SMC2821

ripretinib tablets (Qinlock®)

Deciphera Pharmaceuticals (Netherlands) B.V.

04 July 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the end of life and orphan medicine process

ripretinib (Qinlock®) is accepted for use within NHSScotland.

Indication under review: for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

In a randomised, double-blind, phase III study, ripretinib significantly improved progression free survival compared with placebo in patients with advanced GIST who had received treatment with at least three prior kinase inhibitors.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Co-Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Ripretinib is a switch-control tyrosine kinase inhibitor (TKI) that inhibits KIT proto-oncogene receptor tyrosine kinase and platelet derived growth factor alpha (PDGFRA) kinase, including wild type, primary and secondary mutations. By locking the kinase in the inactive state via a dual mechanism of action, it prevents downstream signalling and cell proliferation which slows tumour growth and reduces symptoms of the disease. Ripretinib also inhibits other kinases in vitro, such as PDGFRB, TIE2, VEGFR2 and BRAF.[1, 2]

The recommended dose of ripretinib is 150 mg once daily taken orally at the same time each day with or without food. Treatment should continue for as long as benefit is observed or until unacceptable toxicity. For further information please refer to the summary of product characteristics (SPC) including recommendations on missed doses and dose modifications for adverse reactions.[1]

1.2. Disease background

Gastrointestinal stromal tumours (GIST) are rare cancers with an estimated incidence rate of 650 clinically meaningful new cases in the UK each year. They are a form of sarcoma and are the most common malignant mesenchymal tumour found in the gastrointestinal tract. The median age at diagnosis is approximately 60 to 65 years, although the range is wide, and they are slightly more prevalent in males. On diagnosis, mutational analysis is conducted to indicate prognosis and predict sensitivity to treatment choice. Most GIST are associated with a KIT (approximately 75%) or PDGFA (approximately 10%) gene mutation, although other rare variants can include succinate dehydrogenase (SDH), neurofibromatosis 1 (NF1), BRAF or RAS gene mutations. Prognostic factors include tumour size and location, mitotic rate and mutational status. Larger tumours (>2 cm) with a high mitotic rate have an increased risk of metastasising compared with smaller tumours, and small bowel or rectal GIST are higher risk than gastric GIST. Metastatic or unresectable GIST that has progressed following treatment with three TKIs is associated with a poor prognosis; progression free survival (PFS) with third line treatment is 4.8 months with no overall survival benefit.[2-4]

1.3. Treatment pathway and relevant comparators

Guidelines recommend treatment with TKIs for locally advanced or metastatic GIST, however, response is limited as resistance can develop within a few months. Imatinib is the first line treatment for patients with a KIT/PDGFRA mutation (except a PDGFRA exon 18 D842V mutation). Avapritinib is licensed for unresectable or metastatic GIST with a PDGFRA D842V mutation but is not recommended by SMC in the absence of a submission (SMC2424). Some patients may also be eligible for surgical intervention if progression is limited while continuing imatinib. On further progression, intolerance or resistance to imatinib, sunitinib is accepted for use in the second line (SMC275/06). If progression occurs again, regorafenib is available as third line treatment. There are no standard treatment options in the fourth line and beyond (SMC1031/15). In this setting, patients receive best supportive care which includes symptomatic management with laxatives, analgesics and antiemetics.[2-4] Clinical experts consulted by SMC indicated that no systemic anticancer therapies would be displaced by ripretinib therefore the most relevant comparator is best supportive care.

1.4. Category for decision-making process

Ripretinib meets SMC end of life and orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of ripretinib for the treatment of advanced GIST is from the INVICTUS study.[5] Details are summarised in Table 2.1.

Table 2.1. Overview of the INVICTUS study[5]

Criteria	INVICTUS
Study design	Multicentre, randomised, double-blind, placebo-controlled phase III study.
Eligible patients	• Adults ≥18 years with a histological GIST diagnosis with at least one measurable disease lesion per mRECIST v1.1. • Progressed on imatinib, sunitinib and regorafenib or have documented intolerance to any of these despite dose modifications. • Access to an archival tumour tissue sample if no anticancer therapy had been administered since collection otherwise a fresh tumour tissue sample should be collected. • ECOG performance status of 0 to 2.
Treatments	Blinded period Oral ripretinib 150 mg once daily plus BSC (n=85) or placebo plus BSC (n=44). Treatment was to continue until disease progression, unacceptable toxicity or withdrawal of consent. Open-label period On progression (by BICR), patients in the placebo group could crossover to receive open-label ripretinib, patients receiving ripretinib could dose escalate to 150 mg twice daily.
Randomisation	Patients were randomised 2:1 to receive ripretinib or placebo. Randomisation was stratified according to the number of previous therapies (three versus four or more), and ECOG performance status (0 versus 1 or 2).
Primary outcome	PFS, defined as the interval between the date of randomisation to the date of documented progressive disease or death due to any cause per mRECIST v1.1 assessed by BICR.
Secondary outcomes	ORR, defined as confirmed complete response and partial response assessed by BICR. EORTC-QLQ-C30 role function and physical function, measured as the change from baseline to day 1 of cycle 2. OS, defined as the time between the date of randomisation and the date of death from any cause.
Statistical analysis	Efficacy analyses were performed in the ITT population, which included all patients who underwent randomisation. A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Outcomes were tested in the following sequential order: PFS, ORR, OS and changes in EORTC-QLQ-C30 Role function and physical function.

Key: BICR: blinded independent central review; BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; GIST: gastrointestinal stromal tumour; ITT: intention to treat; mRECIST v1.1: modified response evaluation criteria in solid tumours version 1.1; PFS: progression free survival; ORR: objective response rate; OS: overall survival

The primary analysis of the INVICTUS study was conducted at data cut-off 31 May 2019. At this time, ripretinib significantly improved PFS compared with placebo. The difference between treatments in first secondary outcome of objective response rate (ORR) did not reach statistical significance and further formal statistical testing was stopped. Updated analysis with an additional 19 months of follow-up is also available from a data cut off on 15 January 2021.[5, 6] The results from the later data cut-off have been used to inform the economic analysis. Study results are detailed in Table 2.2.

Table 2.2: Primary and selected secondary outcome results for INVICTUS in the ITT[5, 6]

Data cut-off	**31 May 2019**		**15 January 2021**	
	Ripretinib n=85	**Placebo n=44**	**Ripretinib n=85**	**Placebo n=44**
Median follow-up in double-blind period, months	6.3	1.6	-	-
Primary outcome: PFS per mRECIST v1.1 assessed by BICR (double-blind period)				
PFS events, n(%)	51 (60%)	37 (84%)	71 (84%)	37 (84%)
Median PFS, months	6.3	1.0	6.3	1.0
HR (95% CI), p-value	0.15 (0.09 to 0.25) p<0.001		0.16 (0.10 to 0.27)	
KM estimated PFS at 6 months	51%	3.2%	51%	3.2%
KM estimated PFS at 12 months	-	-	22%	NE
Secondary outcome: ORR assessed by BICR (double-blind period)				
ORR rate[A], %	9.4%[B]	0	12%	0
Secondary outcome: overall survival (double-blind and open-label period)				
Deaths	26 (31%)	26 (59%)	46 (54%)	36 (82%)
Median OS, months	15.1	6.6	18.2	6.3
HR (95% CI)	0.36 (0.21 to 0.62)		0.41 (0.26 to 0.65)	
KM estimated OS at 12 months	65%	26%	65%	30%
KM estimated OS at 24 months	-	-	43%	20%

Key: BICR: blinded independent central review; CI: confidence interval; HR: hazard ratio; ITT: intention to treat; KM: Kaplan-Meier; mRECIST v1.1: modified response evaluation criteria in solid tumours version 1.1; NE: not estimable; ORR: objective response rate; PFS: progression free survival. [A]Non-significant p-value (p=0.05) therefore subsequent results from outcomes included in the statistical hierarchy are descriptive only. [B]All patients achieved a partial response, and no patients achieved a complete response.

At the May 2019 data cut-off, 29 of the 44 patients originally randomised to placebo had progressive disease per BICR and crossed over to receive open-label ripretinib. In post crossover exploratory analysis, these patients had a median time to further progression or death of 4.6 months, two patients achieved a partial response and median overall survival (OS) was 11.6 months. In the 15 patients in the placebo group that did not cross over to ripretinib, median OS was 1.8 months.[7]

2.2. Health-related quality of life outcomes

Health-Related Quality of Life was assessed using the role and physical domains from European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-

item (EORTC-QLQ-C30), the EuroQol 5 dimensions 5 levels (EQ-5D) and EuroQol visual analogue scale (EQ-VAS). These instruments were used from baseline to cycle 2 day one.

In the ripretinib group, physical and role functioning domains of the EORTC-QLQ-C30 remained stable with an increased adjusted mean change in scores of 1.6 and 3.5 respectively compared with a decline in the placebo group (-8.9 and -17.1, respectively). EQ-VAS scores also remained stable in the ripretinib group with an increased adjusted mean change in score of 3.7 versus a decline of 8.9 in the placebo group. For the EQ-5D minimal change from baseline was noted for both the ripretinib group and placebo group respectively (-0.009 versus -0.06).[5, 8, 9]

2.3. Supportive studies

The submitting company also provided real world evidence from a retrospective review of 45 patients with unresectable or metastatic GIST that had received at least two prior treatments who were offered ripretinib on a compassionate basis in a UK hospital between 2020 and 2021. After a median follow-up of 24.2 months, patients who received ripretinib 150 mg once daily had a median PFS of 7.9 months and 17% achieved a partial response. Median OS was 14 months, which included 15 patients with progressive disease who had ripretinib dose escalated to 150 mg twice daily. No new safety signals were reported.[10]

3. Summary of Safety Evidence

Overall, the regulator concluded that the safety profile of ripretinib for the indication under review was acceptable and no major concerns were identified.[2]

In the INVICTUS study at data cut-off 31 May 2019 during the double-blind period, the median duration of treatment was 24 weeks in the ripretinib arm and 6 weeks in the placebo arm. Any treatment-emergent adverse event (AE) was reported by 99% (84/85) of patients in the ripretinib arm and 98% (42/43) in the placebo arm and these were considered treatment-related in 85% and 60% in the ripretinib and placebo arms respectively. In the ripretinib and placebo groups respectively, patients reporting a grade 3 or higher treatment-related AE (TRAE) were 25% versus 16%, patients with a dose reduction due to TRAEs were 5.9% versus 2.3%, the proportion of TRAEs that led to dose interruptions were 14% versus 7.0% and patients discontinuing therapy due to an TRAE was 4.7% versus 2.3%.[2, 5]

At the May 2019 data cut off during the double-blind period, the most frequently reported TRAEs of any grade with an incidence >20% in the ripretinib group versus the placebo group were: alopecia (49% versus 2.3%), myalgia (28% versus 9.3%), nausea (26% versus 2.3%), fatigue (26% versus 16%), palmar-plantar erythrodysaesthesia syndrome (21% versus 0) and diarrhoea (21% versus 7.0%). The most frequently reported grade 3 or higher TRAEs with an incidence of ≥2% in the ripretinib group were: lipase increase (4.7% versus 0), hypertension (3.5% versus 0), fatigue (2.4% in both groups) and hypophosphataemia (2.4% versus 0). Safety results from subsequent data cut offs were consistent with this primary analysis.[2, 5, 6]

Adverse events of special interest included dermatological toxicities and cardiac disorders. Cutaneous squamous cell carcinoma was reported in 5.9% in the ripretinib group and no patients in the placebo group. The SPC recommends routine dermatological examinations while on treatment. Hypertension and cardiac failure have been observed with ripretinib and patients should be assessed before and monitored throughout treatment, see the SPC for further information.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- INVICTUS was a phase III study with a randomised, placebo-controlled design. The PFS primary outcome and ORR secondary outcome were measured independently during the double-blind period using modified RECIST v1.1 criteria for radiological findings.[5] This limits the risk of potential bias.
- Treatment with ripretinib was associated with a statistically significant improvement in PFS compared with placebo (6.3 months versus 1.0 month) in patients with GIST who had received at least three prior lines of therapy at the May 2019 primary analysis. The regulator considered these results to be clinically relevant. Prespecified subgroup analyses found consistent results. This was supported by improvements in ORR (9.4% versus 0%) and overall survival (15.1 months versus 6.6 months [includes data from double-blind and open-label periods]) which also favoured ripretinib.[2, 5]
- Results from a later data cut-off (January 2021), with an additional 19 months follow-up, were similar to the primary analysis.[6]
- Results from a UK retrospective real word study were broadly supportive of the results from the INVICTUS study.[10]

4.2. Key uncertainties

- INVICTUS was a small study, with a total of 129 patients included in the efficacy analysis.[2, 5] This increases the risk of prognostic or effect-modifying differences between groups that could introduce uncertainty regarding the relative treatment effect. Subgroup analysis is also limited by the small sample sizes.
- On progression (identified by independent radiological review), study patients were unblinded, those in the ripretinib group could dose escalate and those in the placebo group could crossover to receive ripretinib. The SPC does not recommend this dose escalation on progression and advises treatment is continued for as long as benefit is observed.[1, 5] The impact of this increased dose and the confounding effect crossover has on survival results is uncertain and may affect the generalisability of study results to patients receiving the licensed dose in practice. Exploratory analyses conducted by the company to quantify the impact of post progression twice daily dosing was uncertain because of the unknown effect of potential imbalances in characteristics that may differ between patients who chose to dose escalate and those who did not. To account for patients in the placebo group crossing over to the ripretinib group on progression, a crossover adjustment for OS using a two-stage approach was carried out and has been included in the economic base-case.
- In INVICTUS, 37% of patients had received at least four previous lines of treatment. As most patients in Scotland typically receive best supportive care after third line treatment, the study population may include a higher proportion of more heavily pre-treated patients than would be observed in clinical practice. Subgroup analysis based on number of prior treatments were consistent with the primary analysis with a greater PFS benefit in patients who had three prior treatments compared with four or more prior treatments however the numbers in each subgroup were small and results are descriptive only.[5]

- There was no statistically significant difference between treatment groups for ORR, the second outcome in the hierarchical testing strategy, and therefore the results of subsequent outcomes, OS and EORTC-QLQ-C30 changes in physical and role functioning are descriptive only.[5]
- There were limitations associated with the retrospective real world study. The uncontrolled design limits comparison relative to standard care and the sample size is small (n=45). A higher proportion (51%) had small bowel GIST than would be seen in clinical practice and 42% had received two prior treatment lines so may have been less heavily pre-treated and do not represent the licensed indication for ripretinib.
- In clinical practice, patients may continue to take regorafenib after disease progression as there are no other standard fourth line treatment options. Several clinicians consulted by SMC indicated that a rechallenge with imatinib may also be trialled in selected patients. There is no direct or indirect evidence comparing ripretinib with these treatment options in the fourth line.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that availability of ripretinib would fill an unmet need because there are no standard treatment options in the fourth line setting. They indicated that it is a therapeutic advance in the management of advanced GIST because of the favourable results of the INVICTUS study with improved survival outcomes and expected symptom benefit. It would be used as a fourth line treatment option as per the licensed indication.

4.4. Service implications

Significant service implications are unlikely as the number of patients eligible for treatment is small. Ripretinib is taken orally and therefore inpatient administration is not required. There is an established network of GIST clinics across Scotland and clinicians are familiar with the management of common side effects.

*Other data were also assessed but remain confidential.**

5. Patient and clinical engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **ripretinib**, as an **orphan and end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- GIST is a rare and life limiting condition. Patients that require fourth line treatment have a poor prognosis. The burden of disease and previous treatment has a significant impact on the physical, emotional and mental wellbeing of patients and their carers.
- There is no standard fourth line treatment option after progression on imatinib, sunitinib and regorafenib. Patients currently receive best supportive care or occasionally may be rechallenged with imatinib which is associated with low response rates. PACE participants would welcome an additional line of therapy for this small group of patients who have progressed or have been unable to tolerate previous lines of treatment.

- Ripretinib may improve survival outcomes, alleviate symptoms of disease and allow a sustained quality of life. Patients may remain independent for longer, require less support from carers for day-to-day activities and can continue to live a normal life. Knowing there is an effective fourth line treatment available gives patients hope and could alleviate some of the psychological stress associated with limited further treatment options.
- PACE clinicians noted that ripretinib is generally well-tolerated and most side effects are mild in severity. Patients would attend hospital appointments monthly to assess efficacy and monitor for side effects.
- The most appropriate place in the treatment pathway for ripretinib is in the fourth line setting, for patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib.

Additional Patient and Carer Involvement

We received a joint patient group submission from Sarcoma UK and GIST Cancer UK, which are both registered charities. Sarcoma UK has received 0.5% pharmaceutical company funding in the past two years, with none from the submitting company. GIST Cancer UK has not received any pharmaceutical company funding in the past two years. Representatives from both patient groups participated in the PACE meeting. The key points of their joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	40 years
Population	Adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors including imatinib.
Comparators	BSC – which includes pain management (co-codamol, tramadol, paracetamol, morphine, dexamethasone) as well as laxatives, antiemetics and antinausea agents.
Model description	Partitioned survival model with three health states, progression- free (PF), progressed disease (PD) and death. Progressed disease is split into two sub states for the ripretinib arm, where some patients may choose to continue to take ripretinib even after progression. Cycle length is 28 days with a half cycle correction applied.
Clinical data	Clinical evidence is taken from the INVICTUS study. Study data were used to inform PFS, OS and Time to Treatment Discontinuation (TTD) for both the ripretinib and BSC arms. Frequencies of grade 3 or 4 treatment emergent adverse events (TEAEs) were taken from the INVICTUS study for both the ripretinib and BSC arms. All clinical data used in the economic model were taken from the January 2021 data cut. No indirect treatment comparison was used in this submission.
Extrapolation	For PFS, parametric curves were fitted independently to each arm, where the company chose the log-normal distribution as the base-case curve for both treatment arms, based on statistical and visual fit.

	Due to the design of the INVICTUS study, where patients on the BSC arm could crossover to ripretinib post-progression, the company applied a two-stage crossover approach (with simple re-censoring) to adjust the BSC arm. This reduced the OS time in the BSC. The crossover adjustments do not have an impact on the ripretinib overall survival estimates. After crossover adjustment, parametric curves were fitted independently to each arm, where the company chose the log-logistic curve for both treatment arms, based of statistical and visual fit. In order to capture the additional costs of patients in the ripretinib arm that continue treatment after progression, a composite endpoint of treatment discontinuation and PFS was used to model TTD, in other words the transition of patients from the progressed disease on-treatment to the progressed disease off-treatment. This composite endpoint was extrapolated using an exponential curve, which the company justified as the best fitting curve based on statistical fit and a constant hazard assumption.
Quality of life	EQ-5D data from INVICTUS study was mapped to EQ-5D-3L via Van Hout et al (2012)[11], and used for the progression- free state, which was weighted by the total on- treatment and off- treatment patients, and progressed disease on- treatment health state, which was calculated based on patients who continued to receive ripretinib arm after progression in the ripretinib arm. The utility values for PF and PD on-treatment are 0.723 and 0.701, respectively. In the off-treatment PD state for ripretinib arm and the PD for the BSC arm, an EQ-5D-3L based health state utility value of 0.647 (calculated using repeated measures analysis) was employed from the GRID study.[12] The GRID study investigated regorafenib (third line) versus placebo in patients with metastatic/unresectable GIST who have progressed on or were intolerant to imatinib and who have progressed on sunitinib. Adverse event disutilities were sourced from various sources as no specific disutility values could be identified for GIST patients.
Costs and resource use	Costs included acquisition, administration, health state costs, adverse event costs and end of life costs for both arms of the study. Both treatment arms included pain management costs. The treatment duration was based on the TTD curve, where patients who continued ripretinib after progression incurred additional medicine costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

Abbreviations: BSC = best supportive care; GIST = gastrointestinal stromal tumour; OS = overall survival; PD = progressed disease; PF = progression free; PFS = progression-free survival; TTD = time to treatment discontinuation

6.2. Results

The base case incremental cost-effectiveness ratio (ICER) with PAS was £39,474 per quality adjusted life year (QALY) gained. The associated life year gained was 2.685.

The main cost drivers are from the large differences in acquisition costs, which are to be expected against BSC. Due to the continued treatment after progression assumption and the improved PFS, the ripretinib arm have a higher cost over a longer duration.

The main QALY drivers are from the PD health state, particularly the PD off-treatment in the ripretinib arm. This is due to overall survival estimates suggesting that patients in the ripretinib arm would be alive for longer.

6.3. Sensitivity analyses

Sensitivity analyses included deterministic, probabilistic and scenario analysis. The deterministic sensitivity analysis highlighted that the key driver of the results was the utility value for PD Off-Treatment health state (ripretinib arm). The table below illustrates selected scenario analysis.

Table 6.3 Scenario analysis for ripretinib versus BSC with PAS

	Parameter	Base case	Scenario	ICER (£/QALY)
1	Overall Survival curves (applied to both ripretinib and BSC)	OS: Log-logistic curve	OS: exponential	50,383
2			OS: Weibull	50,603
3	Progression free survival curves (applied to both ripretinib and BSC)	PFS: Log normal	PFS: exponential	39,158
4			PFS: Log-logistic	41,209
5			PFS: Generalised gamma	39,207
6	Time to Treatment Discontinuation curves	TTD: exponential	TTD: Weibull	39,214
7			TTD: Log-logistic	45,869
8			TTD: Log-normal	43,958
9	Crossover adjustments	Two-stage approach with simple re-censoring	Unadjusted analysis for BSC OS	59,725
10			OS: RPSFTM-adjusted without re-censoring	40,681
11	Utilities	For PD off treatment and PD for BSC, the GRID study was used as a source	For PD off treatment and PD for BSC, the INVICTUS study was used as a source (0.634)	39,971
12		PD on treatment utility sourced from INVICTUS (0.701)	Assumed the PD on treatment, PD off treatment and PD (BSC) utilities are all 0.647 from GRID study.	39,877
13	Time horizon	40-year time horizon	10-year time horizon	45,293
14	Combined scenario	OS: log-logistic curve + TTD: exponential	OS: exponential + TDD: log-logistic	57,802

Abbreviations: BSC = best supportive care; GIST = gastrointestinal stromal tumour; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressed disease; PF = progression free; PFS = progression-free survival; RPSFT = rank preserving structural failure time model; TTD = time to treatment discontinuation

6.4 Key strengths

- The chosen comparator of BSC seems reasonable and thus there is direct evidence against a relevant comparator.
- The partitioned survival model was an appropriate choice, like other submissions with similar indications. The choice to split the progressed disease state into two sub states to account for the costs associated with patients who continue treatment after progression was appropriate. The SMC experts have indicated that this would be reasonable to assume that fourth line treatment patients would continue treatment post-progression, however they do not specify a how long this added treatment duration would be.

6.5 Key uncertainties

- There was additional uncertainty introduced through the extrapolation methods used to project OS in the ripretinib arm. While all parametric curves have a good visual and statistical fit to the Kaplan-Meier data, the submitting company chose the log-logistic curve for the base case analysis which aligned with the upper end of the company's clinical advisory board estimates, projecting 8.4% of patients alive at 10 years. More conservative curves, scenarios 1 and 2 in table 6.3, predicted lower long-term survival with around 2% and 1%, respectively, alive at 10 years, which is in line with the company's clinical advisory board reported lower bound estimate, resulted in an upward shift in the ICER.

- The company's approach to modelling TTD has an impact on the ICER. Specifically, the use of the log-logistic curve (scenario 7), which extends the time patients remain in the on-treatment health state, results in increased costs thereby increasing the ICER. The company argued that this curve is implausible, citing its non-monotonic hazard and unimodal shape, and suggest the exponential curve in the base case is the most suitable, which predicts a much shorter duration for patients remaining on treatment after progression. There is uncertainty around the true duration of treatment post progression in clinical practice, so it is uncertain which curve is the most appropriate.

- The crossover adjustment introduces uncertainty around the overall survival estimated for the placebo arm. The submitting company selected the two-stage crossover method, justifying it as the least weak approach given the limited data availability, while ruling out the inverse probability of censoring weights (due to small proportion of patients not crossing over) and rank-preserving structural failure time (RPSFT) because the common treatment effect assumption would not hold. However, feedback from the SMC statistician suggests that the common treatment effect assumption could have been relaxed within the RPSFT method. The company did provide these scenarios, which showed minimal changes to the ICER. However, the lack of comparative plots across adjustment methods and absence of external validation leaves the face validity of the adjusted results uncertain. It is clear from scenario 9, the unadjusted analysis results in a significant increase in the ICER. Therefore, the crossover method may have over-adjusted the data and introduces uncertainty about the appropriateness of the overall survival estimates.

- In the INVICTUS Study, if patients in the ripretinib group progressed there was the option to also increase the dose from 150 mg once a day to twice a day, which is not recommended by the SPC. The company conducted a post-hoc analysis to understand the effects of double dosing but ultimately the analysis is associated with considerable uncertainty. The company justified not adjusting for double dose patients in the economic model by highlighting the complexity of multiple treatment switches, selection bias caused by broken randomisation, and the absence of data on all potential treatment effect modifiers. The company claim that these limitations make it difficult to produce reliable and robust estimates, without adding further uncertainty. Even so, the lack of adjustment for the double dosed patients may have introduced bias and artificially inflated the survival benefit of ripretinib.

- There is uncertainty about whether continued treatment of third line regorafenib or a re-challenge of imatinib could be considered as relevant comparators. It is unclear how the inclusion of these comparators would impact the economic results.

- The utility values used in the base case appear high and may have been overestimated.

From deterministic sensitivity analysis, it was clear one of the main drivers of the results is the utility value for the progressed disease off-treatment health state. The company provided additional scenario analysis (scenarios 11 and 12), which showed modest increases in the ICER when the source of the PD health states was altered. While these scenarios suggest only a limited impact on the results, there remains some uncertainty around the appropriateness of the utility values in the context of an end of-life setting.

*Other data were also assessed but remain confidential.**

7 Conclusion

The Committee considered the benefits of ripretinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy was satisfied. In addition, as ripretinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted ripretinib for use in NHSScotland.

8 Guidelines and Protocols

The British Sarcoma Group published 'Gastrointestinal stromal tumour (GIST): British Sarcoma Group clinical practice guidelines' in June 2024.[3]

The European Society of Medical Oncology (ESMO) published 'Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guideline for diagnosis, treatment and follow-up' in September 2021.[4]

9 Additional Information

9.1 Product availability date

20 December 2021

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28 days (£)
Ripretinib	**150 mg once daily, taken orally.**	**17,173**

Costs from BNF online on 28/10/24. Costs do not take any patient access schemes into consideration.

10 Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 13 patients eligible for treatment with ripretinib in each year to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 08 April 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.