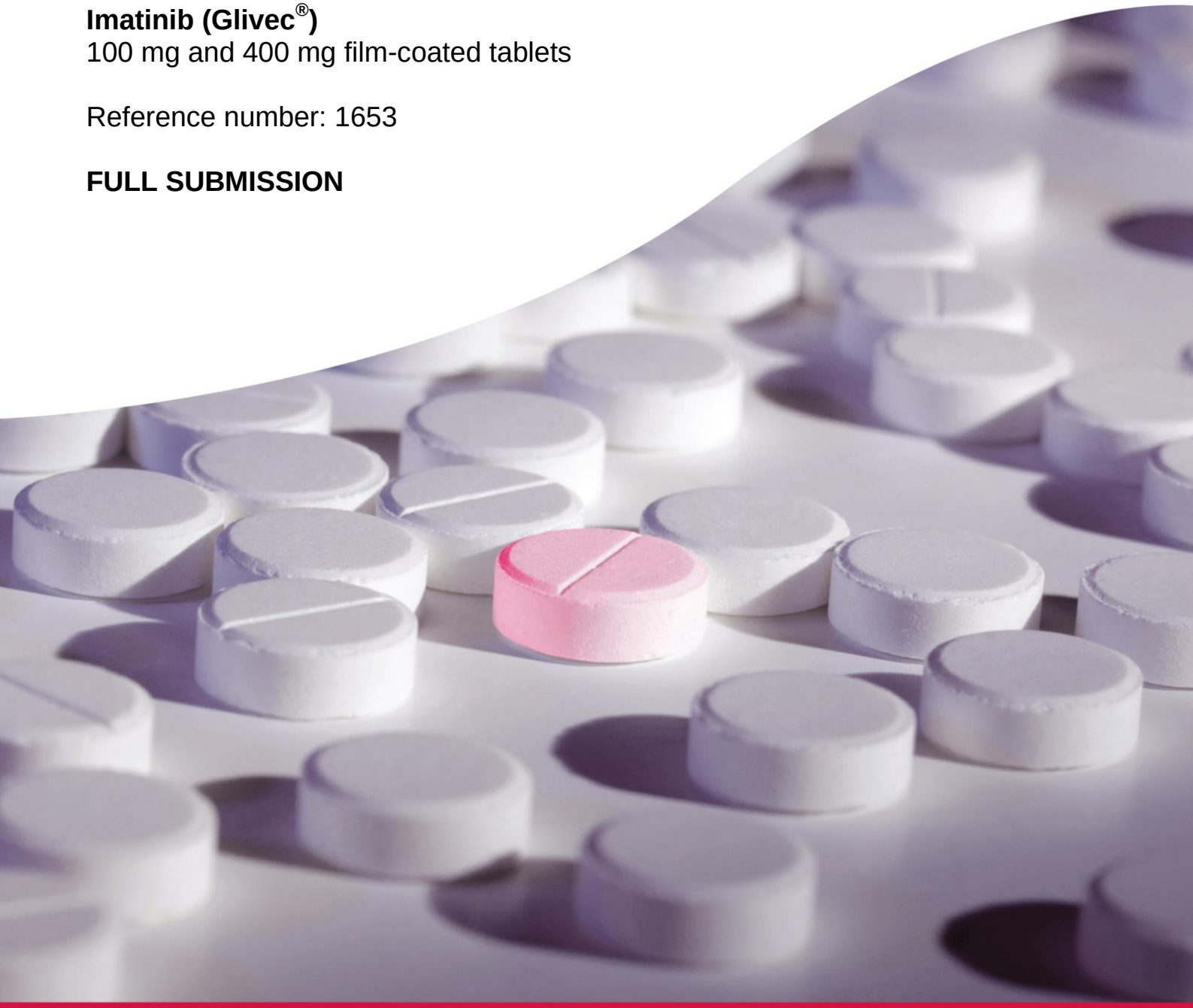
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Imatinib (Glivec®)
100 mg and 400 mg film-coated tablets

Reference number: 1653

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Imatinib (Glivec®) 100 mg and 400 mg film-coated tablets

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd on 19 December 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Imatinib (Glivec®) for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive gastrointestinal stromal tumours. Patients who have low or very low risk of recurrence should not receive adjuvant treatment[2].
Dosing	The recommended dose of imatinib in the indication under consideration is 400 mg once-daily. Optimal treatment duration is not yet established. Length of treatment in the clinical trial supporting this indication was 36 months. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2].
Marketing authorisation date	29 April 2009[3] (licensed for the treatment of Philadelphia chromosome positive [Ph^+] chronic myeloid leukaemia on 7 November 2001)[2,4].

2.0 DECISION CONTEXT

2.1 Background

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal tumours of the gastrointestinal (GI) tract[5–7], affecting an estimated 13 people per 100,000 in Europe[8], with approximately 900 new diagnoses made in the UK each year[9]. GISTs can arise anywhere along the GI tract, but are most commonly found within the stomach and small intestine[5,7]. Surgical resection is the primary course of treatment for patients presenting with localised GIST; however, post-operative recurrence or metastasis occurs in approximately 50% of GIST patients within 5 years[10]. Efforts have been made to identify individuals at risk of recurrence or metastases and current recommendations are based on tumour size, tumour location and mitotic index[11].

Approximately 85% of GISTs contain an activating mutation in either of the receptor protein-tyrosine kinases, KIT (CD117) or PDGFRα[11], and this activation of KIT is considered to be integral to the development of GISTs[12,13]. Imatinib is a protein-tyrosine kinase inhibitor with activity against several receptor protein-tyrosine kinases, including KIT, and acts to inhibit proliferation and promote apoptosis of GIST cells expressing a KIT-activating mutation in vitro[2]. Imatinib is the first licensed therapy for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of GIST[1].

Guidance produced by the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (2009)[12] and the European Society for Medical Oncology (ESMO; 2012)[14] recommends that adjuvant imatinib should be considered for GIST patients at high risk of recurrence, but should not be considered when the risk of recurrence is low[12,14]. The National Institute of Health and Care Excellence (NICE) has previously assessed the evidence for the use of imatinib as an adjuvant treatment for GIST for a duration of one year[15]. NICE Technology Appraisal (TA) 196 concluded that imatinib is

not recommended for use, based on evidence supporting a maximum of 12 months treatment. In 2012, new clinical trial data were published detailing evidence for the use of adjuvant imatinib treatment over 36 months[7], which forms the basis of this submission.

The applicant company has highlighted that the submission focuses on the use of imatinib as an adjuvant treatment of GIST patients who are considered to be at high risk of relapse following resection, according to the Miettinen 2006 criteria (see Glossary)[1].

2.2 Comparators

The comparator included in the company submission was best supportive care (BSC)[1].

2.3 Guidance and related advice

- NICE. Single TA in progress. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (review of TA 196). Expected publication date: October 2014.
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN guidelines®). Soft tissue sarcoma (2013)[16].
- European Society for Medical Oncology (ESMO). Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2012)[17].
- NCCN. NCCN task force report: update on the management of patients with GIST (2010)[5].
- NICE. TA 196. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (2010)[15].
- NICE. TA 209. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of NICE Technology Appraisal guidance 86 [2010])[18].
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland. Guidelines for the management of gastrointestinal stromal tumours (2009)[12].
- Scottish Pathology Network. Guidelines for the management of gastrointestinal stromal tumours (GIST) in Scotland (2009)[19].
- NICE. TA 86. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (2004)[20].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In support of the use of adjuvant imatinib for the indication under consideration, the company submission provides data collated from two independent randomised controlled trials (RCTs): ACOSOG Z9001, which compared 12 months of imatinib adjuvant treatment versus placebo; and SSGXVIII/AIO, which evaluated adjuvant imatinib treatment for a treatment duration of 36 months versus 12 months. The submission included a systematic literature review which identified 12 non-RCTs with the aim of providing further evidence for the efficacy of adjuvant imatinib treatment in patients with resectable GIST; however these will not be discussed further. The company submission also provided an indirect comparison (36 months versus BSC) and supporting evidence from a current ongoing trial (EORTC 62024)[1].

3.1 Clinical effectiveness studies

3.1.1 ACOSOG Z9001

This study was a randomised, phase III, double-blind, placebo-controlled, multicentre RCT that compared 12 months of treatment with adjuvant imatinib versus placebo in patients following the surgical removal of KIT-positive, localised primary GIST ≥ 3 cm in

size [1,21]. Patients (n = 713) were randomised to receive either imatinib 400 mg per day (n = 359) or placebo (n = 354) for 12 months, and monitored for a period of five years from the start of treatment[21]. The median time to follow-up was 14 months[1,21]. Following tumour recurrence, patients were eligible to receive imatinib 400 mg per day if they had completed 12 months of imatinib therapy or if they had been assigned to the placebo group, and patients who experienced tumour recurrence whilst receiving imatinib therapy could have their dose increased to 800 mg per day. The study was unblinded early after an interim analysis demonstrated the benefit of adjuvant imatinib treatment, following which patients randomised to placebo who had not had disease recurrence were eligible to receive imatinib for 12 months[1,21].

The original primary endpoint was overall survival (OS; see Glossary for endpoint definitions); however, prior to the interim analysis this was amended to recurrence-free survival (RFS), following discussion with the Cancer Therapy Evaluation Program and the US Food and Drug Administration due to a lower than expected mortality rate[21]. In the intent-to-treat (ITT) population, imatinib significantly prolonged estimated one-year RFS compared to placebo (97.7% versus 82.3%; hazard ratio [HR] 0.35 [see Table 1]), and the differences remained large up to 30 months (84.2% versus 69.6%), before decreasing progressively[11,21]. No significant difference in OS was detected[1,21].

The company submission includes a post hoc analysis of endpoint data in patients at high risk of recurrence following GIST resection, as determined using the Miettinen 2006 criteria (see Glossary)[1]. In the high risk population (n = 165), the one-year rates of RFS were 98.7% in the imatinib group (n = 84) and 56.1% in the placebo group (n = 81)[1]. Additionally, there was no significant difference in OS between the two treatment groups[1].

3.1.2 SSGXVIII/AIO

This study was a randomised, phase III, open-label, multicentre prospective study which evaluated adjuvant imatinib for a treatment duration of 12 or 36 months in adult patients considered to be at high risk of recurrence (according to modified US National Institutes of Health (NIH) consensus criteria [see Glossary]) following the surgical removal of KIT-positive GIST[7]. Patients (n = 397) were randomised to receive imatinib for a treatment duration of either 12 months (n = 199) or 36 months (n = 198), with a median follow-up of 54 months[7]. The primary efficacy endpoint was RFS (see Glossary for endpoint definitions) in the full population, while secondary endpoints included OS[7]. Imatinib treatment for 36 months significantly prolonged five-year RFS compared with 12 months of treatment (65.6% versus 47.9%; HR: 0.46)[7]. In addition, 36-month imatinib treatment significantly prolonged five-year OS compared to 12-month imatinib treatment (92.0% versus 81.7%; HR: 0.45 [see Table 1])[1,7].

The company submission includes a post-hoc analysis of the subgroup of patients classified as high risk according to the Miettinen 2006 criteria (139 patients in the 36-month group and 142 in the 12-month group)[1]. In this high risk population, RFS at five years was significantly longer in the 36-month group compared with the 12-month group (55.4% versus 35.1%; HR: 0.43)[1]. In addition, OS at five years in the high risk population was significantly prolonged in the 36-month group compared with the 12-month group (89.5% versus 74.2%; HR: 0.39)[1].

Table 1. Overview of primary and secondary efficacy endpoints from the ACOSOG Z9001 and SSGXVIII/AIO studies[1,7,11,21]

Treatment arm	RFS		OS	
	Full population	High risk*	Full population	High risk*
ACOSOG Z9001 (One-year analysis for RFS and two-year analysis for OS)				
Imatinib (12 months)	97.7%	98.7%	98.8%	100%
Placebo	82.3%	56.1%	97.6%	94.7%
Treatment difference	HR: 0.35 (95% CI: 0.22−0.53) p < 0.0001	HR: 0.27 (95% CI: 0.15−0.48) p < 0.0001	HR: 0.66 (95% CI: 0.22−2.03) p = 0.47	p = 0.0764
SSGXVIII/AIO (Five-year analysis)				
Imatinib (36 months)	65.6%	55.4%	92.0%	89.5%
Imatinib (12 months)	47.9%	35.1%	81.7%	74.2%
Treatment difference	HR: 0.46 (95% CI: 0.32−0.65) p < 0.001	HR: 0.43 (95% CI: 0.30−0.62) p < 0.0001	HR: 0.45 (95% CI: 0.22−0.89) p = 0.02	HR: 0.39 (95% CI: 0.19−0.79) p = 0.007

* Determined using the Miettinen 2006 criteria[5,22].
CI: confidence intervals; HR: hazard ratio; OS: overall survival; RFS: recurrence-free survival.

3.1.3 Indirect comparison

In the submission, the applicant company included an indirect comparison, informed by the ACOSOG Z9001 study and SSGXVIII/AIO study, which compared adjuvant imatinib treatment (12 months or 36 months duration) with placebo. A traditional approach to conducting indirect comparisons was considered inappropriate by the applicant company, as visual inspection of the study-derived Kaplan-Meier curves for RFS did not support the assumption of constant proportional hazards usually required to undertake the analysis. Based on these Kaplan-Meier curves, the applicant company concluded that a sensible approach would be to estimate the relative hazards separately for two distinct periods:

- the period of time in which patients received adjuvant imatinib treatment (on-treatment period);
- the period immediately after completion of adjuvant imatinib treatment (off-treatment period).

During the on-treatment period, the HR for risk of recurrence in patients receiving adjuvant imatinib (both treatment durations) compared with placebo was estimated to be 0.111 (95% CI: 0.043−0.281). The estimated HRs for the off-treatment periods for patients receiving either 12 months or 36 months of adjuvant treatment versus placebo were 0.519 (95% CI: 0.297−0.906) and 0.344 (95% CI: 0.160−0.741), respectively.

3.1.4 EORTC 62024

Study EORTC 62024 is an ongoing, randomised, phase III, open-label trial investigating the efficacy and safety of adjuvant imatinib treatment for 24 months in patients following surgical removal of GIST and considered to be at intermediate or high risk of recurrence according to NIH consensus criteria. Patients (n = 908) were randomised to receive imatinib or no further treatment[1,23].

The primary endpoint was OS; however, due to the prognostic improvement in patients, the study independent data monitoring committee authorised that the primary endpoint be changed to imatinib failure-free survival (IFS; see Glossary for endpoint definitions)[1]. The results of this study are unpublished at present, but the results of a planned interim analysis have been reported as a congress presentation[1]. According to the analysis, no significant differences between treatment groups were evident for IFS at five years in the full population (87% in the imatinib group versus 84% in the observation group), or in the subgroup of patients classified as high-risk according to the NIH consensus criteria (77% versus 73%, respectively). However, adjuvant imatinib therapy

significantly improved RFS at five years in the full population (69% in the imatinib group versus 63% in the observation group; $p < 0.001$)[1,23].

3.2 Comparative safety

At the time of licensing, the Committee for Medicinal Products for Human Use concluded that the safety profile of imatinib is similar to the known safety profile in advanced GIST and no unexpected adverse events (AEs) were identified[11].

3.2.1 ACOSOG Z9001

In the safety population (comprising all patients receiving one or more doses of their assigned treatment; n = 682), almost all (95%; 333/337 in imatinib group versus 314/345 in placebo group) patients had at least one adverse event (AE)[21]. The occurrence of AEs was the most common reason for treatment discontinuation in the imatinib group, and tumour recurrence was the most frequent cause of discontinuation in the placebo arm[1,21]. Grade 3−5 AEs occurred in 104 (30.9%) patients in the imatinib group and 63 (18.3%) in the placebo group. Severe AEs occurring more frequently in the imatinib group included neutropenia (3.6% versus 1.2%), abdominal pain (3.6% versus 1.7%), dermatitis (3.3% versus 0%), diarrhoea (3.0% versus 1.4%), increased alanine aminotransferase (2.7% versus 0%) and nausea (2.4% versus 1.2%)[21]. In the imatinib group, 5 (1%) patients died (considered unrelated to GIST) and in the placebo group there were 8 (2%) deaths, 5 of these were considered related to GIST[21].

3.2.2 SSGXVIII/AIO

In the safety population (comprising all patients who took at least one dose of study medication)[7], almost all patients had at least one AE (198/198 in the 36-month group versus 192/194 in the 12-month group)[1,7], of which significantly more in the 36-month group were classed as grade 3–4 (32.8% versus 20.1%; $p = 0.006$)[7]. The incidence of death in the 36-month group was 12 (7 considered related to GIST) and 25 in the 12-month group (14 considered related to GIST), while the number of patients who discontinued imatinib due to AEs was 27 in the 36-month group versus 15 in the 12-month group[1]. AEs occurring more frequently in the 36-month group included anaemia (80.3% versus 72.2%), periorbital oedema (74.2% versus 59.3%), elevated blood lactate dehydrogenase (60.1% versus 43.3%) and diarrhoea (54.0% versus 43.8%)[7].

3.3 AWTTC critique

- Imatinib represents the only licensed medication for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of GIST[9]. Guidelines provided by the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland and ESMO recommend the use of adjuvant imatinib in GIST patients considered to be at high risk of recurrence[12,14].
- The licensed indication for imatinib is the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT-positive GIST[2], which can include patients at high or intermediate/moderate risk of GIST relapse[1]. However, the applicant company has highlighted that the submission focuses on the use of imatinib as an adjuvant treatment of GIST in patients who are considered to be at high risk of relapse following resection, according to the Miettinen 2006 criteria[1]. Clinical expert opinion sought by the All Wales Therapeutics and Toxicology Centre (AWTTC) confirms this criteria is relevant to current clinical practice in Wales.
- Studies ACOSOG Z9001 and SSGXVIII/AIO did not stratify patients using the Miettinen 2006 criteria and the data on the high risk population are derived from post hoc analyses.
- SSGXVIII/AIO is the first, large-scale, randomised controlled trial to demonstrate that 36 months of adjuvant imatinib treatment significantly improves patient outcomes in terms of RFS and OS when compared with 12 months of treatment, although it should be noted that this effect is based on

a relatively small number of deaths: 12 and 25 patients died in the 36 month and 12 month groups respectively.

- Surgical resection is the primary course of treatment for patients presenting with localised GIST[12], and in Wales there is currently no approved licensed adjuvant treatment. As no head-to-head studies exist to compare the clinical efficacy and safety of 36-month imatinib treatment with that of placebo, the company submission included a non-traditional indirect comparison[1]. The full methodology and analysis were not provided by the company and therefore it was not possible to make an assessment of the robustness of the approach. Conclusions drawn from the indirect comparison should be viewed in the light of these limitations.
- The licensed dose of imatinib for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT-positive GIST is 400 mg per day[2]. However, some patients in study ACOSOG Z9001 could have their dose increased to 800 mg per day should disease recurrence occur[21].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of adjuvant imatinib treatment for 36 months compared to no adjuvant treatment (i.e. surgical resection alone) in GIST patients at high risk of recurrence[1], as defined by the Miettinen 2006 criteria[22]. Given that there is no direct comparative evidence, the company includes an indirect comparison, utilising evidence for the use of adjuvant imatinib treatment for 12 months as a bridge between the two treatment arms.

The model uses a Markov approach to estimate the incremental costs and health outcomes over a lifetime horizon (50 years). During each monthly cycle of the model, patients can remain recurrence-free, have a recurrent GIST (first or second recurrence), have progressive disease (and be treated with BSC) or die (from GIST or other causes). Patients enter the model in the "no recurrence and no treatment/on imatinib adjuvant therapy" health states. Patients who discontinue adjuvant therapy due to AEs move to the "no recurrence and no treatment" health state. Upon successful completion of the adjuvant treatment period, patients move to the "no recurrence and completed adjuvant imatinib therapy" health state. Patients who have a first recurrence move to either the "post-recurrence and on imatinib 400 mg", "post recurrence and on sunitinib" or "BSC" health state, and patients with a second recurrence then move to either the "sunitinib second-line treatment" or "BSC" health state. Patients may die from any health state at any time.

Data used to populate the model were obtained largely from the pivotal phase III trials of adjuvant imatinib (ACOSOG Z9001 and SSGXVII/AIO) and supplemented by published literature and assumptions about clinical practice. The applicant company differentiated between the on-treatment period and the off-treatment period. Data from the ACOSOG Z9001 trial was used to estimate the treatment effect during the on-treatment period. The applicant company submitted a non-traditional indirect comparison (between placebo versus 12 months of adjuvant treatment [ACOSOG Z9001] and 12 months of adjuvant imatinib versus 36 months of adjuvant therapy [SSGXVII/AIO]) in order to estimate the treatment effect during the off-treatment period (see Section 3.1.3).

A frequentist indirect comparison was used as inspection of the published Kaplan-Meier curves for RFS derived from the adjuvant imatinib studies demonstrated that the

assumption of constant proportional hazards did not hold and thus a network approach was not feasible. The company advised that a three step approach was used: (i) estimating the Kaplan-Meier curves for the post-treatment phase for patients who are recurrence-free for the duration of the relevant treatment period; (ii) estimating the HR (for the post-treatment phase) from the new Kaplan-Meier curves; and (iii) estimating the treatment effect of 36 months of adjuvant imatinib versus no adjuvant treatment using a frequentist indirect treatment comparison via a fixed effects model. However, the full methodology and analysis were not available for review.

4.1.2 Results

Results of the base case analysis suggest an incremental cost-effectiveness ratio (ICER) for adjuvant imatinib for 36 months compared to no adjuvant treatment (i.e. surgical resection alone) in GIST patients at high risk of recurrence to be £8,390 per quality-adjusted life-year (QALY) gained (Table 2). The company also reported the results of supplementary analyses for adjuvant imatinib for 12 months compared to no adjuvant treatment and for adjuvant imatinib for 36 months compared to adjuvant imatinib for 12 months. The results were £3,509 per QALY gained and £16,006 per QALY gained, respectively. However, given the methodology used and the assumptions made, particularly with respect to estimation of the treatment effect, the results are subject to uncertainty and risk of bias.

Table 2. Company-reported results of the base case analysis[1].

	Imatinib adjuvant treatment (36 months)	No adjuvant treatment
Total costs	£78,068	£47,292
Total LYs	9.46	5.08
Total QALYs	7.50	3.83
ICER (£/LY gained)	£7,021	
ICER (£/QALY gained)	£8,390	
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; LY: life-year.		

A number of sensitivity analyses have been conducted by the company to address uncertainty in model parameters. Of the 42 analyses included in the deterministic sensitivity analysis, the parameters having most impact on cost-effectiveness were the time horizon and treatment effect over time. The cost per QALY gained is under £20,000 in all instances except for when the time horizon is reduced to five years, when the off-treatment hazard ratio is set to the upper CI and when both the on- and off-treatment hazard ratios are set to the upper CI. The six analyses that affect the cost-effectiveness the most are presented in Table 3.

Table 3. Company-reported results of the most influential parameters on cost-effectiveness in the deterministic sensitivity analysis[1].

	Cost per QALY gained
Base case analysis	**£8,390**
Time horizon reduced to 5 years	£31,718
Time horizon reduced to 10 years	£14,184
Off-treatment hazard ratio set to lower CI	£4,268
Off-treatment hazard ratio set to upper CI	£21,557
Both on- and off-treatment hazard ratio set to lower CI	£4,098
Both on- and off-treatment hazard ratio set to upper CI	£29,496
CI: confidence interval	

Scenario analyses have been conducted based on: (i) the parametric distribution used to estimate RFS; (ii) the dose of imatinib following recurrence; (iii) the proportion of

patients moving to BSC following recurrence; and (iv) survival post-recurrence. Using a range of different parametric distributions to estimate RFS increased the cost per QALY gained to between £9,382 and £14,359. Allowing dose escalation to 800 mg per day of imatinib in the metastatic setting reduced the cost per QALY gained to £7,152. Adjusting the proportion of patients moving to BSC following recurrence whilst on imatinib or adjuvant imatinib had virtually no impact on the cost per QALY gained. Allowing for extended survival in the post-recurrence health states reduced the cost per QALY gained to £6,900.

Probabilistic sensitivity analysis undertaken for the base case analysis indicates that the probability that adjuvant imatinib treatment for 36 months is cost-effective compared to no adjuvant treatment is 58.3% and 69.1% at cost-effectiveness thresholds of £20,000 and £30,000 per QALY gained, respectively.

4.1.3 AWTTC critique

The company's estimate of the cost-effectiveness of adjuvant imatinib treatment for 36 months compared with no adjuvant treatment is dependent on the HRs for on- and off-treatment periods. Given the limitations in the methodology used to estimate these HRs, there is significant uncertainty and risk of bias.

Strengths of the company's economic evidence include:

- The model structure is clear and largely in line with other models related to adjuvant therapy for patients with resectable GIST.
- The company has attempted to address the decision problem in a reasonable way despite limitations in the available data. In particular, the company has attempted to address a number of the criticisms of earlier versions of the model, albeit for slightly different indications and/or patient populations.

Limitations of the economic evidence include:

- The use of a non-traditional indirect comparison to estimate the treatment effect during the off-treatment period adds uncertainty to the analysis. As the full methodology and analysis were not available for review, it is difficult to assess the robustness of the approach.
- The lack of available data from the SSGXVIII/AIO trial, to estimate the treatment effect during the on-treatment period adds uncertainty to the analysis.
- The trial data used in the model were based on a post hoc subgroup analysis of patients at high risk of recurrence (i.e. those considered high risk according to the Miettinen 2006 criteria[22]). The resulting ICER may therefore not be reflective of the whole licensed indication.
- Lack of utility estimates from the imatinib clinical trials meant that utility values were obtained from a range of sources, adding uncertainty to the model. The sensitivity analyses undertaken to address this suggested that this is likely to have a limited impact on the results. However, the range of sensitivity analyses undertaken could have been more extensive.
- The applicant company has made a number of assumptions in estimating the costs used in the model. In particular, they have based the frequency of particular items of resource utilisation on guidelines rather than actual use. However, this is likely to have a limited impact on the results.
- Although the patient population in the economic analysis is a subgroup itself, the company has not attempted to identify any other meaningful sub-groups in whom cost-effectiveness maybe differentiated.
- The company's analysis only includes direct medical costs to the NHS in Wales and did not include costs to Personal and Social Services in Wales. However, this is likely to have a limited impact on the results.

4.2 Review of published evidence on cost-effectiveness

The company has highlighted two published CUAs, which evaluated the cost-effectiveness of 36 months of adjuvant imatinib compared with 12 months of adjuvant imatinib[24,25]. Both studies were sponsored by Novartis Pharmaceuticals UK Ltd and used data solely from the SSGXVIII/AIO trial and thus did not require any form of indirect comparison. The model structures were similar with one study being conducted from the perspective of the Dutch healthcare system[24] and the other study conducted from the perspective of the US third party payer[25]. The main difference between the two studies was that the Dutch study used data from the SSGXVIII/AIO trial for only those patients who were considered to be at a high risk of recurrence using the Miettinen criteria, whereas the US study used data from the whole trial population.

The discounted lifetime QALYs for 36 months of adjuvant imatinib versus 12 months of adjuvant imatinib were 6.55 and 5.18 for the Dutch study, with a 1.5% discount rate for QALYs[24]; and 8.53 and 7.18 for the US study, with a 3% discount rate for QALYs[25]. The lifetime discounted QALYs reported in the company submission were 7.50 and 6.07 for 36 months of adjuvant imatinib versus 12 months of adjuvant imatinib, (at a discount rate of 3.5%), hence falling within the results of the two published studies.

The ICERs for 36 months of adjuvant imatinib versus 12 months of adjuvant imatinib were €29,872 per QALY gained for the Dutch study[24] and $62,600 per QALY gained for the US study[25]. The Dutch study reported that the probability of 36 months of adjuvant imatinib being cost-effective compared with 12 months of adjuvant imatinib ranged from 12.2% to 80.4% at willingness to pay thresholds ranging from €20,000 to €50,000 per QALY gained[24]. The equivalent figure from the US study was 100% at a willingness to pay threshold of $100,000 per QALY gained[25].

Standard literature searches conducted by AWTTC have not identified any additional published evidence on the cost-effectiveness of imatinib within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on an incidence of GIST of 14.5 per million[26], the applicant company assumes that there are 45 new cases of GIST diagnosed every year in Wales. Of those, around 13 (29.7%) are in the high risk category as per the Miettinen criteria[22]. The applicant company assumes that two thirds of tumours are resectable, resulting in nine patients per year who are eligible for adjuvant treatment with imatinib. Upon All Wales Medicines Strategy Group (AWMSG) endorsement, the company assumes uptake of 80% in year one increasing to 95% in year five. Patients prescribed adjuvant imatinib treatment will receive treatment for a maximum of 36 months. The company includes discontinuation rates from the economic model in Section 4. Thus the number of patients receiving adjuvant imatinib treatment will increase from six in year one to 21 in year five. The budget impact analysis included relevant direct medical costs, which were derived from the economic model discussed above (see Section 4).

5.1.2 Results

The applicant company estimated the number of patients and costs for the use of imatinib as adjuvant treatment, for up to 36 months, of adult patients at high risk of relapse following resection of KIT-positive GIST. The estimated number of patients and the associated costs as described by the applicant company in their budget impact analysis are summarised in Table 4. The total cost includes drug costs (including administering and monitoring costs) and other direct medical costs, such as outpatient

visits, GP visits and CT scans. The company reported that approximately 94% of direct costs are accounted for by drug costs. The overall net costs are in comparison to no adjuvant treatment.

Table 4. Company-reported costs associated with use of imatinib as adjuvant treatment (36 months) versus no adjuvant treatment[1].

	Year 1 (2014)	Year 2 (2015)	Year 3 (2016)	Year 4 (2017)	Year 5 (2018)
Number of new eligible patients (all indications)	45	45	45	45	45
Total number of eligible patients (indication covered in this submission and includes discontinuation rates)	8	15	22	22	22
Treated (%)	80	85	90	90	95
Treated patients	6	13	20	20	21
Net costs					
Total cost	£145,354	£261,824	£409,052	£423,905	£439,945
Overall net cost	£101,379	£171,126	£268,883	£278,238	£288,782

5.1.3 AWTTC critique

The applicant company estimated the eligible patient numbers based on incidence rates and assumptions, rather than attempt to estimate the actual number of eligible patients in Wales. The applicant company states that only patients presenting with new disease that is resectable will be prescribed the medication.

In addition:

- The company has assumed the same discontinuation rates for adjuvant imatinib treatment as in the economic model. The company also presented a scenario excluding discontinuation which resulted in a higher overall net cost.
- Cost estimates have been derived from the economic model discussed in Section 4. Thus limitations and uncertainties in costs observed in the economic model will also feed through to the budget impact estimates. Consequently, there is some uncertainty associated with the estimates of overall net cost.
- The company appears to have overestimated the cost in year one by assuming that all patients will have their adjuvant imatinib treatment initiated at the beginning of that year. In reality, initiation of treatment will take place over the course of the year.

5.2 Comparative unit costs

Apart from imatinib, there are no pharmacological treatments licensed for the adjuvant treatment of adult patients with GIST. Instead, current standard treatment in Wales is observation after surgery i.e. no adjuvant treatment. Consequently, only the cost of imatinib is highlighted in Table 5 below. This is based on a 30-day treatment period. Given once daily, drug treatment alone would be £62,983 for a patient receiving imatinib for the full 36-month treatment period (£20,994 per year).

Table 5. Example of cost per patient per 309-day treatment period for adjuvant treatment of adult patients with GIST.

	Example dose	Approximate 30-day costs*
Imatinib (Glivec®) 400 mg film-coated tablets	400 mg once daily	£1,724.39
* Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of February 2014[27]; costs of administration and monitoring are not included.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, imatinib (Glivec®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that imatinib (Glivec®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted EORTC 62024 (see section 3.1.4) as an ongoing study[1]; however it is uncertain at present when the results of this trial are likely to be published.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 24 January 2014
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Imatinib failure-free survival (IFS)
This indicates the time at which patients had to be changed to treatment with a different tyrosine kinase inhibitor due to disease relapse or recurrence[23].

Overall survival (OS)
In the ACOSOG Z9001 study, OS was defined as the time from patient registration to death from any cause[21]. In the SSGXVIII/XIO study, OS was defined as the time period from the date of randomisation to death censoring patients who were alive on the date of last follow-up[7].

Recurrence-free survival (RFS)
In the ACOSOG Z9001 study, RFS was defined as the time period from patient registration to the development of tumour recurrence or death from any cause[21]. In the SSGXVIII/XIO study, RFS was defined as the time period from the date of randomisation to the date of first documentation of recurrence (with cytological or histological confirmation or with radiological evidence) or death, whichever occurred first[7].

The Miettinen 2006 criteria
This criteria categorises patients according to three independent predictors of RFS: tumour size, mitotic count and tumour location[1,5,22].

US National Institutes of Health (NIH) Consensus Criteria
This criteria, often referred to as the Fletcher criteria 2002[28], uses two risk factors to assign risk category: tumour size and tumour mitotic count as determined per 50 high power fields of the microscope[1].

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