

# Lenalidomide with rituximab for previously treated follicular lymphoma

Technology appraisal guidance

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[www.nice.org.uk/guidance/ta627](https://www.nice.org.uk/guidance/ta627)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Recommendations

- 1.1 Lenalidomide with rituximab is recommended, within its marketing authorisation, as an option for previously treated follicular lymphoma (grade 1 to 3A) in adults. It is only recommended if the company provides lenalidomide according to the commercial arrangement.

## Why the committee made these recommendations

Follicular lymphoma is usually treated with an anti-CD20 antibody (such as rituximab) with chemotherapy. Treatment options are limited, especially if the disease relapses early after a rituximab-based treatment. Lenalidomide is the first approved targeted treatment for follicular lymphoma that is not an anti-CD20 antibody. Lenalidomide is taken orally, and when used with rituximab is a chemotherapy-free combination.

Clinical-effectiveness evidence shows that, when people take lenalidomide with rituximab, their follicular lymphoma does not progress as quickly as when they take rituximab with chemotherapy. There is also evidence that lenalidomide with rituximab helps people live longer than rituximab with chemotherapy, although it is too early to tell for how much longer.

Lenalidomide with rituximab costs more than rituximab with chemotherapy. However, its cost-effectiveness estimate is within the range that NICE normally considers an acceptable use of NHS resources. Therefore, lenalidomide with rituximab is recommended.

## 2 Information about lenalidomide with rituximab

### Marketing authorisation indication

- 2.1 Lenalidomide (Revlimid, Celgene) with rituximab is indicated 'for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3A)'.

### Dosage in the marketing authorisation

- 2.2 The recommended starting dosage of lenalidomide is 20 mg, orally once daily on days 1 to 21 of repeated 28-day cycles for up to 12 cycles of treatment. The recommended starting dosage of rituximab is 375 mg/m<sup>2</sup> intravenously every week in cycle 1 (days 1, 8, 15, and 22) and day 1 of every 28-day cycle for cycles 2 to 5.

### Price

- 2.3 Lenalidomide is available as a 21-capsule pack. The cost per pack is £4,168.50 (20 mg; excluding VAT; BNF online, accessed January 2020). The company has a [commercial arrangement](#). This makes lenalidomide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount. The list price of rituximab (MabThera) is £349.25 per two 100-mg vials and £873.15 per one 500-mg vial (excluding VAT; BNF online, accessed January 2020). Napp and Sandoz have agreed a nationally available price reduction for biosimilar rituximab with the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence.

## 3 Committee discussion

The [appraisal committee](#) considered evidence submitted by Celgene, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

After technical engagement, there were remaining areas of uncertainty associated with the analyses presented. The committee took these into account in its decision making. It discussed the following issues (issues 1 to 6), which were outstanding after the technical engagement stage.

### The condition and current treatment

#### **There is an unmet need for new treatment options for this disease**

- 3.1 The clinical and patient experts noted that people with previously treated follicular lymphoma have limited treatment options. The choice of treatment for previously treated follicular lymphoma depends on individual circumstances and takes into account previous chemotherapy, the age and fitness of the patient, plus clinician and patient preferences. The patient experts explained that chemotherapy has unpleasant side effects and any treatment that avoided chemotherapy would be welcomed. The committee concluded that lenalidomide with rituximab would be welcomed as a new treatment option for people with previously treated follicular lymphoma.

#### **Current treatment for follicular lymphoma is rituximab with chemotherapy (CHOP or CVP)**

- 3.2 The clinical experts noted that rituximab monotherapy, which is the comparator used in the AUGMENT trial used in this appraisal (see [section 3.3](#)), would rarely be given to people whose disease had relapsed. The company included

obinutuzumab with bendamustine as a comparator, but this combination is only recommended for use in the Cancer Drugs Fund. The committee did not consider obinutuzumab with bendamustine to be used in routine commissioning and did not consider it a relevant comparator. The committee understood that rituximab with either CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or CVP (cyclophosphamide, vincristine and prednisolone) is used to treat follicular lymphoma in people who have had at least 1 previous treatment. The clinical experts noted that the company's proposed treatment pathway originally separated treatments for previously treated follicular lymphoma depending on whether the disease was refractory to rituximab or not. The clinical experts considered that being refractory to rituximab or not was not a clinically appropriate way to separate treatment choices, and that time until relapse after initial chemo-immunotherapy may be more relevant for determining treatment choices in clinical practice. The committee agreed that the most appropriate comparators for this appraisal were rituximab with chemotherapy (CHOP or CVP).

## Clinical effectiveness

### **Clinical evidence for lenalidomide with rituximab and rituximab with chemotherapy is compared using a matching-adjusted indirect comparison**

- 3.3 The evidence for lenalidomide with rituximab came from AUGMENT, a phase 3 multicentre randomised controlled trial that used rituximab monotherapy as the comparator. In the absence of direct comparative evidence of lenalidomide plus rituximab compared with rituximab plus CHOP (R-CHOP) or rituximab plus CVP (R-CVP), the company provided a matching-adjusted indirect comparison to compare both treatments. Data for R-CHOP and R-CVP are from either Van Oers et al. (2006) or the Haematological Malignancy Research Network (HMRN) registry. The committee agreed that using the Van Oers data was not appropriate, because patients were not from the UK and had not had previous treatment with rituximab. The committee concluded that the HMRN registry data were most suitable for R-CHOP and R-CVP because the data were from the UK and include people who had had previous treatment with rituximab.

## **R-CHOP and R-CVP are assumed to be clinically equivalent**

- 3.4 The company combined the R-CHOP and R-CVP populations for the matching-adjusted indirect comparison to increase the sample size of the comparator. The matching-adjusted indirect comparison showed an improvement in progression-free survival for lenalidomide with rituximab compared with R-CHOP and R-CVP (exact data are confidential and cannot be reported here). It also showed an improvement in overall survival for lenalidomide with rituximab compared with R-CHOP and R-CVP (exact data are confidential and cannot be reported here). Median progression-free survival and overall survival could not be estimated because the follow-up data were immature (not yet complete). When assessing the validity of combining R-CHOP and R-CVP, the committee understood that observed data for R-CHOP in the HMRN registry for overall survival, progression-free survival and time to next anti-lymphoma treatment appeared similar to R-CVP. The committee also understood that Cox proportional hazards model analyses of overall survival, progression-free survival and time to next anti-lymphoma treatment showed no statistically significant difference in outcomes between R-CHOP and R-CVP. The clinical experts noted that, in untreated follicular lymphoma, R-CHOP and R-CVP are not clinically equivalent. They considered that R-CHOP has a longer time to treatment failure than R-CVP (despite similar response rates) and progression-free survival is longer with R-CHOP. They also noted that R-CHOP is given to younger, fitter patients who can tolerate the additional chemotherapy component (doxorubicin) in CHOP, while R-CVP is given to older, less fit patients. The clinical experts acknowledged that there was no evidence for R-CHOP and R-CVP in previously treated follicular lymphoma. They accepted that, without any other data sources, it may be appropriate to assume R-CHOP is clinically equivalent to R-CVP. The committee concluded that it was appropriate to assume R-CHOP is clinically equivalent to R-CVP in the economic model.

## **The matching-adjusted indirect comparison is as closely matched as possible**

- 3.5 The ERG noted that the matching-adjusted indirect comparison did not account for all potentially relevant matching criteria. Potentially relevant matching criteria included the diameter of the largest node, haemoglobin levels, duration since last



treatment, high lactate dehydrogenase levels, and Follicular Lymphoma International Prognostic Index (FLIPI) risk group status. The committee understood that the most important criteria identified by clinical experts were included in the matching-adjusted indirect comparison, and that other potentially relevant matching criteria were not collected by HMRN. The committee agreed that, given the data limitations, the matching-adjusted indirect comparison could not be improved further.

## Economic model

### The partitioned survival model structure is appropriate

- 3.6 The company used a partitioned survival model to determine the difference in overall survival and progression-free survival for lenalidomide with rituximab and R-CHOP and R-CVP. The ERG said that a state transition model would have helped to assess the validity of the extrapolations in overall survival and progression-free survival in the partitioned survival model. Following technical engagement, the company provided a state transition model for lenalidomide with rituximab compared with rituximab monotherapy (not R-CHOP and R-CVP). The committee did not consider this appropriate because rituximab monotherapy is not a relevant treatment for patients in the NHS. The committee also noted that a state transition model for lenalidomide with rituximab compared with R-CHOP and R-CVP would have its own uncertainty because of the limitations in the data. The AUGMENT data were immature, with a maximum follow up of 3.9 years, and the R-CHOP and R-CVP data were from a small effective sample. The committee agreed that accurately modelling transitions between intermediate health states would be difficult, and providing a state transition model would not help validate the partitioned survival model. The committee concluded that a partitioned survival model was appropriate, and that a state transition model was not needed on this occasion.

## **Health-related quality-of-life values for lenalidomide with rituximab should be capped in the economic model**

- 3.7 Patients in AUGMENT had health-related quality-of-life values that were higher than the general population for the same age group, in all health states. The clinical experts said that someone with follicular lymphoma would not have higher quality of life than a member of the general population in any health state. At best, their quality of life would be equal to a member of the general population at the same age. The company proposed capping the least severe health-related quality-of-life values (values for progression-free survival) in the economic model to published age-matched UK general population values. The company calculated the quality of life for the post-progression (on or off treatment) health states by adding relative decrements in quality of life observed in AUGMENT to the progression-free survival value. The committee agreed that capping the progression-free survival health state in the economic model to general population values, and using relative decrements from AUGMENT for other health states, was appropriate.

## **A 5-year treatment effect duration for lenalidomide with rituximab is appropriate**

- 3.8 The clinical experts said that overall-survival estimates for lenalidomide with rituximab will be better than overall-survival estimates for R-CHOP and R-CVP for several years once treatment begins. However, these estimates will gradually decline over time and eventually become the same as overall-survival estimates for R-CHOP and R-CVP. The clinical experts noted that it is uncertain how long the overall-survival benefit for lenalidomide with rituximab will last, but said that it will likely start to reduce 5 to 10 years after treatment starts. The company and the ERG's estimates of treatment effect duration was 5 years in its base cases. The committee noted that this was the most conservative estimate, given the clinical expert opinion of 5 to 10 years. The committee concluded that a treatment effect duration of 5 years was appropriate, with no evidence to the contrary.

## **The exponential distribution is appropriate for extrapolating**

## overall survival

- 3.9 NICE's Decision Support Unit technical support document 14 states that, if parametric models are fitted separately to individual treatment arms, it is advisable to use the same type of distribution for extrapolating both arms. For overall survival, the company selected the exponential distribution for both arms to best reflect the average 20-year prognosis for follicular lymphoma when treated with R-CHOP and R-CVP. The clinical experts noted that the Weibull distribution may have also been appropriate for both arms, and the committee noted that it was a slightly better statistical fit than the exponential distribution. The committee also noted that the Weibull distribution produced a higher cost-effectiveness estimate in the probabilistic sensitivity analysis results than it did in the deterministic sensitivity analysis results. The committee was aware that this was caused by lenalidomide with rituximab having lower quality-adjusted life years (QALYs) than R-CHOP and R-CVP in the probabilistic sensitivity analysis results compared with the deterministic sensitivity analysis results. More specifically, lenalidomide with rituximab had lower quality of life or extension of life than R-CHOP and R-CVP in 267 of the 1,000 iterations in the probabilistic sensitivity analysis. The clinical experts said that this was not clinically plausible. The committee agreed that the reduction in QALYs for lenalidomide with rituximab in the probabilistic sensitivity analysis results (when using a Weibull distribution for overall survival) was unusual. The committee noted that this might have been due to an error in the model or an unstable covariance matrix. Because of this, the committee did not consider the output of the probabilistic sensitivity analysis to be robust, and did not think it appropriate to use the Weibull distribution. The committee considered that the exponential distribution had good statistical fit for the observed Kaplan–Meier data and concluded that the exponential distribution was appropriate for extrapolating overall survival.

## Different methods are needed to extrapolate progression-free survival for lenalidomide with rituximab and R-CHOP and R-CVP

- 3.10 The standard approach for extrapolating survival curves is to fit a parametric distribution to the available data, which is then used to estimate survival at any point in time. This method was used to fit the Weibull function for R-CHOP and R-CVP. However, the committee noted that all the standard parametric

extrapolations for lenalidomide with rituximab estimated worse progression-free survival outcomes compared with R-CHOP and R-CVP. The clinical experts said that it was clinically implausible for the average progression-free survival of lenalidomide with rituximab to be worse than the average progression-free survival of R-CHOP and R-CVP. The committee understood that the relatively worse progression-free survival estimates for lenalidomide with rituximab may have been a result of the immature follow-up data from the AUGMENT trial (3.9-year follow up), compared with the longer follow up for R-CHOP and R-CVP (11.6 years). To avoid the implausible crossing of progression-free survival curves, the company used the observed AUGMENT data, and then, in the absence of further trial data, the company fitted a Weibull distribution to the end of these data. The ERG noted that this approach generated a larger progression-free survival benefit for lenalidomide with rituximab than applying the standard parametric distributions. Additionally, the ERG was concerned that, by extrapolating from the end of the observed AUGMENT data when there were fewer patients to inform the extrapolation, the mean progression-free survival benefit for lenalidomide with rituximab may have been further overestimated. The committee agreed that using the observed AUGMENT data with a Weibull distribution extrapolation was the most appropriate method for estimating progression-free survival for lenalidomide with rituximab. This was because this method takes account of the clinical plausibility of a progression-free survival benefit for lenalidomide with rituximab. The committee concluded that the AUGMENT data should have been extrapolated from the midpoint, rather than from the end, because this would have reduced the uncertainty in the extrapolation by using a relatively larger sample size.

## Cost-effectiveness estimate

### Lenalidomide with rituximab is a cost-effective use of NHS resources

- 3.11 [NICE's guide to the methods of technology appraisal](#) says that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER.

Therefore, because of the uncertainty in the equivalence of R-CHOP and R-CVP (see [section 3.4](#)), matching-adjusted indirect comparison (see [section 3.5](#)) and treatment effect duration (see [section 3.8](#)), the committee agreed that an acceptable ICER would be around the lower end of the £20,000 to £30,000 per QALY gained range. The company's deterministic base case showed that the ICER for lenalidomide with rituximab compared with R-CVP was £20,156 per QALY gained (including the patient access scheme for lenalidomide). The ERG presented 6 analyses, each using a different parametric distribution to extrapolate overall survival. The ERG's analyses also included the confidential commercial arrangement for obinutuzumab and biosimilar rituximab. The ICERs were within or below the range that NICE usually considers an acceptable use of NHS resources (the exact ICERs are confidential and cannot be reported here). The committee agreed that an extrapolation with an exponential distribution was appropriate for overall survival in both lenalidomide with rituximab and R-CHOP and R-CVP. The committee also agreed that AUGMENT data with a Weibull distribution (extrapolated from AUGMENT data midpoint) was the most appropriate for estimating progression-free survival for lenalidomide with rituximab, and that a standard parametric Weibull distribution should have been used to extrapolate R-CHOP and R-CVP (see [sections 3.9 and 3.10](#)). These assumptions generated a most plausible ICER that was below the range that NICE usually considers an acceptable use of NHS resources (the exact ICER is confidential and cannot be reported here). The committee therefore recommended lenalidomide with rituximab as an option for previously treated follicular lymphoma (grades 1 to 3A).

## 4 Implementation

- 4.1 [Section 7\(6\) of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – a new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously treated follicular lymphoma and the healthcare professional responsible for their care thinks that lenalidomide with rituximab is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

### **Joel Russell**

Technical lead

### **Sally Doss**

Technical adviser

### **Louise Jafferally**

Project manager

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