Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2229

brentuximab vedotin 50mg powder for concentrate for solution for infusion (Adcetris®)

Takeda UK Ltd.

6 December 2019

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

brentuximab vedotin (Adcetris®) is accepted for restricted use within NHSScotland.

Indication under review: The treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

SMC restriction: for the treatment of patients with advanced CTCL, defined as mycosis fungoides stage IIB and above, primary cutaneous anaplastic large cell lymphoma or Sézary Syndrome.

In an open-label, phase III study in patients with previously treated CD30+ CTCL, the objective response rate maintained for at least four months was significantly higher in patients who received brentuximab vedotin than physician's choice of one of two treatments.

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

Chairman
Scottish Medicines Consortium

Indication

Brentuximab vedotin is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.[1]

Dosing Information

The recommended dose is 1.8mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with CTCL should receive up to 16 cycles.

If the patient's weight is more than 100kg, the dose calculation should use 100kg.

Brentuximab vedotin should be administered under the supervision of a physician experienced in the use of anti-cancer agents.

Further details are included in the summary of product characteristics (SPC).[1]

Product availability date

March 2019.
Brentuximab vedotin has conditional marketing authorisation from the European Medicines Agency. It meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Brentuximab vedotin is an antibody drug conjugate which is composed of a monoclonal antibody covalently linked via an enzyme-cleavable linker to the antimitotic small molecule monomethyl auristatin E. It delivers an antineoplastic agent to CD30-expressing tumour cells resulting in selective apoptotic cell death. CD30 is a type I transmembrane glycosylated protein and is expressed on cell subsets of non-Hodgkin Lymphoma, including cutaneous T-cell lymphoma (CTCL).[2, 3]

The submitting company has requested that SMC considers this product when positioned for use in patients with advanced CTCL, defined as mycosis fungoides stage IIB and above, primary cutaneous anaplastic large cell lymphoma (ALCL) or Sézary Syndrome.

Evidence for this indication is from ALCANZA, an open-label, randomised phase III study. ALCANZA recruited patients with mycosis fungoides or primary cutaneous ALCL who had received at least one previous systemic therapy (or radiotherapy for those with primary cutaneous ALCL). They were required to have CD30+ disease (≥10%), histologically confirmed by central review. Patients had Eastern Cooperative Oncology Group performance status 0 to 2 and adequate hepatic and renal function.[2, 3]

Eligible patients were randomised equally to receive brentuximab vedotin, or physician's choice of either bexarotene or methotrexate, stratified by disease diagnosis (mycosis fungoides or primary cutaneous ALCL). Brentuximab vedotin 1.8mg/kg intravenous infusion was given on day 1 of each 21-day cycle for up to 16 cycles (approximately 48 weeks). In patients above 100kg the dose was based on 100kg. Methotrexate 5mg to 50mg orally was given once weekly as a single dose for up to 48 weeks. Dosage

adjustments to achieve optimal clinical response at the lowest effective dose were allowed. Bexarotene 300mg/m^2 orally was given once daily for up to 48 weeks. The dose could be reduced to 200mg/m^2/day or 100mg/m^2/day if needed or treatment could be temporarily suspended for toxicity. In addition, for patients receiving bexarotene, treatment with fenofibrate 145mg to 200mg for 7 days and a low dose of synthetic thyroxine (T4) was required.[2, 3]

The primary outcome was the proportion of patients achieving an objective global response (complete or partial response) lasting at least four months determined by an independent review facility. This was assessed in the intention-to-treat (ITT) population, defined as all randomised patients who had CD30+ disease according to the Ventana antiCD30 assay (n=128). A fixed sequence testing procedure was used for primary and secondary outcomes to control for type I error.

At the primary analysis, after a median follow-up of 22.9 months, the difference in objective response rate maintained for at least four months between groups was statistically significant favouring brentuximab vedotin.[2, 3]

There were three key secondary outcomes: The proportion of patients achieving a complete response as their best response, progression-free survival (PFS), and symptom burden measured by change in the seven item symptom domain of health-related quality of life measure, Skindex-29, questionnaire.[2, 3] The primary outcome and selected secondary outcomes are detailed in Table 1 below. Overall survival was not a specified study outcome but at the primary analysis, median overall survival had not been reached in either group.[3] Results are available from the final analysis, median follow-up for overall survival was 48.4 months in the brentuximab vedotin group (n=64) and estimated 3-year overall survival was 64%.[4]

Table 1: Primary outcome and selected secondary outcomes from ALCANZA in the ITT population.[2, 3]

	Brentuximab vedotin (n=64)	Bexarotene or methotrexate (n=64)	Difference or hazard ratio (95% Confidence Interval [CI])	p value
Objective response rate lasting at least 4 months	56% (36/64)	12% (8/64)	44% (29 to 58)	p<0.001
Complete response	16% (10/64)	1.6% (1/64)	14% (-4 to 32)	p=0.0046
Median PFS	16.7 months	3.5 months	0.27 (0.17 to 0.43)	p<0.001
Number of patients with a PFS event	30	44	-	-
Mean maximum reduction in symptom domain of Skindex-29 Score	-28.0	-8.6	-	p<0.001

PFS: progression-free survival.

In the Skindex emotions and functioning domain and the skin symptoms domain, no notable differences between groups were observed. Overall, no significant differences were observed between groups in the

Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire and the European Quality of Life 5-Dimension Three Level Version (EQ-5D-3L).[3]

In a subgroup of patients with advanced disease (defined as mycosis fungoides stage IIB or higher and all primary cutaneous ALCL, n=95), after a median of 33.9 months of follow up, objective response rate maintained for at least four months was achieved by 59% (29/49) of the brentuximab vedotin group and 8.7% (4/46) of the bexarotene/methotrexate group. A complete response was achieved by 20% (10/49) and 2.2% (1/46) of patients and median PFS was 16.5 months and 3.5 months respectively.[5]

Limited evidence for patients with Sézary Syndrome comes from a single-arm, phase II study (NCT01396070) which recruited patients with mycosis fungoides and Sézary Syndrome with negligible to 100% CD30 expression levels, who had failed at least one prior systemic therapy. Patients received brentuximab vedotin 1.8mg/kg every 3 weeks for up to 16 doses. An objective global response was observed in 70% (21/30) of patients. Only three study patients had Sézary Syndrome: one had a complete response, one partial response and one progressive disease.[6]

Summary of evidence on comparative safety

The European Medicines Agency (EMA) noted that safety data from the brentuximab vedotin group of ALCANZA are largely consistent with those of the earlier studies. Overall, they considered that no new safety concerns have been identified with brentuximab vedotin treatment in mycosis fungoides and primary cutaneous ALCL patients and that the safety profile of brentuximab vedotin was similar to that observed in other indications.[3]

In the safety population of ALCANZA, adverse events (AEs) were reported in 95% (63/66) of patients in the brentuximab vedotin group and 90% (56/62) of the bexarotene/methotrexate group. Treatment related AEs were reported in 86% and 71% of the respective groups. Serious adverse events were reported in 29% of both groups. An AE leading to discontinuation occurred in 24% and 8.1% of the groups.[2]

Peripheral sensory neuropathy was the most commonly reported AE in the brentuximab vedotin group, in 45% (30/66) of patients, compared with 4.0% (1/25) of patients who received methotrexate and none (0/37) who received bexarotene. Nine patients in the brentuximab vedotin group discontinued treatment due to peripheral neuropathy compared with none in the bexarotene/methotrexate group. Other commonly reported AEs included nausea (36% of the brentuximab vedotin group, 16% of the methotrexate group, 11% of the bexarotene group), diarrhoea (29%, 4%, 8%), fatigue (29%, 20%, 32%), vomiting (17%, 8%, 3%), pruritus (17%, 8%, 16%), pyrexia (17%, 28%, 11%), alopecia (15%, 4%, 3%), and decreased appetite (15%, 4%, 5%).[2] Neutropenia or decreased neutrophil count were reported for 9% of patients in the brentuximab vedotin group and 6% of patients in the physician's choice group. Infusion-related reactions occurred in 14% of patients treated with brentuximab vedotin.[3]

Summary of clinical effectiveness issues

Primary cutaneous lymphomas are defined as non-Hodgkin lymphoma that present in the skin with no evidence of extra-cutaneous disease at diagnosis. CTCL represent approximately 75% to 80% of all primary cutaneous lymphomas. CTCL is a heterogeneous group of neoplasms with significant variation in clinical presentation, histologic appearance and prognosis. Initial symptoms may include plaques/patches or nodules, progressing to skin tumours with more advanced disease. The most common type of CTCL, approximately 50% to 60%, is mycosis fungoides. Primary cutaneous ALCL accounts for around 13% and Sézary Syndrome, which is closely related to mycosis fungoides, accounts for around 3%. [3, 7]

There is no standard treatment for CTCL due to the heterogeneity and small patient numbers. Treatment aims are to control disease and symptoms. Treatment choice is based on disease stage (for mycosis fungoides/Sézary Syndrome) or type. Skin directed therapy (topical agents, phototherapy and radiotherapy) may be used for early-disease. Advanced disease often requires systemic treatment. First and second line systemic treatments can include bexarotene, methotrexate, interferon alfa, chemotherapy, and entry into clinical trials. Reduced intensity allogeneic haemopoietic stem cell transplant (HSCT) is a potential second or third line treatment option for selected patients with advanced disease to consolidate treatment response.[7] Bexarotene has previously been accepted for use in Scotland as a second line treatment for patients with advanced (stages IIb or III) cutaneous T-cell lymphoma (SMC 14/02). Other systemic treatments are used on an off-label basis. Brentuximab vedotin is the first in class for this indication. Brentuximab vedotin meets SMC orphan criteria.

The submitting company has requested that SMC considers this product when positioned for use in patients with advanced CTCL defined as mycosis fungoides stage IIB and above, primary cutaneous ALCL or Sézary Syndrome.

The availability of brentuximab vedotin would provide an additional licensed treatment option for patients with CD30+ CTCL. It is administered as an intravenous infusion every three weeks which may impact on the patients and service.

Key strengths

- In the key ALCANZA study a difference in objective response rate maintained for at least four months of 44% was observed favouring treatment with brentuximab vedotin over relevant comparators, physician's choice of bexarotene or methotrexate. The difference was statistically significant and considered by the EMA to be clinically relevant. Based on pre-specified subgroup analysis, the primary outcome was consistent over mycosis fungoides and primary cutaneous ALCL patients and over physician's choice of treatment.
- Superiority of brentuximab vedotin over bexarotene/methotrexate was also demonstrated for the key secondary outcomes: proportion of patients achieving a complete response, PFS and change in the symptom domain of the Skindex-29 Score.

Key uncertainties

- The licensed indication is broader than the study population. ALCANZA recruited patients with CD30-positive mycosis fungoides or primary cutaneous ALCL. Efficacy and safety data for other types of CTCL are limited. The EMA concluded that available data appears in support for the extrapolation of efficacy to other subtypes.[3]
- Evidence to support the proposed positioning for patients with advanced CTCL comes from a subgroup analysis that was not pre-specified. Randomisation into the study was not stratified by disease stage and therefore the treatment groups in this subgroup analysis may not be balanced.[2] Objective response rate maintained for at least four months and secondary outcomes in patients with advanced disease were similar to those in the ITT population.
- The key study was not powered to detect differences in overall survival. Overall survival could be confounded by subsequent treatments particularly as a large proportion of patients in the bexarotene/methotrexate group receive subsequent treatment with brentuximab vedotin. The EMA noted that, although immature, the overall survival data did not show a detrimental effect and considered this uncertainty acceptable.[3]
- The company noted that it was not possible to conduct an indirect comparison versus interferon alfa due to insufficient evidence.

Where a medicine has conditional marketing authorisation, SMC has the opportunity to issue interim accepted advice subject to re-evaluation where the committee considers that the clinical case is not demonstrated and the requirements for additional evidence that have been specified by the EMA (known as specific obligations) are expected to address key uncertainties in the evidence presented by the submitting company.

Brentuximab vedotin was granted a conditional marketing authorisation from the EMA in 2012. There are no specific obligations relating to this indication and interim acceptance would offer no advantage in this instance.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing brentuximab vedotin with physician's choice of either bexarotene or methotrexate for adults with advanced CTCL, defined as mycosis fungoides stage IIB and above, primary cutaneous ALCL or Sézary Syndrome. As noted above, in Scotland a mix of therapies is used to treat this population, including bexarotene or methotrexate. SMC clinical experts advised that there is no clear comparator.

The cost-utility analysis was primarily based on evidence from the advanced subgroup population of the ALCANZA study. A National Health Service (NHS) Scotland perspective was taken and the model was run over a time horizon of 45 years, equivalent to lifetime. A partitioned survival model was used to undertake the analysis, adapting the model developed for the NICE submission (TA577) to the Scottish

context. The model has five health states: pre-progression, post-progression, allogeneic HSCT, relapse following allogeneic HSCT and death. The mean age at entry to the model was 57 years.

Key evidence to inform the economic model - PFS, overall survival, time on treatment (ToT) - was derived from the individual patient level data from the ALCANZA study. As the economic model is concerned with the advanced CTCL subgroup (Stage IIB to IVB and primary cutaneous ALCL) the data used were those from the advanced CTCL Interim Analysis 2 (IA2) subgroup. This informed the pre-transplant and transplant-ineligible pathways within the economic model. The Objective Response Rate (ORR) data from ALCANZA was used to determine eligibility for a transplant in the pre-progression health state (partial or complete response). Extrapolation of data was modelled for PFS and overall survival from the ALCANZA trial exploring 6 alternative parametric distributions for each model. A Weibull distribution for PFS was fit to both brentuximab vedotin and the comparators based on goodness-of-fit statistics, visual inspection, and clinical plausibility. The overall survival data were highly immature and subject to cross over between arms. Methods to deal with cross over were applied but due to small sample size and large cross-over (46%), the results were logically and clinically implausible. Therefore it was assumed that overall survival was equivalent in both arms and survival in the model for both treatments was based on parametric curves fitted to the comparator arm; the log-logistic was selected in the base case as the most likely to represent long-term outcomes. This is a reasonable assumption given the lack of evidence of a difference in overall survival between arms and the highly uncertain analyses, and was further supported from a following data cut. Time on treatment data from the ALCANZA trial were complete and therefore the full Kaplan Meier data was utilised.

In the ALCANZA trial only four of the 24 UK patients were bridged to allogeneic HSCT. In the model, patients in the pre-progression state were assumed to be potentially eligible for allogeneic HSCT if they had a partial or complete response by 18 weeks (6 cycles); 68.8% and 17.8% in the brentuximab vedotin and comparator therapies arms respectively. The model assumes that 40% of these patients with a PR or CR would be eligible for allogeneic HSCT, and therefore the base case model assumed 28% of brentuximab vedotin patients and 7% of bexarotene or methotrexate patients will be eligible for allogeneic HSCT. There is considerable uncertainty surrounding these estimates and whether they would be seen in practice.

PFS and overall survival outcomes for the allogeneic HSCT and post-transplant outcomes were informed by retrospective chart review of data from 53 patients from six UK centres who were treated with allogeneic HSCT from 2003-2018 (EORTC 2018 dataset)[8], with a median follow-up of 3.3 years. Extrapolation of data was modelled for PFS and OS exploring six alternative parametric distributions for each model. The Gompertz curve was used to model outcomes associated with PFS after an allogeneic HSCT in the base case, as it reflected the decreasing probability of relapse reducing over time to a zero probability and was supported by goodness of fit statistics. For overall survival post allogeneic HSCT the log-normal curve was selected in the base case.

Health related quality of life data were collected within the ALCANZA trial using the EQ-5D-3L, at baseline, every second cycle, at end of treatment and at post treatment follow-up. Utility values were calculated using the UK-5D-3L value set, and while brentuximab vedotin had slightly higher utility at

baseline than the comparators, no significant differences were observed between groups. The company also undertook a mixed effects regression model which derived utility values based on Skindex-29 results. Other approaches to utility value estimation were undertaken in sensitivity analysis, but did not result in large changes in the cost-effectiveness results. Values from published sources were used for the end stage management and post-allogeneic HSCT states of the model, and while appropriate given a lack of other sources, remain a source of uncertainty. [9] [10] It was assumed that the impact of AEs on quality of life was included in the EQ-5D responses and in the regression equation fit to the ALCANZA data.

The costs included in the model are those related to treatment acquisition costs, administration, adverse events, pre-progression and progression state resource use, allogeneic HSCT, subsequent therapies, end stage management and a cost of terminal care. Due to the likely small patient numbers, the base case accounted for medicines wastage by assuming no vial sharing. Resource use estimates were taken from various sources including published and clinical experts' opinion which were validated with UK and Scottish clinicians.

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.

The base case 'with PAS' analysis estimated a reduction in overall costs of £110,939 per patient and a quality adjusted life year (QALY) gain of 1.04, therefore, brentuximab vedotin is shown to dominate the comparator therapies. It should be noted that as the base case model assumed no difference in overall survival between arms in the non-allogeneic HSCT pathway in the model, all the life years gained benefits are derived from the allogeneic HSCT assumptions and data.

The base case and key sensitivity analyses results are shown in table 2.

Table 2: Base case and sensitivity analysis results at PAS price, brentuximab vedotin versus bexarotene or methotrexate.

	Base case / Scenario analysis	**Incremental cost-effectivenss ratio (ICER) With PAS**
	Base case result	Brentuximab vedotin dominates (NMB:£ 142,092)
1	Eligible proportion for allogeneic HSCT (lower, upper estimates)	Brentuximab vedotin dominates (NMB:£ 125,674 - 159,052)
2	Post-progression - CTCL specific end stage care cost	Brenutixmab vedotin dominates (NMB: £109,876 – 174,308)
3	5 year time horizon	Brenutixmab vedotin dominates (NMB: £122,317)
4	Use of Kaplan-Meier data directly for PFS	Brenutixmab vedotin dominates (NMB: £135,483)
5	Independent curve fits to observed data (Weibull for brentuximab vedotin)	Brenutixmab vedotin dominates (NMB: £138,893)
6	Allogeneic HSCT rates: 7.1% in comparator arm, 16.7% in brentuximab vedotin arm	Brenutixmab vedotin dominates (NMB: £93,948)
7	Allogeneic HSCT rates: 5% in comparator arm, 16.7% in brentuximab vedotin arm	Brenutixmab vedotin dominates (NMB: £105,024)

8	Allogeneic HSCT after 30-weeks (10-cycles)	Brenutixmab vedotin dominates (NMB: £136,912)
9	Costs - lower bound estimates from resource use questionnaire	Brenutixmab vedotin dominates (NMB: £93,994)
10	Requested scenario: exclusion of allogeneic HSCT states in the model	Brenutixmab vedotin dominates (NMB:£56,813)

NMB=net monetary benefit (positive values indicate a benefit for brentuximab vedotin over the comparator). NMB is a re-arrangement of the ICER whereby the QALY gains are converted into monetary terms, using a willingness to pay of £30,000/QALY. The NMB is calculated using the following formula *NMB= £30,000*QALY-£cost*

In the one way sensitivity analysis the variables with the greatest impact on model outcomes were those associated with the cost of end-stage care health state, the proportion eligible for allogeneic HSCT and the cost of medium Allevyn dressings. These were found to be the most influential on the net monetary benefit (NMB). However, of all the parameters varied, none resulted in a negative NMB i.e. brentuximab vedotin was cost-effective in all cases. The NMB was relatively insensitive to all other parameters. Likewise, a wide range of scenario analyses were undertaken, none of which resulted in a negative NMB or changed the brentuximab vedotin dominant outcome.

In terms of weaknesses or limitations with the analysis, these mostly relate to uncertainty in the clinical data:

- The population of interest in the economic analysis was based on a small subgroup of the ALCANZA study which was not pre-specified. As such there is uncertainty associated with the clinical data used in the analysis
- There is uncertainty regarding the data used to support the rate of transplant used in the model, yet many benefits in the model are derived from this element. Clinical experts have advised that bridging benefits to allogeneic HSCT are highly likely and scenario analyses undertaken by the company which explored lower eligibility probabilities showed brentuximab vedotin to remain cost-effective (table 2 scenarios 6 and 7).
- The model results are driven by the large positive treatment effect of brentuximab vedotin which both extends PFS (less people progress where utility is very low and cost high) and also enables more patients to be eligible for allogeneic HSCT, which in the model is associated with extended survival, and improved quality of life. The inclusion of allogeneic HSCT in the model is likely to be appropriate given clinical experts' comments that bridging is likely to be a key benefit of brentuximab vedotin. As many of the benefits derived in the model are driven from allogeneic HSCT a worst case scenario analysis was requested to explore exclusion of the allogeneic HSCT pathway to see the impact on model results. Scenario 10 in Table 2 shows brentuximab vedotin remains a dominant strategy, with a cost saving and some small QALY gains driven by quality of life improvements through avoiding progression and end stage disease. The ALCANZA trial evidenced significant PFS gains (HR 0.27), and in the model the progression state has much greater cost in progression and for end stage management and lower quality of life, therefore the high treatment cost of brentuximab vedotin is offset against the large cost savings of avoiding progression in this scenario.
- The economic model only considered bexarotene and methotrexate as comparators. Clinical expert advice is that there is no clear comparator for Scotland. Interferon alfa could also be used, but is not licensed for this indication.

- The overall survival data from the advanced subgroup ALCANZA IA2 data cut are highly immature, with only approximately 30% of events having taken place. The sample size in each group is also very small and the data were subject to high cross over rates (46%) from the physician's choice arm once patients progressed. However, it was assumed that overall survival was equivalent in both arms, which is appropriate given this highly uncertain data.

The Committee also considered the benefits of brentuximab vedotin in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the potential to bridge to a definitive therapy was satisfied. In addition, as brentuximab vedotin is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and after application of the appropriate SMC modifiers, the Committee accepted brentuximab vedotin for restricted use in NHSScotland.

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

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group:

- We received a patient group submission from Lymphoma Action, which is a registered charity.
- Lymphoma Action has received 8.55% pharmaceutical company funding in the past two years, including from the submitting company.
- People with cutaneous T-cell lymphoma (CTCL) usually live with their condition for many years, and experience symptoms flaring up from time to time.
- Psychological and social wellbeing are significantly affected, particularly at more advanced stages. Patients can suffer severe discomfort, itching, pain and fatigue with subsequent impact on employment, leisure activities, relationships and day-to-day living.
- Current treatment options may impact on quality of life. Access to specialist treatments may require travelling to centres some distance from home. Skin care regimens and wound dressing in later stages are time-consuming for both the patient and their family or carer.
- One of the major drawbacks of current treatment options is the lack of a durable response. Many patients respond briefly to treatment but only have a short period before symptoms recur and they require further treatment.
- Patients are keen for effective therapeutic options that could give them the opportunity for prolonged disease control and symptom relief leading to improvements in quality of life.

Brentuximab vedotin represents a valuable option for people who have had limited response to other treatments.

Additional information: guidelines and protocols

The British Association of Dermatologists (BAD) and UK Cutaneous Lymphoma Group (UKCLG) published updated Guidelines for the management of primary cutaneous lymphomas in September 2018.[7] This guidance recommends that:

- Treatment aims are to control disease and symptoms with the minimum of interventions.
- For stage IA to IIA mycosis fungoides skin directed therapy (SDT) are the standard of care. Total skin electron beam radiotherapy (TSEB) and biologic therapy are options for refractory disease.
- Patients with stage IIB mycosis fungoides can have an unpredictable clinical course: some patients develop only small and infrequent skin tumours and often obtain durable responses to localized radiotherapy and other SDT options for persistent patches and plaques; other patients develop extensive bulky skin tumours and rapidly progressive disease requiring TSEB and systemic chemotherapy.
- Following treatment, patients with advanced mycosis fungoides may develop recurrent, low-grade disease where SDT is a treatment option.
- Patients with erythrodermic mycosis fungoides (stage III) and Sézary Syndrome (stage IVA1) often require single or combination systemic therapies such as methotrexate, photopheresis, bexarotene and interferon alfa as first-line treatment.
- Clinical trials and alemtuzumab are also options for Sézary Syndrome (stage IVA1-2).For stage IVA2–B mycosis fungoides / Sézary Syndrome, radiotherapy (including TSEB) for selected stage IV patients and single-agent chemotherapy regimens are the preferred option, but response duration is often short.
- Brentuximab vedotin offers an effective option for refractory stage IB disease and advanced stages of mycosis fungoides / Sézary Syndrome with tumour CD30 expression.
- All patients with early refractory or advanced mycosis fungoides / Sézary Syndrome should be offered participation in clinical trials.
- Reduced-intensity allogeneic HSCT should be considered for selected groups of patients with advanced mycosis fungoides / Sézary Syndrome to consolidate treatment responses.
- Treatment for CD30+ primary cutaneous anaplastic large cell lymphoma (ALCL) consists of surgical excision and/or radiotherapy for localized disease.
- Combination chemotherapy or brentuximab vedotin may be appropriate for patients with CD30+ primary cutaneous ALCL with extensive cutaneous disease or those with systemic progression."[7]

Additional information: comparators

Bexarotene, off-label methotrexate or interferon alfa.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
brentuximab vedotin	**1.8mg/kg intravenous infusion every 3 weeks for up to 16 cycles.**	**120,000**
bexarotene	300mg/m^2 orally daily. Treatment should be continued as long as the patient is deriving benefit.	22,050

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 20/09/19. Costs do not take any patient access schemes into consideration. Cost calculated for 48 weeks of treatment. Body weight of 70kg used for brentuximab vedotin dose and body surface area of 1.8m^2 used for dose of bexarotene.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 11 patients per annum to which confidential estimates of treatment uptake were applied**.**

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

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

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This assessment is based on data submitted by the applicant company up to and including 13 November 2019.

**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.