Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2293

venetoclax 10mg, 50mg, 100mg film-coated tablets (Venclyxto®)

AbbVie Ltd.

06 November 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 considered under the orphan equivalent process

venetoclax (Venclyxto®) is accepted for restricted use within NHSScotland.

Indication under review: In combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Venetoclax-obinutuzumab, compared with chlorambucil-obinutuzumab, significantly improved progression-free survival in adults with CLL and co-morbidities.

SMC restriction: for use in (1) patients without del (17p)/TP53 mutation who are not fit to receive FCR (fludarabine, cyclophosphamide and rituximab) chemo-immunotherapy and (2) patients with del (17p)/TP53 mutation.

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

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

Chairman
Scottish Medicines Consortium

Indication

In combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).[1]

Dosing Information

Venetoclax 20mg daily for one week, then 50mg daily for one week, then 100mg daily for one week, then 200mg daily for one week, then 400mg daily thereafter. Dosing should commence on day 22 of cycle 1. The tablets should be taken with a meal to reduce the risk of lack of efficacy. The tablets should not be chewed, crushed, or broken before swallowing. During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.

Venetoclax is given for a total of twelve 28-day cycles, with the first six cycles in combination with obinutuzumab intravenous (IV) infusion 100mg on day 1 of cycle 1, followed by 900mg which may be administered on day 1 or day 2, then 1000mg on days 8 and 15 of cycle 1 and on day 1 of each subsequent 28-day cycle, for a total of 6 cycles.

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

Product availability date

9 March 2020

Venetoclax meets SMC orphan equivalent criteria in this indication.

Summary of evidence on comparative efficacy

Venetoclax is an inhibitor of B-cell lymphoma-2 (BCL-2), an anti-apoptotic protein that is over-expressed in CLL cells where it mediates tumour cell survival and has been associated with resistance to chemotherapies. Venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.[1] The submitting company has requested that venetoclax be considered when positioned for use in two subgroups:

(1) patients without del (17p)/TP53 mutation who are not fit to receive FCR (fludarabine, cyclophosphamide and rituximab) chemo-immunotherapy and
(2) patients with del (17p)/TP53 mutation

An open-label phase 3 study (CLL14) recruited adults with previously untreated CD20+ CLL and coexisting conditions, with a total score >6 on the Cumulative Illness Rating Scale (CIRS) and/or creatinine clearance (CrCl) <70 mL/min (but not <30mL/min) who required treatment (Binet stage C or symptomatic). Randomisation was stratified by Binet stage (A, B or C) and geographic region (US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern Europe; or Latin America). Patients were equally assigned to twelve 28-day cycles of venetoclax orally (commencing on day 22 of cycle 1 with weekly-increasing daily doses of 20mg, 50mg,

100mg, 200mg and then 400mg daily thereafter) or chlorambucil orally at 0.5mg/kg on days 1 and 15 of each cycle. All patients concurrently received obinutuzumab IV (100mg on day 1 and 900mg on day 2 [or 1000mg on day 1], 1000mg on day 8 and 1000mg on day 15 of cycle 1, then 1000mg on day 1 of cycles 2 through 6). The primary outcome, investigator-assessed progression-free survival (PFS), defined as time from randomisation to the first occurrence of progression or relapse using International Workshop on CLL (iwCLL) 2008 guidelines or death from any cause. This was assessed in the intention-to-treat (ITT) population, which comprised all randomised patients.[2,3]

At the interim analysis (data cut-off August 2018), after a median follow-up of 28.1 months, venetoclax-obinutuzumab compared with chlorambucil-obinutuzumab significantly prolonged PFS as detailed in Table 1. As this crossed the pre-specified early stopping boundary, it became the primary analysis of PFS.[2,3] An updated analysis (data cut-off August 2019) after median follow-up of 39.6 months had similar results.[2,4]

Table 1: Investigator-assessed progression-free survival (PFS) in CLL14 study.[2-4]

	August 2018 cut-off (primary analysis)		**August 2019 cut-off**	
	Venetoclax-obinutuzumab	**Chlorambucil-obinutuzumab**	**Venetoclax-obinutuzumab**	**Chlorambucil-obinutuzumab**
	N=216	**N=216**	**N=216**	**N=216**
Events	30	77	AiC	AiC
HR (95% CI), p-value	0.35 (0.23 to 0.53), p<0.001		0.31 (0.22 to 0.44), p<0.001#	
Median* (months)	NE	NE	NE	35.6
2-year PFS rate*	88%	64%	88%	64%
3-year PFS rate*			82%	50%

CI = confidence interval; * estimates from Kaplan-Meier analysis; # = descriptive p-value; NE = not evaluable; HR = hazard ratio' AiC = academic in confidence

Subgroup analyses of PFS at the August 2019 data cut-off provide some evidence of the treatment effect in the subgroups of proposed positioning. The CLL14 study did not provide evidence in fit patients either with or without del(17p)/TP53 mutation.

Secondary outcomes were assessed at the primary analysis of PFS (August 2018 cut-off) in the hierarchical order listed in Table 2. Most of these were significantly improved with venetoclax-obinutuzumab versus chlorambucil-obinutuzumab. There was no significant difference in overall survival (OS), though data were considered immature. PFS improvements with venetoclax-obinutuzumab were supported by benefits assessed at the end-of-treatment visit (3 months after completion or termination of treatment) in the following secondary outcomes: rates of overall response (defined as investigator-assessed complete response [CR], complete response with incomplete bone marrow recovery [CRi] or partial response [PR] on iwCLL 2008 guidelines); complete response (investigator-assessed CR or CRi); and undetectable minimal residual disease (uMRD) in bone marrow and peripheral blood in the total study population and in those with CR. Minimal residual disease (MRD) negativity was defined as less than one cell in 10,000 leukocytes measured by allele-specific oligonucleotide polymerase chain reaction.[2,3]

Table 2: Secondary outcomes of CL114 at data cut-off August 2018.[2,3]

Outcome#	Venetoclax-obinutuzumab	Chlorambucil-obinutuzumab	Treatment effect* (95% CI)
	N=216	N=216	
PFS by IRC, events	29	79	0.33 (0.22, 0.51)
uMRD bone marrow	123 (57%)	37 (17%)	40% (31, 48)
Combined response (CR and CRi)	107 (50%)	50 (23%)	26% (17, 35)
uMRD peripheral blood	163 (76%)	76 (35%)	40% (31, 49)
uMRD bone marrow in CR	73 (34%)	23 (11%)	23% (15, 31)
uMRD peripheral blood in CR	91 (42%)	31 (14%)	28% (19, 36)
Overall response	183 (85%)	154 (71%)	13% (5.5, 21)
Overall survival	20	17	1.24 (0.64, 2.40)

PFS = progression-free survival; IRC = independent review committee assessed; uMRD = undetectable minimal residual disease assessed 3 months after completion of treatment; CR = complete responders; CRi = complete response with incomplete bone marrow recovery. Complete and overall responses were investigator-assessed. # PFS and overall survival outcomes are expressed as number of events, all other outcomes are expressed as responders (%); * Treatment effect expressed as difference in event rates, except for PFS and overall survival, which are expressed as hazard ratios.

Health Related Quality of Life (HRQoL) was assessed using MD Anderson Symptom Inventory (MDASI), European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Quality of Life 5 Dimensions 3 Level version (EQ-5D-3L). These did not show a difference between treatments.[2]

An open-label phase Ib dose-finding and safety study (GP28331) provided supportive data. It recruited patients with relapsed or refractory or previously untreated CLL. All treatment-naïve patients responded to treatment with venetoclax-obinutuzumab and 78% (25/32) achieved a CR/CRi. Responses were similar among the subgroup of patients with del(17p)/TP53 mutation.[2]

The submitting company presented two naïve indirect comparisons of venetoclax-obinutuzumab (data from CLL14 study[2-4]) versus ibrutinib in treatment-naïve patients with CLL and del(17p)/TP53 mutation. In the indirect comparison supporting the base case economic analysis, the source of data for ibrutinib was a retrospective observational cohort study[5] and in a supportive analysis the source was a phase II study (NCT01500733).[6] The company concluded that there was much uncertainty in these indirect comparisons and results should be interpreted with caution. However, they note that the comparisons suggest similar PFS and OS with venetoclax-obinutuzumab versus ibrutinib.

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review concluded that there were no new safety concerns for venetoclax identified in CLL14 and GP28331. Venetoclax-obinutuzumab was considered not less toxic than chlorambucil-obinutuzumab, the current standard of care in previously untreated

CLL patients with coexisting conditions. Neutropenia, leading to severe infections, was the key issue in the safety profile of venetoclax-obinutuzumab.[2]

In the CLL14 study at the first analysis (data cut-off August 2018) all patients had completed treatment and the median time since completion of treatment was 17.1 months. Within the venetoclax-obinutuzumab and chlorambucil-obinutuzumab groups 94% (200/212) and 99% (213/214) patients reported an adverse event, which were related to treatment in 90% and 94% of patients and were of grade 3 or 4 severity in 79% and 77% of patients, respectively. Serious adverse events were reported by 49% and 42%, respectively, and were treatment-related in 26% of patients in both groups.

In CLL14 (August 2018 cut-off), within the venetoclax-obinutuzumab and chlorambucil-obinutuzumab groups 16% (34/212) and 15% (33/214) had an adverse event leading to withdrawal of any study treatment and 74% and 68% had a dose interruption, respectively.[2]

In CLL14 (August 2018 cut-off), within the venetoclax-obinutuzumab and chlorambucil-obinutuzumab groups, haematological adverse events were reported by 68% and 64%, including neutropenia (58% and 57%), thrombocytopenia (24% and 23%) and anaemia (16% and 19%). Gastrointestinal adverse events were reported by 42% and 35%, including diarrhoea (28% and 15%), nausea (19% and 22%) and constipation (13% and 8.9%). Other common adverse events included pyrexia (23% and 15%), fatigue (15% and 14%), cough (16% and 12%) and headache (11% and 9.8%). Infusion-related reactions (with obinutuzumab) were reported by 45% and 51% of patients, respectively.[2,3]

Adverse events of infections of at least grade 3 severity occurred in 19% and 16% of patients in the respective groups, with pneumonia the most common (4.2% in both groups). Sepsis was reported by more patients in the venetoclax-obinutuzumab group than in the chlorambucil-obinutuzumab group: seven (3.3%) versus two (0.9%) patients. [2,7]

Adverse events with a fatal outcome occurred in 16 (7.5%) and eight (3.7%) patients at the August 2019 cut-off in the venetoclax-obinutuzumab and chlorambucil-obinutuzumab groups, respectively. The most frequently reported adverse event leading to death was sepsis: five patients (2.4%) and one patient (0.5%) in the respective groups. Cardiac arrest was reported in one patient in each group.[2]

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

Summary of clinical effectiveness issues

The treatment approach for first-line therapy in CLL is evolving. In patients with early CLL without symptoms, active surveillance is employed until disease-related symptoms develop. In patients with early CLL and active disease or in patients with advanced CLL, treatment depends upon the presence of TP53 mutations. The British Society for Haematology (BSH) guideline recommends FCR as initial therapy for previously untreated fit patients without TP53 mutations and bendamustine-rituximab as an acceptable alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions, more advanced age, concerns with marrow capacity or patient

preference. In less fit patients, chlorambucil-obinutuzumab is recommended and bendamustine-rituximab might be considered as an alternative. Ibrutinib is also an acceptable treatment option. In extremely frail patients, single agent chlorambucil may be used in those who are intolerant of anti-CD20 antibodies or when intravenous therapy is considered unsuitable, corticosteroid monotherapy can be considered, but rituximab monotherapy is not recommended. In patients with TP53 mutation, ibrutinib is the treatment of choice. Idelalisib-rituximab is a suitable alternative for patients for whom ibrutinib is deemed inappropriate.[8]

Venetoclax is the first BCL-2 inhibitor licensed for the first-line treatment of CLL. It is licensed for use in combination with obinutuzumab, which is an anti-CD20 antibody.[9] Venetoclax meets SMC orphan equivalent criteria in this indication. The submitting company has requested that venetoclax be considered when positioned for use in two subgroups:

(1) patients without del (17p)/TP53 mutation who are not fit to receive FCR therapy, for which the main comparator is chlorambucil-obinutuzumab and
(2) in patients with del (17p)/TP53 mutation, for which the main comparator is ibrutinib.

In the CLL14 study, venetoclax-obinutuzumab significantly increased PFS compared with the current standard of care in this group, chlorambucil-obinutuzumab, with HR of 0.35 (95% CI: 0.23 to 0.53) and 0.31 (95% CI: 0.22 to 0.44) at the August 2018 and August 2019 cut-offs, respectively. Effects on PFS were supported by benefits in response rates and uMRD. OS data were immature. Quality of life measures indicated no difference between the treatment groups.[2,3]

The CLL14 study included treatment-naïve patients with CLL who were less fit and would generally not be suitable for treatment with FCR.[2,3] However, the licence is not limited to those unsuitable for FCR as the EMA considered that efficacy could be extrapolated to fit patients.[1,2] The CLL14 study does not provide evidence in patients who would be eligible for venetoclax-obinutuzumab within the licence and are fit and suitable to receive FCR. This is not an issue in patients without del(17p)/TP53 mutation, as the proposed positioning restricts use to those not suitable for FCR. However, the positioning in patients with del (17p)/TP53 mutation includes both fit and unfit patients.

The evidence base in patients with del (17p)/TP53 mutations had a limited sample size of patients in CLL14. Subgroup analysis of PFS indicated that treatment benefits with venetoclax-obinutuzumab versus obinutuzumab-chlorambucil were generally consistent across the following subgroups: sex; age; Binet stage at screening; cytogenetic subgroups as per hierarchy; del (17p)/TP53 mutation; and immunoglobulin heavy chain variable region (IgVH) mutational status.[2,3] Subgroup analyses of PFS in patients with and without del (17p)/TP53 mutation provide evidence of treatment effects within the subgroup of patients without del (17p)/TP53 mutation who were not fit to receive FCR. In the other subgroup of the proposed positioning, patients with del (17p)/TP53 mutation, there is no direct comparative evidence versus the ibrutinib, the current standard of care. To address this, the submitting company provided naïve indirect comparisons.

The naïve indirect comparisons of venetoclax-obinutuzumab versus ibrutinib were limited by weaknesses characteristic of these types of analysis, which do not adjust for differences across the treatment arms. The comparisons were also limited by small sample sizes and one of the studies of ibrutinib was a retrospective observational cohort study. The indirect comparisons did not

include response rates, safety outcomes or quality-of-life outcomes. The confidence intervals around the results were wide and included one. Due to these limitations, the conclusions are uncertain.

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

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 equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- CLL is an incurable haematological cancer with few effective treatment options and these can be further limited by the potential for adverse effects in CLL patients, who tend to be older and have co-morbidities.
- Venetoclax-obinutuzumab expands the limited treatment options available to CLL patients (1) without del (17p)/TP53 mutation who are not fit to receive FCR, where it markedly prolongs progression-free survival compared with a standard first-line therapy; and (2) with del (17p)/TP53 mutation, where it provides an effective alternative to the current standard of care, which may not be suitable for certain patient groups, such as those with cardiac arrhythmias or receiving anticoagulants.
- Venetoclax-obinutuzumab substantially prolongs progression-free survival and provide a significantly prolonged remission, where the patient is well and able to undertake work or participate in family and social activities. It also increases the likelihood of achieving undetectable minimal residual disease, which is associated with a good long-term prognosis. It is considered to have a less severe adverse effects than chemotherapy-based regimens. These benefits can also provide the patient and their family with relief from anxieties about the future and about accessing optimum treatment.
- Venetoclax-obinutuzumab is a fixed time-limited one-year treatment, which allows patients to enjoy their prolonged remission while off-treatment and this has immense psychological benefits, with reduced anxiety and the chance to make plans. It has advantages over alternative treatments that are given until disease progression or unacceptable toxicity. By limiting the exposure to medicines, the risk of adverse events is reduced, the risk of inducing drug resistant disease is decreased and the range of potential subsequent treatment options is maintained.
- Venetoclax is considered a convenient orally administered medicine. After the initial dose-increasing (five week) phase, patients only attend hospital for intravenously administered obinutuzumab once a month for five months. This has benefits for both the patient and their carer. There is established clinical experience within NHS Scotland of using venetoclax and potential adverse effects are considered manageable.

Additional Patient and Carer Involvement

We received a patient group submission from Leukaemia CARE and a joint patient group submission from the Chronic Lymphocytic Leukaemia Support Association (CLLSA) and Lymphoma Action. All three organisations are registered charities. Leukaemia CARE has received 14.3% pharmaceutical company funding in the past two years, including from the submitting company. CLLSA has received 68% pharmaceutical company funding in the past two years, including from the submitting company. Lymphoma Action has received 9.8% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from CLLSA and Leukaemia CARE participated in the PACE meeting. The key points of the joint submission from CLLSA and Lymphoma Action and the submission from Leukaemia CARE have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis of venetoclax-obinutuzumab for the treatment of adult patients with previously untreated CLL. The base case analysis used chlorambucil-obinutuzumab as the comparator for the non-del (17p)/TP53 mutation population, and ibrutinib as the comparator for the del (17p)/TP53 mutation population.

A partitioned survival cohort simulation model was used. The model consisted of three mutually exclusive health states; pre-progression (starting health state), post-progression and death. The cycle length was 28 days, with patients either remaining in state, transitioning to post-progression or death at the end of each cycle. The model projected two primary outcomes – OS and PFS. An NHS perspective and a 30-year time horizon were selected in the base case of the economic model.

Clinical evidence informing the base case analysis for the non-del (17p)/TP53 mutation population was taken from the interim analysis of the ongoing CLL14 study. [2,3] This included parameters for baseline patient characteristics, PFS, time on treatment, time to next treatment (TTNT) and incidence of adverse events.

Extrapolation of OS and PFS was required. Parametric models were fitted to the CLL14 Kaplan-Meier (KM) data using a model independent of the proportional hazards assumption for PFS, and a dependent model for OS. The most appropriate distributions for OS and PFS were selected based on external validity and clinical plausibility.

For the del (17p)/TP53 mutation population, in the absence of direct comparative evidence between venetoclax-obinutuzumab and ibrutinib, the company presented two naïve indirect comparisons. The KM curves from the CLL14 mutation positive venetoclax-obinutuzumab subpopulation were naïvely compared to those from the ibrutinib studies to obtain a HR between mutation positive patients on venetoclax-obinutuzumab in the CLL14 trial with patients in the ibrutinib studies.

Base case utilities were obtained from a past NICE appraisal.[11] These are outlined in Table 3. Utility values elicited from the CLL14 study were implausibly high and were therefore not used in the base case analysis.

Table 3: Base case utility values

Health state	Base case utility value
Pre-progression while on IV treatment	0.670
Pre-progression off-treatment	0.760
Pre-progression oral treatment	0.710
Post-progression	0.600

Acquisition and administration costs for venetoclax and all comparators were included in the analysis, as were the costs associated with any subsequent treatments. Unit costs for managing adverse events, disease management, and a one-off cost for terminal care were also accounted for.

A 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 list price of the medicine.

PAS discounts are in place for obinutuzumab and ibrutinib and these were included in the results used for decision-making by using estimates of the relevant PAS prices. SMC is unable to include the results which used an estimate of the PAS prices for obinutuzumab and ibrutinib due to commercial confidentiality and competition law issues. As the submitting company also indicated that results using the list prices for all medicines should be regarded as commercially confidential regrettably no cost-effectiveness results can be presented.

The company provided deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA) and scenario analysis. In the DSA, for the non-del (17p)/TP53 population, pre-progression survival utility value had the greatest impact on incremental QALYs and was also the overall driver of the ICER. For the del (17p)/TP53 population, the OS HR had the greatest impact on incremental costs, QALYs and net monetary benefit. The PFS HR had greatest impact on the ICER.

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

- Robust evidence about the long-term effectiveness of venetoclax-obinutuzumab for non-del (17p)/TP53 population is lacking. The CLL14 study data are immature. Median OS and TTNT have not been reached in either arm and median PFS is only available for the chlorambucil-obinutuzumab arm. There is a lack of available data from the comparator studies for the comparison of ibrutinib versus venetoclax-obinutuzumab for the del (17p)/TP53 population.
- Due to the absence of mature study data, there is uncertainty around the treatment effect on OS and therefore, further uncertainty around the extrapolated OS. The extrapolated OS

is close to the level of background mortality, and given that CLL patients tend be older than 70 years with comorbidities, the likelihood of death from all-cause mortality is high. Hence, the base case analysis assumed no difference in OS between venetoclax-obintuzumab and chlorambucil- obintuzumab. However, the effect of using alternative distributions for the OS dependent survival model (assuming either no treatment effect or treatment effect) does not lead to large changes in incremental results.

- The base case analysis found treatment with venetoclax to be associated with lower total costs compared with chlorambucil-obinutuzumab, due to substantially lower subsequent treatment costs in the non-del (17p)/TP53 population. Accrued costs were lower due to the superior PFS achieved by patients on venetoclax, which delays initiation of potential second-line treatment, and due to the fixed treatment duration of venetoclax compared to treatments such as ibrutinib. The modelling of subsequent treatment costs was contingent on the type of subsequent treatment mix received, the TTNT curves, and duration of second-line treatment. There is some uncertainty about the extrapolation of TTNT due to the lack of mature study data as well as potential variation in the types of subsequent treatment mix. However, sensitivity analysis on this aspect was reassuring.
- Base case utilities were obtained from a past NICE appraisal TA343 – chlorambucil-obinutuzumab for untreated CLL. These were preferred to the utility values elicited from the CLL14 study which were notably higher than those used in previous appraisals and also higher than UK-age adjusted general population values. The post-progression utility values from CLL14 were also unreliable due to the low number of patients progressing during the trial period. The impact of applying higher CLL14 based utility values was tested in the scenario analysis (scenario 3), but did not alter the conclusion of venetoclax-obinutuzumab dominance. Nevertheless, pre-progression survival utility value was a key driver of the ICER in the deterministic sensitivity analysis so parameter uncertainty remains an issue. Further, base case utility values did not vary by TP53 mutation status. It is unclear whether this is a safe assumption as the CLL14 utilities, whilst unreliable, did differ substantially for the two subpopulations.
- The sample size of the del (17p)/TP53 mutation subpopulation in the CLL14 was small and mutation status was used as a covariate when conducting the survival modelling. The predicted relative treatment difference between venetoclax-obinutuzumab and ibrutinib in terms of OS/PFS HRs is highly uncertain due to ibrutinib data being from single arm studies. In addition, the naïve comparison method was selected since adjusting for prognostic factors was not feasible. No conclusions can be made about the relative PFS of ibrutinib vs venetoclax-obinutuzumab in the del (17p)/TP53 patient group as the results of the naïve comparison was not statistically significant.

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 equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted venetoclax for restricted use in NHSScotland.

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

Additional information: guidelines and protocols

In 2018, the British Society for Haematology (BSH) published a 'Guideline on the treatment of chronic lymphocytic leukaemia'. This recommends FCR as initial therapy for previously untreated fit patients without TP53 and bendamustine plus rituximab as an acceptable alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions, more advanced age, concerns with marrow capacity or patient preference. In less fit patients chlorambucil-obinutuzumab is recommended and bendamustine-rituximab might be considered as an alternative. Also, ibrutinib is an acceptable treatment option. Chlorambucil in combination with rituximab is not routinely recommended. In extremely frail patients single agent chlorambucil may be used in those who are intolerant of anti-CD20 antibodies or when intravenous therapy is considered unsuitable, corticosteroid monotherapy can be considered, but rituximab monotherapy is not recommended. In patients with TP53 mutation, ibrutinib is the treatment of choice. Idelalisib-rituximab is a suitable alternative for patients for whom ibrutinib is deemed inappropriate.[8]

In 2015, the European Society of Medical Oncology (ESMO) published a 'Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up', which was updated in 2017. For patients with Binet stage A and B with active disease or Binet stage C, this recommends FCR as the standard first-line therapy for fit patients without TP53 deletion or mutation, with bendamustine-rituximab an option for fit elderly patients. In those with co-morbidities, chlorambucil-obinutuzumab is recommended as the standard approach. It notes that patients with TP53 deletion or mutation have a poor prognosis even after FCR therapy. Therefore, it is recommended that these patients are treated with novel inhibitors (ibrutinib; idelalisib and rituximab) in front-line and relapse settings. For fit patients responding to inhibitor treatment, an allogeneic haematopoietic stem-cell transplantation (HSCT) may be discussed, using individual and transplant-related risk factors.[10]

Additional information: comparators

Comparators are different for the two subgroups of the proposed positioning. In patients with del (17p)/TP53 mutation, the main comparator is ibrutinib. In patients without del (17p)/TP53 mutation who are not fit to receive FCR, the main comparator is chlorambucil-obinutuzumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Venetoclax Obinutuzumab	From day 22 of cycle 1 a daily oral dose of 20mg increasing at weekly intervals to 50mg, 100mg, 200mg, then continuing at 400mg daily to the end of twelve 28-day cycles. Intravenous infusion of 100mg on day 1 of Cycle 1, followed by 900 mg (on day 1 or 2), then 1,000mg on days 8 and 15 of cycle 1 and on day 1 of each subsequent 28-day cycle, for six cycles.	79,696

Costs from BNF online on 24 July 2020. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*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 11 September 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.