Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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venetoclax, 10mg, 50mg and 100mg film-coated tablets (Venclyxto®)

SMC No. (1249/17)

AbbVie Ltd

07 July 2017

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 end of life and orphan medicine process

venetoclax (Venclyxto®) is accepted for use within NHS Scotland.

Indication under review: as monotherapy for the treatment of chronic lymphocytic leukaemia (CLL):

- in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.
- in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

In phase II, non-comparative studies of patients with relapsed / refractory CLL, treatment with venetoclax was associated with clinically meaningful overall response rates.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of venetoclax. 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.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Published 07 August 2017

Indication

As monotherapy for the treatment of chronic lymphocytic leukaemia (CLL):

- in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.
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Dosing Information

The starting dose is 20mg of venetoclax once daily for seven days. The dose must be gradually increased over a period of five weeks up to the recommended daily dose of 400mg as described in the summary of product characteristics. Patients should swallow the tablets whole with water at approximately the same time each day. The tablets should be taken with a meal to reduce the risk of lack of efficacy.

The 5-week dose-titration schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of tumour lysis syndrome. Please refer to summary of product characteristics for advice on the prevention and management of tumour lysis syndrome associated with venetoclax.

Treatment should be continued until disease progression or no longer tolerated by the patient.

Treatment with venetoclax should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.[1]

Product availability date

01 January 2017

Venetoclax received a positive scientific opinion for the above indication under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 23 August 2016.

Venetoclax has been designated as an orphan medicine by the European Medicines Agency (EMA) and also meets SMC end-of-life criteria.

Venetoclax has conditional marketing authorisation from the EMA.

Summary of evidence on comparative efficacy

Venetoclax is a selective inhibitor of the B-cell lymphoma-2 (Bcl-2) protein. Bcl-2 is an anti-apoptotic protein which is commonly over-expressed in chronic lymphocytic leukaemia (CLL) cells and Bcl-2 mediates tumour cell survival and chemotherapy resistance. Inhibition of Bcl-2 triggers apoptosis, programmed cell death.[1, 2]

There are no directly comparative efficacy data. Key evidence for venetoclax in CLL is from two open-label, multicentre, non-comparative phase II studies, M13-982 and M14-032.[2-4]

M13-982 recruited adults with relapsed and/or refractory (to at least one line of therapy) CLL with 17p deletion and clinically measurable disease. Patients were required to have adequate coagulation, renal, hepatic and bone marrow function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. All patients received venetoclax orally once daily until disease progression, unacceptable toxicity or other reasons as specified in the protocol. The dose of venetoclax was titrated at weekly intervals over four to five weeks from 20mg to 400mg daily (as per the licensed dosage regimen). Protocol-specified strategies to prevent and manage tumour lysis syndrome were implemented dependent upon assessment of patient's underlying risk. These included: adequate hydration, regular laboratory monitoring, initiation of allopurinol or other uric acid-reducing agent for up to five weeks, hospital admission prior to dose titration (risk dependent); dialysis facilities were required to be available. In addition to the main cohort of patients (n=107), a safety expansion cohort (n=51) was also recruited.[2, 4]

The primary outcome was the overall response rate (ORR) assessed by independent review committee, and the primary analysis was conducted in the first 70 enrolled patients in the main cohort who had received at least one dose of venetoclax and who had a tumour staging assessment after 36 weeks. At the April 2015 data cut-off (median duration of therapy: 12.1 months) for the primary analysis, the ORR was 77% (54/70).[4] Results of secondary outcomes assessed in the full study population at later data cut-off dates are presented in Table 1 below.

Table 1: Secondary outcomes from study M13-982[2, 5]

Outcome[#]	**Full study population (n=158)***
Investigator-assessed ORR	77% (122/158)
Median duration of response	26.5 months
Minimal residual disease negative (peripheral blood)	24% (38/158)
Median investigator-assessed PFS	27.2 months (number of events not reported)
12-month survival (Kaplan meier estimate June 2015)	87%

[#]January 2016 data cut-off date unless specified. *includes data from main cohort and safety extension cohort. ORR = overall response rate. PFS = progression-free survival.

Health-related quality of life (HrQoL) data were collected as exploratory endpoints. Several tools were used including the M.D. Anderson Symptom Inventory (MDASI), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30), the EORTC QLQ CLL16 questionnaire, and the EuroQol 5-dimension (EQ-5D) generic instrument.[2] For all time-points, the mean changes from baseline for both scales of the MDASI (symptom severity and symptom interference) did not exceed the minimally important difference of 0.98 points.[5] Changes from baseline in global health status, fatigue, emotional functioning, role functioning and social functioning as measured by EORTC QLQ-C30 were considered to be clinically important based on the minimum change threshold of five points.[6] Clinically important changes in fatigue, future health worries,[6] disease symptoms and social problems[5] were also captured by the EORTC QLQ CLL16 questionnaire. Improvements in the EQ-5D score and visual analogue scale scores were also observed.[5]

M14-032 is an ongoing phase II, multi-centre, non-randomised study that recruited patients with CLL with an indication for treatment and who had developed refractory or relapsed disease after B-cell receptor pathway inhibitor treatment (eg ibrutinib or idelalisib). Patients had ECOG performance status of 0, 1, or 2, adequate bone marrow-function, coagulation, renal and hepatic function. All patients received venetoclax which was titrated at weekly intervals from 20mg daily to 400mg daily. The study included a main cohort (n=64) of whom 43 had most recently failed ibrutinib treatment and 21 had most recently failed idelalisib therapy. There is a safety expansion cohort; no efficacy outcome data for this cohort were presented.[2, 3]

The primary outcome of the study was ORR, measured up to two years after the last patient was enrolled in the study. This was assessed by the local investigator. ORR by independent review committee (IRC) was supportive. Results for ORR in the main cohort (by most recent B-cell receptor inhibitor) at the most recent data cut-offs are presented in Table 2. Median time on study at the February 2016 cut-off was 9.3 months and 5.6 months in the ibrutinib failure and idelalisib failure subgroups respectively. At the June 2016 cut-off, the respective median times on study were 12.4 months and 9.3 months.[2, 3]

Table 2: Tumour responses in study M14-032 in the main cohort.[2]

		ORR % (complete remission rate %)	
		February 2016	**June 2016**
Ibrutinib failure (n=43)	Investigator-assessed	60% (4.7%)	67% (7.0%)
	IRC-assessed	70% (2.3%)	70% (2.3%)
Idelalisib failure (n=21)	Investigator-assessed	33% (9.5%)	57% (14%)
	IRC-assessed	48% (0)	62% (0)

ORR = overall response rate, IRC = independent review committee.

The ORRs in subgroups defined by presence of 17p deletion or *TP53* mutation (June 2016 data cut-off) were similar in magnitude to the ORRs in the main cohort. In patients with CLL harbouring 17p deletion or *TP53* mutation (n=23), ORRs were 65% (investigator-assessed) and 70% (IRC-assessed). In patients with neither 17p deletion, nor *TP53* mutation (n=41), ORRs were 63% and 66%, respectively.

At the February 2016 data cut-off, the majority of responses were maintained at six months (91% to 100% of patients in the ibrutinib failure and idelalisib failure subgroups). Six-month overall survival was 91% and 95% in the ibrutinib and idelalisib failure subgroups, respectively. Twelve-month overall survival was 88% and 95%.[14] Six-month progression free survival (PFS) rates were 81% to 88% dependent upon the subgroup and method of assessment (IRC or local investigator).[2]

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

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details.

At a February 2016 data cut-off, pooled analysis of 296 patients who received venetoclax 400mg across three monotherapy studies (M13-982, M14-032 and a phase I study) was presented to the EMA which provided adverse event profiles based on median exposure of 11.4 months. Treatment-emergent adverse events were reported in 99% (293/296) of patients, and 76% of patients reported grade 3 or 4 treatment-emergent adverse events. Adverse events led to discontinuation in 9.1% of patients, dose interruption in 35% of patients and dose reduction in 12% of patients. Treatment-emergent adverse events leading to death occurred in 25 patients (8.4%). Deaths of patients were not considered likely to be related to venetoclax treatment at the licensed dose. There was a case of death related to tumour lysis syndrome in a patient who was given 1,200mg daily.[2]

The most frequent treatment-emergent adverse events of grade 3 or 4 in severity were predominantly haematological. Neutropenia was reported in 37% (febrile neutropenia was less common, occurring in 5.7% of patients), anaemia in 15% and thrombocytopenia in 14% of patients. Grade 3 or 4 adverse events likely to impact on daily life such as diarrhoea, fatigue and abdominal pain were reported in fewer than 5% of patients. Grade 3 or 4 pneumonia occurred in 5.1% of patients.

Grade 3 or 4 tumour lysis syndrome was infrequent and was reported in 3.4% (10/296) of patients.[2]

Summary of clinical effectiveness issues

CLL is the most common form of adult leukaemia and mainly affects older people, with a median age of diagnosis of 72 years in the European Union.[2] It is characterised by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymph organs.[7] Clinical signs and symptoms associated with CLL include lymphadenopathy, infection, symptoms of anaemia, and systemic symptoms such as night sweats, weight loss and tiredness.[8]

Aside from stem-cell transplant, treatments for CLL are not curative. Treatment is given usually when a patient becomes symptomatic and first-line options are based upon patient's fitness and presence of adverse genetic markers (17p deletion and *TP53* mutation) and include chemoimmunotherapy regimens (fludarabine, bendamustine, or chlorambucil-based regimens) or the B-cell receptor inhibitors (ibrutinib or idelalisib plus rituximab). Treatment of relapse and refractory disease depends also upon the duration of response to previous lines of therapy; the duration of response tends to reduce with each course of treatment.[7, 9] Clinical experts consulted by SMC advised that there is an unmet need in patients who have failed B-cell receptor inhibitors or are not eligible for these treatments (median overall survival following failure of B-cell receptor inhibitors is between 3.1 and 17.6 months[15,16,17]) and there is a lack of effective options for these patients. They advised that the range of treatments offered to patients include palliative care, or high-dose corticosteroids. In the case of B-cell receptor inhibitor failure, a trial with the other agent (eg idelalisib plus rituximab in patients who have failed treatment with ibrutinib) may be

considered. Alemtuzumab was previously licensed for the treatment of CLL but the marketing authorisation was withdrawn by the company for commercial reasons, not related to efficacy or safety. It is now available for patients with CLL, through a patient access programme and is sometimes used. An allogeneic stem-cell transplant may be considered for selected, fit patients.

Venetoclax is the first-in-class Bcl-2 inhibitor to be marketed in the UK. The EMA granted a conditional marketing authorisation on the basis that it is an orphan medicine, it is intended to be used in a life-threatening disease, the risk-benefit balance was considered positive, it is likely to fulfil an unmet need for treatment post-B-cell receptor inhibitors and the outstanding clinical data are achievable and unlikely to pose an unreasonable risk to public health.[2] In addition to orphan medicine status, venetoclax meets SMC end-of-life criteria.

The magnitude of clinical benefit associated with venetoclax is uncertain; the key evidence in CLL is from non-comparative studies, and overall survival data are immature.

Tumour response rates in the phase II studies (Tables 1 and 2) were considered by the EMA to be clinically meaningful. Tumour responses are likely to be durable; in M13-982, the median PFS has been estimated to be 27 months, and in M14-032 over 90% of tumour responses were maintained at six months. The EMA commented that durable tumour responses are likely to lead to symptomatic improvement (including haematological parameters) and are considered to be informative even with single-arm studies.[2]

Exploratory investigations of the impact of venetoclax on HrQoL suggests modest improvements in global QoL, disease symptoms, social-, emotional-, and role-functioning, although not all patient-reported outcomes had clinically important changes (eg the M.D. Anderson Symptom Inventory).

There are limited data for patients who have failed prior B-cell receptor inhibitors, the results available from the M14-032 study are based on a relatively small sample size. Additional data from an extension to M14-032 have been requested by the EMA as part of the conditional marketing authorisation.[2] M14-032 provides limited data for patients with CLL in the absence of 17p deletion or *TP53* mutation.

The company considers M13-982 to be the key study providing data for the population with CLL harbouring 17p deletion or *TP53* mutation and who are unsuitable for B-cell receptor pathway inhibitor. M13-982 recruited patients with CLL harbouring 17p deletion and / or *TP53* mutation; it did not specifically recruit patients considered not suitable for B-cell receptor inhibitors, and unsuitability was not clearly defined.

Less than 10% of patients in the phase II studies were ECOG performance status 2 at baseline. In addition, the phase II studies excluded patients with clinically significant co-morbidity such as cardiac disability (New York Heart Association class ≥2). The data may therefore not generalise to patients in NHS Scotland who may be frailer and less fit than those recruited to the studies.

To support the economic case for venetoclax, the company conducted naïve indirect treatment comparisons of venetoclax with palliative care and best supportive care (BSC). Data from the two phase II studies and a phase I study[10] of venetoclax were pooled into two analysis sets: patients with 17p deletion and / or *TP53* mutation, and patients with neither of the genetic aberrations of the *TP53* gene. BSC was considered to consist of rituximab plus methylprednisolone, and data from the control group of CLL 116,[11] a study comparing idelalisib plus rituximab with rituximab monotherapy were used as a proxy for this comparator. Retrospective observational data from

the UK CLL registry study were used to provide data for the indirect comparison with palliative care.[12]

In addition to the naïve methodology used, a number of limitations with the analyses were identified. The venetoclax data were not specific to patients who were either unsuitable for B-cell receptor inhibitors or who had failed B-cell receptor inhibitors. The study with rituximab monotherapy was not in a population which would be eligible for venetoclax; it recruited patients who could be randomised to idelalisib treatment and patients with a history of prior B-cell receptor inhibitor therapy were excluded. As a result, the comparison of venetoclax with BSC in this analysis may not be applicable for the indication under review. Both naïve comparisons did not match for baseline characteristics / prognostic factors; although the palliative care registry data were selected based on the eligibility criteria of the venetoclax studies.

Clinical experts consulted by SMC considered venetoclax to be a therapeutic advancement due to encouraging response rates in phase II studies.

Practical implications for patients and the service relate to the associated risk of tumour lysis syndrome and associated mitigating factors recommended for venetoclax (dose titration and other prophylactic measures based on underlying risk). Implications include hospital admission and regular monitoring during the first five weeks of treatment.[1]

The tumour lysis syndrome prophylactic measures minimise the risk of this important adverse event of venetoclax treatment. Haematological adverse events, particularly neutropenia, were the most frequently reported adverse events, but clinical events (eg febrile neutropenia) were less common.

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 venetoclax, as an orphan and end-of-life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- CLL is a highly debilitating and incurable disease. Symptoms of CLL (eg fatigue, risk of infection and pain) have a substantial impact on quality of life.
- There is a psychological impact on patients who live with, on the whole, an incurable disease; there can be stress and anxiety from the uncertainty of the management approach of watch and wait. The disease can also have an impact on patients' ability to contribute to society.
- Venetoclax is a convenient oral treatment option which addresses an unmet need for patients who have limited effective treatment options.
- PACE participants indicated that venetoclax treatment would be associated with substantial symptomatic improvement which can benefit patients and carers. Reduction in fatigue associated with the disease would allow patients to be more active, giving them the energy to return to conducting everyday tasks and possibly return to work.
- While patients experience side effects, these were considered to be manageable.
- Reduced requirement for blood product support and inpatient treatment for infection are anticipated in comparison to alternative supportive / palliative treatment with corticosteroids.

- PACE participants outlined how the data on Minimal Residual Disease negativity and risk of tumour-lysis syndrome are indicators of the effectiveness of venetoclax in this patient population.

Additional Patient and Carer Involvement

We received patient group submissions from: the Chronic Lymphocytic Leukaemia Support Association (CLLSA), Bloodwise and Leukaemia CARE. All three are registered charities. CLLSA has received 65% pharmaceutical company funding in the past two years, including from the submitting company. Bloodwise has received 0.6% pharmaceutical company funding in the past two years, including from the submitting company. Leukaemia CARE has received 10.6% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from all three charities participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing venetoclax with BSC and palliative care for use in patients with CLL as outlined in the marketing authorisation. BSC was defined as treatment with rituximab, with or without high dose methylprednisolone, and 50% of patients were assumed to receive rituximab monotherapy. Palliative care was defined as no active treatment and included only disease management and terminal care costs. The model results were estimated separately for patients with and without 17p deletion / *TP53* mutation.

A partitioned survival model was used over a lifetime (50-year) time horizon with health states consisting of PFS, progressed disease and death. Disease progression was modelled as in the venetoclax clinical studies and a cycle length of 28 days was used as this is consistent with the treatment cycle length of venetoclax. Area under the curve survival analysis was then used to extrapolate the proportion of patients in each health state over the model time horizon.

For the venetoclax arm of the model in patients with 17p deletion / *TP53* mutation, clinical data were based on a pooled analysis of 3 venetoclax studies (M13-982, M14-032 and a phase I dose ranging study M12-175). [2-4, 10] For patients without 17p deletion / *TP53* mutation, using pooled analysis of the M14-032 and M12-175, a Cox proportional hazard model was fitted to estimate OS as a function of the 17p deletion/ TP53 mutation. For the BSC arm, the company selected the rituximab arm of the CLL 116 phase III study (which compared idelalisib plus rituximab with rituximab alone) as a proxy for the efficacy of BSC in the model, with efficacy estimated separately by genetic mutation status. [11] In order to estimate the efficacy of palliative care, data from the UK CLL forum were used and adjusted to better reflect the inclusion and exclusion criteria of the venetoclax studies.[12] This resulted in a dataset of 40 patients which was used to model survival for patients receiving palliative care in the model. No comparative data or formal indirect comparisons were provided to compare venetoclax with BSC or palliative care. Naive comparisons were conducted where the data from the venetoclax single-arm studies, the rituximab arm of the CLL 116 study and the CLL forum registry data were used to extrapolate PFS and OS curves over the model time horizon.

In the venetoclax arm, PFS and OS data from a pooled analysis of patients with 17p deletion / *TP53* mutation in the venetoclax studies were extrapolated over the model time horizon using the Weibull curve, which was selected based on a combination of goodness of fit statistics, plausibility of the survival estimates, and examination of the hazard plot. Using the Weibull curve

resulted in a 10-year survival rate of 12% and 10-year PFS rate of 2%. In order to estimate PFS and OS for non-17p deletion / *TP-53* mutation patients, the pooled data were analysed and a Cox proportional hazard model was fitted to estimate OS as a function of genetic mutation status. This showed the OS hazard ratio of having 17p deletion / *TP53* mutation is 1.908 and the inverse of this hazard ratio was applied to the OS curves to estimate venetoclax PFS and OS for patients without17p deletion / *TP53*mutation.

For BSC, the company used data from the rituximab monotherapy arm from the manufacturer's submission to NICE for idelalisib. These data were extrapolated using the Weibull model based on goodness of fit statistics and plausibility of survival estimates. Alternative curves were explored in the sensitivity analysis and the results showed some sensitivity to using alternative extrapolation approaches. Survival analysis was performed separately for patients with and without genetic mutations. Finally, the adjusted dataset from the UK CLL forum was extrapolated using an exponential curve based on face validity. This resulted in median OS estimated at 13.17 months.

The pre-progression utility value was estimated from EQ-5D-5L data collected in the M14-032 and M13-982 studies. The weighted average pre-progression utility value was estimated to be 0.853. The post-progression utility values was 0.6 based on a published study. Both pre- and post- progression utility values were age-adjusted, resulting in values ranging from 0.853 to 0.689 in PFS and between 0.6 and 0.485 in the post-progression health state. No disutilities due to adverse events were applied in the base case analysis.

Medicine costs included acquisition, administration and adverse event costs. Administration costs were included for BSC but did not include wastage as the company stated vial sharing is common practice. The costs of tumour lysis syndrome prophylaxis were also included based on the patient's risk, with 19% of patients in the lower risk group and 81% in the greater risk group. The average cost of tumour lysis syndrome prophylaxis applied in the model was £2,215 and was varied in the sensitivity analysis. Routine care and a range of monitoring and test costs were included. Terminal care costs were also included.

A Patient Access Scheme (PAS) was submitted by the company and accepted by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Results for the 17p deletion / *TP53* mutation subgroup:

For the comparison with BSC, the company estimated an incremental cost-effectiveness ratio (ICER) of £63,147 based on an incremental cost of £148,166 and a quality-adjusted life-year (QALY) gain of 2.346 and a life year gain of 3.105.

For the comparison with palliative care, the company estimated an ICER of £69,114 based on an incremental cost of £164,641 and a QALY gain of 2.382 and a life year gain of 2.98.

Table 3: Key sensitivity analysis for 17p deletion / *TP53* mutation patients- without PAS

Scenario	ICER venetoclax without PAS vs BSC	ICER venetoclax without PAS vs palliative care
Reducing venetoclax OS using 95% CI	£80,401	£87,788
Increasing BSC OS using 95% CI	£80,668	n/a
Increasing venetoclax PFS using 95% CI	£71,744	£77,319
UK CLL forum OS hazard rate	n/a	£81,140
Time horizon reduced to 10 years	£65,386	£71,605
Treatment effect of venetoclax restricted to 6 years	£69,549	£76,236
Venetoclax PFS and OS extrapolation using loglogistic	£66,467	£70,983
Venetoclax PFS and OS extrapolation using Gompertz	£67,491	£75,076
Utility values from published study (PFS 0.8, PPS 0.6)	£66,134	£73,078
Palliative care OS extrapolation using loglogistic	n/a	£134,702
Palliative care OS extrapolation using lognormal	n/a	£140,508

Results for patients without 17p deletion / *TP53* mutation:

For the comparison with BSC, the company estimated an ICER of £69,576 based on an incremental cost of £236,950 and a QALY gain of 3.406 and a life year gain of 4.511.

For the comparison with palliative care, the company estimated an ICER of £64,195 based on an incremental cost of £257,388 and a QALY gain of 4.009 and a life year gain of 5.204.

In both subgroups, the majority of the life year and QALY gains with venetoclax are obtained in the PFS health state. The results of the key sensitivity analyses are presented in table 4.

Table 4: Key sensitivity analysis for patients without 17p deletion / *TP53* mutation - without PAS

Scenario	ICER venetoclax without PAS vs BSC	ICER venetoclax without PAS vs palliative care
Increasing 17p deletion / *TP53* PFS hazard ratio	£96,527	£88,527
Reducing 17p deletion / *TP53* OS hazard ratio	£92,161	£100,567
Reducing venetoclax OS using 95% CI	£88,527	£78,329
Increasing BSC OS using 95% CI	£93,360	n/a
Time horizon reduced to 10 years	£77,388	£69,850
Treatment effect of venetoclax restricted to 6 years	£87,055	£76,254

Utility values from published study (PFS 0.8, PPS 0.6)	£73,040	£67,582
Palliative care OS extrapolation using loglogistic	n/a	£90,394
Palliative care OS extrapolation using lognormal	n/a	£92,032

The following limitations were noted:

- There are no comparative study data available to compare venetoclax with BSC or palliative care. Estimates of comparative efficacy are based on naïve comparisons of the single-arm venetoclax studies with other data sources used to proxy the efficacy of the comparator treatments. There are also a number of limitations with the venetoclax data as noted in the clinical effectiveness section above, including the immaturity of the OS data and the lack of data in the licensed population.
- There are also some limitations with the data sources used in the comparator arms. For example, the patients in the CLL 116 study used to proxy BSC would not be eligible to receive venetoclax in practice as all patients were suitable to receive treatment with a B-cell receptor inhibitor. It could be argued that the post-progression survival data from the idelalisib arm of the CLL 116 study may be more appropriate as these data would represent survival for patients who have failed on a B-cell receptor inhibitor. The life years estimated in the BSC arm may lack face validity as they are less than the palliative care arm where no active treatment was received (0.98 vs 1.12 undiscounted), suggesting the model may underestimate survival with BSC. Finally, the data source used to estimate the efficacy of palliative care includes patients with and without genetic mutations, which will introduce some bias in the model estimates as the venetoclax data are modeled separately by genetic mutation status.
- The large incremental life year and QALY gains with venetoclax estimated in the model are based on these naïve indirect comparisons and, given the clinical data limitations, are particularly uncertain. As shown in tables 3 and 4, the results are particularly sensitive to varying the OS estimates using the 95% confidence intervals and for the comparison with palliative care the extrapolation approach is also a key driver. For the subgroup of patients without 17p deletion / *TP53* mutation, the results are also sensitive to the relative efficacy of venetoclax in patients with and without genetic mutations.
- The treatments included in BSC (rituximab with or without high-dose methylprednisolone) were not specifically mentioned by SMC clinical experts and may not reflect BSC in clinical practice. Other treatment options such as high-dose corticosteroids, alemtuzumab, the B-cell receptor inhibitors (idelalisib and ibrutinib) and stem-cell transplant were mentioned by SMC clinical experts. For patients who have failed on or are unsuitable for one B-cell receptor inhibitor, the other B-cell receptor inhibitor could be a treatment option in practice. The timing of the publication of SMC advice on the B-cell receptor inhibitors preclude them being considered as comparators according to SMC process, but they may be used in clinical practice for some patients.
- The PFS health state utility value may lack face validity as the values used throughout the model time horizon are consistently higher than the age-matched general population utility values. The results showed some upward sensitivity to changes to the utility values.

The Committee considered the benefits of venetoclax in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that, as venetoclax 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 modifiers, the Committee accepted venetoclax for use in NHS Scotland.

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

Additional information: guidelines and protocols

The British Society for Haematology provided an interim update to its guideline "Investigation and management of chronic lymphocytic leukaemia" in 2015.[9] Recommendations of relevance to the indication under review are summarised in the table below.

Table 5: relevant recommendations from the British Society for Haematology[9]

Clinical scenario	Recommendation(s)
Presence of 17p deletion or *TP53* mutation in adults unsuitable for B-cell receptor pathway inhibitor	If idelalisib plus rituximab or ibrutinib are not available, then treatment with alemtuzumab +/- corticosteroids remains preferable to chemotherapy.
Presence of 17p deletion or *TP53* mutation in adults who have failed a B-cell receptor pathway inhibitor	No firm recommendations can be made as to how patients relapsing after treatment with ibrutinib or idelalisib plus rituximab should be managed.
Absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor	

The European Society for Medical Oncology published clinical practice guidelines for diagnosis, treatment and follow-up of chronic lymphocytic leukaemia in 2015.[7] In patients who have failed a B-cell receptor pathway inhibitor (eg idelalisib plus rituximab/ofatumumab or ibrutinib), the recommendation is to either switch to an alternative B-cell receptor pathway inhibitor or to use a B-cell lymphoma-2 (Bcl-2) inhibitor (eg venetoclax) within a clinical study setting. Patients who then respond to a switch in B-cell receptor inhibitor or to the Bcl-2 inhibitor should be considered for allogeneic haematopoetic stem-cell transplant (if fit enough). The guideline made no recommendation for treatment options in patients unsuitable for B-cell receptor pathway inhibitors and in the presence of 17p deletion or *TP53* mutation.

Additional information: comparators

There are no standard treatment options available. Treatment options advised by clinical experts include high-dose corticosteroids (eg methylprednisolone), idelalisib plus rituximab (on failure of ibrutinib), and ibrutinib (in idelalisib failure).

Cost of relevant comparators

Medicine	Dose Regimen	Cost per 28-day cycle (£)
venetoclax	**20mg orally once daily, titrated at weekly intervals to 400mg daily**	**Cycle 1: 1,108** **Cycles 2 onwards: 4,789**
idelalisib plus rituximab	idelalisib: 150mg orally twice daily rituximab: IV infusion of 375mg/m^2 on day 1, then 500mg/m^2 every two weeks for four doses, then 500mg/m^2 every four weeks for three doses (total of eight doses).*	Cycle 1: 5,876 Cycle 2: 6,400 Cycles 3 to 6: 4,653 Cycles 7 onwards: 2,907
ibrutinib	420mg orally once daily	4,292
methylprednisolone	1g/m^2 IV on days 1 to 5 every 28 days	164

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS.co.uk on 03 April 2017, except for methylprednisolone (from eVadis, extracted on 03 March 2017). Costs calculated using body surface area of 1.8m^2, and the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. *Rituximab dosing as per idelalisib study 312-0116.

Additional information: budget impact

The company estimated there would be 322 patients eligible for treatment in year 1 and 409 in year 5, to which confidential estimates of treatment uptake were applied.

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 commercially confidential.**

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This assessment is based on data submitted by the applicant company up to and including 19 May 2017.

**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 drug 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.