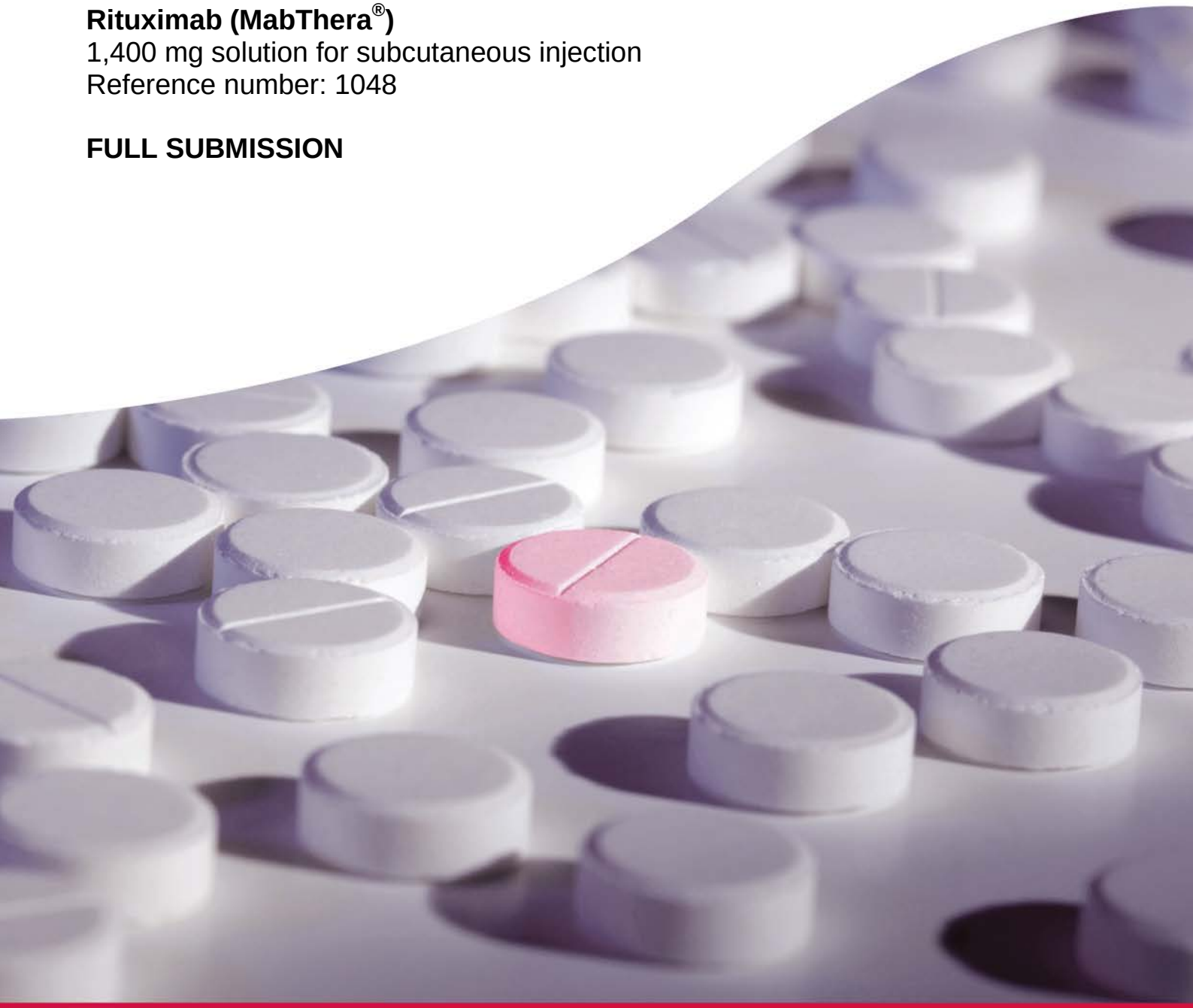
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Rituximab (MabThera®)
1,400 mg solution for subcutaneous injection
Reference number: 1048

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Rituximab (MabThera®) 1,400 mg solution for subcutaneous injection

This assessment report is based on evidence submitted by Roche Products Limited on 21 July 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Rituximab (MabThera®) solution for subcutaneous injection is indicated in adults for non-Hodgkin's lymphoma (NHL): for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy; as maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy; and for the treatment of patients with CD20-positive diffuse large B cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy[2].
Dosing	A fixed dose of 1,400 mg is recommended irrespective of the patient's body surface area. Rituximab subcutaneous (SC) formulation should be administered as subcutaneous injection only, over approximately five minutes into the abdominal wall. Prior to treatment with the SC formulation, all patients must always receive a full dose of rituximab by intravenous (IV) infusion, using the IV formulation. The recommended dose in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients with follicular lymphoma is: first cycle with rituximab IV formulation 375 mg/m^2 body surface area, followed by subsequent cycles with the SC formulation injected at a fixed dose of 1,400 mg per cycle for up to eight cycles. The recommended dose for maintenance therapy for previously untreated and relapsed/refractory follicular lymphoma who have responded to induction treatment is 1,400 mg once every two months and once every three months, respectively; until disease progression or for a maximum of two years. The recommended dose for the treatment of diffuse large B cell NHL in combination with CHOP chemotherapy is 375 mg/m^2 body surface area IV formulation for the first cycle, followed by subsequent cycles with the SC formulation injected at a fixed dose of 1,400 mg per cycle, for up to a total of eight cycles. See the Summaries of Product Characteristics (SPCs) for full dosing details of SC[2] and IV[3] formulations.
Marketing authorisation date	21 March 2014[4]

2.0 DECISION CONTEXT

2.1 Background

Non-Hodgkin's lymphoma (NHL) is the sixth most common cancer in the UK[5]. NHLs are a heterogeneous group of disorders with the most common subtypes in the UK being diffuse large B cell lymphomas and follicular lymphomas[5]. Radiotherapy, immunotherapy and chemotherapy are established in the treatment of NHL[6]. Treatment of NHL may involve several phases: induction therapy, assessment of disease, response to treatment, maintenance therapy, treatment at the point of first relapse, consolidation post-relapse and palliative treatment.

Rituximab is a monoclonal antibody that binds to cluster of differentiation 20 (CD20) protein, present on the cell surface of B-lymphocytes[7]. Rituximab then eliminates these B cells via a number of different possible mechanisms, including mediated cell lysis and apoptosis[2,7]. Rituximab subcutaneous (SC) formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme which enables the SC injection of large volumes and acts as a permeation enhancer[2,7].

2.2 Comparator

The comparator included in the company submission was rituximab (MabThera®) intravenous (IV) formulation.

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE) Technology Appraisal 243. Rituximab for the first-line treatment of stage III or IV follicular lymphoma: (review of NICE technology appraisal guidance 110) (2012)[8].
- National Comprehensive Cancer Network (NCCN). Non-Hodgkin's Lymphomas. (2012)[6].
- Diffuse large B-cell lymphoma: European Society for Medical Oncology (ESMO) Clinical practice Guidelines for diagnosis, treatment and follow-up (2012)[9].
- NICE Technology Appraisal 226. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma (2011)[10].
- Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2010)[11].
- NICE Technology Appraisal 137. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma: Review of technology appraisal guidance 37 (2008)[12].
- NICE Technology Appraisal 65. Rituximab for aggressive non-Hodgkin's lymphoma (2003)[13].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission compares rituximab SC formulation with rituximab IV formulation. The main evidence presented is from the pivotal phase III SABRINA study (BO22334)[1,14]. Supportive evidence is provided from the phase Ib SparkThera study (BP22333)[1,15].

3.1 SABRINA study (BO22334).

SABRINA is a two-stage, multicentre, randomised, open-label, phase III study to investigate the pharmacokinetics, efficacy and safety of rituximab SC versus rituximab IV. In stage 1, patients with previously untreated follicular lymphoma received induction therapy with rituximab in combination with either cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or cyclophosphamide, vincristine, prednisone (CVP) chemotherapy[1,14]. In stage 2 an additional 283 patients received induction treatment and maintenance treatment (if eligible) with either rituximab SC or IV. Maintenance

treatment with either rituximab SC or IV was also given in stage 2 to eligible patients who had received induction treatment in stage 1[16].

In stage 1 (induction phase), patients were randomised to receive either 1,400 mg fixed dose of rituximab SC (n = 63) or 375 mg/m^2 rituximab IV (n = 64), plus CHOP or CVP. All patients received one dose of rituximab IV in cycle 1 followed by the allocated treatment in cycles 2–8, where each chemotherapy cycle lasted 21 days. In both arms 63% of patients received CHOP chemotherapy and 37% received CVP. Patients showing a full or partial response in the induction phase were treated in the maintenance phase in stage 2. At the time of writing this report stage 2 results have not been published in a peer-reviewed journal[1,14].

Non-inferiority of rituximab SC compared to the IV formulation was demonstrated for the stage 1 primary endpoint for the per protocol population; the lower limit of the 90% confidence intervals (CI) of the geometric mean ratio of observed rituximab serum trough concentrations (C_{trough}) at cycle 7 (before cycle 8 dosing) exceeded the pre-specified margin of 0.8[14]. Secondary endpoints included the rituximab serum area under the concentration time curve (AUC) at cycle 7 and overall response (patients achieving a complete response, unconfirmed complete response or partial response) in the intention-to-treat population[1,14]. See Table 1 for results.

Table 1. Results of the SABRINA phase III study[1,14].

	Rituximab SC + chemotherapy	Rituximab IV + chemotherapy	Geometric mean ratio SC/IV* (90% CI)
Primary endpoint			
C_{trough} (micrograms/ml at cycle 7; geometric mean)	134.58 (n = 54)	83.13 (n = 48)	1.62 (1.36–1.94)
Secondary endpoint			
AUC (micrograms.days/ml) cycle 7; geometric mean)	3,779 (n = 55)	2,734 (n = 58)	1.38 (1.24–1.53)
Overall response (investigator assessment)	57/63 (90%)	54/64 (84%)	-
*based on logarithmic scale, adjusted for tumour load at baseline.			

The applicant company provided a congress abstract which reports pooled efficacy and safety analyses from stage 1 and stage 2 of the SABRINA study. Overall response rates at the end of the induction, were supportive of the stage 1 results[16].

3.2 SparkThera (BP22333)

Supportive evidence is provided from this two-stage phase Ib study to investigate the pharmacokinetics, safety and tolerability of rituximab SC formulation used as maintenance treatment in patients with first-line or relapsed follicular lymphoma[1,15]. Stage 1 was a dose-finding study. In stage 2, patients (n = 154) with follicular lymphoma received either 1,400 mg rituximab SC or 375 mg/m^2 rituximab IV on day 1 of each cycle for their remaining maintenance cycles, stratified by regimen (every 2/3 months). The primary endpoint, non-inferiority of rituximab SC compared to rituximab IV, was demonstrated; the lower limits of the two-sided 90% CIs for the geometric mean C_{trough} ratios exceeded the protocol-specified non-inferiority limit[15].

3.3 Comparative safety

The safety populations for both the SABRINA and SparkThera studies included all participants who received at least one dose of rituximab SC or rituximab IV. With the

exception of administration-related reactions (ARRs), the overall adverse event (AEs) profile of rituximab SC was comparable to rituximab IV in both studies[7].

In the SABRINA study, AEs considered by the study investigator to be related to treatment by rituximab and occurring within 24 hours of drug administration were recorded as ARRs. In stage I a greater number of ARRs occurred in SC-treated patients compared to those receiving the IV formulation (31/60 [50%] versus 21/65 [32%], respectively)[14].

The most common ARRs, occurring in the SC and IV arms respectively in stage I of the SABRINA study were erythema (8% versus 3%), pruritus (6% versus 3%), chills (3% versus 6%), injection-site erythema (10% versus 0%) and vomiting (3% versus 6%)[1]. Three (5%) patients in the SC arm and one (2%) patient in the IV arm had grade 3 administration-related reactions[14]. The number of patient discontinuations considered related to study treatment, were zero in the SC arm and two in the IV arm[1,14]. Febrile neutropenia was the most common serious adverse event (SAE), occurring in 6/62 (10%) of patients in the SC arm and 2/65 (3%) of patients in the IV arm[1,14].

Safety evidence from stage 2 of the SparkThera study supported the findings of the SABRINA trial. A similar incidence of SAEs were reported in the rituximab SC arm compared to the IV arm (9/77 [12%] versus 11/77 [14%], respectively) and there was a higher incidence of ARRs (24/77 [31%] versus 3/77 [4%], respectively)[15].

3.4 AWTTC critique

- Rituximab has become standard of care for neoplastic B-lymphocyte derived diseases such as follicular lymphoma[7]. The Committee for Medicinal Products for Human Use (CHMP) reports that rituximab SC could be seen as an improvement in patient care compared to the IV formulation. CHMP concluded that at least equal efficacy has been demonstrated for the SC formulation and, except for local reactions, the safety profile is considered similar at this time. Further data on efficacy in terms of time related endpoints, long-term safety and immunogenicity of the SC formulation of rituximab will be provided from on-going trials[7].
- CHMP state that the data in patients with follicular lymphoma can be extrapolated to the other NHL indications using the same dose and regimens; therefore extrapolation to CD20-positive diffuse large B cell NHL is acceptable. However, for rituximab monotherapy in the treatment of patients with stage III-IV follicular lymphoma where patients require a more intensive dosing regimen (every week for four weeks), no study data were available for the SC formulation[7]. Consequently rituximab SC is not licensed as monotherapy for the treatment of patients with stage III-IV follicular lymphoma who are either chemoresistant, or are in their second or subsequent relapse after chemotherapy[2,7]. However, rituximab IV is licensed and recommended by NICE in this setting[3,12].
- The clinical evidence for rituximab SC is based on the SABRINA study, a pharmacokinetic clinical bridging study demonstrating non-inferiority of SC versus IV rituximab. Clinical efficacy endpoints were reported as secondary outcomes and the patient numbers in stage 1 of the study were small. Published results from stage 2 are not currently available; pooled efficacy data following induction and safety results reported in a congress abstract are in line with results of stage 1.
- A time and motion study, supported by the company, showed that rituximab SC was associated with reduced active health care professional time and costs, as well as reduced patient time in the treatment room, versus the IV formulation[17]. Following a typical initial IV infusion of 4–6 hours, the SC formulation can be administered over five minutes, whilst infusion using the IV formulation typically takes 2–4 hours[1,7]. However, other cytostatic agents would still require IV

administration[7]. The company also highlight a congress abstract reporting interim data from an ongoing patient preference study. They conclude that patient's primary reason for preferring the SC route versus IV was 'less time in the clinic' followed by 'less emotional distress' and 'more comfortable administration'[18].

- Rituximab SC formulation has a fixed dosing regimen removing the risk of dosing errors based on body surface area as required for the IV formulation. However, prior to SC treatment, all patients must receive a full dose of IV rituximab[2].
- CHMP notes that the ARRs reported in the studies for rituximab SC are clinically manageable as they were neither serious nor severe. However such management may impact the convenience of patients and may require healthcare resource[7].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submitted a cost minimisation analysis (CMA) comparing the annual medicine and non-medicine costs of rituximab SC with rituximab IV[1]. The company justifies the choice of CMA on the basis of the results from the SABRINA trial. No clinical outcomes or AEs are modelled.

Costs are calculated for induction therapy (eight treatment cycles) and maintenance therapy (six treatment cycles). Medication costs for rituximab IV are calculated assuming a BSA of 1.86 m^2 per patient, dose of 375 mg per m^2, vial costs of £174.63 per 100 mg and no vial wastage. Medication costs for rituximab SC for induction assume an initial dose of rituximab IV and seven cycles of SC fixed-dose 1,400 mg rituximab. Costs for use as maintenance therapy assume six cycles of SC fixed-dose 1,400 mg rituximab. Costs for rituximab SC are calculated using a confidential, discounted price available under a Wales Patient Access Scheme (WPAS). Resource use and costs to administer IV and SC rituximab are derived from a time and motion study, recording staff time to prepare and administer the medicines in three English centres[17]. The CMA adopts an NHS Wales perspective and a one year time horizon is applied[1].

4.1.2 Results

The company's base case results, using the WPAS price for SC rituximab, are provided in Table 2[1]. [Commercial in confidence data removed]. The difference between the induction and maintenance treatment cycles arises because the initial treatment in the induction arm is IV as per licence. Preparation and administration costs per cycle are assumed to be lower by £115 with SC administration compared to IV (£31 versus £146).

Table 2. Results of base case cost per patient per course of rituximab using WPAS price.

	Induction 8 cycles*		Difference SC−IV	Maintenance 6 cycles		Difference SC−IV
	IV	SC†		IV	SC	
Medicine costs per patient						
Cost per cycle	£1,218	§	§	£1,218	§	§
Full treatment costs	£9,744	§	§	£7,308	§	§
Preparation and administration costs per patient						
Cost per cycle	£146	£31	−£115	£146	£31	−£115
Full treatment costs	£1,171	£365	−£806	£879	£188	−£691
Total Costs						
Cost per cycle	**£1,364**	§	§	**£1,364**	§	§
Full treatment costs	**£10,915**	§	§	**£8,187**	§	§

*****Results apply to the use of rituximab as induction therapy for previously untreated or relapsed/refractory patients with stage III-IV follicular lymphoma in combination with chemotherapy and for the treatment of patients with CD20 positive diffuse large B-cell NHL in combination with CHOP.
†7 cycles SC and 1 cycle IV; § Commercial in confidence data removed

With the WPAS, the SC formulation has lower medicine and administration costs per cycle. [Commercial in confidence data removed]

Table 3 presents the results from a range of sensitivity analyses. The CMA is sensitive to changes in BSA, with higher BSA increasing the cost of IV but not the cost of SC treatment. The savings are also sensitive to the approach used to measure active healthcare professionals (HCP) time to administer IV rituximab.

Table 3. Results of selected scenario and sensitivity analyses.

Scenario and sensitivity analyses	Net cost per treatment (SC–IV) per patient		Plausibility
	Induction	Maintenance	
Base case	*	*	Assumes staff are actively treating only one patient for duration of rituximab IV infusion.
BSA: Females 1.71 m^2, males 1.95 m^2 (base 1.73 m^2 and 1.97 m^2) and different mix of males to females so mean BSA actually higher in sensitivity analysis.	*	*	Assumes staff are actively treating only one patient for duration of rituximab IV infusion.
3.5 patients treated at any given time. Monitor IV infusion time reduced from 148 mins to 42.2 mins per patient and non-drug costs with rituximab IV reduces from £146 to £73 per patient per cycle.	*	*	More plausible however based on the use of rituximab as maintenance treatment
Active time is defined as when HCPs are physically present with patients. Time taken to monitor an infusion of IV rituximab reduced from 148 mins to 4 mins, reducing total process duration for IV admin from 223 mins to 79 mins. Non-drug costs with IV reduces from £146 to £46 per patient per cycle.	*	*	More plausible however based on the use of rituximab as maintenance treatment
*Commercial in confidence data removed.			

4.1.3 AWTTC critique

The CMA presented by the company is only appropriate if the company has demonstrated rituximab SC is therapeutically equivalent to rituximab IV with respect to all dimensions of health outcomes (benefits and harms) and any relevant issues concerning patient preference that may impinge on these outcomes. The clinical evidence is based on a pharmacokinetic clinical bridging study demonstrating pharmacokinetic non-inferiority of SC formulation versus IV formulation. However, a greater number of ARRs occurred in the SC-treated patients compared to those receiving IV. The study was of a short duration with only 127 participants and results of the stage 2 maintenance phase (providing further efficacy information) are awaited.

The base case cost savings could potentially be biased. Firstly, the base case assumes healthcare professionals are actively treating only one patient at a time for the duration of a rituximab IV infusion. Secondly, the time and motion study excluded induction therapy with IV rituximab[17]. Hence there are uncertainties applying the conclusions drawn from this study to the use of rituximab SC in combination with chemotherapy.

Strengths of the economic evidence include:

- Medicine costs, resource use and unit costs are derived from valid sources.
- Sensitivity analyses include the results of two scenarios presented in the time and motion study which adopt alternative definitions of the time to administer IV rituximab compared to the base case[17].

Weaknesses of the economic evidence include:

- Without longer-term efficacy and safety data for rituximab SC to compare to existing data for the IV preparation it is not possible to judge whether a cost utility analysis would be more appropriate.
- The cost savings estimated from the time and motion study are potentially biased because:
  - –The study only measured use as maintenance therapy; induction therapy (in combination with other chemotherapy regimens) was excluded. Therefore, there are uncertainties regarding the overall savings associated with SC rituximab in combination with chemotherapy.
  - –Some staff, for example those involved in preparing treatment during the time and motion trial, are graded higher, with higher associated costs than those carrying out similar activities in clinical practice.
  - –The base case analysis assumed that one nurse actively treated one patient only for the duration of the administration of the infusion, although in practice this is unlikely to be the case. The alternative scenarios could therefore be more plausible than the base case analysis.
- Sensitivity analyses did not consider patient groups with a mean BSA lower than that adopted in the base case. For example, assuming a mean BSA of 1.71 m^2 (from the first sensitivity analysis for females) the medicine only cost of IV rituximab is £1,120 per cycle, [Commercial in confidence data removed].
- Results for maintenance therapy (i.e. six treatment cycles for a one year time horizon) are based on the use of rituximab as maintenance treatment in patients with previously untreated follicular lymphoma whose disease has responded to induction treatment. For maintenance treatment in patients with relapsed or refractory follicular lymphoma whose disease has responded to induction therapy, the recommended regimen is based on treatment every 3 months (i.e. four treatment cycles for a one year time horizon). These results are not presented. However, cost savings would be still be expected (based on

the company estimates) due to the lower cost of preparation/administration and lower acquisition cost of SC rituximab when applying the WPAS price.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified no relevant economic evaluations comparing rituximab SC to the IV preparation.

5.0 SUMMARY OF THE EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company's own market research informed estimates that 382 patients are treated with rituximab IV, all of whom are anticipated to switch to SC administration[1]. Of the 382 patients, 111 have untreated stage III-IV follicular lymphoma, 81 receive maintenance therapy and 190 have CD20 positive diffuse large B cell NHL. The company states these are consistent with the estimated incidence of NHL in Wales (592), adjusted for those with follicular lymphoma who are treated with medication and the percentage receiving rituximab. No change in patient numbers are forecast over the next five years. The company applied the unit costs per cycle provided in Table 2 to these patient groups to estimate net costs and savings from adopting rituximab SC. The results are presented in Table 4. [Commercial in confidence data removed]

Table 4. Company-reported costs of SC rituximab at WPAS price compared to IV rituximab.

	All patients N = 382		Difference SC−IV
	IV	SC	
Medicine costs	£3,525,020	*	*
Administration costs	£423,769	*	*
Total cost	**£3,948,788**	*****	*****
*Commercial in confidence data removed.			

5.1.3 AWTTC critique

The company's estimate of 592 incident patients with NHL is comparable to the estimate of 578 patients with the disease in 2012 reported by the Welsh Cancer Intelligence and Surveillance Unit[19] . Other data are from market research information which has not been provided by the company and cannot therefore be validated. The unit costs are consistent with those adopted in the CMA. No additional sensitivity analyses are provided. The weaknesses associated with the CMA apply to the budget impact forecasts.

5.2 Comparative unit costs

Table 5 provides unit costs for rituximab IV and SC (based on list price).

Table 5. Examples of medicine acquisition costs.

Medicine	Example dose	Mean cost per cycle
Rituximab SC	1,400 mg per cycle	£1,345*
Rituximab IV	375 mg/m^2 per cycle	£1,218*†
*Cost based on MIMS list prices as of September 2014[20]; † Based on body surface area (BSA) 1.86m^2.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, rituximab (MabThera®) solution for SC injection is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that rituximab (MabThera®) solution for SC injection will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted three ongoing studies that are likely to be available within 6–12 months. In Q3 2014 the second stage of the SABRINA study will provide data on patients receiving rituximab SC or rituximab IV as maintenance therapy for up to 2 years[1].

The company reports that interim results from the MabEase study (MO28107, NCT01649856), a phase IIIb open-label study of the use of rituximab SC versus IV with CHOP as first-line induction therapy in patients with CD20-positive diffuse large B-cell lymphoma, will be available in Q4 2014[1,21].

Interim results from the Mabcute study (MO25455, NCT01461928), a phase IIIb observation study of maintenance therapy in patients with relapsed or refractory NHL who have responded to induction and two-year maintenance with rituximab SC, will be available in Q2 2015[1,22].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 4 August 2014
Date range of evidence search: No date limits were applied to database searches.

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