Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2252

gilteritinib 40mg film-coated tablets (Xospata®)

Astellas Pharma Ltd

7 August 2020

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

ADVICE: following a full submission assessed under the end of life and orphan medicine process.

gilteritinib (Xospata®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia with a FLT3 mutation.

In an open-label, phase III study, gilteritinib improved overall survival compared with salvage chemotherapy in patients with relapsed or refractory acute myeloid leukaemia with a FLT3 mutation.

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

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

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia with a FLT3 mutation.[1]

Dosing Information

Before taking gilteritinib, relapsed or refractory acute myeloid leukaemia patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test.

The recommended starting dose of gilteritinib is 120mg (three 40mg tablets) orally once daily, swallowed whole, with or without food. In the absence of a response after 4 weeks of treatment, the dose can be increased to 200mg (five 40mg tablets) once daily if tolerated or clinically warranted. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response.

Treatment should be initiated and monitored by a physician experienced in the use of anticancer therapies.

See summary of product characteristics (SPC) for further information including dose modification for special circumstances and monitoring.[1]

Product availability date

October 2019

Gilteritinib has been designated an orphan medicine by the European Medicines Agency (EMA) for the treatment of acute myeloid leukaemia. It also meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Acute myeloid leukaemia is a rare and aggressive malignancy of the blood and bone marrow. It is characterised by differentiation and proliferation of malignant, abnormal myeloid progenitor cells, which accumulate in the bone marrow and suppress the production of normal blood cells. Approximately 30% of acute myeloid leukaemia patients have an FMS-like tyrosine kinase 3 (FLT3) mutation in whom prognosis is generally poorer. Gilteritinib is an oral protein kinase inhibitor which acts to block FLT3. It also inhibits tyrosine kinase AXL which has been implicated in FLT3 inhibitor resistance.[1, 2]

The evidence comes from the open-label, randomised, phase III study, ADMIRAL, in 371 patients with relapsed or refractory acute myeloid leukaemia. Eligible patients were aged ≥18 years with acute myeloid leukaemia refractory to one or two cycles of anthracycline-based chemotherapy or haematologic relapse after a complete remission. In addition, patients were required to have centrally assessed FLT3 mutations (FLT3 ITD or FLT3 TKD D835 or FLT3 I836). Patients were randomised, in a ratio of 2:1, to receive gilteritinib (120mg orally daily) or salvage chemotherapy. The gilteritinib dose could be increased to 200mg daily in patients who did not achieve a composite complete remission. Salvage chemotherapy comprised one of four regimens preselected by the investigator. This included two high-intensity regimens: mitoxantrone, etoposide and cytarabine (MEC) or fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin (FLAG-IDA); and two low-intensity regimens: low dose-cytarabine or azacitidine. Responding patients could have a transplant and those in the gilteritinib group could restart treatment 30 to 90 days after successful haematopoietic stem cell transplant (HSCT).[1, 3]

There were two primary outcomes: overall survival (defined as the time from randomisation to death due to any cause) and the rate of complete remission or complete remission with partial haematological recovery (see table 1 footnote for definition). Analysis was performed in the intention to treat (ITT) population, which included all randomised patients with the final analysis performed after 258 deaths had occurred (data cut-off September 2018). The study used a hierarchical statistical testing strategy with no formal testing of outcomes after the first non-significant outcome in the hierarchy.[2, 3]

At the final analysis (September 2018), median overall survival and complete remission or complete remission with partial haematological recovery were significantly longer in the gilteritinib group compared with the salvage chemotherapy group. The first key secondary outcome, event-free survival (defined as freedom from treatment failure or death) was not significantly different between treatment groups. Following the hierarchical statistical testing strategy, no formal testing of subsequent outcomes, including complete remission and duration of remission, were performed and results reported are descriptive only and not inferential (no p-values reported). Details are presented in table 1 below.

Table 1: Primary and key secondary outcomes in the intention to treat population of the ADMIRAL study at final analysis (September 2018)[2, 3]

	Gilteritinib (n=247)	Salvage chemotherapy (n=124)	Hazard ratio/ difference (95% CI)
Overall survival			
Median follow-up for overall survival analysis	17.8 months		
Deaths (n)	171	90	
Median overall survival	9.3 months	5.6 months	0.64 (0.49 to 0.83), p<0.001

Estimated survival rate at 12 months	37%	17%	
Estimated survival rate at 24 months	19%	14%	
Complete remission or complete remission with partial haematologic recovery (CR/CRh)			
CR/CRh, % (n/N)	34% (84/247)	15% (19/124)	19% (9.8 to 27)
Secondary outcomes			
Events (relapse, treatment failure death) (n)	189	62	
Event-free survival	2.8 months	0.7 months	0.79 (0.58 to 1.09)
Complete remission rate, % (n/N)	21% (52/247)	10% (13/124)	11% (2.8 to 18)

HR = hazard ratio, CI = confidence interval, KM = Kaplan-Meier, CR/CRh = complete remission and complete remission with partial hematological recovery; Complete remission (CR) = absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukaemia; complete remission with partial haematologic recovery (CRh) = marrow blasts <5%, partial haematologic recovery absolute neutrophil count ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.

Other secondary outcomes included duration of complete remission, which was longer in the gilteritinib group compared with the salvage chemotherapy group (median 14.8 months versus 1.8 months).[2]

During the study, 26% (63/247) of gilteritinib patients and 15% (19/124) of salvage chemotherapy patients underwent transplantation. When overall survival analysis was censored at the point of transplantation, the median overall survival remained longer in the gilteritinib compared with the salvage chemotherapy group (8.3 months versus 5.3 months; hazard ratio 0.58 [95% CI:0.43 to 0.76]). In the subgroup of transplanted patients, median overall survival was 19.9 months and not estimable respectively; hazard ratio 1.33 (95% CI: 0.55 to 3.22). [2-4]

A number of patient-reported outcomes were assessed as exploratory outcomes. The severity of fatigue was assessed using the Brief Fatigue Inventory (BFI); general health related quality of life was assessed using the EuroQol Group 5-Dimension (EQ-5D); the severity of dyspnoea was assessed using the Functional Assessment of Chronic Illness Therapy-Dyspnea Short Forms (FACIT-Dys-SF) and the leukaemia-specific signs and symptoms were assessed using the Functional Assessment of Cancer Therapy - Leukaemia (FACT-Leu) total score and dizziness and mouth subscales. There were similar changes from baseline to day 1 of cycle 2 in the gilteritinib and salvage chemotherapy groups in terms of BFI, FACIT-Dys-SF and FACT-Leu. The median change from baseline to day 1 of cycle 2 in the EQ-5D-5L visual analogue scale (VAS) score was 0 in the gilteritinib group and -3.0 in the salvage chemotherapy group.[2]

The company submission included brief details of a naïve, unadjusted indirect comparison of overall survival for gilteritinib with best supportive care. This included two studies; the ADMIRAL

study and a retrospective analysis of data from 393 patients on further treatment following first relapse anthracycline-based chemotherapy. The company assumed that the salvage chemotherapy group of the ADMIRAL study (high and low-intensity) (n=124) had similar efficacy to the low-dose cytarabine group of the Sarkozy study (n=48) and calculated a hazard ratio for best supportive care versus gilteritinib of 2.86.[3, 5]

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

Summary of evidence on comparative safety

In the ADMIRAL study, the median duration of treatment was longer in the gilteritinib group (18 weeks) compared with the salvage chemotherapy group (4 weeks). Any treatment-emergent adverse event (AE) was reported by 100% (246/246) of patients in the gilteritinib group and 98% (107/109) in the salvage chemotherapy group and these were treatment-related in 84% and 65% respectively. In the gilteritinib and salvage chemotherapy groups respectively, patients reporting a grade 3 or higher treatment-emergent AE were 96% versus 86%, and these were treatment-related in 62% and 52% of patients respectively. A serious treatment-emergent AE was reported in 83% of gilteritinib patients and 31% of salvage chemotherapy patients and these were treatment-related in 36% and 15% of patients respectively. Treatment-emergent AEs led to discontinuation of study treatment in 24% of gilteritinib patients and 12% of salvage chemotherapy patients, 11% and 4.6% of patients respectively had treatment-related AEs which led to discontinuation.

The most frequently reported AEs of any grade in the gilteritinib group versus the salvage chemotherapy group respectively were: anaemia (47% versus 35%), febrile neutropenia (47% versus 37%), pyrexia (43% versus 29%), alanine aminotransferase increased (42% versus 9.2%), aspartate aminotransferase increased (40% versus 12%), diarrhoea (33% versus 29%), constipation (31% versus 15%), hypokalaemia (29% versus 31%), cough (29% versus 10%), fatigue (28% versus 13%) decreased platelet count (23% versus 26%) and thrombocytopenia (26% versus 17%).[2, 3]

In the gilteritinib group, 4.9% of patients had a prolonged corrected QT interval and the SPC recommends that an electrocardiogram should be performed before and during treatment.[1, 3]

Gilteritinib has also been associated with differentiation syndrome which involves rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. The SPC includes details for management.[1, 2]

Summary of clinical effectiveness issues

Treatment of acute myeloid leukaemia aims to induce a clinical remission and prevent relapse and HSCT is the only curative option. Intensive induction chemotherapy is the initial treatment in sufficiently fit patients but approximately 30% of adult acute myeloid leukaemia patients are refractory to induction therapy and of those who achieve a complete remission, approximately 75% will relapse. The 5-year survival after first relapse is approximately 10%. Around 30% of acute myeloid leukaemia patients have a mutation of the FLT3 gene, which is associated with a higher risk of relapse and lower survival. The first generation FLT3 inhibitor, midostaurin, has been licensed and accepted for use by SMC for the first-line treatment of acute myeloid leukaemia patients with FLT3 mutation in combination with intensive induction chemotherapy. There is currently no standard of care for relapsed or refractory acute myeloid leukaemia with FLT3 mutations and patients are managed within a clinical study, with salvage chemotherapy or best supportive care. Gilteritinib is the first medicine to be licensed for the treatment of relapsed or refractory acute myeloid leukaemia in patients with FLT3 mutation. Prevalence is estimated to be approximately 1.4 per 10,000 in Europe. Gilteritinib meets SMC orphan and end of life criteria. Clinical experts consulted by SMC considered that there is an unmet need for effective treatments for this patient population.

The ADMIRAL study provides evidence of significantly improved overall survival and complete remission rates with full or partial haematologic recovery with gilteritinib compared with salvage chemotherapy in patients with relapsed or refractory acute myeloid leukaemia with FLT3 mutation. The median absolute survival benefit of 3.7 months was considered clinically relevant by the EMA given the poor prognosis in this patient population. Subgroup analyses suggested a consistent treatment effect across several prognostic factors such as age, response category to first line therapy, acute myeloid leukaemia risk score, and for patients eligible for low (39%) and high intensity (61%) treatment. In the small subgroup of patients who had received a previous FLT3 inhibitor (n=46), median overall survival numerically favoured gilteritinib (hazard ratio 0.70 [95% CI: 0.35 to 1.44]); in those who had not received a previous FLT3 inhibitor (n=325), the hazard ratio was 0.62 (95% CI: 0.47 to 0.82). The ADMIRAL study found no significant difference between the treatment groups in event-free survival and further statistical analysis was stopped. More patients in the gilteritinib than salvage chemotherapy groups (26% versus 15%) were able to have HSCT. Initial outcomes were considered generally similar but the survival data are limited by the small numbers of patients and the effects of continued treatment with gilteritinib post-HSCT are unclear (63% [40/63] of transplanted patients continued to take gilteritinib).[2, 3]

There were a number of limitations in the study including its open-label design, which the EMA considered acceptable given the differences in administration of the gilteritinib and the different salvage chemotherapy regimens. However, this may have introduced potential bias in subjective outcomes and in safety. Most of the patients in the salvage chemotherapy group, particularly those in the high-intensity group, finished study treatment after two cycles. Therefore the duration of follow-up for remission was shorter than in the gilteritinib-treated patients and the

results for duration of remission in salvage chemotherapy group are less robust (the 95% CI around the median could not be estimated). Patient reported outcomes were assessed as exploratory outcomes and found similar results in both treatment groups. However, some of the assessments were not disease-specific and may not have been sensitive enough to measure the treatment effect.[2, 3]

There were some differences between the ADMIRAL study population and patients likely to be treated in practice, which may affect the generalisability of the study results. Study patients were considered refractory if they had received one or two cycles of induction therapy and this differs from the European guidelines, which recommends two cycles. More study patients classified as primary refractory (62% [90/146]) had only received one cycle of high-intensity chemotherapy and may affect the generalisability of study results to patients who may have received two cycles in practice. Midostaurin may be used as part of first-line treatment but in ADMIRAL, only 12% of patients had received previous FLT3 inhibitor treatment and the results may be less generalisable to a population in which midostaurin is more widely used. However, subgroup analysis suggests a similar treatment effect in those who have and who have not received a previous FLT3 inhibitor. The majority of study patients (84%) had good performance status (ECOG 0 or 1) and it is unclear if the study results would be generalisable to those who are less fit.

The ADMIRAL study provides direct comparison with salvage chemotherapy regimens likely to be used in practice. Evidence versus best supportive care, also considered a relevant comparator, was based on the result of the naïve indirect comparison. However, the lack of a search strategy, the methods used and differences between the studies and their populations, (particularly only 7.4% of the retrospective analysis patients having FLT3 mutation) make the result highly uncertain.

The introduction of gilteritinib would offer the first licensed medicine for the treatment of relapsed or refractory acute myeloid leukaemia in patients with FLT3 mutation. In comparison to current active treatment options, mainly salvage chemotherapy, gilteritinib improved overall survival. In addition, it offers the convenience of oral administration, allowing patients to be treated at home, compared with the multiple injections needed for the salvage chemotherapy regimens. Clinical experts consulted by SMC considered that gilteritinib was a therapeutic advancement due to increase in overall survival, and would replace salvage chemotherapy either as palliative care or as a bridge to transplant for a small number of suitable patients.

Patient and clinician engagement (PACE)

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

The key points expressed by the group were:

- Relapsed or refractory AML is a devastating disease with a poor prognosis, and significant symptom burden. Symptoms include: fatigue, breathlessness, bleeding and bruising, fever / night sweats, musculoskeletal pain, infections, memory loss, loss of concentration, pruritus, and sleeping problems. FLT3 mutation positive AML is present in around 30% of patients and is associated with poorer prognosis.
- There is an unmet need for effective personalised treatments for relapsed or refractory AML with FLT3 mutation. Current conventional salvage chemotherapy is associated with considerable toxicity and poor response.
- Gilteritinib is the first medicine to be licensed for patients with relapsed or refractory FLT3 mutation positive AML and offers a survival benefit over salvage chemotherapy.
- Gilteritinib should allow a higher number of suitable patients to proceed to potentially curative transplant compared with conventional salvage chemotherapy.
- As the first targeted therapy for these patients, gilteritinib has a more favourable toxicity profile than conventional salvage chemotherapy. Gilteritinib may offer patients a better quality of life and more time at home with their families.
- It is an oral therapy which can be administered as an outpatient treatment with less impact on health care resources than conventional salvage chemotherapy regimens**.**

Additional Patient and Carer Involvement

We received a patient group submission from Leukaemia CARE, which is a registered charity. Leukaemia CARE has received 14.3% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from Leukaemia CARE participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing gilteritinib to salvage chemotherapy and best supportive care (BSC) in the licensed indication population. The four salvage chemotherapy comparators were low-dose cytarabine, azacitidine, MEC, and FLAG-Ida. As the sample size of the clinical study was powered to detect a difference in clinical benefits between gilteritinib and the

overall salvage chemotherapy arm, the base case results were presented for a 'weighted comparator'. Weights for the four salvage treatments were based on the ADMIRAL study.

The economic model presented was a hybrid decision tree and partitioned survival model. All patients entered the model under the 'treatment without HSCT' state. The decision tree component was used to stratify a proportion of patients who subsequently received HSCT. A three state partitioned survival model was applied to both the treatment with and without HSCT groups. The partition model predicted the long-term survival status of patients conditional on HSCT status. A lifetime horizon (40 years) was used.

Clinical evidence informing the base case analysis was obtained from the ADMIRAL study. This included parameters for overall survival and event-free survival (EFS) for those without HSCT, post-progression treatment, time to HSCT, resource use, adverse event risks and patient utilities. For the 'with HSCT' patients, post-transplant EFS and overall survival was estimated using data from a published study that was not specific to the target patient population.[6] A naïve indirect comparison was performed to determine comparative efficacy against BSC. Patients who remained alive in the model at year three were considered to be effectively cured. These patients were assumed to have no further risk of relapse but were associated with a higher risk of death (standardised morality ratio of two).

The utility values used in the economic model were based on the ADMIRAL study (EQ-5D-5L cross-walked to EQ5D-3L). Adverse event disutilities were also included, as was a disutility associated with the six-month period following HSCT.

Medicine acquisition and administration costs for gilteritinib and all comparators were included in the analysis as were monthly costs of medical care (e.g. outpatient visits, emergency visits, diagnostic procedures, laboratory tests, transfusions), monthly hospitalisation cost by regimen (before relapse/progression), one-off cost for terminal care, HSCT and FLT3 mutation testing. Post-progression treatment costs related to medicines acquisition and administration, hospitalisation, and complications were also applied.

A simple Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a discount is offered on the price of the medicine. A PAS discount is in place for azacitidine and this was included in the results used for decision-making by using estimates of the comparator PAS price. As such, the results reflecting the weighted average comparator and the individual comparison against azacitidine can only be presented using list prices for all medicines.

The base case analysis presented by the submitting company produced an incremental cost-effectiveness ratio (ICER) of £77,818 per quality-adjusted life-year (QALY) against the weighted comparator and £74,814 against azacitidine. The company also presented cost-effectiveness results against individual comparators and BSC, which are presented in table 3 below:

Table 3: Base case cost effectiveness results against individual comparators at PAS price

Treatment	ICER (£/QALY)
gilteritinib	-
FLAG_IDA	47,277
MEC	48,543
low-dose cytarabine	52,943
BSC	35,645

Table 5: Selected sensitivity analyses results vs weighted comparator

	Scenario	ICER (£/QALY) (list price)
	Base case	*77,818*
1	No HSCT for all treatments	179,737
2	Subsequent HSCT rate - comparators (upper 95% CI)	106,097
3	Subsequent HSCT rate - gilteritinib (lower 95% CI)	104,676
4	Only HSCT for patients who achieved composite complete remission	72,073
5	Alternative gilteritinib OS curve (without HSCT) – Weibull	115,066
6	Time Horizon: 20 years	85,986
7	Alternative Health State Utility Input Source - Joshi 2019	82,583
8	Treatment wastage – 7 days	80,842
9	Including BSC in weighted comparator	74,916
10	Assume earlier cure point – 2 years	84,908
11	Assume later cure point – 5 years	92,212
12	ADMIRAL data for HSCT OS with 3 year cure point	104,066
13	ADMIRAL data for HSCT OS with 2 year cure point	63,624

Table 6: Selected sensitivity analyses results vs BSC

	Scenario	ICER (£/QALY) (PAS price)
	Base case	*35,645*
1	No HSCT for all treatments	82,390
2	Subsequent HSCT rate - gilteritinib (lower 95% CI)	40,182
3	Only HSCT use for patients who achieved composite complete remission	39,106
5	Alternative gilteritinib OS curve (without HSCT) – Weibull	41,780
6	Time Horizon: 20 years	39,196

7	Alternative health state utility input source - Joshi 2019	37,924
8	Treatment wastage – 7 days	36,533

There were a number of limitations with the analysis which include the following:

- The population in the key clinical study may not be reflective of patients seen in clinical practice due to the expected uptake of midostaurin. In ADMIRAL, 13% of the gilteritinib group and 11.3% of the salvage chemotherapy had received prior FLT3 inhibitors. Whether prior exposure to midostaurin would affect response to gilteritinib is uncertain. If the proportion of patients being treated first with midostaurin is greater in clinical practice then the efficacy of gilteritinib may be different to that observed in the trial. Generalisability is of further concern in this case because patients on gilteritinib were more likely to be eligible for HSCT. Scenario analysis showed that the model was sensitive to the rate of patients going on to receive HSCT, with a rate lower than that observed in ADMIRAL having a significant increase in ICER.
- The assumption of the 3-year cure point, whilst plausible, is not based on any evidence from the clinical study. The cure point impacts on the extrapolation of overall survival and EFS by limiting parametric curves to three years. The length of the cure point is a driver of cost-effectiveness, with scenario analysis showing changing this assumption to 2-years leads to a nearly 19% decrease in the ICER. The company believes that a cure point of 18-24 months is realistic based on evidence from the wider literature and a post-hoc analysis of the mature ADMIRAL data indicated a cure point of 22 months for those patients who underwent a transplant. However it is unclear if this timeline represents an optimistic scenario.
- The use of external data to model survival for patients receiving HSCT is problematic as patients in the Evers et al study[6] did not all have FLT3 mutations and therefore were not totally representative of patients eligible for gilteritinib. The ADMIRAL data were immature and unreliable due to limited follow up. Applying the ADMIRAL data to the post-HSCT group led to a substantial rise in the ICER. The latest analysis of the ADMIRAL data reporting two year follow-up found that survival was similar to that of Evers et al[6], but still had an upward influence on the ICER.
- It was assumed that gilteritinib would be used as maintenance therapy after HSCT and the model attributed an additional survival benefit of maintenance therapy to patients after HSCT. A hazard ratio was calculated via an indirect comparison between ADMIRAL data and data from Evers et al[6], which was then applied to the model predicting overall survival for the with HSCT group. An updated analysis based on mature survival data from ADMIRAL had an upward influence on the ICER.
- BSC is a relevant comparator but the indirect comparison used to determine its relative efficacy was not reliable. There is additional uncertainty about whether BSC should be included as part of the blended comparator, but this would be contingent on being able to address concerns regarding estimating comparative efficacy.
- The costs of gilteritinib and chemotherapy were applied as one-off costs in the first cycle of the model only. This was done for simplicity since the mean treatment durations for chemotherapy patients were one to two months. This deviates from generally accepted practice of applying costs at each cycle and has implications in terms of inaccurate discounting and treatment

duration not being linked to progression. However, costs are not a key driver of the model. Some concerns were expressed by the NDC in relation to the face validity of the utility values used in the model in terms of them being optimistic. Alternative values were used in a sensitivity analysis.

The Committee also considered the benefits of gilteritinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission and the potential to bridge to a definitive therapy. In addition, as gilteritinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

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

Additional information: guidelines and protocols

Current guidelines pre-date the availability of gilteritinib for the treatment of FLT3 mutation positive relapsed or refractory acute myeloid leukaemia.

The European LeukemiaNet (ELN) consensus guidance Diagnosis and management of acute myeloid leukaemia in adults: 2017 ELN recommendations from an international expert panel was published in November 2016. The ELN notes that in relapsed and primary refractory patients, poorer outcomes are associated with shorter duration of first complete remission, increased age, nonfavourable karyotype and history of previous HSCT. Since no standard chemotherapy regimen has emerged, the guidance recommends that patients should be entered into a clinical trial whenever possible. The guidance also provides details of a number of possible salvage chemotherapy regimens. There are no recommendations for relapsed or refractory acute myeloid leukaemia patients who have a FLT3 mutation.[7]

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. This recommends that for carefully selected refractory patients with a human leukocyte antigen (HLA) matched donor, an allogenic stem cell treatment may be offered, despite the limited chance of success. In patients who were not found to be suitable, the guideline suggests best supporting care or palliative systemic treatment be offered. For patients with relapse after a first remission, intensive re-induction may be offered and the chances of success are better after longer duration of first remission. Patients in second or subsequent remission may still qualify for allogeneic HSCT with a family or unrelated HLA-matched donor, or with cord blood derived stem cells. There are no recommendations for relapsed or refractory acute myeloid leukaemia patients who have a FLT3 mutation.[8]

Additional information: comparators

Clinical study, salvage chemotherapy regimens and best supportive care.

List price of medicine under review

Medicine	Dose Regimen	Cost per 28 days (£)
gilteritinib	**120mg orally once daily**	**14,188**

Costs from BNF online on 3 February 2020. Costs do not take any patient access scheme into consideration.

Additional information: budget impact

The submitting company estimated there would be 27 patients eligible for treatment with gilteritinib in each year. The estimated uptake rate was 40% in year 1 and 70% in year 5 with a discontinuation rate of 0% applied each year. This resulted in 11 patients estimated to receive treatment in year 1 rising to 19 patients in year 5.

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.

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

References
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This assessment is based on data submitted by the applicant company up to and including 12 March 2020.

**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*

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

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

Advice context:

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

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