SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
www.scottishmedicines.org.uk
NHS SCOTLAND
Delta House • 50 West Nile Street • Glasgow • G1 2NP • Tel 0141 225 6999 • Chairman: Dr Alan G MacDonald

midostaurin 25mg soft capsules (Rydapt®) SMC No 1330/18

Novartis Pharmaceuticals UK Limited

4 May 2018

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 assessed under the ultra-orphan and end of life medicine process

midostaurin (Rydapt®) is accepted for use within NHS Scotland.

Indication under review: In combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FMS-like tyrosine kinase 3 (FLT3) mutation-positive.

In a randomised, double-blind, phase III study of adults (aged <60 years) with FLT3 mutation-positive AML, the addition of midostaurin to standard intensive chemotherapy regimen resulted in improved overall survival when compared with addition of placebo.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of midostaurin. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

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

Chairman,
Scottish Medicines Consortium

Published 11 June 2018

Indication

In combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FMS-like tyrosine kinase 3 (FLT3) mutation-positive.[1]

Dosing Information

The recommended dose of midostaurin is 50mg orally twice daily.

Midostaurin is dosed on days 8 to 21 of induction and consolidation chemotherapy cycles, and then for patients in complete response, every day as single agent maintenance therapy until relapse for up to 12 cycles of 28 days each. In patients receiving a haematopoietic stem cell transplant (SCT), midostaurin should be discontinued 48 hours prior to the conditioning regimen for SCT.

Before taking midostaurin, AML patients must have confirmation of FLT3 mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test.

Treatment with midostaurin should be initiated by a physician experienced in the use of anti-cancer therapies.

See summary of product characteristics (SPC) for further information including dose modification for specific clinical circumstances.[1]

Product availability date

April 2018
Midostaurin is an EMA designated orphan medicine and meets SMC ultra-orphan and end-of-life criteria for this indication.

Background

Midostaurin is an inhibitor of multiple tyrosine kinases, including FLT3 and KIT kinase. Inhibition of FLT3 receptor signalling induces cell cycle arrest and apoptosis in leukaemic cells that express mutant receptors (FLT3 ITD or FLT3 TKD) or those that overexpress FLT3 wild-type receptors.[1]

Midostaurin for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

AML are a heterogeneous group of haematopoietic stem cell disorders characterised by incomplete maturation of blood cells and decreased production of normal haematopoietic elements. Diagnosis is based on the presence of ≥20% blasts in blood or marrow, or regardless of blast percentage: select cytogenetic abnormalities or myeloid sarcoma. Symptoms commonly experienced by patients, resulting from the associated pancytopenia, include fatigue, dyspnoea, infection and bleeding.[2] Incidence increases with age, male sex and European descent.[2, 3] Scottish cancer statistics for 2015 report that 183 people were diagnosed with AML, 105 of whom were male. In all patients, median age range for

diagnosis was 70 to 74 years.[4] Prognosis at the point of diagnosis is affected by patient and AML-related factors. Patient factors that adversely affect prognosis include increasing age, poorer performance status, and poor general health. Hyperleukocytosis at presentation, and cytogenetic abnormalities such as FLT3 mutation are associated with poorer prognosis.[3, 5] The five-year survival rate for AML is 19%.[6]

Choice of treatment is determined by the fitness of the patient to receive intensive induction chemotherapy; this includes a risk assessment of treatment-associated mortality, particularly in older patients, those with poorer performance status, or complicating co-morbidities. Patients with adverse cytogenetic or molecular genetics may not be considered good candidates for intensive treatment on the balance that the benefits may be reduced to the extent that they do not outweigh the associated risks of treatment. Intensive treatment is given with curative intent.[3, 5] Intensive induction treatment usually comprises anthracycline plus cytarabine. Dosing schedules vary across centres. In Europe a "3+7" induction regimen (three days of daunorubicin and seven days of cytarabine) is given. In the UK, induction regimens tend to follow the protocols of the collaborative AML studies (eg AML 17), which use a "3+10, 3+8" schedule.[7] Consolidation therapy is indicated upon clinical and haematological remission and may include SCT.[3, 5]

Midostaurin is the first FLT3 tyrosine kinase inhibitor to be licensed for the management of AML. It meets SMC ultra-orphan and end-of-life criteria when used for the treatment of AML.

Clinical experts consulted by SMC advised that there is an unmet need for patients with FLT3-mutated AML due to the increased risk of relapse in this patient group when managed with standard chemotherapy regimens.

A patient and clinician engagement (PACE) meeting was held to consider the added value of midostaurin in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the fact that AML is a rapidly progressing form of leukaemia; approximately half of patients are diagnosed following emergency presentation, and approximately 80% commence treatment within a week of diagnosis. Current therapies are extremely toxic and frequently require prolonged inpatient admission. In addition to the significant symptom burden, the emotional impact of diagnosis can affect the mental health of patients; approximately half of patients with AML report anxiety or depressive feelings. Emotional stress also affects carers and family members. Patients with AML often have difficulty performing some activities of daily living; approximately 40% have problems taking care of themselves. Work / education is also affected with either reduction of hours or cessation altogether, with associated financial consequences.

Impact of new technology

Summary of evidence on comparative efficacy

The key evidence for midostaurin in adults with FLT3 mutant AML is the multicentre, randomised, double-blind, placebo-controlled, phase III RATIFY study.[8]

RATIFY recruited adults (18 to 59 years of age) with newly diagnosed FLT3 mutated (ITD or TKD subtypes) AML. Patients with acute promyelocytic leukaemia were excluded. No prior chemotherapy for leukaemia or myelodysplasia was permitted, excluding: emergency leukapheresis, emergency treatment for hyperleukocytosis with hydroxyurea for ≤5 days, cranial radiotherapy for central nervous system leukostasis (one dose only), or growth factor / cytokine support.[6, 8]

Patients were randomised in a 1:1 ratio (in blocks of six) to receive midostaurin (n=360) or placebo (n=357) used in combination with standard intensive chemotherapy (Table 1). Randomisation was

stratified by subtype of FLT3 mutation (TKD versus ITD high ratio [>0.7] versus ITD low ratio [0.05 to 0.7]).

Table 1: Treatment regimen for RATIFY[8]

Phase of treatment	Standard chemotherapy	Randomised treatment
Induction (up to two cycles)	daunorubicin 60mg/m^2 IV once daily (days 1 to 3) cytarabine 200mg/m^2 continuous IV infusion (days 1 to 7)	midostaurin 50mg or placebo twice daily (days 8 to 21)
Consolidation (four 28-day cycles)	cytarabine 3,000mg/m^2 IV every 12 hours (days 1, 3, and 5)	midostaurin 50mg or placebo twice daily (days 8 to 21)
Maintenance (up to twelve 28-day cycles)	-	midostaurin 50mg or placebo twice daily

Treatment comprised three phases (induction, consolidation and maintenance); patients advanced to the next phase following achievement of complete remission (CR). CR was defined as <5% blasts in the marrow or extramedullary leukaemia, absolute neutrophil count >1.0x10^9/L, platelet count >100x10^9/L and absence of blasts in the peripheral blood. A second cycle of induction was indicated for patients who did not achieve CR after the first; those who failed to achieve CR after the second cycle had treatment discontinued. Patients who remained in CR after consolidation moved to the maintenance phase.

At any time during the study, randomised treatment (midostaurin / placebo) was withheld or dose reduced in the presence of QTc-interval prolongation and / or grade ≥3 non-haematological adverse events. Use of stem-cell transplant (SCT) was not stipulated in the protocol, but could be employed at the local investigator's discretion, and resulted in discontinuation of study treatment. [6, 8]

The primary outcome was overall survival which was defined as the time from randomisation until death from any cause; this was assessed in the intention to treat population, all randomised patients.[8]

As a result of lower than expected event accrual rate, the study's main analysis (data cut-off 1st April 2015) was chosen (approximately 4.5 years after the final patient was recruited in October 2011) since it was considered that the planned 509 events were not likely to occur within a reasonable timeframe.[8] At this data cut-off there had been 171 deaths in the midostaurin group (48%) and 186 deaths in the placebo group (52%). A statistically significant improvement in overall survival (OS) was found in favour of midostaurin treatment; hazard ratio (HR) 0.77 (95% confidence interval [CI]: 0.63 to 0.95), p=0.0078.[6] Later analysis at a data cut-off in September 2016 forms the basis of the economic analysis presented to SMC. Results at this data cut-off are presented in Table 2.

Table 2: Updated overall survival analysis in RATIFY (data cut-off 05 September 2016).[6]

Overall survival		midostaurin (n=360)	placebo (n=357)
Event rate, n (%)		176 (49%)	189 (53%)
HR (95% CI)		0.79 (0.64 to 0.97), p=0.0109	
Median survival		74.7 months	25.6 months
KM-estimated survival at	Two years	61%	51%
	Three years	54%	47%
	Five years	51%	43%

HR = hazard ratio, CI = confidence interval, KM = Kaplan-Meier

The key secondary outcome of the study was event-free survival, and midostaurin was associated with a statistically significant benefit compared with placebo. Event-free survival was defined as the time to relapse, death from any cause or failure to achieve, within 60 days of commencement of induction therapy, CR. Results for this and other secondary outcomes are presented in Table 3.

Table 3: Secondary outcomes of RATIFY.[6]

		midostaurin (n=360)	placebo (n=357)
Event-free survival	Event rate	71%	78%
	Failure to achieve CR within 60 days	41%	46%
	Relapse	25%	25%
	Death	5.0%	6.7%
	Median	8.2 months	3.0 months
	HR (95% CI)	0.78 (0.66 to 0.93), p=0.0024	
Overall survival (censored at SCT)	Event rate	20%	23%
	Median survival	NR	NR
	HR (95% CI)	0.75 (0.54 to 1.03), p=0.037	
Event-free survival (censored at SCT)	Event rate	62%	68%
	Median	8.3 months	2.8 months
	HR (95% CI)	0.81 (0.68 to 0.98), p=0.012	
CR within 60 days of commencing induction therapy	Proportion of patients	59% (212/360), p=0.07 vs. placebo	54% (191/357)
DFS	Event rate	51% (109/212)	60% (114/191)
	Median	26.7 months	15.5 months
	HR (95% CI)	0.71 (0.55 to 0.92), p=0.005	

		midostaurin (n=360)	placebo (n=357)
CIR	Median	NR	17.6 months
	HR (95% CI)	0.68 (0.52 to 0.89), p=0.0023	
SCT	Proportion of patients	59% p=0.25 vs. placebo	55%

HR = hazard ratio, CI = confidence interval, SCT = stem-cell transplant, NR = not reached, CR = complete remission, DFS = disease-free survival (the time from date of first CR [within 60 days] to relapse or death from any cause), CIR = cumulative incidence of relapse (the time from date of first CR [within 60 days] to relapse or death due to AML).

A single-arm, phase II study (NCT01477606) provides supporting data for the use of midostaurin in patients with AML.[9, 10] The study recruited adults (aged 18 to 70 years) with newly diagnosed FLT3-ITD positive AML, ECOG performance status 0 to 2, who were considered eligible for intensive chemotherapy. All patients received induction therapy comprising daunorubicin (60mg/m^2, days 1 to 3), cytarabine continuous infusion (200mg/m^2, days 1 to 7) and midostaurin 50mg twice daily (day 8 to 48 hours prior to next treatment cycle). A second cycle of induction was given if there was partial remission. Consolidation comprised SCT, or in those not eligible for transplant, high-dose cytarabine in combination with midostaurin. Following SCT / consolidation chemotherapy, patients were managed with midostaurin maintenance for up to 12 months. The primary outcome was event-free survival analysed in two subgroups (age 18 to 60 years, and age 61 to 70 years). Interim analysis of the initial cohort of 145 patients enrolled in the study (32% of whom were >60 years of age) provided data with a median follow-up of 25.2 months. The event-free survival rate at two years was 35% for the whole cohort and 27% in those aged >60 years. Median event-free survival in the older group was 9.3 months. In those aged >60 years, approximately two thirds of patients achieved CR and SCT was received by 23%. Median OS in the full cohort was 24.7 months, and 15.5 months in those >60 years.[6]

Summary of evidence on comparative safety

In the RATIFY study 680 patients were included in the safety set, defined as patients who had received at least one dose of randomised treatment (midostaurin or placebo on day eight), 345 patients in the midostaurin group and 335 patients randomised to the placebo group.[6]

The median cumulative dose of randomised treatment was 4,150mg and 2,800mg in the midostaurin and placebo groups, respectively. Median relative dose intensities for each group were 95% for the study overall.[6]

All patients experienced at least one adverse event (AE) of any grade; grade ≥3 AEs were reported in all but one patient in the safety set. Events tended to occur in the induction and consolidation phases, and less frequently reported during maintenance.[6] These grade ≥3 AEs were reported in similar proportions of patients in each treatment group with the exception of rash / desquamation, occurring in 14% of midostaurin patients and in 7.6% of placebo patients.[8]

The most common grade ≥3 AEs were haematological; thrombocytopenia in 97% of patients in each group, neutropenia in 95% and 96% of midostaurin and placebo patients respectively, and anaemia in 93% and 88% respectively.[8]

Other common grade ≥3 AEs included febrile neutropenia (82% of patients in each group), infection (52% and 50% of midostaurin and placebo patients respectively), lymphopenia (19% and 22% respectively), diarrhoea (16% and 15%), hypokalaemia (14% and 17%) and pain (13% and 12%). Other grade ≥3 AEs which may impact on patients' quality of life such as fatigue, nausea and mucositis were reported in fewer than 10% of patients in the midostaurin group.[8]

Summary of clinical effectiveness issues

RATIFY demonstrated that the addition of midostaurin to standard intensive chemotherapy for AML was associated with a statistically significant improvement in OS (HR 0.79).[6] The Kaplan-Meier curves for both treatment groups plateaued around the time of median survival; survival estimates at landmarks better describe the magnitude of benefit for this outcome. Estimated survival rates at three and five years were 7% and 8% higher, respectively, in patients managed with midostaurin, a clinically important treatment effect. OS benefit was shown whether patients went on to receive SCT or not.

Aside from mortality benefits, midostaurin improved event-free survival, DFS, and risk of relapse (CIR), when compared with standard chemotherapy. It was relatively well tolerated, with the exception of a higher incidence of rash.

No health-related quality of life data were gathered in the RATIFY study.

An uncertainty of the study's findings was an apparent lack of effect (in terms of OS) in females (n=398, HR 1.01). The European Medicines Agency (EMA) noted that the difference may have been related to use of SCT and the difference in treatment effect was not observed in subgroup analyses of secondary outcomes, concluding that there was sufficient evidence of benefit of midostaurin in females. Any effect of patient sex is under investigation in ongoing clinical studies.[6]

The standard chemotherapy regimen employed in RATIFY closely resembles the "3+7" regimens advocated in European guidelines.[5, 8] British guidelines note that there is no evidence that cytarabine given for 10 days is superior to a 7-day course.[11]

The main limitation of the evidence with respect to generalisation to NHS Scotland is the recruitment of patients in RATIFY based on their age. Eligibility of patients for intensive chemotherapy induction / consolidation relates to their fitness, level of frailty, and not just their age. The phase II study provides supporting evidence of the effectiveness of midostaurin in an older cohort, but these are non-comparative data.

Clinical experts consulted by SMC advised that midostaurin is a therapeutic advancement due to the OS benefit when compared with standard chemotherapy.

As an oral treatment, there are unlikely to be implications with regard to administration of dosages. The introduction of midostaurin is likely to have service implications for the diagnostics services of the NHS. At present, only ITD mutations of FLT3 are screened for upon diagnosis (since this has prognostic implications for patients). With the availability of a targeted treatment for FLT3-mutated AML, regardless of mutation type, laboratories will need to also test for the TKD mutation, and also report results in time for commencement of midostaurin on the relevant day of the first induction cycle.

At the PACE meeting, it was noted that midostaurin is associated with modestly improved survival and a reduced risk of relapse, without any substantial increase in side effects when compared with intensive chemotherapy. Since it is well tolerated, midostaurin treatment is not expected to be detrimental to a patient's quality of life compared with standard intensive chemotherapy. Although the introduction of a maintenance phase, prolongs the treatment duration, oral treatment is convenient for patients. In addition the requirement for regular outpatient monitoring and dispensing of midostaurin is unlikely to be any more burdensome than the regular follow-up required in those who are in remission after intensive induction and consolidation treatment for AML.

Patient and clinician engagement

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of midostaurin as an ultra-orphan medicine in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- AML is a devastating disease with a particularly poor prognosis, and significant symptom burden such as fatigue, breathlessness, bleeding and bruising, fever / night sweats, musculoskeletal pain, infections, memory loss, loss of concentration, pruritus, and sleeping problems. In addition there are important emotional and financial stresses that have considerable impacts on patients, their families and carers.
- FLT3 mutation is associated with increased risk of relapse with standard treatment; patients are offered stem cell transplant where possible.
- There has been limited progress with regards to therapeutic advances in AML over the last couple of decades. Current therapies are extremely toxic and frequently require prolonged inpatient admission. At present there are no FLT3 targeted therapies available for this patient group.
- Midostaurin is associated with a modest improvement in overall survival and reduced risk of relapse, without substantial additional side effects, when compared with standard therapy. PACE participants spoke of the fear of relapse that patients, and their families, experience.
- There is unlikely to be a detrimental effect on quality of life since it is well tolerated, the oral dosage is convenient and treatment requires a modest increase in outpatient attendance during the maintenance phase when compared with routine care.
- It would be used in a relatively small cohort of the patient population; those with FLT3 AML who were not recruited to clinical studies.

Additional Patient and Carer Involvement
We received patient group submissions from Bloodwise and Leukaemia CARE. Both organisations are registered charities. Bloodwise has received 0.9% pharmaceutical company funding in the past two years, including from the submitting company. Leukaemia CARE has received 11.6% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Leukaemia CARE participated in the PACE meeting. The key points of both submissions have been included in the full PACE statement considered by SMC.

Value for money

The submitting company presented a cost-utility analysis comparing the use of midostaurin as induction, consolidation and maintenance therapy (for those achieving complete remission) to standard of care (SOC) induction and consolidation treatment with daunorubicin and cytarabine in AML FLT3 mutation-positive patients. Midostaurin was used in combination with SOC in the induction and consolidation treatment phases. The comparator is likely to be reasonable for some patients, but SMC clinical experts noted that patients are often treated as part of clinical studies.

A partitioned survival model over a lifetime (53-year) horizon was used. The model included the following health states: initial treatment, relapse, complete remission, SCT and death. The key clinical data (OS) used in the model were taken from the RATIFY study. The submitting company performed an age-adjustment to the OS data in an attempt to better reflect the likely age of patients who may be treated in clinical practice. This was achieved by using a pooled and weighted population from both

RATIFY and the single-arm, phase II study (NCT01477606). The analysis used propensity score matching to compare people in the phase 2 study (older population aged up to 70) with historical controls. The pooled population was weighted 59% to the older population of the phase II study population and 41% to the younger (RATIFY). To extrapolate the survival data in the model, a 'cure assumption' was applied such that the rate of death from the general population was used after the end of the trial data. This led to the initial gain in OS being maintained over the lifetime horizon. The use of SCT was estimated from RATIFY data.

Utility values in the model were taken from a variety of literature sources and were said to capture any treatment-related AEs eg values of 0.83, 0.53, and 0.759 were used for the remission, relapse and post-SCT recovery states respectively.

Costs in the model related to medicines acquisition costs, background disease management costs, costs of SCT and terminal care costs. Data from RATIFY were used to estimate midostaurin and SOC medicines costs and included dose reductions and treatment wastage and included up to 18 cycles of midostaurin monotherapy treatment. The analysis included the cost of FLT3-ITD testing. Background disease management costs were estimated from a survey conducted by the submitting company.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

In terms of results, the base case incremental cost-effectiveness ratio (ICER) with PAS was £18,481 per quality adjusted life year (QALY) compared to SOC. The majority of the QALY gain was achieved from the SCT state of the model and the key cost driver of the model was the cost of the midostaurin therapy itself (particularly the costs in the maintenance phase of treatment).

Extensive one-way (deterministic), probabilistic and scenario-based sensitivity analyses were provided. The key sources of upward sensitivity and associated ICERs are noted in the Table 4:

Table 4: key sensitivity analyses results

Scenario	Sensitivity analysis	ICER with PAS
1	SCT rate (use of confidence interval range)	£29,187
2	Post SCT utility; reduced to 0.68	£19,774
3	Complete remission utility; reduced to 0.75	£18,992
4	Removal of the age-adjustment factor for OS (ie use of RATIFY ITT data only)	£31,046
5	Assuming a mortality rate twice the rate of the normal population rate	£21,662
6	Use of a 'within trial' time horizon	£35,774
7	Use of a 10 year time horizon	£27,648
8	Age-adjustment of utility values	£19,290

ICER = incremental cost-effectiveness ratio, SCT = stem-cell transplant, OS = overal survival, ITT = intention to treat

A number of weaknesses and uncertainties with the analysis are noted:

- The results were very sensitive to the method used to adjust overall survival in an attempt to better reflect the older population in whom the treatment is likely to be used in practice. The method would appear to result in improved outcomes compared to use of the RATIFY study data alone. The SMC

statistician advised that there were a number of important weaknesses with the method of adjustment which adds uncertainty to the analysis. These included: the use of historical control patients spanning back to the 1990s and as such may not be reflective of current management; relatively small patient numbers in the elderly patient group; lack of robustness in the calculation of propensity scores; and the potential that the population weighting for the younger population should have been 54%. Use of the unadjusted RATIFY population increased the ICER to £31,046.

- The model used a 'cure assumption' and the results were sensitive to assuming that the rate of mortality was higher in the patient population compared to the background rate of mortality for the general population. SMC clinical experts indicated that it would be reasonable to expect a higher mortality rate than for the general population and therefore the base case ICER is likely to be an underestimate.
- The model structure does not appear to allow for the possibility of patients relapsing from the SCT health state, and SMC clinical experts have advised that relapse post-SCT is a valid clinical possibility. While the risk of relapse would apply to patients from both arms of the model entering the SCT state there was a higher rate of SCT in the midostaurin arm so the potential for over-estimation of outcomes could have greater impact on midostaurin. Additional analysis was provided by the company to address this aspect and it resulted in an increase in the ICER to £19,638
- The deterministic sensitivity analysis showed little impact on the ICER from changing utility values in the SCT states; this was a little surprising given that the majority of the QALY gains in the analysis were attributable to the SCT states. The company indicated the pattern of results is a consequence of the modelling structure with all SCT patients remaining in that state until death and also a very different OS curve between arms of the model (in favour of midostaurin). While this is noted as an explanation, given our concerns about the estimated OS gain, it reinforces the uncertainty with the predicted gains in the model.
- The analysis does not include costs related to TKD mutation testing. While this does not influence the ICER, the issue of testing has important implications for the service in terms of implementation.

The company provided additional analysis to show the combined impact of the key uncertainties or limitations in the analysis. This revised case used only data from the RATIFY study in patients with a higher mean age and applied a higher mortality rate, resulting in a with PAS ICER of £39,882. Adjusting the modelling to also include relapse post-SCT increased this combined ICER further to £42,579.

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

Impact beyond direct health benefits and on specialist services

At the PACE meeting, it was noted that patients are likely to be inpatients for a significant proportion of induction and consolidation phases of treatment whether they have standard intensive chemotherapy with or without midostaurin. The 12-month maintenance phase with midostaurin monotherapy would be managed on an outpatient basis with regular monitoring for full blood counts and remission status. When compared with the follow-up given to patients following standard induction and consolidation, this would be a modest increase in attendance and was not considered to be burdensome to patients.

Improvement in the outcomes of treatment for patients would have a positive effect on the emotional impact of AML on carers and family members.

Costs to NHS and Personal Social Services

The submitting company estimated there would be 18 patients eligible for treatment with midostaurin per year. The estimated uptake rate was 13.4% in year 1 (2 patients) and 67% in year 5 (12 patients).

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

The submitting company did not estimate any costs outside the NHS.

Conclusion

The Committee also considered the benefits of midostaurin in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied. In addition, as midostaurin is an ultra-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 modifiers, the Committee accepted midostaurin for use in NHS Scotland.

Additional information: guidelines and protocols

The European LeukemiaNet (ELN) consensus guidance Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel was published in November 2016.[5] The guidance recommends that patient diagnostic work-up "should include screening for mutations in FLT3 (both for internal tandem duplications [ITD] together with data on the mutant-to-wild type allelic ratio,57-60 and tyrosine kinase domain [TKD] mutations at codons D835 and I836); activating mutations of FLT3 are not only prognostic, but may beneficially be affected by tyrosine kinase inhibition." The guidance also includes a recommendation based on the results of the RATIFY study and recommends that "patients with FLT-mutated AML may be considered to receive intensive chemotherapy in combination with midostaurin." Standard intensive induction chemotherapy is recommended to comprise seven days of cytarabine continuous infusion (100 to 200mg/m^2) and three days of anthracycline (eg daunorubicin 60mg/m^2). Consolidation therapy recommended in the guidelines include allogeneic SCT (adverse- or intermediate-risk genetics), or between two and four cycles of intermediate dose cytarabine.[5]

The European Society for Medical Oncology (ESMO) published guidance titled "Acute myeloblastic leukaemias in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in August 2013.[3] The ESMO guidance recommends cytogenetic and molecular genetic testing as part of the diagnostic work-up of AML. The guidance also recommends that "induction chemotherapy should include an anthracycline and cytarabine with the particularly well-known and time-honoured '3+7' regimen…Consolidation therapy in AML is warranted once patients have reached clinical and haematological remission. There is no consensus on a single 'best' post-remission treatment." ESMO guidance was published in 2013, predates the availability of midostaurin and thus no recommendations regarding its use are made.[3]

Additional information: comparators

Midostaurin would be given in addition to existing intensive chemotherapy regimens (eg daunorubicin and cytarabine). The cost table below includes schedules used in the RATIFY study and schedules used in the UK based on AML study protocols.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
midostaurin	**Induction (21-day cycle)** **50mg orally twice daily on days 8 to 21**	**5,610**
	Consolidation (28-day cycle) **50mg orally twice daily on days 8 to 21**	**5,610**
	Maintenance (28-day cycle) **50mg orally twice daily on days 1 to 28**	**11,220**
daunorubicin cytarabine (RATIFY)	Induction (21-day cycle) daunorubicin 60mg/m^2 IV on days 1 to 3 cytarabine 200mg/m^2 IV on days 1 to 7	1,307
	Consolidation (28-day cycle) cytarabine 3g/m^2 IV twice daily on days 1, 3 and 5	215
daunorubicin cytarabine (AML studies)	Induction Cycle 1 daunorubicin 60mg/m^2 IV on days 1 to 3 cytarabine 100mg/m^2 IV twice daily on days 1 to 10 Cycle 2 Daunorubicin 50mg/m^2 IV on days 1 to 3 Cytarabine 100mg/m^2 IV twice daily on days 1 to 8	Cycle 1 1,365 Cycle 2 1,131
	Consolidation cytarabine 3g/m^2 IV twice daily on days 1, 3 and 5	215

Doses are for general comparison and do not imply therapeutic equivalence. Costs for midostaurin from eMC Dictionary of Medicines and Devices Browser on 02 May 2018, all other costs from the BNF on 02 February 2018. Costs calculated using the full cost of vials / ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

References

1. Novartis Europharm Limited. Summary of product characteristics - midostaurin (Rydapt) 25mg soft capsules. 25 October 2017 [cited 22 January 2018]; Available from: www.ema.europa.eu.
2. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995- . Record No. 114798, Acute myeloid leukemia (AML); [updated 09 Jan 2018]; [about 25 screens]. Available from http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=114798. Registration and login required. [cited 22 January 2018].
3. Fey MF, Buske C, on behalf of the EGWG. Acute myeloblastic leukaemias in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013;24 Suppl 6:vi138-43.
4. ISD Scotland. Cancer Statistics. Acute myeloid leukaemia: ICD-10 C92.0. Annual incidence. [cited 22 January 2018]; Available from: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Leukaemias/#myeloid.
5. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T*, et al.* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-47.
6. European Medicines Agency. Assessment Report: Rydapt (EMA/CHMP/516229/2017). 2017 20 July 2017 [cited 23 January 2018]; Available from: www.ema.europa.eu.
7. ISRCTNregistry. AML17: a programme of treatment development in younger patients with Acute Myeloid Leukaemia and high-risk myelodysplastic syndrome. [cited 05 February 2018]; Available from: http://www.isrctn.com/ISRCTN55675535.
8. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD*, et al.* Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377:454-64.
9. Protocol in acute myeloid leukemia with FLT3-ITD (NCT01477606). 11 September 2017 [cited 31 January 2018]; Available from: www.clinicaltrials.gov.
10. Schlenk RF, Fiedler W, Salih HR, Wulf G, Thol F, Kundgen A*, et al.* Impact of age and midostaurin-dose on response and outcome in acute myeloid leukemia with FLT3-ITD: Interim-analyses of the AMLSG 16-10 trial. Blood Conference: 58th Annual Meeting of the American Society of Hematology, ASH. 2016;128(22).
11. British Committee for Standards in Haematology, Milligan D, Grimwade D, Cullis J, Bond L, Swirsky D*, et al.* Guidelines on the management of acute myeloid leukaemia in adults. Br J Haematol. 2006;135:450-74.

This assessment is based on data submitted by the applicant company up to and including 16 March 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

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

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order

to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

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

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