Cost-effectiveness of larotrectinib (Vitrakvi®) for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of larotrectinib (Vitrakvi®). Following assessment of the Applicant's submission, the NCPE recommends that larotrectinib (Vitrakvi®) not be considered for reimbursement, unless cost effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Bayer Limited) Health Technology Assessment of Vitrakvi®. 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.

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

National Centre for Pharmacoeconomics **November 2021**

Summary

In February 2021, Bayer Limited submitted a health technology assessment (HTA) dossier on larotrectinib for the treatment of adult and paediatric patients with neurotrophic tyrosine receptor kinase (NTRK) gene fusion positive solid tumours and whose disease is locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options available. Larotrectinib was granted conditional marketing authorisation by the European Medicines Agency (EMA) on 19 September 2019. Larotrectinib is a NTRK inhibitor; it inhibits the formation of oncogenic TRK proteins involved in tumour formation. Larotrectinib is available as an oral formulation in capsules and also as a solution for paediatric use. Larotrectinib is recommended at a dose of 100mg twice daily in adult patients and at a dose of 100mg per m^2 twice daily in paediatric patients. Treatment with larotrectinib is continued until disease progression occurs or there is unacceptable toxicity. The Applicant is seeking reimbursement for larotrectinib on the High Tech Drug Arrangement.

NTRK gene fusions occur in less than 1% of all cancers and have a higher prevalence in rarer tumour sub-types. The prognostic effect of NTRK gene fusions across all tumour types is unknown. Larotrectinib is the first NTRK-targeted antineoplastic agent to be licensed by the EMA. Currently, patients with NTRK gene fusion positive cancers are treated with standard of care (SOC) treatments depending on the tumour type and the line of therapy. The Applicant anticipates that larotrectinib will be used at later lines of therapy, in line with the licensed indication. However, the Review Group consider there to be potential for larotrectinib to be used in earlier lines of therapy, once a NTRK gene fusion positive cancer has been identified. There is also considerable uncertainty and cost associated with NTRK testing in Ireland. Currently, NTRK testing is routinely carried out as standard on non-small cell lung cancer samples as part of a next generation sequencing (NGS) panel. For other tumour types, the Applicant proposes that NGS panel testing will be performed on tumour samples associated with a high prevalence of NTRK gene fusions and in cancers where NGS panel testing platforms are available, at the request of the physician. For remaining tumour types, the Applicant states that immunohistochemistry (IHC) testing will be used to screen

for NTRK gene fusion cancers, with positive screens then undergoing a NGS panel as a confirmatory test.

1. **Comparative effectiveness of larotrectinib**

The clinical efficacy of larotrectinib, in adult and paediatric patients, is evaluated in three basket clinical trials. The basket trials are single arm, open label and are currently ongoing (19 tumour types included based on latest datacut; 20 July 2020). LOXO-TRK-14001, a phase one trial, consists of a dose escalation stage (n=61) and a dose expansion stage (n=9; ongoing) in adults aged 18 years or older with locally advanced or metastatic solid tumours. Presence of NTRK gene fusion is not a requirement. SCOUT (LOXO-TRK-15003), in patients aged one month to 21 years, has a phase one portion (consisting of a dose escalation stage (n=24) and a dose expansion stage (n=5; ongoing)) and an ongoing phase two portion (n=14). SCOUT included patients with central nervous system (CNS) tumours. Presence of a NTRK gene fusion is not a requirement for all participants. NAVIGATE (n=63) is a phase two trial in patients aged 12 years and older with documented NTRK gene fusion. It should be noted across all the basket trials that larotrectinib was permitted as first line therapy if there were no suitable curative therapies available (LOXO-TRK-14001; SCOUT) or if the patient was unlikely to derive clinical benefit from standard of care therapies (NAVIGATE). Safety was the primary endpoint of LOXO-TRK-14001 and the phase one stage of SCOUT. For the phase two stage of SCOUT, the overall response rate (ORR) in patients with a NTRK gene fusion, was the primary endpoint. Similarly, ORR as confirmed by independent central review was the primary endpoint in NAVIGATE. Progression-free survival (PFS) and overall survival (OS) were secondary endpoints in NAVIGATE, while quality of life was a secondary endpoint in SCOUT and an exploratory endpoint in NAVIGATE.

For regulatory approval, the data were pooled across the three studies and the primary endpoint across the pooled analysis was ORR by independent central review. Secondary endpoints of the pooled analyses included: ORR based on investigator assessment for patients with non-CNS primary tumours; time to response; duration of response (DOR); time on treatment; progression-free survival (PFS) (including PFS rate at six and 12 months), and overall survival (OS). The primary analysis set (PAS; n=55; data cut-off date 19 February 2018) was a pooled analysis of patients enrolled across the three studies who met the

following criteria: documented NTRK gene fusion; non-CNS primary tumour with one or more measurable lesions as assessed by RECIST criteria and in receipt of at least one dose of larotrectinib. Data based on the extended PAS dataset (ePAS2; n=93) were presented to the CHMP with a data cut-off date of 30 July 2018. However, the CHMP also requested data be provided on the population with primary CNS tumours (supplementary analysis set 3 (SAS3); n=9; 30 July 2018). For this submission, the Applicant provided data from updated, extended datacuts with a data cut-off date of 20 July 2020; ePAS5 (n=192) and SAS3 (n=33). Table 1 provides details of baseline characteristics and ORR data across the datasets provided for regulatory approval and updated datasets provided as part of the submission.

Table 1 Selected baseline characteristics and efficacy outcome data from datasets used for regulatory approval (ePAS2 + SAS3) and more recent datacuts used in the submission (ePAS5 +SAS3; 30 July 2020).

	Datasets used for regulatory approval		**Datasets used for HTA submission**	
	ePAS2* n=93	**SAS3* n=9**	**ePAS5[α] n=192**	**SAS3[α] n=33**
Baseline Characteristics				
Mean age (SD)	37.9 years (26.1)	28.4 years (32)	35.1 years (26.8)	16.9 years (20.2)
ECOG PS zero, n (%)	42 (45%)	5 (56%)	98 (51%)	18 (55%)
ECOG PS one, n(%)	41 (44%)	3 (33%)	70 (36%)	10 (30%)
Number of tumour types	14	1	18	1
No prior systemic therapy, %	23%	0%	27%	15%
Efficacy				
Complete response, n(%)	15 (16%)	0 (0%)[β]	44 (23%)	3 (9%)[β]
Partial response, n(%)	51 (55%)	1 (1%) [β]	82 (43%)	5 (15%)[β]
ORR, % (95% CI)	72% (62% to 81%)	11% (0% to 48%)[β]	72% (65% to79%)	24% (11% to 42%)[β]

ePAS=extended primary analysis set; **SAS**=supplementary analysis set; **SD**=standard deviation; **ECOG**=Eastern Cooperative Oncology Group; **PS**=performance status; **HTA**= health technology assessment; **CI**=confidence interval; **ORR**=overall response rate.
*Data cut-off date 30 July 2018
[α]Data cut-off date 20 July 2020
[β]Efficacy outcomes were based on investigator's assessment and not independent central review as in PAS datasets.

The median PFS (investigator assessment) was 33.4 months (95% CI 22.5 to 43.5) in the ePAS5 dataset and 18.3 months (95% CI 6.7 to not estimable) in the SAS3 dataset. The median follow-up for OS was 24 months and 16.5 months, in the ePAS5 and SAS3 datasets, respectively. The median OS was not estimable in either dataset.

For the cost-effectiveness evaluation, PFS and OS data was pooled across tumour types and weighted depending on the distribution of 12 of the 19 included tumour types across the clinical trials (ePAS5 + SAS3; 30 July 2020). The Review Group considered it more

appropriate to conduct a Bayesian hierarchical model (BHM) to estimate treatment effectiveness, as this method may better account for heterogeneity in treatment effectiveness. The Applicant stated that it was not feasible to perform a BHM using time-to-event data within the timeframe of the HTA. Previous BHM analyses using the ORR indicate that pooled analysis from the clinical trials may overestimate treatment effectiveness, due to over-representation of rarer tumour types with high NTRK frequency. A systematic literature review (SLR) was commissioned by the Applicant to identify clinical evidence of all relevant comparators for the larotrectinib HTA submission to the National Institute for Health and Care Excellence (NICE), last updated in January 2019. However, limited evidence was identified through this route. The Applicant conducted a naïve indirect treatment comparison, sourcing comparator efficacy estimates from NICE technology appraisals, in the first instance, followed by the SLR. The Applicant identified comparator efficacy estimates for 12 tumour types included in the model, with one comparator chosen by the Applicant for each respective tumour type. For melanoma and breast tumour type, mixed chemotherapies were used, based on the comparators used in NICE technology appraisals. The Review Group queried whether this allowed for representation of all relevant comparators; the Applicant stated this was to avoid additional complexity in the model.

The Review Group had a number of concerns with the clinical evidence for larotrectinib including: a lack of unbiased comparative efficacy data compared with standard of care; a lack of accounting for heterogeneity in the clinical trials; a lack of generalisability of clinical evidence to the patient population expected to be treated in Irish clinical practice; immature survival data and the non-systematic sourcing of comparator efficacy estimates. It is also unknown whether NTRK gene fusions are oncogenic drivers in all tumour types. The Review Group considers the comparative effectiveness analysis of larotrectinib to be highly uncertain and caution should be exerted when using results of this analysis for decision making.

2. Safety of drug

The safety data for larotrectinib are derived from a pooled analysis of 196 adult and paediatric patients who were NTRK gene fusion positive and received at least one dose of larotrectinib as part of one of the three basket clinical trials (data cut-off date: 15 July 2019).

Treatment emergent adverse events (TEAEs) were experienced by 77% of the population. TEAEs led to permanent discontinuation in 5% of the population. Nearly half of the safety population experienced grade three and four adverse events (AEs) (49%); although a smaller proportion were larotrectinib-related (14%). The most common grade three and four AEs across the entire safety population were blood disorders including anaemia (8%), reduced neutrophil count (8%) and decreased lymphocyte count (5%).

The summary of product characteristics (SPC) states, that for patients experiencing a grade three or four TEAE, larotrectinib should be withheld until the TEAE is resolved. Treatment should resume at the next dose modification if resolution occurs within four weeks. The recommended dose modifications for larotrectinib are outlined in the SPC. If the TEAE does not resolve within four weeks, or after the third dose modification, larotrectinib should be permanently discontinued.

Safety data for comparators were derived from the respective sources that informed clinical data and the same limitations with generalisability of inputs to the NTRK positive population remain.

3. Cost effectiveness of larotrectinib

Methods

The cost-effectiveness of larotrectinib was assessed using a three-state partition survival model with a cycle length of seven days and a lifetime horizon (80 years). There are three mutually-exclusive health states; patients enter the model in the progression-free health state and can either stay in the progression-free health state, transfer to the progressed disease state or the absorbing death health state. Reverse transitions are not possible. The proportion of patients within each health state is estimated directly from the extrapolated PFS and OS curves for larotrectinib and comparators, respectively. The Review Group considered the Applicant's choice of extrapolation curves to be reasonable, although validation with clinical opinion was not possible. There are 12 comparator sub-engines in the model; the contribution of each sub-engine to the overall pooled comparator is weighted by the distribution of each tumour type across the pooled dataset (ePAS5 + SAS3).

It is assumed that patients continue on treatment until they reach the progressed health state. The population included were reflective of the licensed indication, although only 12 of the 19 tumour types represented in the trials were included in the model. Some of the tumour groups in the trial were rolled into other tumour sub-engines due to similar SOC therapies whereas others had their weighting equally distributed across tumour sub-engines. The population comprised 55% adults and 45% paediatrics.

The Applicant conducted a SLR to identify relevant health-related quality of life (HRQOL) data in patients with a NTRK gene fusion positive cancer. Treatment-specific health state utility values were applied in the Applicant's base case analysis. Larotrectinib health-state utility values were sourced from the SCOUT and NAVIGATE clinical trials (n=112; 888 assessments). A key limitation of the derivation of health-state utility values from the larotrectinib trials is the small number of patients and assessments contributing to the analyses, along with the heterogeneity in HRQOL assessments. The Review Group noted the SLR for utility values did not include search terms broad enough to identify HRQOL data for comparators, due to restriction to NTRK gene fusion positive cancer. Therefore, health state utility values for comparators were sourced from NICE technology appraisals. The Review Group noted a number of errors in the comparator health state utility values used in the model which were corrected in the Applicant's corrected base case. The Review Group consider the health state utility values for tumour-specific comparators to be highly uncertain. The Review Group did not consider it appropriate to assume treatment-specific health state utility values for larotrectinib treated patients, particularly for the progressed health state, given the lack of direct comparative evidence. In the NCPE adjusted base case, the Review Group applied treatment-independent health state utility values in the progressed health state.

The NTRK testing cost per patient was estimated based on testing rate assumptions by the Applicant, incorporating NTRK frequency rates across tumour types. The cost of NTRK testing, incorporating the cost of negative tests, was applied to all larotrectinib-treated patients in the NCPE adjusted base case.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's corrected base case are presented in Table 2 and Table 3, respectively. The Review Group highlight that while the NCPE adjusted base case reflects the preferred model inputs of the Review group for two parameters (NTRK testing costs and treatment-independent progressed disease health-state utility value), considerable uncertainty remains with the resulting ICER. The main reasons for this include: an inability to alter the structure of the cost-effectiveness model; the non-systematic sourcing of inputs; the unknown prognostic effect of NTRK gene fusions in general and across tumour types; a lack of direct comparative evidence; a lack of effort to address the issues with evidence from a basket trial (statistical methods) and the modelled population not reflecting the population expected to be treated with larotrectinib in Irish clinical practice.

Table 2 Deterministic incremental cost-effectiveness results based on the NCPE adjusted base-case

Treatment	Total Cost	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Pooled comparators	€73,695	1.463	-	-	-
Larotrectinib	€581,983	4.565	€508,288	3.102	**€163,864/QALY**

QALY= quality adjusted life year; **ICER**=incremental cost-effectiveness ratio
Note: A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded so calculations will not be directly replicable.

Table 3 Deterministic incremental cost-effectiveness results based on the Applicant's corrected base-case

Treatment	Total Cost	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Pooled comparators	€73,695	1.463	-	-	-
Larotrectinib	€567,488	5.275	€493,793	3.812	**€129,543/QALY**

QALY= quality adjusted life year; **ICER**=incremental cost-effectiveness ratio
Note: A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded so calculations will not be directly replicable.

Sensitivity analysis

In the NCPE adjusted base case, the probabilistic ICERs were similar to the deterministic ICERs. In the NCPE adjusted base case, the probability of larotrectinib being cost-effective at a willingness-to-pay threshold of €45,000/QALY is 7.89%. At a willingness-to-pay threshold of €20,000/QALY, the probability is 0.20%.

Under the NCPE adjusted base-case, the most influential parameter (in the one-way sensitivity analyses) was the annual discount rate for outcomes. Other influential parameters included the inputs for the larotrectinib Weibull curves (for OS and PFS). The

Review Group also varied the utility values for larotrectinib in scenario analyses, such that treatment-independent health state utility values were applied to larotrectinib for both the progression-free and progressed disease health states, which increased the ICER to €180,177/QALY. Decreasing the time horizon to 20 years and 10 years increased the ICER to €173,280/QALY and €207,095/QALY, respectively.

4. Budget impact of larotrectinib

The price to wholesaler of one pack (56 capsules) of the 100mg capsules, 25mg capsules and 20mg/mL oral solution (100mL) are as follows: €12,042.01; €3,010.53 and €4,413.68. VAT is not applicable as larotrectinib is an oral drug. The total annual treatment cost for adults and paediatrics if using the 100mg capsules is €161,697.56 per patient. The total annual per patient treatment cost if the 25mg capsules or 100mL oral solution are used in paediatric patients, assuming a mean body surface area of 0.74m^2 is €121,460.17 and €177,723.72, respectively. Based on the proportion of patients using each formulation in the trials, the mean annual treatment cost of larotrectinib is estimated to be €163,552.20 per patient. The Applicant estimated the treatment duration with larotrectinib based on the restricted median PFS in the pooled analysis, estimated to be 15 months. The Applicant estimated the weighted average per patient treatment course cost for larotrectinib based on median PFS, to be €182,736. The Review Group considered it more appropriate to estimate the mean treatment duration for larotrectinib based on the mean PFS in the cost-effectiveness model which is estimated to be 42 months, or 46 x 28-day treatment cycles. The Review Group estimates the weighted mean per patient treatment course cost to be €572,684. The mean treatment duration of comparator therapies was based on the mean PFS curve for each of the 12 tumour sub-engines, unless the SPC or regimen protocol specified an alternative treatment duration.

The Applicant estimates that 14 patients with NTRK gene fusion positive cancer will be identified and treated with larotrectinib in year one, rising to 17 in year five. Estimations of the eligible patient population with NTRK gene fusion positive cancer are underpinned by assumptions relating to NTRK testing and positivity rates, which the Review Group consider to be highly uncertain. The Applicant estimated the cumulative five-year gross drug budget

impact of larotrectinib to be €14.10 million. In the NCPE adjusted base case, the cumulative five-year gross drug budget impact is estimated to be €31.96 million.

The Applicant estimates the cumulative five-year net drug budget impact of larotrectinib to be €12.15 million (including VAT, where applicable). The Review Group estimate the five-year net drug budget impact of larotrectinib to be €24.74 million (including VAT, where applicable). The Applicant considered the additional costs associated with NTRK testing and the other costs offsets; the Applicant net healthcare budget impact is estimated to be €22.21 million. The Review Group estimate the net healthcare budget impact to be €34.74 million. The Review Group considers budget impact estimates to be uncertain given the assumptions made by Applicant relating to NTRK testing rates and the estimated number of patients that will be treated with larotrectinib each year.

5. Patient submissions

No patient submissions were received in support of this submission.

6. Conclusion

Following the NCPE Review Group assessment of the available evidence, the NCPE recommends that larotrectinib (Vitrakvi®) not be recommended for reimbursement, unless cost effectiveness can be improved relative to existing treatments*. This recommendation is dependent on the ability to address some of the uncertainties including the clinical evidence, the prognostic benefit of treating NTRK, testing and transferability of evidence across tumour types.

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