

3. Cost effectiveness of selumetinib

Methods

A three-state partitioned survival model was submitted by the Applicant. The partitioned-survival model includes three mutually exclusive health states; Progression-Free (or

stabilised disease), Progressed Disease and Death. Progressed Disease is defined as a 20% or more increase in PN volume compared with baseline, or compared with best response to selumetinib treatment among selumetinib responders. All patients enter the model in the Progressed Disease state. Each patient in the selumetinib-treated arm then enters the Progression-Free health state during the first cycle, and is assumed to be on treatment. Patients can discontinue selumetinib treatment and remain in the Progression-Free health state or transition to the Progressed Disease health state or Death. Patients in the selumetinib-treated arm are assumed to be off treatment if they are in the Progressed Disease health state. Patients in the BSC arm are assumed to commence the model in the Progressed Disease health state and they can either remain in this health state or transition to the Death state. As such, the model structure differs for both arms.

PFS for the selumetinib-treated arm is estimated via parametric extrapolation of patient-level PFS data from the 31 March 2021 data cut-off of the SPRINT phase II, stratum one trial. The Applicant assumes that progression will plateau at 18 years of age, such that patients treated with selumetinib cannot transition into the Progressed Disease state in adulthood. There is no robust evidence to support implementation of the progression plateau at 18 years; this assumption is highly uncertainty. In the NCPE adjusted base case, patients treated with selumetinib can continue to transition into the Progressed Disease health state until 24 years of age, at a lower rate of progression than patients aged less than 18 years. The Review Group highlight that this is a simplifying assumption intended to capture the likelihood that PN growth may continue into adulthood. However, the progression rate and timepoint at which progression may plateau for patients treated with selumetinib is unknown. Scenario analyses explored this uncertainty. General population mortality was estimated using Central Statistics Office Irish lifetables. Excess mortality due to NF1 PN disease was incorporated into the model by applying the same standardised mortality ratio to both the selumetinib and BSC arms.

Health-state utility values, applied in the model, were derived from a time-trade off study using two vignettes (that attributed a wide range of benefits to selumetinib treatment). The vignettes were not evidence-based. The Applicant also assumed that a caregiver utility would apply to 1.5 caregivers per patient treated with selumetinib. The Applicant's assumptions, regarding caregiver utility, were not substantiated by robust evidence. A caregiver utility is not assumed in the NCPE adjusted base case, although scenario analyses

explore the impact of a caregiver utility on cost-effectiveness results.

The Applicant assumed there will be a selumetinib treatment duration cap of five years. The SPRINT study did not include a treatment duration cap, nor is a stopping rule specified in the SmPC for selumetinib. There is potential for life-long treatment with selumetinib, although treatment should not be initiated in patients aged 18 years and older. Clinical opinion indicates that potentially, selumetinib treatment will be stopped if PN stabilisation occurs, although re-treatment could commence if PN re-growth occurred. The model does not consider the possibility of re-treatment with selumetinib. The NCPE adjusted base case does not include a stopping rule for selumetinib treatment.

The following changes were implemented in the NCPE adjusted base case: removal of the stopping rule for selumetinib; the annual rate of progression in the selumetinib arm for adults aged 18 to 24 years; allowing for transition to the progressed state between 18 and 24 years of age; removal of caregiver utility and an assumption of 100% relative dose intensity.

Results

The results of the Applicant's and NCPE adjusted base case deterministic cost-effectiveness analysis are presented in Tables 1 and 2. The Review Group had serious concerns that the model did not adequately describe the condition, nor capture the effect of selumetinib treatment on PN-related outcomes, therefore cost-effectiveness estimates are considered to be very uncertain.

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

Treatments	Total costs		Incremental costs		ICER (€/QALY)
	(€)	Total QALYs	(€)	Incremental QALYs	
BSC	12,950	14.54	-	-	-
Selumetinib	554,728	21.12	541,777	6.58	82,373

BSC: best supportive care; QALY: quality adjusted life years

^a Corresponding probabilistic ICER using 10,000 iterations =€77,215/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.

Table 2: NCPE adjusted base case incremental cost-effectiveness results^a

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	12,950	10.75	-	-	-
Selumetinib	1,116,608	13.64	1,103,658	2.90	380,985

BSC: best supportive care; QALY: quality adjusted life year

^a Corresponding probabilistic ICER using 10,000 iterations =€395,340/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.

Sensitivity analysis

Deterministic one-way sensitivity analysis indicates that the most influential parameters in the model for the NCPE adjusted base case were curve parameters for the time to treatment discontinuation curve and the discount rate for outcomes. The most influential parameters in the Applicant base case model were the number of caregivers to whom the utility decrement was applied to in the BSC arm, the value of the absolute reduction in utility applied and the discount rate for outcomes.

4. Budget impact of selumetinib

The price-to-wholesaler per 10mg pack of selumetinib (60 capsules) is €5,152.64 and €12,882.59 per 25mg pack (60 capsules). Using NCPE preferred assumptions, the estimated mean annual treatment cost of selumetinib per patient, aged 10 years, is €204,001, while the estimated mean annual cost per patient, aged 18 years, is €305,642.

All budget impact estimations are highly uncertain. When the Applicant's assumptions regarding market share and treatment discontinuation are applied, only seven patients are anticipated to be treated with selumetinib annually. The Applicant's projections lack face validity given that the number of patients anticipated to be treated, across all five years, are lower than the number of patients currently being treated, in Ireland, as part of an Early Access Programme for selumetinib. In addition, as of August 2024, over 90% of patients initiated on this Early Access Programme continue to receive treatment with selumetinib, with the first patient commencing treatment in 2019. In the NCPE adjusted base case, it is estimated that 13 patients will be treated with selumetinib in year one, rising to 15 in year five. The NCPE adjusted base case assumes that all patients remain on treatment over the five-year time horizon. The cumulative five-year gross drug budget impact, based on the Review Group's assumptions, is estimated to be €14,718,806 (VAT not applicable). The

Applicant estimates a gross drug budget impact of €8,887,580 over five years. Given that selumetinib is an add-on treatment to BSC, the net budget impacts are the same as the respective gross budget impacts.

5. Patient Organisation Submission

A patient organisation submission was received from the Neurofibromatosis Association of Ireland.

6. Conclusion

The NCPE recommends that selumetinib (Koselugo®) 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.*