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Technology Appraisals and Guidance Information Services

Static List Review (SLR)

Title and TA publication number of static topic:	**TA137; Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma**
Final decision:	The guidance will remain on the ‘static guidance list’

1. Publication date:	February 2008 (This guidance updates and replaces NICE technology appraisal 37 (The clinical effectiveness and cost effectiveness of rituximab for follicular lymphoma) published in May 2002).
2. Date added to static list:	March 2011
3. Date the last searches were run:	October 2010
4. Current guidance:	1.1 Rituximab, within its marketing authorisation, in combination with chemotherapy, is recommended as an option for the induction of remission in people with relapsed stage III or IV follicular non- Hodgkin’s lymphoma. 1.2 Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non- Hodgkin's lymphoma in remission induced with chemotherapy with or

	without rituximab. 1.3 Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).
5. Research recommendations from original guidance:	None
6. Current cost of technology/ technologies:	One 100m-g vial is £174.63 and one 500m-g vial is £873.15 ('British national formulary' [BNF] edition 70).
7. Cost information from the TA (if available):	The cost of one 100-mg vial is £174.63 and one 500-mg vial is £873.15 (excluding VAT; 'British national formulary' [BNF] edition 53).
8. Alternative company(ies):	None
9. Changes to the original indication:	MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
10. New relevant trials:	A Phase 3 Open-Label Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Chemotherapy in Subjects With Previously Untreated Follicular Lymphoma (NCT01476787) Enrolment: 254 Estimated Study Completion Date: June 2024 This study is ongoing, but not recruiting participants Comparing Two Schedules of Rituximab Maintenance in Rituximab-Responding

	Patients With Untreated, Chemotherapy Resistant or Relapsed Follicular Lymphoma: A Randomized Phase III Trial (NCT00227695) Estimated Enrolment: 270 Estimated Study Completion Date: September 2017 This study is ongoing, but not recruiting participants. A Study of Patient Preference With Subcutaneous Versus Intravenous MabThera/Rituxan (Rituximab) in Patients With CD20+ Diffuse Large B-Cell Lymphoma or CD20+ Follicular Non-Hodgkin's Lymphoma Grades 1, 2 or 3a (NCT01724021) Enrolment: 746 Estimated Study Completion Date: March 2017 This study is ongoing, but not recruiting participants. A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Placebo in Subjects With Relapsed/Refractory Indolent Lymphoma (NCT01938001) Estimated Enrolment: 350 Estimated Study Completion Date: December 2021 This study is currently recruiting participants The Asymptomatic Follicular Lymphoma (AFL) Trial: A Phase III Study of Single-Agent Rituximab Immunotherapy Versus Zevalin Radioimmunotherapy for Patients With New, Untreated Follicular Lymphoma Who Are Candidates for Observation (NCT02320292) Estimated Enrolment: 128 Estimated Primary Completion Date: January 2026 This study is currently recruiting participants

	A Phase 3, Randomized, Double-Blind Study Of PF-05280586 Versus Rituximab For The First-Line Treatment Of Patients With CD20-Positive, Low Tumor Burden, Follicular Lymphoma (NCT02213263) Estimated Enrollment: 394 Estimated Study Completion Date: September 2017 This study is currently recruiting participants A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Duvelisib in Combination With Rituximab vs Rituximab in Subjects With Previously Treated Follicular Lymphoma (NCT02204982) Estimated Enrolment: 400 Estimated Study Completion Date: January 2024 This study is ongoing, but not recruiting participants A Two-stage Phase III, International, Multi-center, Randomized, Controlled, Open-label Study to Investigate the Pharmacokinetics, Efficacy and Safety of Rituximab SC in Combination With CHOP or CVP Versus Rituximab IV in Combination With CHOP or CVP in Patients With Previously Untreated Follicular Lymphoma Followed by Maintenance Treatment With Either Rituximab SC or Rituximab IV (NCT01200758) Enrolment: 410 Estimated Study Completion Date: November 2017 This study is ongoing, but not recruiting participants A Phase 3 Open Label Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Chemotherapy Followed by Rituximab in Subjects With Previously Untreated Follicular Lymphoma (RELEVANCE) (NCT01650701)

	Enrolment: 1031 Estimated Study Completion Date: June 2024 This study is ongoing, but not recruiting participants A Randomized Phase III Trial Evaluating Two Strategies of Rituximab Administration for the Treatment of First Line/Low Tumor Burden Follicular Lymphoma (Follicular Lymphoma IV/SC Rituximab Therapy) (NCT02303119) Estimated Enrolment: 202 Estimated Study Completion Date: January 2021 This study is currently recruiting participants. A Randomized, Controlled, Double-Blind Phase III Trial to Compare the Efficacy, Safety and Pharmacokinetics of GP2013 vs. MabThera® in Patients With Previously Untreated, Advanced Stage Follicular Lymphoma (NCT01419665) Estimated Enrolment: 618 Estimated Study Completion Date: March 2018 This study is ongoing, but not recruiting participants A Phase 3, Randomised, Parallel-group, Active-controlled, Double-blind Study to Compare Efficacy and Safety Between CT-P10 and Rituxan in Patients With Low Tumour Burden Follicular Lymphoma (NCT02260804) Estimated Enrolment: 104 Estimated Study Completion Date: August 2020 This study is not yet open for participant recruitment A Multicenter, Phase III, Randomized Study to Evaluate the Efficacy of Response-adapted Strategy to Define Maintenance After Standard Chemoimmunotherapy in Patients With Advanced-stage Follicular Lymphoma (NCT02063685)

	Estimated Enrolment: 602 Estimated Study Completion Date: July 2019 This study is currently recruiting participants Lenalidomide Plus Rituximab Followed by Lenalidomide Versus Rituximab Maintenance for Relapsed/Refractory Follicular, Marginal Zone or Mantle Cell Lymphoma. (MAGNIFY) (NCT01996865) Estimated Enrolment: 500 Estimated Study Completion Date: March 2023 This study is currently recruiting participants A Phase 3, Randomized, Double-blind Study of Duvelisib Administered in Combination With Rituximab and Bendamustine vs Placebo Administered in Combination With Rituximab and Bendamustine in Subjects With Previously-Treated Indolent Non-Hodgkin Lymphoma (NCT02576275) Estimated Enrolment: 600 Estimated Study Completion Date: May 2024 This study is currently recruiting participants A Multicenter Open-label Randomized Study of BCD-020 (Rituximab, CJSC BIOCAD, Russia) Efficacy and Safety in Comparison With MabThera (F. Hoffmann-La Roche Ltd., Switzerland) in Monotherapy of CD20-positive Indolent Non-Hodgkin's Lymphoma (NCT01701232) Estimated Enrollment: 134 Estimated Study Completion Date: December 2016 This study is currently recruiting participants

	A Phase 1/3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Demonstrate Equivalence of Pharmacokinetics and Noninferiority of Efficacy for CT-P10 in Comparison With Rituxan, Each Administered in Combination With Cyclophosphamide, Vincristine, and Prednisone (CVP) in Patients With Advanced Follicular Lymphoma (NCT02162771) Estimated Enrolment: 134 Estimated Study Completion Date: June 2020 This study is ongoing, but not recruiting participants A Multicentre, Phase III, Open Label, Randomized Study in Previously Untreated Patients With Advanced Indolent Non-Hodgkin's Lymphoma Evaluating the Benefit of GA101 (RO5072759) + Chemotherapy Compared to Rituximab + Chemotherapy Followed by GA101 or Rituximab Maintenance Therapy in Responders (NCT01332968) Enrolment: 1401 Estimated Study Completion Date: March 2017 This study is ongoing, but not recruiting participants A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas (NCT01732913) Estimated Enrolment: 375 Estimated Study Completion Date: June 2022 This study is currently recruiting participants A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas (NCT01732926)

	Enrolment: 475 Estimated Study Completion Date: August 2022 This study is ongoing, but not recruiting participants A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib), in Combination With Either Bendamustine and Rituximab (BR) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects With Previously Treated Indolent Non-Hodgkin Lymphoma (iNHL) (NCT01974440) Enrolment: 403 Estimated Study Completion Date: August 2021 This study is ongoing, but not recruiting participants A Randomized Multicenter Study Comparing Pixantrone + Rituximab With Gemcitabine + Rituximab in Patients With Aggressive B-cell Non-Hodgkin Lymphoma Who Have Relapsed After Therapy With CHOP-R or an Equivalent Regimen and Are Ineligible for Stem Cell Transplant (NCT01321541) Estimated Enrolment: 260 Estimated Study Completion Date: June 2017 This study is currently recruiting participants A Multi-center, Prospective, Randomized Phase III Study of the Safety and Efficacy of R-CEOP-90/R-CEOP-70 Versus R-CHOP-50 in the Treatment of Diffuse Large B-cell Lymphoma and Follicular Lymphoma Grade 3B (NCT01852435) Estimated Enrollment: 600 Estimated Study Completion Date: April 2017

	This study is currently recruiting participants A Trial Assessing Efficacy and Toxicity of a Combination of Rituximab and Lenalidomide (R2) vs Rituximab Alone as Maintenance After Chemoimmunotherapy With Rituximab-Bendamustine for Relapsed/Refractory FL Patients Not Eligible for ASCT (NCT02390869) Estimated Enrolment: 253 Estimated Study Completion Date: September 2019 This study is currently recruiting participants
11. Relevant NICE guidance (published or in progress):	NICE advice [ESNM46] Non-Hodgkin's lymphoma: rituximab subcutaneous injection Published date: September 2014 NICE technology appraisal guidance [TA306] Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B‑cell lymphoma Published date: February 2014. 'The guidance on this technology will be considered for review when the PIX306 trial results are available and at the latest in November 2016.' NICE technology appraisal guidance [TA243] Rituximab for the first-line treatment of stage III-IV follicular lymphoma Published date: January 2012 Review decision - August 2014 - moved to the 'static guidance list'. NICE technology appraisal guidance [TA65] Rituximab for aggressive non-Hodgkin's lymphoma Published date: September 2003. Static List Review Decision - May 2014: The guidance will remain on the 'static guidance list'. The guidance will then be incorporated into the forthcoming clinical guideline for non-Hodgkin's lymphoma, which is due to be published in July 2016. NICE technology appraisal guidance [TA226] Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma Published date: June 2011. Review decision - August 2014 - moved to the 'static guidance list'.

	NICE guidelines [CSG3] Improving outcomes in haemato-oncology cancer Published date: October 2003. Currently being updated – see below. NICE technology appraisal guidance [TA328] Idelalisib for treating follicular lymphoma that is refractory to 2 prior treatments (terminated appraisal - no evidence submission was received from Gilead Sciences for the technology) Published date: December 2014 NICE technology appraisal guidance [TA206] Bendamustine for the treatment of indolent (low grade) non-Hodgkin's lymphoma that is refractory to rituximab (terminated appraisal - no evidence submission was received from the manufacturer or sponsor of the technology) Published date: October 2010 Bortezomib for the treatment of relapsed or refractory follicular non-Hodgkin's lymphoma [ID407] NICE technology appraisal guidance Anticipated publication date: TBC Lymphoma (follicular, rituximab-refractory) - obinutuzumab (with bendamustine) [ID841] NICE technology appraisal guidance Anticipated publication date: January 2017 Obinutuzumab in combination with bendamustine for treating rituximab-refractory follicular lymphoma [ID841] NICE technology appraisal guidance Anticipated publication date: January 2017 Haematological cancers - improving outcomes (update) This guidance will fully update the following: CSG 3. NICE clinical guideline. Anticipated publication date: May 2016 Non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma NICE clinical guideline Anticipated publication date: July 2016
12. Relevant safety issues:	“Patients with active hepatitis B disease should not be treated with rituximab - rituximab has been associated with reactivation of hepatitis B virus when used in the indications of cancer and rheumatoid arthritis.” Source: Medicines and Healthcare products Regulatory Agency (2013)

13. Any other additional relevant information or comments:	"A new subcutaneous injection of rituximab was granted a marketing authorisation in March 2014. Rituximab subcutaneous injection (MabThera, Roche Products Limited) is licensed for treating non-Hodgkin's lymphoma in adults including those with: • previously untreated stage III−IV follicular lymphoma in combination with chemotherapy. • follicular lymphoma that responded to induction therapy. • CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy." Source: NICE advice [ESNM46] Non-Hodgkin's lymphoma: rituximab subcutaneous injection Published date: September 2014
14. Technical Lead comments and recommendation:	Since technology appraisal 137 was published the marketing authorisation for rituximab has been updated to include: • 'the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy' and • 'the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy'. However neither of these updates affect technology appraisal 137 and NICE guidance has been produced for rituximab for the first-line treatment of stage III-IV follicular lymphoma, technology appraisal 243. There are currently no biosimilars of rituximab or any other manufacturers of the drug. According to the 'British national formulary' [BNF] (edition 70) the current price of rituximab as a concentrate for intravenous infusion is the same as when the guidance was originally published in 2008, a 100mg vial is £174.63 and a 500mg vial is £873.15. Since technology appraisal 137 was published the company has launched subcutaneous rituximab. The price and concentration differs to the concentrate for

	intravenous infusion with a rituximab (120 mg/mL) 11.7mL vial costing £1344.65 (BNF, edition 70). During a search for new trials, since the publication of technology appraisal 137 and the review proposal paper for technology appraisal 137, in 2010, information about 13 on-going trials were found. However none of them provided relevant information to suggest a review of technology appraisal 137 was required. Ten of the trials were investigating rituximab in a combination treatment with lenalidomide, duvelisib, idelalisib, pixantrone or gemcitabine, 2 studies were comparing subcutaneous treatment with intravenous infusion and 1 was observing different treatment schedules for rituximab. Based on this information a review of the guidance on the basis of the information above would not provide value for the NHS.

SLR paper sign off: Janet Robertson – Associate Director, Technology Appraisals

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Date of IS searching: 16-19 February 2016

Appendix 1 – explanation of options

Options	Consequence	Selected – 'Yes/No'
The guidance will remain on the 'static guidance list'	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The decision to review the guidance will be deferred to specify date or trial	NICE will consider whether a review is necessary at the specified date. NICE will actively monitor the evidence available to ascertain when a consideration of a review is more suitable.	No
A full consideration of a review will be carried out through the Review Proposal Process	There is evidence that could warrant a review of the guidance. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	No
The guidance will be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	No
The guidance should be updated in an on-going	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once	No

clinical guideline.	the guideline is published the technology appraisal will be withdrawn. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	