Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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ponatinib 15mg, 45mg film-coated tablets (Iclusig®) SMC No. (1032/15)

ARIAD pharmaceuticals, Inc.

6 March 2015

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan and end of life process

ponatinib (Iclusig®) is accepted for use within NHS Scotland.

Indication under review: 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.

A non-comparative phase II study of ponatinib was conducted with primary outcomes of major cytogenetic response in patients with baseline chronic phase CML and major haematologic response in patients with baseline accelerated or blast phase CML or Ph+ALL. Ponatinib demonstrated efficacy in heavily pre-treated CML and Ph+ALL patients who had received dasatinib/nilotinib as second line or further line tyrosine kinase inhibitor therapy or who had the T315I mutation.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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Dosing Information

The recommended starting dose is 45mg of ponatinib once daily. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. Dose modifications should be considered for the management of treatment toxicity.

Tablets should be swallowed whole. Patients should not crush or dissolve the tablets. Ponatinib may be taken with or without food.

Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia. Haematologic support such as platelet transfusion and haematopoietic growth factors can be used during treatment if clinically indicated.

Before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimised during treatment with ponatinib.

Product availability date

August 2013

Ponatinib meets SMC orphan criteria for CML and meets both orphan and end of life criteria for Ph+ALL.

Summary of evidence on comparative efficacy

Ponatinib is the fifth tyrosine kinase inhibitor (TKI) licensed for the treatment of CML, which is a haematopoietic stem cell disease characterised by a proliferation of granulocytes and their immature myeloid precursors including blast cells. CML has three phases: chronic phase (CP), accelerated phase (AP) and blast phase (BP). The patient population for this licensed indication also includes patients with Ph+ ALL. Recent estimates suggest that mean survival following progression to AP is 16 months (10 months in AP and 6 months in BP).[1,2,3] The National Institute for Health and Care Excellence (NICE) has recommended the use of imatinib or nilotinib for first-line treatment of CP CML, and nilotinib in patients with CP or AP CML whose CML is resistant to treatment with standard-dose imatinib or who have imatinib intolerance.[2,3]

One phase II multi-centre, single-arm study has been conducted in patients with CP, AP or BP CML (any phenotype) or Ph+ALL with disease resistant to, or intolerant of, therapy with nilotinib or dasatinib or with the *BCR-ABL* T315I mutation. Patients were required to be ≥18 years old, have an Eastern

Co-operative Oncology Group (ECOG) performance status ≤2, adequate renal and hepatic function, normal pancreatic status and a normal QT interval. After screening, patients were assigned to one of six cohorts based on disease stage and presence of T315I mutation: A (CP CML resistant or intolerant to dasatinib or nilotinib); B (CP CML with T315I mutation); C (AP CML resistant or intolerant to dasatinib or nilotinib); D (AP CML with T315I mutation); E (BP CMP or Ph+ALL resistant or intolerant to dasatinib or nilotinib); and F (BP CML or Ph+ALL with T315I mutation). All patients received oral ponatinib 45mg once daily as long as they continued to receive benefit from it or until disease progression, development of intolerance, withdrawal of consent by the patient or decision by the investigator. Overall, 93% of patients had received ≥2 prior TKIs and 58% had received ≥3 prior TKIs**.** The six cohorts were analysed separately.[4]

For CP CML patients, the primary outcome was major cytogenetic response (MCyR) at any time within the first 12 months of the study. MCyR was defined as complete cytogenetic response (CCyR) (defined as no Ph+ cells) or partial cytogenetic response (PCyR) defined as 1% to 35% Ph+ cells. CP CML patients with PCyR at baseline had to reach CCyR in order to achieve a MCyR. CP CML patients with CCyR at baseline were not included in the study. For patients with AP CML, BP CML or Ph+ALL at baseline, the primary outcome was major haematologic response (MaHR) within the first six months of the study. MaHR was defined as complete haematologic response (CHR) or no evidence of leukaemia and was confirmed by blood analyses after ≥28 days. Patients in these cohorts with MaHR at baseline were not eligible for the study. Fourteen AP CML patients with MaHR were enrolled and were counted as non-responders for MaHR.[4]

After a median follow-up of 15 months, 56% (149/267) (95% confidence interval [CI]: 50% to 62%) of CP CML patients achieved MCyR, 51% in the resistant/intolerant subgroup and 70% in the T315I subgroup. It was estimated that the duration of MCyR lasted ≥12 months in 91% of responders. In the AP CML, BP CML and Ph+ ALL groups, 55% (46/83) (95% CI: 44% to 66%), 31% (19/62) (95% CI: 20% to 44%) and 41% (13/32) (95% CI: 24% to 59%) patients respectively achieved MaHR.[4]

The company also submitted unpublished efficacy data after a median follow-up of 24 months, sourced from an oral presentation at a conference. These results are included in Table 1.[5]

Table 1: Study outcomes by to disease type/stage/mutation (median follow up of 24 months [5]

Study Outcomes	**CP-CML**		**AP-CML**		**BP-CML**		**Ph+ ALL**	
	R/I (N=203)	**T315I (N=64)**	**R/I (N=65)**	**T315I (N=18)**	**R/I (N=38)**	**T315I (N=24)**	**R/I (N=10)**	**T315I (N=22)**
MCyR	56%	72%						
CCyR	48%	70%						
MMR	31%	58%						
MaHR			62%	61%	32%	29%	50%	36%
PFS at 2 years	67%		37%		-		-	
Estimated (KM) median PFS	29 months		15 months		-		-	
OS at 2 years	86%		72%		18%		21%	
Estimated (KM) median OS	NR		NR		7 months		8 months	

MCyR=Major cytogenetic response; CCyR= complete cytogenetic response; MMR=major molecular response; MaHR=major haematologic response; PFS=progression free survival; KM=Kaplan-Meier; OS=overall survival; NR=not reached; R/I=resistant/intolerant.

For CP CML patients, at 24 months follow-up, the median time to response for MCyR was 2.8 months and it was estimated that 89% (95% CI: 82% to 93%) of patients would maintain this response for at least two years. For AP CML patients, the median time to response was 0.7 months and it was estimated that 21% (95% CI: 8% to 37%) of patients would maintain this response for at least two years.[5]

Summary of evidence on comparative safety

In the whole study population (unpublished data at median follow-up of 24 months), the most common non-haematologic serious adverse events were pneumonia 6.2% (28/449), pancreatitis 5.6% (25/449), pyrexia 4.2% (19/449) and abdominal pain 4.0% (18/449). The most common haematologic serious adverse events were anaemia 3.3% (15/449), thrombocytopenia 3.1% (14/449) and febrile neutropenia 2.9% (13/449). Overall, the most common treatment-emergent adverse events (≥20%) were a decreased platelet count, rash, abdominal pain, headache, constipation and dry skin.[5]

At 24 months follow-up (equating to 578 patient-years), arterial thrombosis adverse events occurred in 17% (77/449) of patients and arterial thrombosis serious adverse events occurred in 12% (53/449) of patients. Cardiovascular adverse events occurred in 9.1% (41/449) and cardiovascular serious adverse events in 6.2% (28/449) of patients. Cerebrovascular adverse events occurred in 5.7% (26/449) and cerebrovascular serious adverse events in 4.0% (18/449) of patients. Peripheral vascular adverse events occurred in 6.2% (28/449) and peripheral vascular serious adverse events in 3.6% (16/449) of patients. Venous thromboembolism adverse events occurred in 5.1% (23/449) of patients and venous thromboembolism serious adverse events occurred in 2.9% (13/449) of patients.[5] The Summary of Product Characteristics (SPC) for ponatinib notes that serious vascular occlusion has occurred in patients treated with ponatinib, including cardiovascular, cerebrovascular and peripheral vascular events, and venous thrombotic events. Patients with and without cardiovascular risk factors, including patients aged less than 50 years, experienced these events. Vascular occlusive adverse events were more frequent with increasing age and in patients with prior history of ischaemia, hypertension, diabetes, or hyperlipidaemia.[6]

The rates of treatment-related adverse events resulting in discontinuation were 10% in CP-CML, (and 7% in AP-CML and 3% in BP-CML/Ph+ALL). Myelosuppression was commonly reported in all patient populations; however, discontinuation due to myelosuppression was uncommon (thrombocytopenia 3.6%, neutropenia and anaemia <1% each).[6]

Five deaths were considered by the investigators as being possibly or probably related to ponatinib. In patients with CP CML, one had pneumonia and one had an acute myocardial infarction, one patient with AP CML had fungal pneumonia, one patient with BP CML had a gastric haemorrhage and one patient with Ph+ALL had a cardiac arrest.[4]

It is noted in the European Public Assessment Report that the occurrence of pancreatic events (24%), including pancreatitis (7.4%), is one of the major safety issues of ponatinib use. The EMA noted that this differs from the other TKIs (with less than 1% pancreatitis). However, pancreatitis rarely led to ponatinib discontinuation.[1]

Summary of clinical effectiveness issues

CML and ALL are malignant proliferative diseases of haematopoietic stem cells. Approximately 95% of patients with CML and 20% to 25% of adult patients with ALL have a chromosomal abnormality known as the Philadelphia chromosome (Ph+) caused by reciprocal translocations between chromosomes 9 and 22 resulting in a *BCR-ABL* fusion gene that encodes an active tyrosine kinase protein which causes uncontrolled cell proliferation. The same *BCR-ABL* fusion gene is also found in CML patients without the Philadelphia chromosome who have different translocations. The three phases of CML have different disease characteristics and prognoses. CP CML can last over 10 years though mean survival following progression to AP CML is 16 months (10 months in AP and 6 months

in BP, the latter resembling ALL).[1,2,3] Most patients are diagnosed in CP CML and may be asymptomatic or present with fatigue, anaemia, weight loss, night sweats, or splenomegaly. Ponatinib is a third generation TKI 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] It is the only licensed drug that inhibits T315I mutation gene activity. Although not induced by exposure to TKIs, continual treatment with these drugs increases the proportion of leukaemic cells with the T315I mutation, due to a selection process, and ultimately leads to resistance.[7] Ponatinib meets SMC orphan criteria. It also meets SMC end of life criteria for the Ph+ALL patient group.

Allogenic stem cell transplant (SCT) is the only potentially curative treatment for CML but is associated with morbidity and mortality and is therefore limited by patient fitness as well as the availability of suitable donors.[8] Current drug treatments for CML include the first generation TKI, imatinib (commonly used first-line) and the second generation TKIs, nilotinib (used first- or second-line), dasatinib and bosutinib. Dasatinib is not recommended by NICE multiple technology appraisals 241 and 251 and this advice has been endorsed in Scotland).[2,3] SMC has recently accepted bosutinib for Ph+CML.

SMC clinical experts considered that there is unmet need in this therapeutic area, namely in patients unsuitable for allogenic SCT who have the T315I mutation or who have failed on prior TKI treatment.

The pivotal study was a non-comparative phase II study. There are no direct comparative data with other TKIs. The EMA considered the magnitude of response rates shown in the study to be clinically relevant, especially for, but not restricted to, patients with CML and T315I mutation.[1] Ponatinib has demonstrated efficacy in heavily pre-treated Ph+ leukaemia patients in all stages of disease, i.e., patients who have received dasatinib/nilotinib as second line or further line TKI therapy, and in patients with the T315I mutation.[1] There are limited efficacy data in patients who have only received one prior TKI.

An indirect comparison was conducted in the CP CML cohort. It was necessarily a naïve (unadjusted) indirect comparison because the only available studies are non-comparative or observational. The efficacy of ponatinib was compared with second generation TKIs, bosutinib, dasatinib, and nilotinib in patients with CP CML resistant/intolerant to ≥1 prior second generation TKI. Safety was not compared. An in-press publication of the indirect comparison cites estimated probabilities of CCyR with second generation TKIs of 22% to 26%, compared with 60% (95% credible interval: 52% to 68%) with ponatinib.[9] An unadjusted naïve indirect comparison limits the validity and usefulness of the available comparative results.

SMC clinical experts considered that ponatinib is a therapeutic advancement due to its efficacy in patients with the T315I mutation, and that the place in therapy of ponatinib is in patients with the T315I mutation in particular and also following failure of prior TKIs. They noted that the introduction of this medicine may impact on the patient and/or on service delivery due to monitoring required for adverse cardiovascular events. Serious vascular occlusion has been reported with ponatinib and is being monitored by the regulatory authorities. The patient's cardiovascular status should be assessed before starting ponatinib and regularly monitored during treatment.[6] Ponatinib should not be used in patients with a history of myocardial infarction or stroke, unless the potential benefit of treatment outweighs the potential risk.[6]

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ponatinib, as an orphan medicine and as an end of life medicine for Ph+ALL, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Patients who are resistant to, or intolerant of, existing first and second generation TKIs have a very poor prognosis. Chronic phase CML patients are at risk of progressing to blast crisis. Ph+ALL is associated with a particularly poor prognosis.

- Ponatinib offers extended survival and better symptom control leading to significantly improved quality of life compared to existing very limited treatment options. This is particularly important in patients harbouring the T315I mutation, in whom there is no other effective treatment.

- Anecdotal evidence suggests that cardiovascular side effects associated with ponatinib can be lessened by dose reductions whilst maintaining clinical benefit.

- For younger patients with severe disease who are eligible for stem cell transplantation, ponatinib offers a reduction in the burden of their disease prior to transplant and can be considered as a bridge to a potential cure.

- There is a psychological benefit to patients and their families of knowing that there is a realistic treatment option available to them later in the disease pathway.

- SMC has already accepted imatinib, nilotinib and bosutinib for treatment of CML. Patients who are resistant to, or intolerant of, these TKIs should have access to a further treatment option that has been shown to be effective (or in the case of patients with T315I mutation a first-line option) on equity grounds.

- The PACE group felt strongly that this medicine should be made available in NHS Scotland and that this should be in line with the licensed indication. They stressed that it provides the best option to optimise life expectancy and quality of life in this small group of patients.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing ponatinib with a number of comparators used in CP, AP or BP CML, or in patients with Ph+ALL. For patients treated in CP, the comparators were dasatinib, bosutinib, hydroxycarbamide, interferon alfa and SCT. In the AP and BP models, for patients eligible for SCT, the comparators were SCT and bosutinib followed by SCT, and for patients unsuitable for SCT, the comparators were bosutinib and best supportive care (BSC). In the Ph+ALL model, the comparators were SCT and BSC.

For the CML indication, three separate models were used to estimate the cost-effectiveness of ponatinib when used in different stages of disease. For the Ph+ALL indication, the model used was based on the AP/BP CML model but used Ph+ALL specific data where available. All models used a

lifetime horizon, the duration of which varied depending on the phase patients started ponatinib treatment.

The CP-CML model combined a conventional state transition Markov model with a partitioned survival area under the curve model. The Markov model consisted of the three health states of CP, AP and BP-CML. In the CP health state, patients were categorised according to their response to treatment (CCyR, PCyR, complete haematologic response [CHR] and no response). The progression of patients from CP to AP was modelled according to the level of response. For patients starting treatment with ponatinib in the AP or BP, two separate models were used. Both models included health states for patients on active treatment, BSC and suitable for SCT. The AP model also allowed for patients progressing to BP.

The data for the ponatinib arm of the model were taken from a subgroup of patients in the pivotal study who had received two prior TKIs, which included 91 patients. For the dasatinib arm of the model, a number of data sources were used to estimate response levels. For the bosutinib arm of the model, the data source was a published paper which reported the results of a bosutinib study which was used as part of a submission to NICE. The response rates for hydroxycarbamide and interferon alfa were based on assumption. Outcomes for the SCT arm were taken from published studies.

In the AP, BP and Ph+ALL models, the ponatinib data were also taken from the pivotal study, with efficacy data for bosutinib taken from the NICE submission. The OS estimates for BSC were taken from a published study where patients spent 9.6 months in the AP-CML state and 6 months in the BP-CML state. For PFS, a mean of 3.6 months was assumed. In the Ph+ALL model, efficacy of SCT and BSC were based on literature estimates.

To extrapolate the data beyond the end of the clinical study in the CP model, the company identified data used in the NICE dasatinib and nilotinib technology appraisals in patients who were resistant or intolerant to imatinib. These data reported the proportion of patients who were progression-free at 6 monthly intervals until 48 months. These data were then extrapolated to estimate long-term disease progression from CP to AP/BP. A Weibull distribution was selected to extrapolate progression for CCyR, PCyR and CHR response categories based on visual inspection of the curves and taking clinical plausibility into account. The exponential function was selected for modelling the no response category. The progression rates were then applied to the response rates at 12 months from the pivotal study to predict the long-term outcomes.

The model used age-adjusted population norm utility values and then applied utility decrements for each health state to capture the quality of life impact on patients at the various stages of CML. The utility decrements used in the CP-CML model were taken from a published study which reported utility values using the time trade off method from 100 members of the UK general public. The utility values in the AP and BP-CML model were taken from a separate published study. In the Ph+ALL model, in the absence of utility values specific to ALL patients, the same utility values as BP-CML were assumed.

The analysis included drug costs of ponatinib, dasatinib, bosutinib, interferon alfa, hydroxycarbamide and treatments used as BSC. Costs of treating adverse events were also included. As all treatments are administered orally, no administration costs or drug wastage was included. Monitoring and follow-up costs included outpatient visits, tests and other interventions such as blood and platelet transfusions. The costs of SCT and end of life care were also included. Resource use was included in the model according to disease phase and response to treatment. For the on-treatment period, the resource use estimates were based on data from a Delphi panel.

The base case results according to the various patient groups and comparators are presented below:

Patient Group	Comparators	Incremental cost	Incremental QALYs	ICERs
CP-CML	Dasatinib	£72,696	3.13	£23,242
	Bosutinib	£62,794	3.21	£19,566
	SCT	£9,754	2.54	£3,837
	Hydroxycarbamide	£79,097	5.32	£14,860
	Interferon alfa	-£12,451	5.32	dominant
AP-CML, eligible for SCT	Bosutinib, SCT	£8,436	0.78	£10,734
	SCT	-£13,061	2.6	dominant
AP-CML, unsuitable for SCT	Bosutinib	£10,524	0.95	£10,997
	BSC	£41,727	2.6	£16,029
BP-CML, eligible for SCT	Bosutinib, SCT	£5,768	-0.2	dominated
	SCT	-£67,135	0.29	dominant
BP-CML, unsuitable for SCT	Bosutinib	£1,562	-0.26	dominated
	BSC	£13,191	0.11	£115,835
Ph+ALL	SCT	-£51,204	0.35	dominant
	BSC	£8,767	0.35	£24,870

There are a number of limitations with the analysis:

- Clinical data used in the model were taken from a number of different studies where patient populations and study designs were assumed to be comparable, but evidence was not provided to support this assumption. The only available data were from single arm phase II studies or observational studies, and as a result of the limitations with the data only a naive indirect comparison was conducted. As noted above, there are a number of limitations with the indirect comparison, including heterogeneity in study design and small patient numbers. The model results are driven by differences in response rates which are based on these data sources and are therefore uncertain. Sensitivity analysis requested from the company showed that the ICERs increased to £24k and £16k for the comparisons with bosutinib and hydroxycarbamide respectively when the CCyR with ponatinib was reduced by 20%.
- The model results estimate large gains in survival beyond the treatment period which appeared to lack face validity. In the CP model, large overall survival gains are predicted by extrapolation based on data from a subgroup of CP CML patients following 2 prior TKIs, but these estimates are inconsistent with the expected survival with BSC following progression. In the CP model, the mean gain in overall survival with ponatinib vs hydroxycarbamide was estimated to be 5.85 years (11.6 years vs 5.75 years). Similarly, the model predicted a gain of 3.5 years over bosutinib (11.6 vs 8.1). The overall survival estimate of 11.6 years with ponatinib may be overestimated, particularly given that the mean time on treatment was 4.87 years. In addition, in the AP model a large proportion of the survival gain was accrued by patients surviving for a number of years in the BP health state, which also lacks face validity. Sensitivity analysis was subsequently provided by the company which assumed no additional benefit beyond the treatment period. In this analysis, the overall survival estimates and QALY gains with ponatinib were more conservative which resulted in the ICERs increasing to £25k and £22k in the CP model for the comparisons with bosutinib and hydroxycarbamide respectively.
- The model results by T315I mutation status were not provided. Experts indicate mutation status is an important consideration with regards to treatment efficacy and choice of treatment. The company was asked to provide the results by T315I mutation status but their response indicated it would not be appropriate to provide this analysis as mutation status was not a significant predictor of response and would result in estimates based on small patient numbers. While these points are

acknowledged, SMC clinical experts consider ponatinib has a role in patients with the T315I mutation and therefore it would be helpful to see the cost-effectiveness estimates based on these data. In the absence of such analysis, the overall results versus hydroxycarbamide (as a proxy for BSC) are likely to be the most relevant based on SMC clinical expert responses.

- No additional testing or monitoring costs were included in the ponatinib arm. SMC clinical experts highlighted that the reported adverse events associated with ponatinib may necessitate additional monitoring of patients in practice. Sensitivity analysis was provided by the company which included an additional specialist visit every 3 months in the ponatinib arm and this resulted in a marginal increase in the ICERs.
- In the CP model, the utility gain between the CP and BP health states is larger than seen in other submissions to SMC for this condition. Sensitivity analysis was provided by the company which used more conservative utility values and this resulted in a small increase in the ICERs.
- In order to combine a number of uncertainties identified in the model, a scenario analysis was provided which assumed no additional benefit beyond the treatment period, used more conservative utility values and included additional monitoring costs in the ponatinib arm. In this scenario, for the CP model the ICERs increased to £29k and £25k for the comparisons with bosutinib and hydroxycarbamide respectively. Reducing the time horizon of this analysis to 20 years increased the ICERs to £35k and £31k.

SMC considered the likely range of cost-effectiveness ratios for ponatinib in this setting and the remaining uncertainties in the economic case. The Committee also considered the benefits in the context of the SMC decision modifiers and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied. In addition, as ponatinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifier, the Committee accepted ponatinib for use in NHS Scotland.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from The CML Support Group and Leukaemia CARE, both registered charities.

- Both charities have received pharmaceutical company funding in the past two years with The CML Support Group receiving some from the submitting company.

- Diagnosis with CML is particularly devastating for patients and their families as many display no symptoms when first diagnosed. The widely held belief that Leukaemia diagnosis amounts to death means that people often do not disclose their condition to family and employers for fear of economic and social consequences. This places them under even greater psychological stress.

- While the current tyrosine kinase inhibitors (TKIs) can be effective in many patients, others may be resistant or unable to tolerate the side-effects associated with them. In addition none of the current TKIs have activity against the T315I mutation which a small number of patients have.

- Ponatinib has a different side-effect profile from the other TKIs which may mean that it will be tolerated better by patients who have not tolerated the others, although it has been associated with significant cardiovascular side-effects.

- As ponatinib may be effective in patients with the T315I mutation it gives these patients hope where there was very little.

Additional information: guidelines and protocols

National Institute for Health and Care Excellence (NICE). Technology appraisal 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 (January 2012). It includes the following recommendations:

- Nilotinib is recommended for the treatment of chronic or accelerated phase Philadelphia-chromosome-positive CML in adults:
    - whose CML is resistant to treatment with standard-dose imatinib or
    - who have imatinib intolerance and
    - if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.
- Dasatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase CML in adults with imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib.
- High-dose imatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib.[2]

European Society for Medical Oncology (ESMO). Chronic myeloid leukemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2012).
Chronic phase

- First-line: Imatinib 400mg, or nilotinib 600mg, or dasatinib 100mg
- Second-line:
    - In case of intolerance, switch to another, taking into consideration the side effects of the first tyrosine kinase inhibitor, and comorbidities
    - In case of failure of imatinib, switch to nilotinib, or dasatinib, taking into consideration the presence and the type of BCR-ABL KD mutation
    - In case of failure of nilotinib or dasatinib, switch to dasatinib or nilotinib, taking into consideration the presence and the type of BCR-ABL KD mutation. Consider an allogeneic hematopoietic stem cell transplantation (alloHSCT)
- Third-line
    - In case of failure of two or three tyrosine kinase inhibitor, consider alloHSCT

Accelerated/blast phase

- Tyrosine kinase inhibitor naïve
    - Imatinib 600 or 800mg, or nilotinib 800mg or dasatinib 140mg, and consider alloHSCT
- Tyrosine kinase inhibitor pre-treated
    - Switch to another tyrosine kinase inhibitor, consider chemotherapy and alloHSC T[10]

European leukemianet (ELN). ELN recommendations for the management of chronic myeloid leukaemia (2013).
These guidelines were produced by an ELN expert panel who reviewed prior and new studies, to update recommendations made in 2009.
Chronic phase
First-line (outside of clinical trials):

- imatinib (400mg once daily), nilotinib (300mg twice daily), or dasatinib (100mg once daily).

Second line, intolerance to the first tyrosine kinase inhibitor

- Imatinib, nilotinib or dasatinib

Second line, failure of imatinib first line
- Dasatinib, or nilotinib, or bosutinib, or ponatinib.

Second line, failure of nilotinib first line
- Dasatinib,or bosutinib, or ponatinib.

Second line, failure of dasatinib first line
- Nilotinib, or bosutinib, or ponatinib.

Third line, failure of, or/and intolerance to, two tyrosine kinase inhibitors
- Any one of the remaining tyrosine kinase inhibitors.[8]

Additional information: comparators

Current drug treatments for CML include the first generation tyrosine kinase inhibitor, imatinib (commonly used first-line) and the second generation tyrosine kinase inhibitors, nilotinib (used first- or second-line) and dasatinib (which is not recommended by National Institute for Health and Care Excellence [NICE] multiple technology appraisals [MTA] 241 and 251 and this advice has been endorsed in Scotland).[2,3]

Options in patients with CML and the T315I mutation who are not suitable for allogenic SCT are considered to be palliative/supportive therapy and include hydroxycarbamide and interferon alfa.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 28 days (£)
Ponatinib	**Orally, 45mg once daily**	**4,713**
Bosutinib	Orally, 500mg once daily	3,437
Nilotinib	Orally, 400mg twice daily	2,433
Dasatinib*	Orally 100mg to 140mg once daily (chronic phase CML) or 140mg to 180mg once daily (accelerated, myeloid or lymphoid blast phase CML or Ph+ ALL)	2,338 to 3,507
Interferon alfa 2a (Roferon®)**	Subcutaneously on days 1 to 3; 3 million IU daily, days 4 to 6; 6 million IU per day, days 7 to 84; 9 million IU units per day	1,064 to 1,119
Interferon alfa 2b (Intron A®)**	Subcutaneously, 4 to 5 million IU/m^2 daily (monotherapy)#	873 to 1,164
Hydroxycarbamide***	Orally 20 to 30mg/kg once daily	9 to12

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online on 18.11.14 and based on 70kg body weight or 1.8m^2 body surface area where relevant. CML=chronic myeloid leukaemia; Ph+ ALL=Philadelphia chromosome positive acute lymphocytic leukaemia. Costs are based on the usual maximum licensed doses and do not take into account dose reductions for treatment toxicity. Costs of bosutinib and nilotinib are based on continuation of recommended starting doses. *Not recommended for this indication in Scotland **See relevant Summary of product characteristics for information on treatment beyond 12 weeks. *** Dose for Hydrea® capsules - licensed dose schedules of hydroxycarbamide differ according to product # Intron A cost based on use of 50 million units/ml multidose pens

Additional information: budget impact

For CML patients, the submitting company estimated there would be 18 patients eligible for treatment in each year with an estimated uptake rate of 100% and a 30% discontinuation rate. This resulted in an estimated 12 patients being treated each year.

The company estimated a gross budget impact of £624k each year. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £190k. The costs of displaced medicines were estimated based on a weighted average of relevant treatments.

For the Ph+ALL population, the company estimated there would be 15 patients eligible for treatment in year 1 and 4 patients in year 5 with an estimated uptake rate of 100% in all years and a 78% discontinuation rate. This resulted in an estimated 3 patients being treated in year 1 and 1 patient in year 5.

The company estimated a gross budget impact of £279k in year 1 and £69k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £134k in year 1 and £33k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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4. Cortes JE, Kim DW, Pinilla-Ibarz J et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013; 369: 1783-96.

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6. Ariad Pharmaceuticals, Inc. Summary of product characteristics for ponatinib (Iclusig®).

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9. (In Press) Lipton JH, et al. Comparative efficacy of tyrosine kinase inhibitor treatments in the third-line setting, for chronic-phase chronic myelogenous leukemia after failure of second-generation tyrosine kinase inhibitors. Leuk Res (2014),

10. Baccarani M, Pileri S, Steegmann JL, et al. Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii72-7

This assessment is based on data submitted by the applicant company up to and including 09 January 2015.

Drug 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.

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.