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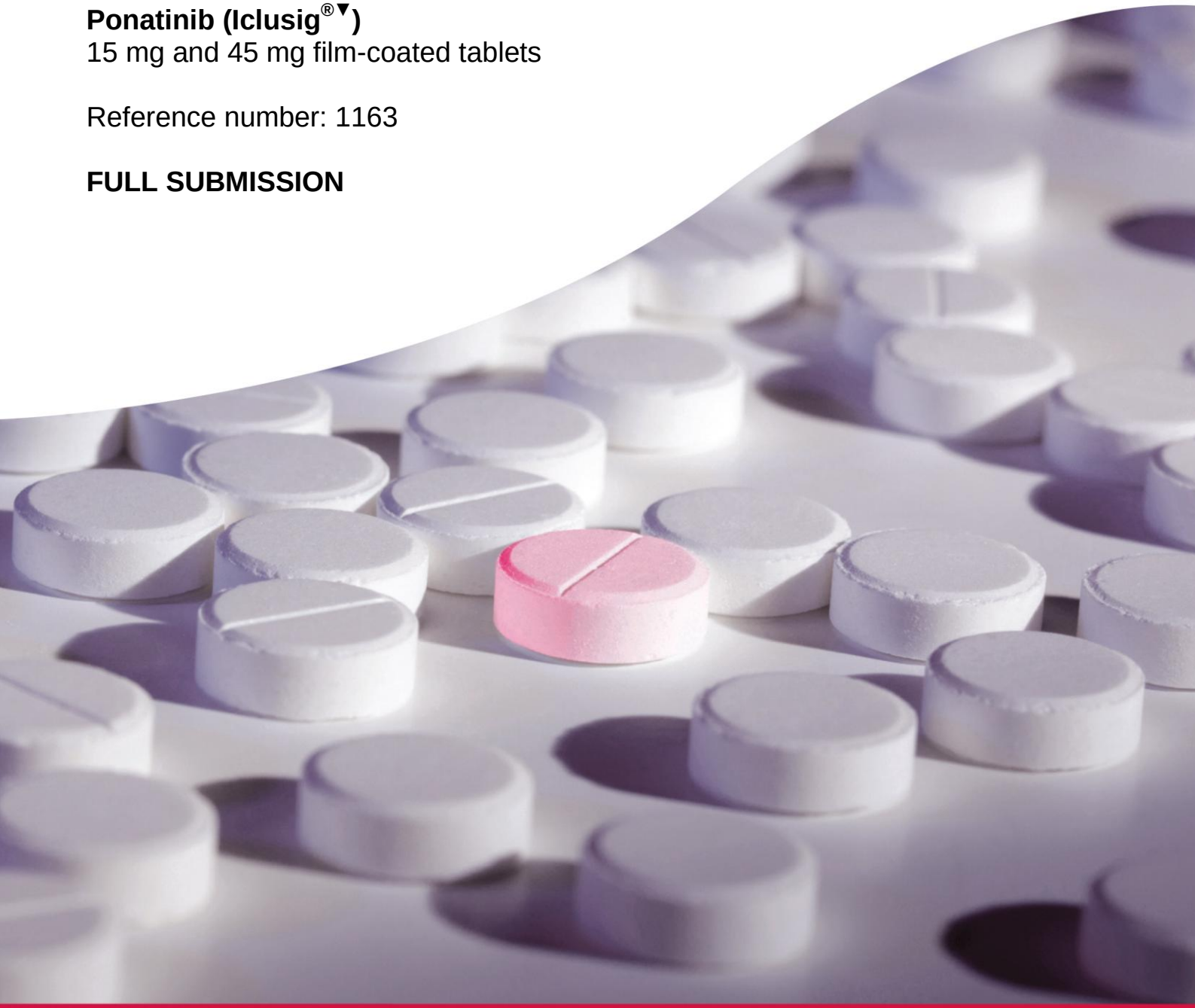
AWMSG SECRETARIAT ASSESSMENT REPORT

Ponatinib (Iclusig®▼)
15 mg and 45 mg film-coated tablets

Reference number: 1163

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Ponatinib (Iclusig®▼) 15 mg and 45 mg film-coated tablets

This assessment report is based on evidence submitted by ARIAD Pharma UK Ltd on 4 July 2014 and 12 August 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ponatinib (Iclusig®▼) is indicated in adult patients with: • Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation; • Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph^+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation[2].
Dosing	The recommended starting dose of ponatinib is 45 mg once daily. Refer to the Summary of Product Characteristics (SPC) for dose modifications and further information[2].
Marketing authorisation date	1 July 2013[3]

2.0 DECISION CONTEXT

2.1 Background

Chronic myeloid leukaemia (CML) is a cancer of myeloid blood cells characterised by a proliferation of granulocytes in blood and bone marrow[4]. CML is a progressive disease typically consisting of three phases: chronic phase (CP), accelerated phase (AP) and blast phase (BP: see Glossary for definitions)[4,5]. Acute lymphoblastic leukaemia (ALL) is an aggressive type of blood cancer characterised by the excess production of immature lymphoblasts[6]. Approximately 95% of patients diagnosed with CML[7] and 20-30% of adult patients with ALL[4,7] possess an acquired chromosomal abnormality, known as the Philadelphia chromosome (Ph), caused by a reciprocal translocation between chromosomes 9 and 22. This translocation results in a *BCR-ABL* fusion gene that encodes an active tyrosine kinase protein. This protein leads to uncontrolled cell proliferation[4,7–10].

Guidance issued by National Institute for Health and Care Excellence (NICE) recommends standard dose imatinib or nilotinib as first-line treatment options for CML[11]. Nilotinib is also recommended for second-line use where treatment with imatinib is not tolerated or where there is resistance[4]. Bosutinib, dasatinib and high dose imatinib are not recommended by NICE[4,12]. Like imatinib, nilotinib, bosutinib and dasatinib, ponatinib is a tyrosine kinase inhibitor (TKI). Ponatinib is a third generation TKI and was designed to inhibit the kinase activity of the *BCR-ABL* gene and all mutant variants, including the (T)hreonine-315-(I)soleucine (T315I) mutation, in patients failing multiple TKIs[1,7].

2.2 Comparators

The comparators included in the company submission for CML were:

- Dasatinib (Sprycel®)
- Bosutinib (Bosulif®▼)
- Hydroxycarbamide
- Interferon alfa
- Allogenic stem cell transplantation (allo-SCT)

The comparators included for Ph^+ ALL were:

- A six-week course of chemotherapy (vincristine and prednisone)
- Allo-SCT

2.3 Guidance and related advice

- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Lymphoblastic Leukaemia (2014)[13].
- NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Chronic Myelogenous Leukaemia (2014)[14].
- European LeukaemiaNet. European LeukaemiaNet recommendations for the management of chronic myeloid leukaemia (2013)[15].
- NICE. TA299. Bosutinib for previously treated chronic myeloid leukaemia (2013)[12].
- NICE. Technology Appraisal (TA) 241. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance (2012)[4].
- European Society for Medical Oncology (ESMO). Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2012)[5].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of dasatinib (Sprycel®). Dasatinib (Sprycel®) is not recommended for use within NHS Wales for the treatment of adults with Philadelphia chromosome positive (Ph^+) acute lymphoblastic leukaemia (ALL) and lymphoid blast chronic myeloid leukaemia (LB-CML) with resistance or intolerance to prior therapy[16].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The applicant company provided data from an ongoing pivotal clinical study (PACE) which aimed to determine the efficacy of ponatinib. As supporting evidence, the applicant company also conducted a systematic literature review[1].

3.1 PACE study

This is an ongoing phase II, multicentre, international, open-label trial of oral ponatinib in patients with CML (CP, AP or BP) or Ph^+ ALL, who are resistant or intolerant to treatment with either dasatinib or nilotinib, or possess the *BCR-ABL* T315I mutation (as confirmed by direct sequencing)[1]. Patients were heavily treated with prior TKIs and conventional therapies: 37% had received two TKIs (imatinib, dasatinib, nilotinib, or bosutinib) and 55% had received three or more TKIs[1,7,17]. A total of 449 patients received an initial 45 mg dose of ponatinib. Of these, 444 were assigned to one of six cohorts (see Table 1), collectively referred to as the treated population[1,7,17]. The remaining five patients (three in CP-CML and two in AP-CML) were not eligible to be assigned to a cohort, but did receive ponatinib. These patients were therefore included in the safety analysis, but not the pre-specified efficacy analysis[1,18]. All patients

continued to receive treatment until there was evidence of disease progression, development of intolerance, the patient withdrew consent or the investigator decided to terminate treatment[1,7,17].

Table 1. Patient cohorts in the PACE study[1,7,17]

	CP-CML	AP-CML	BP-CML or Ph$^+$ ALL
Resistant or intolerant to dasatinib or nilotinib (noT315I mutation)	Cohort A (n = 203)	Cohort C (n = 65)	Cohort E (n = 48)
T315I mutation	Cohort B (n = 64)	Cohort D (n = 18)	Cohort F (n = 46)

ALL: acute lymphoblastic leukaemia; AP: accelerated phase; BP: blast phase; CML: chronic myeloid leukaemia; CP: chronic phase; Ph$^+$: Philadelphia chromosome-positive.

The primary endpoint was the proportion of patients achieving a response after initiation of treatment (major cytogenetic response [MCyR] in CP-CML by 12 months and major haematological response [MaHR] in AP-CML, BP-CML and Ph$^+$ ALL by 6 months; see Glossary for endpoint definitions). Secondary endpoints included progression-free survival (PFS) and overall survival (OS), as reported in Table 2. In the treated population, ponatinib exhibited clinically meaningful responses across all disease stages (see Table 2) and mutation status (see Table 3). Amongst the 267 patients with CP-CML, 54% had a MCyR. Of the 83 patients with AP-CML and 62 patients with BP-CML, 58% and 31% had a MaHR, respectively[7,19]. For the Ph$^+$ ALL patients, 41% achieved MaHR. The response rates achieved in each of the cohorts met or exceeded the pre-specified statistical criteria for success. Secondary endpoints were supportive of the primary endpoints[1,7,17]. The median relative dose intensity (the proportion of administered doses relative to planned doses) was 0.84. Dose reductions occurred in 55% of the patients and 67% of patients had at least one dose interruption[16].

The submission also included 24-month follow up data presented at conference; the results of which were broadly comparable for the main endpoints[20].

Table 2. Overview of the key efficacy results for the treated population of the PACE study (irrespective of T315I mutation status)[1,7,17]

	CP-CML (n = 267)	AP-CML (n = 83)	BP-CML (n = 62)	Ph+ ALL (n = 32)
Primary endpoints				
MCyR*	149 (56%) (95% CI: 50 to 62)	-	-	-
MaHR†	-	46 (55%) (95% CI: 44 to 66)	19 (31%) (95% CI: 20 to 44)	13 (41%) (95% CI: 24 to 59)
Secondary endpoints				
Median time to MCyR$, months (range)	2.8 (1.6−11.3)	3.7 (0.8−9.7)	1.9 (0.9−5.5)	1.0 (0.9−3.7)
Median time to MaHR$, months (range)	-	0.69 (0.5−5.7)	0.9 (0.4−3.7)	0.7 (0.4−5.5)
Percentage remaining in MCyR at 12 months$‡	91% (95% CI: 85 to 95)	73% (95% CI: NR)	66% (95% CI: NR)	32% (95% CI: NR)
Percentage remaining in MaHR at 12 months$‡	-	48% (95% CI: NR)	42% (95% CI: NR)	8% (95% CI: NR)
PFS at 12 months‡	214 (80%)	46 (55%)	12 (19%)	2 (7%)
OS at 12 months‡	251 (94%)	70 (84%)	18 (29%)	13 (40%)

*Patients with a MCyR by 12 months
†Patients with a MaHR by 6 months
$Responders only
‡ estimated using Kaplain-Meier method
AP: accelerated phase; BP: blast phase; CML: chronic myeloid leukaemia; CP: chronic phase; MaHR: major haematological response; MCyR: major cytogenetic response; NR: not reported; OS: overall survival; PFS: progression-free survival.

Table 3. Major cytogenetic or major haematological response rates in the treated population by T315I mutation status[1,7,17,19]

	No T315I mutation	T315I mutation	Total (± T315I mutation)
CP-CML			
MCyR	104/203 (51%) (95% CI: 42 to 56)	45/64 (70%) (95% CI: 58 to 81)	149/267 (56%) (95% CI: 50 to 62)
AP-CML			
MaHR	37/65 (57%) (95% CI:NR)	9/18 (50%) (95% CI: 26 to 74)	48/83 (55%) (95% CI: 44 to 66)
BP-CML			
MaHR	12/38 (32%) (95% CI: 18 to 49)	7/24 (29%) (95% CI: 13 to 51)	19/62 (31%) (95% CI: 20 to 44)
Ph+ ALL			
MaHR	5/10 (50%) (95% CI: 19 to 81)	8/22 (36%) (95% CI: 17 to 59)	13/32 (41%) (95% CI: 24 to 59)

AP: accelerated phase; BP: blast phase; CP: chronic phase; CML: chronic myeloid leukaemia; MaHR: major haematological response; MCyR: major cytogenetic response; T315I: (T)hreonine-315-(I)soleucine.

3.2 Systematic literature review

In the absence of head-to-head evidence for the efficacy and safety of ponatinib versus other TKIs, the applicant company conducted a systematic literature review. Twelve studies (five single-arm and seven observational studies) met their inclusion criteria in patients with CML or Ph^+ ALL who were resistant/intolerant to prior treatments and these formed the basis of their analysis. The treatments represented were the 2G-TKIs: bosutinib, dasatinib and nilotinib and ponatinib. All studies reported complete cytogenetic response (CCyR) and seven reported MCyR. Analyses of the 12 studies suggests that patients with CP-CML who are resistant or intolerant to prior treatment with 2G-TKIs have a higher CCyR (33.6 to 38.5 percentage points higher) and MCyR (20.3 to 40.5 percentage points higher) rates with ponatinib than with the other 2G-TKIs included in the analysis. The applicant company concluded that based on this available data, ponatinib appears to provide a higher probability of treatment response compared with the 2G-TKIs that are already used in this indication (dasatinib, nilotinib and bosutinib)[1].

3.3 Comparative safety

Based on the pooled safety data submitted as part of the application for marketing authorisation, the Committee for Medicinal Products for Human Use (CHMP) concluded that while the safety profile of ponatinib is similar to that of other TKIs, it differs from them in the incidence of several clinically important events. Pancreatitis, uncommon with other TKIs (< 1%), occurred in about 7.4% of ponatinib-treated patients, but was reversible in the majority of cases and rarely led to discontinuation[7]. Pancreatitis was also the most common treatment-related serious adverse event (SAE) reported in the PACE study; it tended to occur early after treatment initiation (with the majority of cases occurring within the first month)[1,7,17]. All patients (n = 29) with pancreatitis resumed treatment with ponatinib; however, three patients had recurrent events and one patient (with CP-CML) discontinued treatment because of this[1,17]. The SPC for ponatinib provides guidance on how to monitor for this adverse effect and what to do if a rise in serum lipase occurs[2,7].

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularisation procedures have occurred in ponatinib-treated patients. Preliminary data from a now discontinued Phase III comparison of ponatinib with imatinib showed a higher number of vascular events in the ponatinib group. Following a review of updated clinical trial data indicating that blood clots were occurring at a higher rate than was observed at the time of the medicines initial authorisation, CHMP recommended that ponatinib should not be used in patients with a history of a heart attack or stroke, unless the potential benefits to them outweigh the risks. In addition, the cardiovascular risks of all patients should be assessed and measures should be taken to reduce risks before starting and throughout the duration of treatment. Patients who have high blood pressure should have their blood pressure controlled, and treatment should be stopped immediately in any patient with signs of blood clots obstructing arteries or veins[2,21].

CHMP report that treatment-emergent grade 3 or 4 ALT elevations were somewhat more frequent with ponatinib use (8%) compared with dasatinib and nilotinib and similar to bosutinib[7]. In addition, ponatinib is associated with severe myelosuppression (thrombocytopenia, neutropenia and anaemia), which usually occurs within the first three months of treatment. The frequency of severe myelosuppression was greater in patients with AP-CML or BP-CML/Ph^+ ALL than in patients with CP-CML[1,7,17]. CHMP concluded that myelosuppression was generally reversible and usually managed by temporarily suspending treatment or by reducing the dose of ponatinib. Discontinuation rate due to myelosuppression was low (thrombocytopenia: 3.6%; neutropenia: < 1%; and anaemia: < 1%)[7]. Haematological laboratory abnormalities were similar between ponatinib and dasatinib[7].

The lack of a comparative study hampers the assessment of causality of SAEs that are also characteristic features of the disease treated, such as frequently occurring myelosuppression, infections and bleeding. In line with this, lower frequencies were seen during periods of response, i.e. when symptoms of the disease are fewer[7].

3.4 AWTTC critique

- The applicant company state that no head-to-head trials of response to ponatinib versus other TKIs have been conducted in the population of interest (patients resistant or intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate or who have T315I mutation). The applicant did not provide a clinical comparison of ponatinib with hydroxycarbamide, interferon alfa, or allo-SCT[1].
- The applicant company completed a Delphi process to establish what the relevant comparators to ponatinib are in clinical practice in the UK. However, of the five comparators highlighted for CML, dasatinib and bosutinib are not approved for use in Wales based on current NICE advice.
- The prognosis for patients with the T315I mutation is poor due to the lack of available treatment options as these patients are resistant to nilotinib, dasatinib and bosutinib. Currently, the only treatment option available for these patients in Wales is allo-SCT[17]. Ponatinib provides a second option for patients with T315I mutation.
- A post hoc analysis was performed to examine the impact of several predictor variables and outcomes in CP-CML patients in the PACE study. Increasing response rate was correlated with increased dose intensity, younger age, fewer prior therapies and less time since diagnosis. Notably, T315I mutation status was not an independent predictor of response, despite the higher response rates observed in those CP-CML patients with the T315I mutation. This may be explained by the significant association between dose intensity and T315I mutation status, and between age and T315I mutation status. The CP-CML patients with the T315I mutation were younger and able to tolerate higher doses[7].
- The systematic review comprised single arm and observational studies only, no restriction on dosing was applied due to incomplete reporting in the studies. In addition outcomes varied across the studies included and minimal data were provided on patients included in the trials. Overall there is significant uncertainty in the validity of the results reported for the systematic review.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission[1] describes three different economic models: one for the CP CML, one for the AP and BP CML and one for the Ph^+ ALL indication. The company claimed that to analyse the cost-effectiveness of the use of ponatinib for its indication the treatment of patients in different stages of CML could not be incorporated adequately within the same model. Due to the different design and population used as basis of the economic evaluations a separate assessment of each model is presented.

CP-CML model

The economic model for the chronic stage of CML combines a conventional state transition (Markov) model with a partitioned survival (area under the curve [AUC]) model. Dasatinib, bosutinib, SCT, hydroxycarbamide and interferon alfa are the main comparators to ponatinib. The combined model includes four disease states: a chronic phase of CML (CP-CML), two progressed phases (AP-CML and BP-CML), and an absorbing 'dead' state. The CP-CML disease state ("Markov model") is further partitioned according to response to initial CP-CML therapy: CP/CCyR for patients who

achieve a complete cytogenetic response, CP/PCyR for patients with a partial cytogenetic response, CP/CHR for patients with a complete haematological response, and CP/NR for those with no response (NR). Patients enter the model in the CP-CML health state and in the first model cycle are classified by response to therapy. In subsequent cycles patients can remain in the CP-CML health state corresponding to their response category, die, or transition into the progressed disease submodel ("AUC model"). The 'progression' rate from CP-CML to AP-CML is modelled via a surrogate relationship based on the extent of the cytogenetic response, with the risk of progression differing by patients' response status. Patients who progress into the AP-CML health state may remain in this state, transition to BP-CML (where they reside until death) or die from AP-CML. Parametric survival functions are used to estimate the proportion of patients remaining free of endpoints (PFS and OS) which also dictate the rate of transition (probability of remaining in the AP-CML state). A proportion of patients who enter the AP/BP-CML model are also assumed to receive allo-SCT. Patients who receive allo-SCT are assumed to be in one of three health states: dead, alive and in remission, or alive and relapsed. Parametric functions are used to model OS and relapse-free survival for allo-SCT.

Response rates for ponatinib were obtained from analysis of the PACE phase II individual patient level data. Response rates used in the base case analysis were based on patients who had failed two prior TKIs. Response rates for dasatinib and bosutinib were obtained from various published sources. For hydroxycarbamide and interferon alfa it was assumed that 50% of participants experienced minimal treatment response by 12 months. To estimate long-term disease progression out of the CP-CML state, PFS proportions by response category, taken from a study of dasatinib[22] in CP-CML, were extrapolated by fitting standard parametric distributions (exponential, weibull, log-logistic) to each response category.

Time on treatment for ponatinib was obtained from the PACE trial with an adjusted parametric analysis extrapolating time on treatment beyond the PACE follow-up duration (using an exponential distribution). To estimate the time on treatment for the model comparators stratified by response, 'scaling factors' for each comparator were applied to the baseline time on treatment for each response category. Scaling factors were calculated as the ratio of the median time on treatment for the comparator to that for ponatinib as observed in the PACE trial for the subpopulation of all patients pooled across all prior TKI histories. Data from the literature were used to source the median time-on-treatment for dasatinib and for bosutinib. For hydroxycarbamide, and interferon alfa, it was assumed that a clinician would continue to prescribe treatment until progression to AP-CML.

The impact of CML on patients' health related quality of life (HRQoL) was modelled as a decrement from that of an age-matched member of the general population. During each cycle, the model generates an age-adjusted EQ-5D population norm value based on UK data. From the age-adjusted baseline, disease phase-specific utility decrements, derived from the literature, associated with each health state are then applied to model the impact of CML. The following resource use components were included in the analysis: pharmacological therapy (including relative dose intensity for ponatinib, dasatinib and bosutinib); monitoring and follow-up care (modelled as a function of disease phase and response to therapy [CCyR]); adverse events (AEs); general healthcare consumption; and, end-of-life care (value of a 10-day inpatient stay immediately before death). No administration costs were included. All costs used in the model were derived from published or publicly available sources, or based on expert opinion. Drug acquisition costs were sourced from the British National Formulary.

The analysis was conducted from the perspective of NHS Wales using a 40-year time horizon and a cycle length of three months. It was based on a starting age of 56 years

(the median age of patients in the PACE trial who had previously received two prior TKIs). Costs and benefits were discounted at an annual rate of 3.5%.

CP-CML model results

Results of the base case analyses for the chronic stage of CML are summarised in Table 4.

Table 4. Company-reported results of the base case analyses for the chronic stage of CML

Base-case analysis		Drug	Comparator(s)				
		Ponatinib	Dasatinib	Bosutinib	SCT	Hydroxycarbamide	Interferon alfa
On treatment costs (£)		210,775	63,187	71,012	181,104	4,816	25,263
	Difference		*147,587*	*139,762*	*29,671*	*205,958*	*185,511*
Off treatment costs (£)		154,239	229,888	232,029	172,345	282,071	363,191
	Difference		*-75,649*	*-77,790*	*-18,106*	*-127,832*	*-208,952*
Total cost (£)		365,013	293,075	303,041	353,449	286,887	388,454
	Difference		*71,938*	*61,972*	*11,565*	*78,126*	*-23,441*
Total LYG		11.6	8.20	8.10	11.78	5.75	5.75
	Difference		*3.4*	*3.5*	*-0.18*	*5.85*	*5.85*
Total QALYs		8.40	5.27	5.19	5.86	3.08	3.08
	Difference		*3.13*	*3.21*	*2.54*	*5.32*	*5.32*
ICER (£/QALY gained)			**23,000**	**19,310**	**4,549**	**14,678**	**Dominant**

Abbreviations: LYG = life years gained; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SCT = stem cell transplantation

Based on an individual's expected lifetime treatment with ponatinib, results ranged from a saving of £23,441 to an additional cost of £78,126, when compared with other treatments. Ponatinib is modelled to provide patients with additional benefits, ranging from 2.54 to 5.32, in quality-adjusted life-years (QALYs). The base case incremental cost-effectiveness ratio (ICER), therefore, ranges from dominant (versus interferon alfa) to a maximum of £23,000/QALY gained (versus dasatinib).

Deterministic sensitivity analyses were conducted, testing each model parameter to the upper and lower ends of its variation range. The range of variation was set to ± 20% of the base case value. One-way sensitivity analyses were only presented for the comparison with dasatinib, which presented the highest ICER (£23,000/QALY gained). The parameter that induced the strongest variation in the base case ICER was the ponatinib pack price. All other parameters analysed did not have a major influence on the ICER.

Probabilistic sensitivity analyses were also calculated with 1,000 iterations. The corresponding cost-effectiveness planes along with cost-effectiveness acceptability frontiers were presented by the company. The probability of ponatinib being cost effective at a £20,000 per QALY gained threshold were 26.6% versus dasatinib, 48.7% versus bosutinib, 75.9% versus SCT, 71.1% versus hydroxycarbamide and 99.1% versus interferon alfa. Using a threshold of £30,000 per QALY gained the probability of ponatinib being cost effective were 78.0% versus dasatinib, 90.4% versus bosutinib, 87.2% versus SCT, 92.7% versus hydroxycarbamide and 99.9% versus interferon alfa.

AP-and BP-CML model

The economic model for the advanced stages of CML was designed to simulate AP- and BP-CML. Bosutinib, SCT and best supportive care (BSC) (assumed to be hydroxycarbamide) were the main comparators to ponatinib. Comparator treatment sequences for AP and BP CML were based on whether patients were suitable or unsuitable for SCT. For patients who were suitable for SCT, the relevant treatment sequences were:

- Ponatinib, followed by SCT (Ponatinib, SCT) in those patients who respond to it; BSC is applied after ponatinib discontinuation;
- Bosutinib, followed by SCT (Bosutinib, SCT) in those patients who respond to it; BSC is applied after bosutinib discontinuation;
- Entire modeled population starts on SCT; in case of relapse, BSC is applied

For those patients not suitable for SCT, the relevant treatment sequences were:

- Ponatinib treatment, followed by BSC in case of discontinuation
- Bosutinib treatment, followed by BSC in case of discontinuation
- Patients are only given palliative treatment (BSC).

A different model design was used to simulate patients starting treatment in AP-CML compared to those starting in BP-CML. The AP model is a Markov cohort model using six health states (including death). Patients start in AP-CML with an active pharmacological treatment, which can either be ponatinib or bosutinib. If patients respond to treatment and achieve remission, they can undergo SCT. SCT is intended to be a curative intervention and patients are considered 'cured' once they've received this treatment and remain in the SCT state, with improved HRQoL and minimal costs. However, a proportion of patients will experience relapse, and these patients move to the AP SCT relapse state. The AP SCT relapse state is considered identical to the AP active treatment state, the only difference being that after a first transplantation, patients cannot have a second one. This design implies that after a relapse, patients are considered to return to their original disease state (AP) and re-start active treatment. Patients remain in this state until disease progression or discontinuation of

active treatment. Determinants for the disease course include: OS; PFS; time on (active) treatment and relapse-free survival after SCT. OS and PFS determine transition to the death and BP state respectively. Time-on-treatment determines the discontinuation of active treatment and the transition to the AP BSC state.

The BP model was similar to the AP model but limited to just five health states (again, including death). Patients start in the BP active treatment state and, following response to treatment can move to the SCT state. After SCT, patients can either remain in this state as 'cured' or experience a relapse, and move to the BP SCT relapse state. Similar to the AP model, this state is identical to the BP active treatment state except that a further transition to SCT is not allowed. As in the AP model, the time on treatment determines the discontinuation of the active treatment. After discontinuation, patients are assumed to be treated with BSC until death.

The main determinants of the disease course (OS, PFS, time on active treatment, relapse-free survival after SCT) were derived from Kaplan–Meier curves from randomised controlled trials (RCTs). To extrapolate beyond the short time frame of the RCTs a parametric curve fitting approach was adopted (with the exponential function always selected by the company). OS, PFS and time on treatment for ponatinib were obtained from the PACE study. OS, PFS for bosutinib were derived from Study 200 (as reported in the manufacturer's submission to NICE)[12]. Response to active treatment was modelled to determine the transition to the SCT state. MaHR was assumed as a proxy of disease remission. MaHR rates for ponatinib were derived from the PACE study. MaHR rates for bosutinib treatment were obtained from the manufacturer NICE single technology appraisal (STA) submission[12]. Data on OS of CML patients after SCT were obtained from a published study[23] and for hydroxycarbamide both OS and PFS for patients in AP- and BP-CML were based on data used in a previous Health Technology Assessment (which was based on assumed OS and PFS data)[24].

The impact of CML on patients' HRQoL was modeled as a decrement from that of an age-equivalent member of the general population. During each cycle, the model generates an age-adjusted EQ-5D population norm value based on UK data. From the age- and sex-adjusted baseline, disease phase-specific utility decrements, derived from the literature, are applied to take into consideration: the progression of the disease, the occurrence of AEs, the morbidity associated with SCT and leukaemia relapse after SCT.

The following resource use components were included in the analysis: pharmacological therapy (including relative dose intensity for ponatinib, bosutinib and hydroxycarbamide); SCT; monitoring and follow-up (modelled as a function of disease phase and response to therapy [MaHR]); initial allo-SCT and follow-up care (remission); AEs; end-of-life care (value of a 10-day inpatient stay immediately before death). All costs used in the model were derived from published or publicly available sources, or based on expert opinion. Drug acquisition costs were sourced from the British National Formulary. No administration costs were included.

The analysis was conducted from the perspective of NHS Wales. The cohort simulation runs in three-monthly cycles through the entire lifetime of modelled patients. A half-cycle correction is applied. A 3.5% discount rate is applied to both outcomes and costs.

AP-and BP-CML model results

Results of the base case analyses for the advanced stages of CML are summarised in Table 5.

Table 5. Company-reported results of the base case analyses for advanced stages of CML

Phase	SCT eligibility	Comparison	Ponatinib		Comparator		ICER (£/QALY)
			QALY	Cost (£)	QALY	Cost (£)	
AP	Eligible for SCT	(Ponatinib, SCT) vs. (Bosutininb, SCT)	3.13	78,100	2.20	62,399	16,923
		(Ponatinib, SCT) vs. SCT	3.13	78,100	0.72	136,02	Dominant
	Unsuitable for SCT	Ponatinib vs. Bosutinib	3.00	48,607	2.05	38,068	11,013
		Ponatinib vs. BSC	3.00	48,607	0,40	6,394	16,215
BP	Eligible for SCT	(Ponatinib, SCT) vs. (Bosutininb, SCT)	0.38	22,392	0.64	19,616	Not dominant
		(Ponatinib, SCT) vs. SCT	0.38	22,392	0.42	130,556	N/A
	Unsuitable for SCT	Ponatinib vs. Bosutinib	0.37	19,998	0.63	18,424	Not dominant
		Ponatinib vs. BSC	0.37	19,998	0.26	6,407	119,344

Abbreviations: AP = acute phase; BP = blast phase; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year

In the AP-CML analysis for patients suitable for SCT the ICER of 'ponatinib, SCT' versus 'bosutininb, SCT' is £16,923/QALY, in favour of 'ponatinib, SCT', and dominant versus direct SCT. For AP-CML patients unsuitable for SCT the ICER is £11,013/QALY for ponatinib versus bosutinib and £16,215/QALY for ponatinib versus BSC. In the analysis of BP-CML patients suitable for SCT 'ponatinib, SCT' was more costly (total costs of £22,392 versus £19,616) and less effective (QALYs of 0.38 versus 0.64) versus 'bosutininb, SCT'. For BP-CML patients unsuitable for SCT, bosutinib dominated ponatinib (less costly and more effective). When Ponatinib was compared to BSC the ICER was £119,344/QALY.

To assess the influence of each parameter variation on the result of the model one way sensitivity analyses were undertaken with all inputs varied by a ±10% range of the base case value. The analysis was performed for the AP model in patients suitable for transplantation, where 'ponatinib, SCT' was compared with 'Bosutinib, SCT' with a base case ICER of £16,923/QALY. The model was most sensitive to the monthly cost of ponatinib, followed by the survival on treatment with bosutinib. Ponatinib cost variation of ± 10% of its base case value caused a variation in the ICER in the range ± 23%. Other influencing parameters were ponatinib PFS and the MaHR rate used. Probabilistic sensitivity analyses were not presented by the company for this analysis.

Ph^+ ALL model

The economic model for the Ph^+ ALL indication used a design similar to that of the BP-CML model. SCT and BSC were the main comparators to ponatinib. Comparator treatment sequences for the Ph^+ ALL indication were based on whether patients were suitable or unsuitable for SCT. For patients who were suitable for SCT, the relevant treatment sequences were:

- Ponatinib, followed by SCT (Ponatinib, SCT) in those patients who respond to it; BSC is applied after ponatinib discontinuation
- Entire modelled population starts on SCT (SCT).

For those patients not suitable for SCT, the relevant treatment sequences were:

- Ponatinib treatment, followed by BSC in case of discontinuation
- Patients are only given palliative chemotherapy (BSC).

The Ph^+ ALL model is a Markov cohort model using four health states (including death). Patients start in the 'Active Treatment' state if the comparator is ponatinib, in the 'allo-SCT' state if the comparator is allo-SCT and in the 'BSC' state if the comparator is BSC. In the 'Active Treatment' state patients may respond to the treatment and achieve remission. In this case, it is assumed that patients can undergo SCT. Patients who are not responding remain in the 'Active Treatment' state until they discontinue ponatinib (transition to 'BSC' state) or die. Patients in the 'allo-SCT' state and in the 'BSC' state remain there until death.

The main determinants of the disease course (OS, time on active treatment and response to active treatment) were derived from Kaplan–Meier curves from both RCTs and observational studies. To extrapolate beyond the time frame of the published studies, a parametric curve-fitting approach was adopted. Similarly to the approach used in the BP-CML model the exponential function was always selected. OS and time on treatment for ponatinib were obtained from the PACE study. The OS in Ph^+ ALL patients after SCT was derived from a study examining the outcome of 421 patients with ALL (81 patients with Ph^+ ALL) who experienced a first relapse[25]. OS in Ph^+ ALL patients treated with palliative chemotherapy was derived from data from an observational cohort of 37 patients with ALL[26]. MaHR was assumed as a proxy of disease remission with MaHR rates for ponatinib derived from the PACE study.

The impact of Ph^+ ALL on patients' HRQoL was modelled as a decrement from that of an age-equivalent member of the general population. In the absence of data specific for ALL, the same utility as in BP-CML was assumed.

The following resource use components were included in the analysis: pharmacological therapy (including relative dose intensity for ponatinib); SCT; monitoring and follow-up (modelled as a function of disease phase and response to therapy [MaHR]); initial allo-SCT and follow-up care (remission); AEs; end-of-life care (value of a 10-day inpatient stay immediately before death). All costs used in the model were derived from published or publicly available sources, or based on expert opinion. Drug acquisition costs were sourced from the British National Formulary. No administration costs were included.

The analysis was conducted from the perspective of NHS Wales. The cohort simulation runs in three monthly cycles through the entire lifetime of modelled patients. A half-cycle correction is applied. A 3.5% discount rate is applied to both outcomes and costs.

Ph^+ ALL model results

Results of the base case analyses for the Ph^+ ALL indication model are summarised in Table 6.

Table 6. Company-reported results of the base case analyses for the Ph+ ALL indication model

SCT eligibility	Comparison	Ponatinib		Comparator		ICER (£/QALY)
		QALY	Cost (£)	QALY	Cost (£)	
Eligible for SCT	(Ponatinib, SCT) versus SCT	0.74	78,097	0.39	129,192	Dominant
Unsuitable for SCT	Ponatinib versus BSC	0.52	36,452	0.17	27,576	£25,182

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year

In the analysis of Ph+ ALL patients suitable for SCT, 'Ponatinib, SCT' is less costly (total costs of £78,097 versus £129,192) and more effective (QALYs of 0.74 versus 0.39) compared to 'SCT' ('ponatinib, SCT' is dominant versus 'SCT'). In the analysis of Ph+ ALL patients unsuitable for SCT the ICER is £25,182/QALY for ponatinib versus BSC.

To assess the influence of each parameter variation on the result of the model, one way sensitivity analyses were undertaken with all inputs varied by a ±10% range of the base case value. The analysis was performed in patients unsuitable for transplantation, where ponatinib was compared with BSC, with a base case ICER of £25,182/QALY. The most influential parameter was the cost of ponatinib, followed by the utility values used for Ph+ ALL. Ponatinib cost variation of ± 10% of its base case value caused a variation in the ICER in the range ± 13%. Other influencing parameters were time on treatment with ponatinib and the unit cost of one day in hospital. Probabilistic sensitivity analyses were not presented by the company for this analysis.

4.1.2 AWTTC critique

Strengths of the economic evidence include:

- The major costs and consequences associated with treatment appear to have been incorporated into the model.
- The structure of the models seems to be consistent with the natural history of the disease.
- The company conducted a range of sensitivity and scenario analyses to test key assumptions.

Limitations of the economic evidence include:

- Since CML is a chronic disease and the estimated survival of patients from diagnosis is approximately 15–20 years it was necessary to extrapolate clinical-effectiveness data over many years which introduced substantial uncertainty and significant potential for bias.
- There is a lack of long-term progression-free and overall survival data for ponatinib and there are no direct comparative data; hence, there is no direct head-to-head comparison with other treatment agents. Effectiveness data used in the models is taken from various sources for the different interventions. The only data on response to either dasatinib or nilotinib in this setting comes from a small number of studies. Furthermore response rates for hydroxycarbamide and interferon alfa are based on assumptions.
- Based on the results of the systematic literature review provided by the company ponatinib appeared to provide a higher probability of treatment response compared with the 2G-TKIs commonly used in this indication (dasatinib, nilotinib and bosutinib). However, it was unclear whether the studies synthesised in the meta-analysis were methodologically comparable and whether sources of heterogeneity existed.

- The 'progression' rate from CP-CML to AP-CML was modelled via a surrogate relationship based on the extent of the cytogenetic response, with the risk of progression differing for patients achieving different response rates. As such the response profile of each treatment becomes the driver of outcomes through the assumed surrogacy relationship. Since response rates for the model comparators were derived either from small observational studies or based on assumptions the values used are highly uncertain and response rates might have favoured ponatinib.
- There is some uncertainty in the line of treatment that clinicians would use ponatinib if it were recommended by AWMSG as the license does not strictly specify whether the product should be used post second-line failure in CP-CML and AP- BP CML. Also it is unclear if alternative treatment sequences following the failure of 1G- or 2G-TKIs are available in clinical practice in Wales and whether these would have any impact on the cost effectiveness of ponatinib.
- The company restricted their submission in the CP-CML model to use in patients post second-line TKIs failure and in those who have exhausted all other treatment options with 1G- or 2G-TKIs in the progressed phases (AP and BP) of CML which is different from the licenced indication.
- Resource use data were derived using a Delphi Panel approach. It is not clear whether this reflects expected resource use associated with current treatment of CP-CML, AP and BP-CML and Ph^+ ALL in Wales.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of ponatinib within its licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on data from 2003 the company estimated that approximately 2,600 people in England and Wales have CML[27] and 600–800 people are diagnosed each year[4]; with more than 90% of these patients diagnosed with CP-CML[28]. The incidence of CML in Wales is 1.4 and 0.9 per 100,000 males and females, respectively[29]. On the basis of this information, the company estimated the number of patients with CML in Wales to be 189 (prevalent population), with 34 new cases occurring each year (incident population). Based on data from Cancer Research UK from 2008 the company estimated the UK standardised incidence rate for leukemia to be 9.6 per 100,000 population[30], of which 10% of cases to be ALL (0.96 per 100,000 population)[30], and a further 20–30% to be Ph^+ (0.3 per 100,000)[31]. On the basis of this information the company estimated the number of patients with Ph^+ ALL in Wales to be 8 (prevalent population), with 9 new cases estimated each year (incident population).

The number of patients eligible for treatment with ponatinib in Wales was estimated by the company on the basis of the number of new patients and the failure rates with imatinib and nilotinib reported in the literature. The company estimated that out of 34 new CP-CML cases occurring each year in Wales, 25–30% of these would fail first-line treatment with imatinib and[32] over 50% would also eventually fail second-line treatment with nilotinib[33]. This suggested a third-line pool potentially eligible for ponatinib of four patients. The company assumed that these patients would receive ponatinib on an ongoing basis, until discontinuation for toxicity or lack of response. Based on the rate of discontinuation observed in the PACE study, a yearly discontinuation rate of 30% was assumed by the company. The estimated net number of CML patients in each of the first five years after introduction was estimated as follows: 1st year: 4 patients, 2nd year: 7 patients, 3rd year: 9 patients, 4th year: 10 patients and 5th year: 11 patients.

The number of Ph^+ ALL patients eligible for treatment with ponatinib in Wales was also estimated by the company on the basis of the number of incident patients and the failure rates with imatinib and dasatinib reported in the literature. The company estimated that out of 9 new Ph^+ ALL cases occurring each year in Wales, up to 30% would be refractory to imatinib (relapsing after a median of 2.2 months)[8], and over 70% would also fail on second-line treatment with dasatinib[8], suggesting a third-line pool of 1 to 2 patients potentially eligible for ponatinib.

5.1.2 Results

Table 7 presents the budget impact estimates as presented in section 8 of the company's submission. The analysis included the same comparators as those specified in the CP-CML economic evidence submission (dasatinib, bosutinib, hydroxycarbamide, interferon alfa and allo-SCT).

To estimate the incremental cost to the health service of the introduction of ponatinib in Wales, the budget impact to treat the patients who would be eligible for ponatinib therapy was estimated in the presence and in the absence of ponatinib on the market. The company estimated a weighted average cost per year (£35,618) of all the alternative treatments used in clinical practice in Wales (based on physician responses [n=9] to a Delphi questionnaire). The cost for ponatinib was based on the highest possible dosing (45 mg per day - £61,441).

Table 7. Company-reported costs associated with the introduction of ponatinib in Wales for CML patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients* (all indications)	4	7	9	10	11
Number of eligible patients (indication(s) covered in this submission)	4	7	9	10	11
Uptake (%)	100%	100%	100%	100%	100%
Treated patients	4	7	9	10	11
Net costs**	£242,400	£424,200	£545,400	£606,000	£666,600
Cost of alternative treatment ***	£142,472	£249,326	£320,562	£356,180	£391,798
Overall net cost (vs. alternative treatments)	£99,928	£174,874	£224,838	£249,820	£274,802

* Assumes all eligible patients would receive ponatinib
** Assumes highest possible dosing throughout the year and thus the highest possible annual cost of ponatinib.
*** Based on weighted average cost per year of alternative treatments identified from Delphi panel

The overall net cost versus alternative treatments was £99,928 in Year 1 rising to £274,802 in Year 5. For the few Ph^+ ALL patients in Wales expected to be treated with ponatinib, the alternative treatments were salvage chemotherapy or SCT. The company estimated annual costs of £30,300 for the two Ph^+ ALL patients per year eligible for ponatinib (based on a duration of treatment of approximately 3 months and the highest dose of ponatinib – 45 mg per day).

The company assumed the highest possible dose, and thus the highest possible cost, applied for an entire year for ponatinib. However, the company suggested that some patients might only be receiving the 15 mg daily dose of ponatinib in clinical practice (in the PACE trial, 20% of patients' time was spent on the 15 mg daily dose). By using this data, the average annual cost for ponatinib was estimated to be in the range of

£55,000 per year. The company also suggested that the SPC for ponatinib would soon be updated with new dosing guidance for CP-CML recommending a switch to lower doses upon achievement of response which could potentially further decrease the cost per year of ponatinib. As the median time to response in CP CML in the ponatinib trial was approximately three months, this suggests an annual cost of ponatinib in the range of £38,000 (three months of 45 mg daily starting dose, followed by nine months of 15 mg daily).

5.1.3 AWTTC critique

- Due to lack of epidemiological data in patients post second-line TKIs failures in Wales, the estimation of the number of patients eligible for treatment with ponatinib is based on assumptions and data drawn from published studies.
- The number of patients eligible for treatment with ponatinib in Wales was estimated on the basis of the number of new patients and failure with two TKIs as reported in the literature. Patients currently with the condition in Wales (prevalent population) are not included in the budget impact estimates. The data presented by the company might be underestimating the budget impact of introducing ponatinib in Wales.
- The analysis assumed a 100% uptake rate starting from year one, which may overestimate initial uptake.
- A proportion of patients in the ponatinib trial (20% of patients) only used a 15 mg daily dose. It is unclear what the optimal dose regimen for ponatinib in clinical practice in Wales should be.

5.2 Comparative unit costs

Table 8 provides example comparative acquisition costs for ponatinib, dasatinib, bosutinib, hydroxycarbamide, interferon alfa and allo-SCT.

Table 8. Examples of treatment regimen costs

Treatment regimen	Example doses	Annual cost per patient*
Ponatinib 45 mg	45 mg per day	£61,441
Dasatinib 100 mg	100 mg per day	£30,477
Bosutinib 500 mg	500 mg per day	£44,799
Hydroxycarbamide 500 mg	2,000 mg per day†	£154
Interferon alfa 1-mL vial	9,000,000 IU per day	£13,649
Allo-SCT	Intervention	£85,581

*Costs based on BNF list prices as of 26 August 2014[34]. †Assumes 25 mg/kg daily for an average weight of 80 kg[22] Cost for allo-SCT from company's submission.
This table does not imply therapeutic equivalence of the medicines and doses listed.
See all relevant SPCs for full dosing details.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company anticipate that ponatinib (Iclusig®▼) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

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

GLOSSARY

Chronic phase (CP)
This is the initial phase of CML and its duration is variable. The definition of CP implies that none of the criteria for AP are met[35]. In this phase the symptoms are usually mild and non-specific and can include fatigue, weight loss, night sweats, anaemia, a feeling of 'fullness' and a tender lump on the left side of the abdomen caused by enlargement of the spleen[4].

Accelerated phase (AP)
This phase of CML is characterised by 15-29% blasts in blood or bone marrow or > 30% blasts plus promyelocytes in blood or bone marrow, with blasts < 30%; ≥ 20% basophils in blood; persistent thrombocytopenia (< 100 x 10^9/L) unrelated to therapy and clonal chromosome abnormalities in Ph^+ cells (CCA/Ph^+), major route, on treatment[15,35]. Disease progression is more rapid than that in the chronic phase, and immature blast cells in blood and bone marrow proliferate. Symptoms include bruising, bleeding and infections[4].

Blast phase (BP)
This final phase of CML is characterised by ≥ 30% blasts in blood or bone marrow or extramedullary blast proliferation (apart from spleen)[15,35] . There is a rapid increase in immature forms of cells (blasts), which replace normal cells in bone marrow and affect other organs. Symptoms include fever, sweating, pain and enlargement of organs. When this phase is reached CML is often fatal within 3–6 months[4].

Major cytogenetic response (MCyR)
The MCyR was defined as the proportion of patients who achieved a complete cytogenic response (CCyR) or partial cytogenetic response (PCyR) after initiation of study treatment. Patients entering the trial in PCyR had to achieve a CCyR to meet the MCyR endpoint[1].

Major haematological response (MaHR)
The MaHR rate was defined as the proportion of patients who achieved a complete haematological response (CHR) or had no evidence of leukaemia after initiation of study treatment, with one additional assessment at least 28 days later at which the CHR or no evidence of leukaemia criteria were met[1].

Overall survival (OS)
OS is defined as the interval from the first dose of study treatment until death, censored at the last date at which patient was known to be alive[17].

Progression-free survival (PFS)
PFS is defined as the interval from the first dose of study treatment until the criteria for progression or death are met, censored at the last date at which patient was known to be alive[17].

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