SMC2543

ibrutinib film-coated tablets (Imbruvica®)

Janssen-Cilag Ltd.

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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 orphan equivalent medicine process

ibrutinib (Imbruvica®) is accepted for use within NHSScotland.

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

In a phase III study, ibrutinib plus venetoclax resulted in a statistically significant improvement in progression-free survival compared with another combination therapy in a defined group of patients with previously untreated CLL.

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.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Ibrutinib is a covalently binding inhibitor of Bruton's tyrosine kinase (BTK). BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is involved in the pathogenesis of several B-cell cancers, such as Chronic Lymphocytic Leukaemia (CLL).[1, 2] Venetoclax is a selective, orally available, competitive inhibitor of B-cell lymphoma 2 (BCL-2), which liberates pro-apoptotic proteins to trigger apoptosis in cancer cells. Overexpression of BCL-2 is common in CLL and CLL cells typically depend on BCL-2 for survival.[1, 3] Ibrutinib and venetoclax preferentially target distinct cell compartments and CLL sub-populations, effectively eliminating both dividing and resting CLL cells.[1, 4]

When used in combination for CLL, ibrutinib and venetoclax are both administered orally for up to 15 cycles; each treatment cycle is 28 days. Ibrutinib is administered at a dose of 420mg once daily (cycles 1 to 15), whilst venetoclax is administered from cycles 4 to 15. The starting dose of venetoclax is 20mg once daily for 7 days. The dose must be gradually increased over a period of 5 weeks up to the daily dose of 400mg as per the Summary of Product Characteristics.[2, 3]

1.2. Disease background

CLL is the most common form of adult leukaemia, with an approximate incidence rate of 4 new cases per 100,000 people every year.[5-8] CLL predominantly affects people of older age, and is characterised by the clonal expansion of mature B-cells in the blood, bone marrow or lymph nodes. The condition is generally incurable, with a high clinical burden due to its relapsing and remitting nature.[1, 5, 9, 10]

1.3. Treatment pathway and relevant comparators

In the early stages, CLL is usually an indolent disease where active surveillance is employed until disease-related symptoms develop. However, in active or advanced CLL, first-line treatment is recommended based on tumour protein 53 (TP53) status (that is a chromosome 17p deletion [del17p] and/or TP53 mutation); these are known indicators of a high-risk of CLL progression and poor prognosis. Other factors that affect decision-making are age, comorbidities, and patient preference (for example fixed duration or continuous treatment). However, the treatment landscape, and guidelines, for first-line therapy in CLL is constantly evolving.[10]

The submitting company has indicated that the indication under review within this submission consists of the three following populations, who shall be referred to throughout the rest of this document:

The 'FCR (fludarabine, cyclophosphamide, and rituximab)-suitable' population

The submitting company defined this population as those with no chromosome 17p deletion (del17p), with a cumulative illness rating scale (CIRS) ≤6, creatinine clearance (CrCl) ≥70 mL/min, and a European Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, and who are suitable for fludarabine-based therapy. The British Society for Haematology (BSH) guidelines describe this population as 'fit patients with CLL and intact TP53' (that is they have no TP53 mutation); for these patients FCR was the predominant first-line treatment option, and is still a viable option for fit, younger patients with a mutated Immunoglobulin Heavy-Chain Variable region (IGHV) and intact TP53. Venetoclax plus obinutuzumab is an alternative treatment option that is accepted by SMC in

this population (SMC2427).[10] The submitting company deemed FCR and venetoclax plus obinutuzumab to be the only relevant comparators for this population; however, experts contacted by SMC advised that FCR use appears to have significantly diminished in this population, and highlighted that venetoclax plus obinutuzumab is the most relevant comparator in this patient population.

The 'FCR unsuitable' population

The submitting company defined this population as those with no del17p mutation, with a CIRS >6 and/or a CrCl <70 mL/min, and who would be deemed unsuitable for fludarabine-based therapy. The BSH guidelines describe this population as 'less fit (or unsuitable for chemo-immunotherapy) patients with CLL and intact TP53'; most patients with CLL would be classed as 'less fit' with approximately 90% having comorbidities. For these patients, treatment options (which have been approved by SMC for this population) include venetoclax plus obinutuzumab (SMC2293) and acalabrutinib monotherapy (SMC2347).[10] The submitting company also listed obinutuzumab plus chlorambucil (SMC 1008/14) as a comparator. The latest BSH and Scottish guidance does not recommend the use of obinutuzumab plus chlorambucil. Emerging evidence supports the use of the BTK and BCL-2 inhibitors over chemo-immunotherapy.[10] Scottish guidance also lists chlorambucil with or without rituximab (for up to six cycles) as an alternative option for frail patients with comorbidities (CIRS>6 and ECOG PS>2). However, experts contacted by SMC did not consider either of the chlorambucil-based therapies mentioned to be relevant comparators in this population.

The 'high risk' population

The submitting company and BSH both define this population as those with a del17p and/or TP53 mutation.[10] These patients have very poor responses to chemo-immunotherapy and as a result have the poorest prognosis with a median overall survival of 2 to 5 years.[5, 10] Latest Scottish guidance and/or the BSH recommend the following treatment options for this population (that have been accepted by SMC): venetoclax plus obinutuzumab for a fixed duration of 12 months (SMC2293); ibrutinib monotherapy (SMC1151/16); acalabrutinib monotherapy (SMC2346); venetoclax monotherapy, when BTKis are unsuitable (SMC1249/17); and idelalisib plus rituximab (SMC 1026/15), in patients ineligible for all other therapies.[10] Except for idelalisib plus rituximab, and venetoclax monotherapy, the submitting company also considers these all to be relevant comparators for this population.

1.4. Category for decision-making process

Eligibility for a PACE meeting

Ibrutinib meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The direct evidence is derived from the CAPTIVATE and GLOW studies; details of these studies are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	CAPTIVATE study[1, 11]	GLOW study[1, 12]
Study Design	International, non-randomised, non-comparative, open-label, two cohort, phase II study. This submission shall only focus on one of these cohorts (that is the FD cohort).	International, randomised, open-label phase III study.
Eligible Patients	• Aged ≥18 and ≤70 years old.	• Aged ≥65 years old, or aged 18 to 64 years old with at least one of the following: ○ CIRS score >6 ○ CrCl <70 mL/min • No del17p or known TP53 mutation at baseline.
	Applicable to both studies: • Diagnosis of active CLL or SLL that requires treatment as per the iwCLL criteria. • Measurable nodal disease by CT. • No prior therapy for CLL or SLL. • ECOG PS of 0 to 2. • No suspected Richter's syndrome.	
Treatments	As part of a 28-day treatment cycle, all patients in the FD cohort received **oral ibrutinib** 420mg once daily (cycles to 1 to 15) **plus oral venetoclax** (cycles 4 to 15 only). Venetoclax was titrated up from a once daily dose of 20mg to 400mg over 5 weeks, as per the SPC.[2, 3] After completion of the FD regimen, patients who subsequently had confirmed PD by iwCLL criteria could be retreated with ibrutinib monotherapy until PD or unacceptable toxicity. For patients who had PD more than two years after completion of the original FD regimen, retreatment with the FD ibrutinib plus venetoclax regimen could be considered.	As part of a 28-day treatment cycle, patients were randomised equally to receive: • **oral chlorambucil** 0.5mg/kg (on days 1 and 15 of cycles 1 to 6) **plus IV obinutuzumab** 1,000mg (on days 1, 8 and 15 of cycle 1, and day 1 of cycles 2 to 6); or • **oral ibrutinib plus oral venetoclax**, as per the same dosing schedule used in the CAPTIVATE study. After completion of their FD regimen, patients in either group who developed IRC-confirmed PD and had active CLL disease may have been eligible to receive ibrutinib monotherapy until PD or unacceptable toxicity as per the investigator assessment.
Randomisation	Not applicable.	Stratified by IGHV mutational status (mutated vs. un-mutated vs. not available) and presence of del11q (yes vs. no).

Primary outcome	Investigator-assessed CR rate (CR/CRi)[a].	IRC-assessed PFS
Secondary outcomes	This included PFS and overall survival.	MRD negativity rate in the bone marrow; CR rate; ORR; overall survival.
Statistical analysis	The primary and secondary outcomes were evaluated using descriptive statistics.	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The order of the hierarchical statistical testing analysis was: IRC-assessed PFS, then the secondary outcomes as outlined above.

[a]defined as the proportion of patients with a CR or CR with incomplete bone marrow recovery (CRi).

Abbreviations: CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CrCl = creatinine clearance (as per the Cockcroft-Gault equation); CR = complete response; CT = computed tomography; del11q = chromosome 11q deletion; del17p = chromosome 17p deletion**;** ECOG PS = Eastern Cooperative Oncology Group Performance Status; FD = fixed duration; IGHV = immunoglobulin heavy-chain variable region; IRC = independent review committee; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; MRD = minimal residual disease; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; SLL = small lymphocytic lymphoma; TP53 = tumour protein 53

For the 'FCR unsuitable' population, the main direct evidence comes from the intention-to-treat (ITT) population in the GLOW study. Results from two extended follow-ups (August 2021 and January 2022 data cut-offs) of the ITT population are presented in table 2.2. However, only the August 2021 extended follow-up data were used to inform the indirect treatment comparisons and economic analyses; upon request the submitting company advised that there was insufficient time to use the updated data cuts in the economic analyses but did not anticipate it would significantly change the results of the economic analyses.

The results for independent review committee (IRC)-assessed PFS and overall survival, at the January 2022 data cut-off were consistent with the earlier August 2021 data cut; but the differences in overall survival between the two treatment groups were not statistically significant. The absolute difference, in the ibrutinib plus venetoclax and chlorambucil plus obinutuzumab groups respectively, in KM estimated overall survival at 36 months also reduced (90% and 84%).[1]

Table 2.2 Primary and selected secondary outcomes from the GLOW study.[1, 12]

Data cut-off date	August 2021		January 2022	
	Ibrutinib + venetoclax (n=106)	**Chlorambucil + obinutuzumab (n=105)**	**Ibrutinib + venetoclax (n=106)**	**Chlorambucil + obinutuzumab (n=105)**
Median follow-up	34.1 months		38.9 months	
Primary outcome: IRC-assessed progression-free survival				
Events, n	21	68	Not reported	Not reported
HR (95% CI), p-value	0.22 (0.13 to 0.36), p <0.001		0.19 (0.12 to 0.31)	
Median PFS (months)	NR	23.7	Not reported	Not reported
KM estimated PFS at 36 months	79%	28%	79%	30%

Secondary outcome: overall survival				
Deaths, n	11	16	12	22
HR (95% CI), p-value	0.76 (0.35 to 1.64) Not significant		0.58 (0.29 to 1.19) Not significant	
Median overall survival (months)	NR	NR	NR	NR
KM estimated overall survival at 30 months	89%	88%	90%	88%
KM estimated overall survival at 36 months	89%	81%	90%	84%
Abbreviations: CR = complete response; CRi = complete response with incomplete bone marrow recovery; del17p = chromosome 17p deletion; KM = Kaplan-Meier; NR = not reached; PFS = progression-free survival				

The submitting company also provided further follow-up data for overall survival at an August 2022 data cut-off (median follow-up 46.1 months); this showed a statistically significant improvement in overall survival for those treated with ibrutinib plus venetoclax, compared with chlorambucil plus obinutuzumab. The HR (95% CI) was 0.487 (0.26 to 0.91), p=0.021.[13, 14]

The main direct evidence for the 'FCR suitable' and 'high-risk' populations are derived from the fixed duration cohort in the CAPTIVATE study. The submitting company advised that the subgroup of patients with no del17p mutation (n=136) was attributable to the 'FCR suitable' population; this subgroup of patients were used for most analyses in the company submission. The subgroup of patients who had a del17p mutation and/or a TP53 mutation (n=27) was attributable to the 'high-risk' population; efficacy results for this subgroup of patients were comparable to those with no del17p mutation. Results of both of these subgroups are presented in table 2.3 from the primary analysis (November 2020 data-cut off) and the extended follow-up (August 2021 data cut-off).

Table 2.3 Primary and selected secondary outcomes from the subgroup of patients without a del17p mutation, and the subgroup of patients with a del17p and/or TP53 mutation (within the fixed duration cohort in the CAPTIVATE study).

	Patients without a del17p mutation (n=136)		**Patients with a del17p and/or TP53 mutation (n=27)**	
Data cut-off date	November 2020	August 2021	November 2020	August 2021
Median follow-up	27.9 months	38.7 months	27.9 months	38.7 months
Primary outcome: investigator-assessed rate of CR/CRi				
CR/CRi, %	56%	58%	56%	56%
Secondary outcome: investigator-assessed progression-free survival				
Events, n	16	23	*	*
Median PFS	NR	NR	NR	NR
KM estimated PFS at 24 months	96%	-	84%	-
KM estimated PFS at 36 months	-	89%	-	80%
Secondary outcome: overall survival				
Deaths, n	3	3	0	0
Median overall survival	NR	NR	NR	NR
KM estimated overall survival at 24 months	98%	-	96%	-

KM estimated overall survival at 36 months	-	98%	-	96%
Abbreviations: CR = complete response; CRi = complete response with incomplete bone marrow recovery; del17p = chromosome 17p deletion; KM = Kaplan-Meier; NR = not reached; PFS = progression-free survival *considered confidential by company				

2.2. Health-related quality of life outcomes

No health-related quality of life (HRQoL) data were collected in the CAPTIVATE study.[1, 16]

HRQoL was assessed in the GLOW study using the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire. At the August 2021 data cut-off (median follow-up 34.1 months), the results suggest that both treatment groups saw improvements in HRQoL, however no significant differences between treatment groups were observed.[17]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing ibrutinib plus venetoclax with the most relevant treatments in the defined populations, the submitting company presented an indirect treatment comparison (ITC) for the 'FCR-suitable' and 'FCR-unsuitable' populations. An ITC was not carried out for the 'high-risk' patients as they considered this unfeasible due to limited data. The PFS results have been used by the submitting company to suggest that ibrutinib plus venetoclax has better efficacy than FCR (FCR suitable population), whilst having similar efficacy to acalabrutinib monotherapy and venetoclax plus obinutuzumab (FCR unsuitable population) These results have been used to inform the economic base case, details are presented in Table 2.4.

Table 2.4: Summary of indirect treatment comparison

Criteria	Overview
Design	• **'FCR-suitable' population –** an unanchored ITC, using propensity score analysis with ATC weighting and excluding missing covariate values in the base case analysis. • **'FCR-unsuitable' population –** anchored MAICs using chlorambucil plus obinutuzumab as the common comparator and matching on four characteristics in the base case analysis (age, ECOG PS, CIRS, and TP53 mutation status).
Population	Where possible the submitting company tried to achieve the following populations in the ITCs: • **'FCR-suitable' –** patients with no del17p mutation, with a CIRS ≤6, CrCl ≥70mL/min, and ECOG PS<2, and for whom fludarabine-based therapy is deemed suitable. • **'FCR-unsuitable' –** patients with no del17p mutation, with a CIRS >6 and/or CrCl <70mL/min, and for whom fludarabine-based therapy is deemed unsuitable. However, the study populations included in the ITCs were broader than these definitions (see key uncertainties, section 4.2).
Comparators	• **'FCR-suitable' –** compared ibrutinib plus venetoclax with FCR. • **'FCR-unsuitable' –** compared ibrutinib plus venetoclax with: venetoclax plus obinutuzumab, and acalabrutinib monotherapy.
Studies included	• **'FCR-suitable' –** FD cohort from the CAPTIVATE study (ibrutinib plus venetoclax)[11] & E1912 (FCR)[18]. • **'FCR-unsuitable' –** GLOW (ibrutinib plus venetoclax)[12], CLL14 (venetoclax plus obinutuzumab)[19], and ELEVATE-TN (acalabrutinib monotherapy).[20]

Outcomes	**For the both the 'FCR-suitable' and 'FCR-unsuitable' populations:** • Investigator-assessed Progression-free survival (PFS) • Overall survival • Time to next treatment **For the 'FCR-suitable' population only:** • Time to treatment discontinuation • Complete response rate • Safety (including any grade TEAEs, grade 3 to 4 TEAEs, and treatment discontinuation).
Results	**'FCR-suitable':** The results used in the economic base case analysis suggest that ibrutinib plus venetoclax was more effective than FCR. **'FCR-unsuitable':** The results used in the economic base case analysis suggest that ibrutinib plus venetoclax had similar efficacy to venetoclax plus obinutuzumab and acalabrutinib.
Abbreviations: ATC = Average treatment effect in the control population; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance (as per the Cockcroft-Gault equation); del17p = chromosome 17p deletion; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FCR = fludarabine, cyclophosphamide, and rituximab; FD = fixed duration; ITC = indirect treatment comparison; MAICs = matching adjusted indirect comparisons; PLD = patient level data; TEAEs = treatment emergent adverse events.	

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

3. Summary of Safety Evidence

The overall side effect profile was considered to be well characterised and manageable by the regulator, with the option of a treatment holiday noted as a positive. They highlighted that the safety profile of ibrutinib plus venetoclax is less favourable compared with the less effective treatment regimens for patients with CLL. In the GLOW study, they noted a trend towards an increase in treatment associated deaths with ibrutinib plus venetoclax treatment, though there is high uncertainty about the magnitude of the difference and to what extent either agent (ibrutinib or venetoclax) had on the safety profile.[1]

Table 3.1 Summary of treatment emergent adverse events in the CAPTIVATE and GLOW studies.

Data cut-off	**November 2020**	**February 2021**	
	'All-treated' FD cohort in CAPTIVATE[1, 11]	**ITT population in GLOW[1, 12]**	
	Ibrutinib + venetoclax (n=159)	**Ibrutinib + venetoclax (n=106)**	**Chlorambucil + obinutuzumab (n=105)**
Median duration of treatment	13.8 months	13.8 months	5.1 months
Any TEAE	99%	99%	94%
Serious TEAEs	23%	46%	28%
TEAEs leading to a dose reduction of any study drug	21%	26%	21%
TEAEs leading to discontinuation of any study drug	5.0%	21%	7.6%
Deaths within 30 days after the last dose of study treatment	0.3%	6.6%	1.9%
Abbreviations: FD = fixed duration; ITT = intention to treat; TEAE = treatment-emergent adverse event			

Table 3.2 Summary of the most frequent (>10% occurrence) grade ≥3 adverse events, and adverse events of special interest (in the CAPTIVATE and GLOW studies).

Data cut-off	November 2020	February 2021	
	'All-treated' FD cohort in CAPTIVATE[1, 11]	ITT population in GLOW[1, 12]	
	Ibrutinib + venetoclax (n=159)	Ibrutinib + venetoclax (n=106)	Chlorambucil + obinutuzumab (n=105)
Median duration of treatment	13.8 months	13.8 months	5.1 months
Grade ≥3 TEAEs	62%	76%	70%
Grade ≥3 neutropenia	33%	28%	50%
Grade ≥3 diarrhoea	10%	10%	1.0%
Grade ≥3 thrombocytopenia	13%	5.7%	20%
Grade ≥3 adverse events of special interest			
Major Haemorrhage	0.9%	3.8%	1.0%
Tumour Lysis Syndrome	0.3%	0%	5.7%
Atrial fibrillation	1.5%	6.6%	0%
Hypertension	7.1%	8.5%	1.9%
Infections	8.4%	15%	10%
Abbreviations: FD = fixed duration; ITT = intention to treat; TEAE = treatment-emergent adverse event			

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- The GLOW study, which was a phase III, randomised controlled study, provided results applicable to the 'FCR unsuitable' population.[1, 12] Extended follow-up data (median follow-up 46 months) from this study showed a statistically significant improvement in overall survival for those treated with ibrutinib plus venetoclax, compared with chlorambucil plus obinutuzumab. The HR (95% CI) was 0.487 (0.26 to 0.91), p=0.021.[13, 14]

- The GLOW study also showed statistically significant improvement in IRC-assessed PFS. With KM estimated PFS rates at 36 months of 79% and 30%, in the ibrutinib plus venetoclax group and the chlorambucil and obinutuzumab groups respectively, this was also deemed to have demonstrated a significant clinical benefit. PFS benefits were also consistent across subgroups (including IGHV and del11q status).[1]

- Results from the fixed duration cohort of the CAPTIVATE study are applicable to the 'FCR-suitable' and the 'high-risk' populations. Patients with previously untreated CLL who received ibrutinib plus venetoclax and who had no del17p mutation (n=136), had an investigator-assessed rate of CR/CRi of 58% at the extended follow-up (August 2021 data cut-off). In the fixed duration cohort of the CAPTIVATE study, efficacy results for the 'high risk' subgroup of patients (n=27) were comparable to those without del17p mutations (n=136); patients in this subgroup had an investigator-assessed rate of CR/CRi of 56%.[1, 11]

- In the fixed duration cohort of the CAPTIVATE study, the baseline characteristics for the patients without a del17p mutation (n=136) had characteristics broadly representative of an 'FCR suitable' population according to Scottish practice guidelines: no patients were over 71 years of age, all had

an ECOG PS of 0 or 1, and only 4.4% had a CrCl<60 mL/min.[1] Unfortunately, CIRS data was not collected for the CAPTIVATE study unavailable, though the submitting company advise that it is likely that most patients in the CAPTIVATE study would have a CIRS >6.

4.2. Key uncertainties

- In the GLOW study, after 46.1 months of follow-up (August 2022 data cut-off), the medians for PFS and overall survival have not been reached in the ibrutinib plus venetoclax group; the median for overall survival has also not been reached in the chlorambucil plus obinutuzumab group.[13, 14] The regulatory authority has noted that the sample size of the study is relatively small and may be responsible for the lack of PFS and overall survival events.
- Although the open-label design of the GLOW study is unlikely to have significantly affected the primary efficacy outcomes (since the IRC that performed tumour assessment were blinded to study treatment allocation), it may have biased patient-reported outcomes including safety and HRQoL. [1]
- The CAPTIVATE study, was a non-comparative, open-label, phase II study, where the primary and secondary outcomes were evaluated by a non-blinded investigator assessment. This is prone to several biases and interpretation of efficacy and safety data were hampered by the lack of a control group, meaning results are descriptive only. After 38.7 months of follow-up, the medians for progression-free survival and overall survival have not been reached.[1, 11] No HRQoL data were collected in the CAPTIVATE study.[1, 16] The main direct evidence for the 'FCR suitable' and 'high-risk' populations are derived from subgroups of a single cohort within the CAPTIVATE study, with no direct evidence available against any comparator.

The 'FCR suitable' population

- There were no direct comparative data against other medicines that may be used in Scottish practice such as venetoclax plus obinutuzumab. The ITC presented by the company had some limitations; a broader population was included, no indirect evidence for venetoclax plus obinutuzumab, unobserved or unmeasured confounding factors that could not be adjusted for may bias the results and there were some inconsistencies in the results depending on the methods used. Despite these uncertainties, the statistician considered that the company's approach was reasonable.
- Within the fixed duration cohort of the CAPTIVATE study, 57% (78/136) of the patients who did not have a del17p mutation, had an un-mutated IGHV status.[1] These patients will have inferior outcomes with FCR and venetoclax plus obinutuzumab, and since FCR is not recommended as a treatment option by the BSH for patients without an IGHV mutation (and without a del17p or TP53 mutation) then this adds uncertainty about whether this study cohort currently represents an 'FCR suitable' population.[10] The results from the subgroup analyses in CAPTIVATE suggest a potentially higher rate of response and longer PFS in the un-mutated IGHV patients, however the subgroup analyses were not statistically powered to make definitive conclusions about a differential response according to IGHV status, and longer follow-up of these cohorts is needed.[1, 11]
- At the August 2021 data cut-off (median follow-up 38.7 months), sensitivity analyses revealed there were differences in the rates of investigator-assessed (58%) and IRC-assessed (64%) CR/CRi,

in patients without a del17p mutation.[1] This raises some uncertainty about the robustness of the rate of CR/CRi reported.

The 'FCR unsuitable' population

- Clinical experts contacted by SMC confirmed that the comparator chlorambucil plus obinutuzumab is rarely used for these patients. There were no direct comparative data against the most relevant comparators in Scottish clinical practice, venetoclax plus obinutuzumab and acalabrutinib monotherapy. The ITC also has some limitations, with the population being broader, some prognostic characteristics could not be matched and the immature data and evidence of non-proportional hazards added uncertainty. However the scenario analyses were consistent with the base case result and the conclusions were considered reasonable.
- The regulatory authority noted a trend towards treatment associated deaths with ibrutinib plus venetoclax.[1] As a result of these observations, the BSH has advised caution in older patients and/or those with more co-morbidities, and recommended limiting the use of ibrutinib plus venetoclax to fit patients with high-risk CLL (for example those with: an un-mutated IGHV, a TP53 mutation, or an 11q deletion).[10]

The 'high risk' population

- The direct evidence provided for this population consists of only 27 patients from the fixed duration cohort; the regulatory authority noted that the direct evidence for this population is 'scarce' and that uncertainties remain about the persistence of treatment effect with ibrutinib plus venetoclax, especially in those with a del17p and/or TP53 mutation.[1]
- There were no direct comparative data against other medicines that may be used in Scottish practice, such as: venetoclax plus obinutuzumab (fixed duration of 12 months); ibrutinib monotherapy; acalabrutinib monotherapy; and venetoclax monotherapy. The submitting company also did not present any indirect comparative data, as they considered this unfeasible due to limited data available. The company has assumed that the relative efficacy in FCR-unsuitable patients is generalisable to high-risk patients. However, experts contacted by SMC agree that this assumption is highly uncertain.

4.3. Clinical expert input

Clinical experts consulted by SMC provided mixed views on whether ibrutinib in combination with venetoclax represented a therapeutic advancement; the data are promising but there is limited follow-up in the studies, and a lack of head-to-head comparisons with relevant treatments. They consider that the combination would provide an all oral, fixed duration treatment option for patients.

4.4. Service implications

Clinical experts consulted by SMC considered that the oral combination of ibrutinib plus venetoclax could reduce day case needs compared with venetoclax plus obinutuzumab (parenteral). The fixed duration of ibrutinib plus venetoclax could also reduce the number of outpatient appointments required if it was used instead of BTKi monotherapies.

5. 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 **ibrutinib (Imbruvica®),** as an **orphan equivalent** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Chronic lymphocytic leukaemia (CLL) is a low-grade lymphoproliferative disorder where those with progressive disease and adverse genetic features may have their life expectancy significantly reduced due to the condition and its complications, or because of treatment side effects. Results from a 'Living with Leukaemia' highlighted that many patients with CLL feel more anxious and depressed following their diagnosis; describe their guilt at being a "burden to their carers"; and the ongoing stress associated with CLL treatments and the knowledge that their CLL is incurable.
- Despite the availability of very effective first-line treatments for CLL, none of these regimens are all-oral, fixed duration combinations; this means that patients prescribed combination treatment (as well as families and carers) need to attend hospital for the administration and review of at least one of their treatments. Additionally, remission timescales can vary from patient to patient depending on their individual DNA gene profile, therefore any new effective and tolerable treatment combinations are welcome.
- Evidence derived from the CAPTIVATE and GLOW studies showed that ibrutinib plus venetoclax treatment resulted in improved complete response rates (CAPTIVATE) and significantly delayed disease progression against the comparator (GLOW study). While there is no direct comparison with other first-line treatments that are used in Scotland, ibrutinib plus venetoclax does offer the option of an all-oral, fixed-duration therapy that may have a similar efficacy to these treatments.
- The side effect profile of ibrutinib plus venetoclax appears to be comparable to other CLL regimens. Additionally, since ibrutinib plus venetoclax is a time-limited therapy (15 months), it potentially has a reduced risk of toxicities, such as atrial fibrillation and haemorrhage that are associated with the long-term use of Bruton's tyrosine kinase (BTK) inhibitors. It is also recognised that CLL patient's response to vaccination, for example the COVID-19 vaccine, and the ability to clear infections such as COVID-19 is better whilst not on CLL therapy. Therefore, shortening the duration of BTKi therapy is desirable.
- This is an all-oral, fixed-duration treatment regimen, which compared to other currently available first-line therapies, would have less financial and travelling implications for patient's family or carers; especially for those who reside far away from treatment centres. This combination would provide more independence for the patient, and compared to other single-agent BTK inhibitors that are usually given for several years with 3-monthly clinic reviews, ibrutinib plus venetoclax is only given for 15 months in total; this offers patients and their families the opportunity to return back to some form of normality between lines of treatment. A fixed-duration, all-oral, outpatient-based treatment would likely have a significant beneficial effect on patient's family life and their ability to undertake work and leisure activities. It would also allow them to fully contribute to their household and wider society.
- An all-oral treatment option means that, compared to one of the main CLL first-line treatments venetoclax plus obinutuzumab, this could be administered entirely in the outpatient setting, and

would reduce the number of hospital visits, and day case time required for the administration of intravenous therapies like obinutuzumab. These reduced hospital visits would reduce patient expenses from travelling and this, along with the fixed-duration, would improve the financial, emotional, and mental wellbeing of patients and their families.

- Since this will be a treatment that can be delivered as an outpatient, it will likely require less NHS staff resource and time. Additionally, ibrutinib and venetoclax are already used on their own or part of treatment regimens for CLL, so there would be no requirement to train staff on these medicines.

Additional Patient and Carer Involvement

We received patient group submissions from CLL Support and Leukaemia Care. CLL Support is a charitable incorporated organisation and Leukaemia Care is a registered charity. CLL Support has received 47% pharmaceutical company funding in the past two years, including from the submitting company. Leukaemia Care has received 27% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	The economic model considered three populations: • The **FCR-suitable** population were modelled using a 40 year time horizon, with an assumed mean age of 58 at the start of treatment. • The **FCR-unsuitable** and **high-risk** populations were modelled using a 30 year time horizon, with an assumed mean starting age of 71.
Population	The modelled population aligned with the MHRA approved licence for ibrutinib plus venetoclax in patients with previously untreated CLL.[2] The total treatment population was split into three populations: **FCR-suitable** patients, **FCR-unsuitable** patients and **high-risk** patients. The definitions of these populations matched those described throughout the clinical sections of this document (see Section 1.3).
Comparators	A total of 5 comparators were used, which differed across the populations. The comparator and population combinations were as follows: • **FCR-suitable**: FCR and venetoclax plus obinutuzumab • **FCR-unsuitable**: Chlorambucil plus obinutuzumab, venetoclax plus obinutuzumab, and acalabrutinib • **High-risk**: venetoclax plus obinutuzumab, acalabrutinib and ibrutinib
Model description	The company submitted a four state semi-Markov model, which was structurally consistent between all three patient populations. The model contained the states of progression-free on first-line treatment (PF 1L), progression-free on second-line treatment (PF 2L), post-progressed disease

	(PPD) and death. Patients started in the PF 1L state, where they received ibrutinib plus venetoclax or one of the comparators listed above. Upon progression patients moved to the PF 2L state, where they received second-line treatment (ibrutinib, venetoclax plus rituximab or acalabrutinib), or to the PPD state. Those patients in the PF 2L state who progressed moved to the PPD state. Within the PPD state, patients received best supportive care. Patients could transition from all the alive states to the dead state.
Clinical data	A variety of clinical sources were used to describe the efficacy of ibrutinib plus venetoclax in the economic model. The E1912 study[18] was used to inform the efficacy of FCR in delaying progression and the mortality rate of patients receiving FCR during first-line treatment. A propensity scored matched indirect treatment comparison (ITC) combined data from the E1912[18] and CAPITVATE studies[11] to estimate the treatment effect of ibrutinib plus venetoclax on progression-free survival (PFS) relative to FCR in an **FCR-suitable** population. The GLOW study[12] provided comparative PFS data between ibrutinib plus venetoclax and obinutuzumab plus chlorambucil, as well as mortality data during first-line treatment, in an **FCR-unsuitable** population. Anchored match adjusted indirect comparisons (MAICs) combined data from the GLOW,[12] CLL14,[19] and ELEVATE-TN[20] studies to estimate the relative efficacy of venetoclax plus obinutuzumab, obinutuzumab plus chlorambucil and acalabrutinib on PFS in an **FCR-unsuitable** population, relative to ibrutinib plus venetoclax. The RESONATE study[21] was used to estimate the PFS of second-line treatment, as well as the mortality rates for patients in second-line treatment or in the PPD state. Despite the inclusion of patients from the **high-risk population** in the participants of the CAPITVATE study, no direct or indirect evidence on the use of ibrutinib plus venetoclax in **high-risk patients** was used in the modelling. Instead, all inputs for that group were based on an assumption of equal treatment efficacy between the **FCR-unsuitable** and **high-risk patients**.
Extrapolation	**FCR suitable population:** PFS for patients receiving FCR at first-line was extrapolated by fitting a Weibull curve to data from the E1912 study. The PFS for patients receiving ibruitinib plus venetoclax was estimated by applying the hazard ratio from the ITC to the FCR curve. The PFS for patients receiving venetoclax plus obinutuzumab was estimated by combining the results of the ITC and MAIC to estimate the hazard ratio between venetoclax plus obinutuzumab and FCR, despite the MAIC having included FCR-unsuitable patients. The PFS curves defined the exit from the PF 1L state, with three possible destinations – the PF 2L state, the PPD state and the dead state. The mortality rate for patients receiving first-line treatment was estimated from FCR patients in the E1912 study. This was assumed equal across time, and across all treatments received at first-line. After accounting for death, the company assumed that all patients exiting the PF 1L state moved to the PF 2L state, and none moved directly to the PPD state. **FCR unsuitable population:** PFS for patients receiving ibrutinib plus venetoclax was estimated by applying a piecewise exponential curve to data from the GLOW study. The directly observed data was used for the first 15 cycles (3 months), and an exponential distribution applied thereafter. The PFS for the first-line treatment with obinutuzumab plus chlorambucil was estimated by applying a 7-knot spline model to data from the obinutuzumab plus chlorambucil arm of the GLOW study. The PFS for acalabrutinib and venetoclax plus obinutuzumab patients was projected by applying the hazard ratio estimated from the anchored MAICs to a single piece exponential curve estimated from the ibrutinib plus venetoclax data of the GLOW study.

	Mortality during first-line treatment was estimated based on the rates observed in the GLOW study. The mortality rate for obinutuzumab plus chlorambucil patients was estimated directly and assumed constant across time. The mortality rate estimated for ibrutinib plus venetoclax patients was applied for 15 cycles, after which the mortality rates was matched to that observed for obinutuzumab plus chlorambucil. The mortality rates observed for obinutuzumab plus chlorambucil was also applied for venetoclax plus obinutuzumab and acalabrutinib. As in the case of the FCR-suitable patients, after accounting for mortality, all patients existing out of the PF 1L state were assumed to move to the PF 2L state. **High-risk population:** PFS and mortality rates during first-line treatment for the high-risk patients receiving venetoclax plus obinutuzumab and acalabrutinib were assumed equal to FCR-unsuitable patients due to a lack of evidence in that population. Across all the sub-populations and treatment arms, movements out of the PF 2L state were defined by an exponential curve fitted to the data observed for ibrutinib patients who had received 1 or 2 prior lines of therapy in the RESONATE study. Similar, death during second-line treatment was estimated from that same ibrutinib data and applied across all sub-populations and treatment arm combinations. Finally, in the absence of data, the mortality rate for patients in the PPD state was assumed equal to that in the PF 2L state across all sub-populations and treatment arm combinations.
Quality of life	Quality of life was captured through utility values applied to each of the alive states, with additional disutilities for AEs and IV treatment administration. The utility value for the PF 1L state was estimated from EQ-5D questionnaires collected as part of the GLOW study. Utility values for the PF 2L and PPD states were assumed equal and estimated from Holzner et al. (2004).[22] Both those utility values were age adjusted to match the assumed starting ages in the model. The utility values for the high-risk patients were assumed to match those for the **FCR-unsuitable** patients due to the same assumed starting age. Each administration of an IV treatment was associated with a utility decrement which was drawn from a previous HTA submission.[23]
Costs and resource use	Medicine costs included acquisition and administration costs for both first- and second-line treatments, as well as AE costs for first-line treatment only. Patients receiving ibrutinib plus venetoclax, venetoclax plus obinutuzumab, and obinutuzumab plus chlorambucil were assumed at risk of treatment emergent tumour lysis syndrome (TLS), with costs of treatment included. Health state treatment costs were estimated based on various categories of NHS resource use, including tests (blood count, renal, liver function, immunoglobulin, bone marrow), scans (chest x-ray, CT), visits (haematologist, inpatient non-surgical) and blood transfusions. An end-of-life cost was included values at £7,569.[24]
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. The results presented do not take account of the PAS for venetoclax, obinutuzumab and acalabrutinib but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for venetoclax, obinutuzumab and acalabrutinib due to commercial confidentiality and competition law issues.

Abbreviations: AE = adverse event; CLL = chronic lymphocytic leukaemia; CT = computerised tomography; FCR = fludarabine, cyclophosphamide, and rituximab; HTA = health technology assessment; IV = intravenous; MHRA = Medicines and Healthcare products Regulatory Agency.

6.2. Results

The baseline results are presented in Table 6.2.1, 6.2.2 and 6.2.3 for the FCR-suitable, FCR-unsuitable and high-risk populations respectively. No combined economic results across subgroups and comparators was provided. The results in the tables below are inclusive of the PAS discount on ibrutinib, but not those on venetoclax, obinutuzumab, obinutuzumab and acalabrutinib

Table 6.2.1 Base case results – FCR-suitable population (inclusive of PAS discount on ibrutinib only)

Technologies	Life Years Gained	ICER
I+V	-	-
FCR	2.01	£3,795
VenO	1.19	Dominant

Abbreviations: *I+V, ibrutinib plus venetoclax; FCR, fludarabine plus cyclophosphaminde; VenO, venetoclax plus obinutuzumab; QALY, quality adjusted life year; ICER; incremental cost-effectiveness ratio; dominant, cheaper and more effective*

Table 6.2.2 Base case results – FCR-unsuitable population (inclusive of PAS discount on ibrutinib only)

Technologies	Life Years Gained	ICER
I+V	-	-
O-Clb	1.47	Dominant
VenO	0.23	Dominant
Acalabrutinib	-0.15	£137,872,305 (SW quad)

Abbreviations: *I+V, ibrutinib plus venetoclax; O-Clb, obinutuzumab plus chlorambucil; VenO, venetoclax plus obinutuzumab; LY, life years; QALY, quality adjusted life year; ICER; incremental cost-effectiveness ratio; SW quad, South West quadrant of the cost-effectiveness plane (less effective and cheaper)*

Table 6.2.3 Base case results – high-risk population (inclusive of PAS discount on ibrutinib only)

Technologies	Life years Gained	ICER
I+V	-	-
Ibrutinib	-0.15	£280,237,021 (SW quad)
VenO	0.23	Dominant
Acalabrutinib	-0.15	£1837,872,305 (SW quad)

Abbreviations: *I+V, ibrutinib plus venetoclax; VenO, venetoclax plus obinutuzumab; LY, life years; QALY, quality adjusted life year; ICER; incremental cost-effectiveness ratio; SW quad, South West quadrant of the cost-effectiveness plane*

6.3. Sensitivity analyses

Sensitivity analysis suggested that the main driver of economic results were the hazard ratios used to project progression free survival during first line treatment of treatments relative to the base curves and the medicine acquisition costs.

The company also provided a selection of scenarios exploring areas of uncertainty.

Table 6.3.1 Scenario analyses – FCR-suitable population (inclusive of PAS discount on ibrutinib only)

		Comparator	
Scenario description	**Base case description**	**FCR**	**VenO**
Time Horizon 30 years	Time Horizon 40 years	£3,693	Dominant across all presented scenarios
Time Horizon 35 years		£3,755	
HR I+V vs FCR – ITC weighting = ATT	HR I+V vs FCR – ITC weighting = ATC	£14,074	
HR I+V vs FCR – ITC weighting = ATO		£6,830	
HR VenO vs. FCR derived from CL113 study	HR VenO vs. FCR derived indirectly via anchored MAIC	Dominant	
FCR extrapolation - Gompertz	FCR extrapolation - Weibull	£15,419	
FCR extrapolation - Generalized Gamma		£6,431	
80% receiving subsequent treatments	100% receiving subsequent treatments	£7,434	
TFI - 0 Cycles	TFI - 14 Cycles	£241	
IV Wastage - Exclude	IV Wastage - Include	£9,137	
Oral Wastage - Include	Oral Wastage - Exclude	£4,933	
SMR 1.1	SMR 1.0	£3,256	
SMR 1.15		£2,979	
SMR 1.19		£2,754	

Abbreviations: *FCR, fludarabine, cyclophosphamide, and rituximab; VenO, venetoclax plus obinutuzumab; HR, hazard ratio; ITC, indirect treatment comparison; ATC, Average treatment effect in the control population; ATT, Average treatment effect in the treated population; ATO, Average treatment effect in the combined/overall population; MAIC, match adjusted indirect comparison; TFI, treatment free interval; IV, intravenous; SMR, standardised mortality ratio;*

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

Table 6.3.2 Scenario analyses – FCR-unsuitable and high-risk populations (inclusive of PAS discount on ibrutinib only)

		FCR-unsuitable			High-risk		
Scenario description	**Base case description**	**O-Clb**	**VenO**	**Acala.**	**Ibrut.**	**VenO**	**Acala.**
Time Horizon 25 years	Time Horizon 30 years	Dominant across all presented scenarios	Dominant across all presented scenarios	£89m (SW)	£83m (SW)	Dominant across all presented scenarios	£89m (SW)
Time Horizon 20 years				£28m (SW)	£15m (SW)		£28m (SW)
Time Varying HRs - ≤12 months/>12 months	Single HR - Adjusted for age, ECOG, CIRS, and TP53 mutation			Dominant	Dominant		Dominant
Fully adjusted MAIC				Dominant	£280m (SW)		Dominant
Unadjusted MAIC				£1m (SW)	£280m (SW)		£1m (SW)
Cost-minimization acalabrutinib				£92m(SW)	Dominant		£92m (SW)
80% receiving subsequent treatments	100% receiving subsequent treatments			Dominant	Dominant		Dominant
TFI - 0 Cycles	TFI - 14 Cycles			£138m (SW)	£281m (SW)		£138m (SW)
IV Wastage - Exclude	IV Wastage - Include			£138m (SW)	£280m (SW)		£138m (SW)
Oral Wastage - Include	Oral Wastage - Exclude			£138m (SW)	£298m (SW)		£138m (SW)
SMR 1.1	SMR 1.0			£29m (SW)	£16m (SW)		£29m (SW)
SMR 1.15				£22m (SW)	£11m (SW)		£22m (SW)
SMR 1.19				£18m (SW)	£9m (SW)		£18m (SW)

Abbreviations: *I+V, ibrutinib plus venetoclax; VenO, venetoclax plus obinutuzumab; HR, hazard ratio; MAIC, match adjusted indirect comparison; TFI, treatment free interval; IV, intravenous; SMR, standardised mortality ratio; SW quad, South West quadrant of the cost-effectiveness plane*

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

6.4. Key strengths

The main strengths of the analysis were identified as:

- The population included in the economic model matched the licensed indication.
- The model structure appeared to be suitable and did not introduce any obvious source of bias.
- The comparators were appropriate and aligned to those products most likely replaced in Scottish clinical practice.
- The modelling suggested that the economic results were highly stable across a range of scenarios.

6.5. Key uncertainties

The main uncertainties in the analysis were identified as:

- The CAPTIVATE study, which was used as a data source for the FCR-suitable population in the economic model, was considered at high risk of bias due to its open-label design, lack of comparator, and non-blinded investigator assessment.
- There was no direct evidence comparing ibrutinib plus venetoclax to FCR in the FCR-suitable population, leading to the use of a propensity score matched ITC. This analysis introduces uncertainty into the analysis. In particular, there is uncertainty whether the most appropriate weighting method had been used, and unknown and unobserved factors may have biased results.
- There is no direct head-to-head evidence comparing ibrutinib plus venetoclax to venetoclax plus obinutuzumab, and acalabrutinib monotherapy in the FCR-unsuitable population, leading to the use of MAICs. These MAICs have introduced uncertainty into the analysis, particularly through the failure to control for the del17p mutation differences between the included studies. The hazard ratios generated within the MAICs were also wide, and crossed one, indicating no statistical difference between treatments.
- Related to the two points above, the hazard ratios used to project the PFS during first line treatment were key drivers of the economic results. Varying these hazard ratios to the 95% confidence limits led to large changes in the economic results.
- Despite the use of indirect comparisons, several data gaps remained, and the company used assumptions to address them. Several of these assumptions appeared reasonable (including the assumed treatment efficacy of venetoclax plus obinutuzumab between the FCR-unsuitable and the FCR-suitable populations and the outcome equivalence between acalabrutinib and ibrutinib), although they still contributed towards uncertainty in the economic results. Another significant assumption was that the clinical outcomes between the FCR-unsuitable and high-risk patients would be the same, and the suitability of that was questioned by clinical experts consulted by SMC.
- Several of the data sources used to estimate and project PFS are highly immature. While that represented a good clinical outcome for patients, it introduced uncertainty in the estimation of hazard ratios and the fitting of survival curves, which increase the uncertainty in the economic results.

7. Conclusion

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

8. Guidelines and Protocols

The British Society for Haematology (BSH)[10], and the European Society for Medical Oncology (ESMO)[5], published guidelines on the treatment of CLL in 2022 and 2021, respectively.

9. Additional Information

9.1. Product availability date

19 December 2022.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
Ibrutinib plus venetoclax	**As per section 1.1 (see above)**	**118,178**

Costs from BNF online on 04 October 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated 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.**

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This assessment is based on data submitted by the applicant company up to and including 16 June 2023.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.