

Non-Hodgkin's lymphoma: rituximab subcutaneous injection

Evidence summary

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Key points from the evidence

The content of this evidence summary was up-to-date in September 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Rituximab subcutaneous injection ([MabThera](#), Roche Products Limited) was granted a marketing authorisation in March 2014 for treating non-Hodgkin's lymphoma in adults. Rituximab concentrate for solution for intravenous infusion ([MabThera](#), Roche Products Limited) has been available in the UK since June 1998.

Stage 1 of an open-label randomised controlled trial in adults ([SABRINA](#); n=127) with previously untreated follicular lymphoma demonstrated pharmacokinetic non-inferiority of

3-week cycles of fixed-dose subcutaneous rituximab 1400 mg compared with intravenous rituximab 375 mg/m² body surface area. Overall response rate was similar in the 2 groups; however, the trial did not have the statistical power to detect differences between the groups. Administration-related reactions were more common with subcutaneous rituximab compared with intravenous rituximab, although most were mild to moderate.

A time and motion study (Rule et al. 2014) found that administration of subcutaneous rituximab was associated with savings in healthcare professional time and costs compared with intravenous rituximab. However, the study had insufficient power to assess differences between the groups statistically.

<p>Effectiveness</p> <p>Stage 1 of SABRINA (Davies et al. 2014, n=127) found that, compared with intravenous rituximab, fixed dose subcutaneous rituximab:</p> <ul style="list-style-type: none"> • was pharmacokinetically non-inferior for the primary outcome of ratio of observed mean rituximab serum trough concentrations (C_{trough}) between the groups at induction cycle 7 (1.62, 90% confidence interval [CI] 1.36 to 1.94). • was associated with a similar overall response rate (84% with intravenous rituximab compared with 90% with subcutaneous rituximab); however, the trial was not powered to detect differences between the groups. 	<p>Safety</p> <ul style="list-style-type: none"> • In SABRINA, the most common adverse events in the intravenous and subcutaneous rituximab groups were neutropenia (35% in both groups), nausea (23% and 29% respectively) and constipation (26% and 23% respectively). • The summary of product characteristics for rituximab subcutaneous injection states that, during the development programme, the safety profile of the subcutaneous injection was comparable to that of the intravenous infusion, with the exception of local injection site reactions. • In SABRINA, administration-related reactions were more common with subcutaneous rituximab compared with intravenous rituximab (50% compared with 32% respectively; statistical analysis not reported). More than 90% of these reactions were mild-to-moderate.
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Patient factors	Resource implications
<ul style="list-style-type: none"> • Administration of rituximab subcutaneous injection takes approximately 5 minutes, whereas administration of the intravenous infusion can take several hours. • In a time and motion study by Rule et al. 2014, subcutaneous rituximab was associated with a reduction in mean participant time spent in the treatment chair or bed, treatment room and hospital compared with intravenous rituximab. The majority of the time saved was time spent in the treatment chair or bed (mean 45.7 minutes and 238.8 minutes respectively: study not powered to analyse differences). • Some patients may prefer a subcutaneous injection to an intravenous infusion. 	<ul style="list-style-type: none"> • The cost per cycle of intravenous rituximab 375 mg/m² body surface area is estimated to be £1222.40 (based on a body surface area of 1.86 m² and assuming wastage: MIMS, August 2014). • The cost per cycle of subcutaneous rituximab at a fixed dose of 1400 mg is higher at £1344.65 (MIMS, August 2014). However, a commercial pricing agreement is currently in place with NHS England to supply subcutaneous rituximab at a price which provides drug cost savings to NHS England (Roche Products Limited, personal communication, August 2014). • In the time and motion study, administration of subcutaneous rituximab was associated with savings in healthcare professional time (mean 30.9–174.8 minutes) and costs (mean £15.22–£115.17) per patient compared with intravenous rituximab.

Introduction and current guidance

Non-Hodgkin's lymphomas are a diverse group of lymphoproliferative malignancies that are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. Most people with a diagnosis of non-Hodgkin's lymphoma have a B-cell lymphoma. The most common B-cell lymphomas are diffuse large B-cell and follicular lymphoma (NICE clinical guideline final scope on [Non-Hodgkin's lymphoma](#)).

A wide range of treatments is used for managing non-Hodgkin's lymphoma. For people with low-grade non-Hodgkin's lymphoma who are asymptomatic, management includes observation. For people who need treatment, there can be several phases: induction therapy, assessment of disease response to treatment, maintenance treatment, treatment at the point of first relapse, consolidation after relapse and palliative treatment (see the final scope for the NICE clinical guideline on [Non-Hodgkin's lymphoma](#)).

NICE has published the following technology appraisals making recommendations about intravenous rituximab in non-Hodgkin's lymphoma indications:

- [Rituximab for aggressive non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 65.
- [Rituximab for the first-line treatment of stage III–IV follicular lymphoma](#), NICE technology appraisal guidance 243.
- [Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 226.
- [Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 137.

This evidence summary looks at a new subcutaneous injection of rituximab.

[Full text of Introduction and current guidance.](#)

Product overview

Rituximab ([MabThera](#), Roche Products Limited) is a monoclonal antibody that targets the CD20 surface antigen, expressed on normal B-cells and almost all B-cell lymphomas.

The existing intravenous infusion of rituximab ([MabThera](#), Roche Products Limited) is licensed for treating non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis.

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.

[Full text of Product overview](#)

Evidence review

- This evidence summary discusses the results of stage 1 of an ongoing phase III open-label [randomised controlled trial](#) (SABRINA), reported by [Davies et al. \(2014\)](#). The SABRINA trial was designed to demonstrate pharmacokinetic non-inferiority of subcutaneous rituximab compared with intravenous rituximab. Also discussed in the evidence summary is a UK time and motion study ([Rule et al. 2014](#)), which investigated staff time and costs associated with administration of subcutaneous, compared with intravenous rituximab.
- The SABRINA trial included 127 adults (mean age 55.5 years) with previously untreated histologically confirmed CD20-positive grade 1, 2 or 3a follicular lymphoma. Participants were randomised to 8 cycles of intravenous rituximab at a dose of 375 mg/m² body surface area (n=64) or 1 cycle of intravenous rituximab at a dose of 375 mg/m² body surface area followed by 7 cycles of subcutaneous rituximab at a fixed dose of 1400 mg (n=63). All participants also received induction chemotherapy regimens.
- The ratio of observed geometric mean serum trough concentrations of rituximab (C_{trough}) between the subcutaneous and intravenous rituximab groups (the primary outcome) in the per-protocol population was 1.62 (90% CI 1.36 to 1.94). Because the lower limit of the 90% CI exceeded the pre-specified margin of 0.8, subcutaneous rituximab was shown to be pharmacokinetically non-inferior to intravenous rituximab. However this result was not reported in the intention-to-treat population. The [European Medicines Agency guideline on Points to consider on switching between superiority and non-inferiority](#) states that non-inferiority studies should be analysed using both the per-protocol and the [intention-to-treat](#) data sets.

- Secondary efficacy outcomes included overall response rate (the percentage of people achieving a complete, unconfirmed complete or partial response to treatment) at the end of induction treatment. In the intention-to-treat population the overall response rate was similar in the 2 groups (84% in the intravenous rituximab group compared with 90% in the subcutaneous rituximab group in the investigator assessment); however, the trial did not have the statistical power to detect differences between the groups. No other clinical efficacy results or patient-oriented outcomes such as progression-free survival or overall survival were reported in the stage 1 analysis. Quality of life was not assessed.
- In SABRINA, treatment-related adverse events were more common in the subcutaneous rituximab plus chemotherapy group compared with the intravenous rituximab plus chemotherapy group (73% [45/62] and 46% [30/65] respectively). However, the proportion of people who experienced a serious adverse event did not differ between the groups. The most common adverse events in the intravenous rituximab and subcutaneous rituximab groups were neutropenia (35% in both groups), nausea (23% and 29% respectively) and constipation (26% and 23% respectively).
- Administration-related reactions were more common with subcutaneous rituximab compared with intravenous rituximab occurring in 50% and 32% of participants respectively; however more than 90% of these reactions were mild-to-moderate.
- Stage 1 of the SABRINA trial had a number of limitations. Clinical efficacy results reported in the trial (such as overall response rate and complete response rate) were secondary, not primary endpoints. The short duration of the study and small size (it included only 127 participants) meant it was not powered sufficiently to assess differences between the treatment groups for these outcomes. In addition, it was an open-label study, which could have introduced bias.
- In SABRINA, overall exposure to rituximab was higher in people in the subcutaneous than the intravenous group because of the fixed-dose. The EPAR states that, because of this, long-term safety issues which potentially could affect overall survival cannot be excluded for subcutaneous rituximab.

- In the time and motion study reported by [Rule et al. 2014](#), administration of subcutaneous rituximab was associated with savings in healthcare professional time (time savings: 174.8 minutes, 95% CI 172.5 to 177.1 minutes) and costs (cost savings: £115.17, 95% CI £98.95 to £136.93) per patient compared with intravenous rituximab, assuming that during administration of intravenous rituximab, the healthcare professional was actively treating the participant for the total duration of the infusion time, taking up 100% of their time. In alternative analyses that made different assumptions about the amount of time the healthcare professional spent actively monitoring the participant receiving intravenous rituximab infusion, the mean healthcare professional time and costs saved were less (mean time saved: 30.9–69.4 minutes; mean costs saved: £15.22–£41.94). However, the significance of any differences between the groups could not be assessed in this study because the small number of observations (13–38 depending on treatment group and observation area) meant it had insufficient power.
- Subcutaneous rituximab was also associated with a reduction in mean participant time spent in the treatment chair or bed, treatment room and hospital overall. The majority of the time saved was time spent in the treatment chair or bed (mean 238.8 minutes with intravenous rituximab, compared with 45.7 minutes with subcutaneous rituximab; difference: 193.1 minutes, 95% CI 177.9 to 206.6 minutes).

[Full text of Evidence review.](#)

Context

The subcutaneous injection of rituximab provides an alternative route of administration to the intravenous infusion. The cost per cycle of intravenous rituximab at a dose of 375 mg/m² body surface area per cycle (based on a body surface area of 1.86 m² and assuming wastage) is estimated to be £1222.40 ([MIMS](#), August 2014). The cost per cycle of subcutaneous rituximab at a fixed dose of 1400 mg per cycle is higher at £1344.65 ([MIMS](#), August 2014). A commercial pricing agreement is currently in place with NHS England to supply subcutaneous rituximab at a price which provides drug cost savings to NHS England (Roche Products Limited, personal communication, August 2014).

[Full text of Context.](#)

Estimated impact for the NHS

Subcutaneous rituximab may provide a potential alternative to intravenous rituximab for treating non-Hodgkin's lymphoma. It offers a quicker, less invasive mode of administration; however, administration-related reactions are more common with the subcutaneous injection compared with the intravenous infusion. Before starting rituximab subcutaneous injections, all patients must have received a full dose of rituximab intravenous infusion to facilitate the management of any administration reactions.

The drug cost of rituximab subcutaneous injection is higher than the intravenous infusion. However a commercial pricing agreement is currently in place with NHS England to supply subcutaneous rituximab at a price which provides drug cost savings to NHS England (Roche Products Limited, personal communication, August 2014). The subcutaneous injection offers benefits in terms of healthcare professional time and associated costs saved compared with administration of the intravenous infusion. However these benefits may not be as great if rituximab is used with other drugs given intravenously.

Local decision makers will need to consider the available evidence when making decisions about using subcutaneous rituximab, in the setting of their local care pathways and usual rituximab-containing treatment schedules. The likely benefits of its use will need to be balanced against the increased risk of administration-related reactions, current lack of longer-term efficacy and safety data, and the absence of direct patient-oriented outcomes such as overall survival and quality of life in non-Hodgkin's lymphoma.

[Full text of Estimated impact for the NHS.](#)

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

Non-Hodgkin's lymphomas are a diverse group of lymphoproliferative malignancies that are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. Most people with a diagnosis of non-Hodgkin's lymphoma have a B-cell lymphoma. The most common B-cell lymphomas are diffuse large B-cell and follicular lymphoma. Other less common types of B-cell lymphoma include mantle cell lymphoma, marginal zone lymphoma, and Burkitt's lymphoma (NICE clinical guideline final scope for [Non-Hodgkin's lymphoma](#)).

The Ann Arbor staging system is the most commonly used staging system to classify the spread of non-Hodgkin's lymphoma and ranges from stage I to stage IV with stage IV indicating more advanced disease ([National Cancer Institute at the National Institutes for Health: Stage information for adult non-Hodgkin's lymphoma](#)).

Non-Hodgkin's follicular lymphoma can also be graded according to how aggressive the disease is, with grade 1 (sometimes called low-grade) being indolent and grade 3 (sometimes called high-grade) being aggressive ([National Cancer Institute at the National Institutes for Health: Cellular classification of adult non-Hodgkin's lymphoma](#)).

According to data published by [Cancer Research UK](#), non-Hodgkin's lymphoma accounts for 4% of cancers in men and women in the UK, with 12,783 new cases and 4646 deaths recorded in 2011. The incidence of non-Hodgkin's lymphoma increases with age.

A wide range of treatments is used for managing non-Hodgkin's lymphoma. For people with low-grade non-Hodgkin's lymphoma who are asymptomatic, management includes observation. For people who need treatment, there can be several phases: induction therapy, assessment of disease response to treatment, maintenance treatment, treatment at the point of first relapse, consolidation after relapse and palliative treatment (see the NICE clinical guideline final scope for [Non-Hodgkin's lymphoma](#)).

A NICE guideline on [Non-Hodgkin's lymphoma](#) is in development (expected date of publication December 2015). Several NICE technology appraisals have been published recommending various treatments for non-Hodgkin's lymphoma.

Rituximab (intravenous infusion) is recommended for use in combination with a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) for the first-line treatment of CD20-positive diffuse large-B-cell lymphoma at clinical stage II, III or IV. Rituximab is not recommended for use when CHOP is contraindicated ([Rituximab for aggressive non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 65).

Rituximab (intravenous infusion), in combination with certain chemotherapy regimens, is recommended as an option for treating symptomatic stage III and IV follicular lymphoma in previously untreated people ([Rituximab for the first-line treatment of stage III–IV follicular lymphoma](#), NICE technology appraisal guidance 243).

Rituximab (intravenous infusion) maintenance therapy is recommended as an option for treating people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy ([Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 226).

Rituximab (intravenous formulation), within its [marketing authorisation](#) at the time of appraisal, 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. In addition, maintenance treatment with rituximab monotherapy is recommended as an option for people with relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab. Monotherapy is also recommended as an option for treating people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted ([Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 137).

Monotherapy with pixantrone is recommended as a third- or fourth-line treatment option for adults with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma, when the person has previously been treated with rituximab, and as long as the manufacturer provides pixantrone with the discount agreed in the patient access scheme ([Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma](#), NICE technology appraisal guidance 306).

This evidence summary looks at a new subcutaneous injection of rituximab.

Product overview

Drug action

Rituximab ([MabThera](#), Roche Products Limited) is a monoclonal antibody that targets the CD20 surface antigen, expressed on normal B-cells and almost all B-cell lymphomas. Rituximab probably induces the death of CD20-positive cells by a combination of mechanisms including antibody-directed cytotoxicity, complement-dependent cytotoxicity, and the induction of apoptosis. Rituximab also appears to sensitise cells to the action of conventional cytotoxic drugs ([Rituximab for aggressive non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 65).

Licensed therapeutic indication

Rituximab concentrate for solution for intravenous infusion ([MabThera](#), Roche Products Limited) was originally granted a European Union marketing authorisation in June 1998. The marketing authorisation has been extended several times since first authorisation and currently (August 2014) rituximab intravenous infusion is licensed for treating non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. The dose of rituximab intravenous infusion for non-Hodgkin's lymphoma indications is 375 mg/m² body surface area; the frequency of dosing depends on the indication. Administration can take several hours.

In March 2014, marketing authorisation was granted for a new subcutaneous injection of rituximab. 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 chemotherapy.

Before starting rituximab subcutaneous injections, all patients must have received a full dose of rituximab intravenous infusion to facilitate the management of any administration

reactions. The recommended dose of rituximab subcutaneous injection is 1400 mg per cycle irrespective of the patient's body surface area. It is administered over approximately 5 minutes.

It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous) is being administered, as prescribed.

Course and cost

The cost per cycle of rituximab subcutaneous injection (based on a fixed dose of 1400 mg per cycle) is £1344.65 excluding VAT ([MIMS](#), August 2014).

The cost per cycle of rituximab intravenous infusion at a dose of 375 mg/m² body surface area, calculated based on a body surface area of 1.86 m² is £1222.40 (assuming wastage; [MIMS](#), August 2014).

According to the [summary of product characteristics \(SPC\) for rituximab subcutaneous injection](#), for induction therapy in previously untreated or relapsed or refractory follicular lymphoma or in diffuse large B-cell non-Hodgkin's lymphoma, the recommended dose of rituximab in combination with chemotherapy is:

- 375 mg/m² body surface area for the first cycle using rituximab intravenous infusion, followed by up to 8 cycles using rituximab subcutaneous injection at a fixed dose of 1400 mg per cycle. Therefore, the cost per course would be £10,634.95 in a person with a body surface area of 1.86 m².

For maintenance treatment in people with previously untreated follicular lymphoma whose disease has responded to induction treatment, the recommended dose of rituximab subcutaneous injection is:

- 1400 mg once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of 2 years. The annual cost of treatment would be £8067.90.

For maintenance treatment in people with relapsed or refractory follicular lymphoma whose disease has responded to induction treatment, the recommended dose of rituximab subcutaneous injection is:

- 1400 mg once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of 2 years. The annual cost of treatment would be £5378.60.

A commercial pricing agreement is in place with NHS England to supply subcutaneous rituximab at a price which provides drug cost savings to NHS England (Roche Products Limited, personal communication, August 2014).

Evidence review

This evidence summary discusses the results of stage 1 of an ongoing randomised open-label phase III trial ([SABRINA](#)), reported by [Davies et al. \(2014\)](#). Stage 1 was primarily designed to assess the pharmacokinetic non-inferiority of subcutaneous rituximab injection compared with the standard intravenous infusion for treating follicular lymphoma; safety and efficacy responses were reported as secondary outcomes. Stage 2 of the trial, which is ongoing, will provide further data on efficacy and safety.

This evidence summary also discusses a UK time and motion study ([Rule et al. 2014](#)) that investigated staff time and costs associated with administration of subcutaneous, compared with intravenous rituximab.

Three other trials of subcutaneous rituximab in non-Hodgkin's lymphoma are underway, [MabCute](#), [MabEase](#), and [PrefMAB](#).

SABRINA ([Davies et al. 2014](#))

- Design: phase III open-label [randomised controlled trial](#) consisting of 2 stages. Stage 1 involved induction therapy with intravenous or subcutaneous rituximab in combination with chemotherapy for 8 cycles. People whose disease completely or partially responded in stage 1 continued rituximab alone as maintenance therapy every 8 weeks for up to 12 cycles in stage 2. The trial was conducted in 67 centres, across 23 countries worldwide.

- Population: 127 adults (mean age 55.5 years) with previously untreated histologically confirmed CD20-positive grade 1, 2 or 3a follicular lymphoma. Participants had to have an Eastern Cooperative Oncology Group performance status of between 0 and 2 (scale of 0–4 with 0 indicating normal activity and 4 indicating bedridden and possibly needing hospitalisation), bidimensionally measured disease (by computerised tomography or magnetic resonance imaging scan), life expectancy of at least 6 months, adequate haematological function for at least 28 days, and 1 or more of the following: bulky disease, B symptoms such as fever, night sweats and weight loss, increased serum lactate dehydrogenase or β 2-microglobulin concentrations, involvement of at least 3 nodal sites, symptomatic spleen enlargement, compressive syndrome, or pleural or peritoneal effusion. People with presence or history of central nervous system disease, transformation to high-grade non-follicular lymphoma, or malignancies other than follicular lymphoma were excluded.
- Intervention and comparison: participants were randomised centrally to intravenous (n=64) or subcutaneous rituximab (n=63). People in the intravenous rituximab group received induction therapy with 8 cycles of intravenous rituximab at a dose of 375 mg/m² body surface area, in addition to cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP; 63% of participants) or cyclophosphamide, vincristine, prednisone (CVP; 37% of participants) chemotherapy. People in the subcutaneous rituximab group received induction therapy with 1 cycle of intravenous rituximab at a dose of 375 mg/m² body surface area (to allow for management of potential administration-related reactions) plus CHOP (63% of participants) or CVP (37% of participants) chemotherapy, followed by 7 cycles of subcutaneous rituximab at a fixed dose of 1400 mg plus chemotherapy. Each cycle lasted 21 days. The method of randomisation described suggests allocation was concealed, although it is not explicitly stated in the methods.

- Outcomes:** The primary endpoint for stage 1 of the trial was the ratio of the observed geometric mean serum trough concentrations of rituximab (C_{trough}) between the groups at induction cycle 7 (before cycle 8 dosing). In order to show non-inferiority of subcutaneous treatment compared with intravenous treatment, the lower limit of the 90% confidence interval (CI) of the geometric mean C_{trough} ratio had to be at least 0.8. Analysis of the primary outcome was completed in the per-protocol population only. The paper does not report if any sensitivity analyses were performed. Secondary endpoints included rituximab serum concentration area under the concentration time curve (AUC) at cycles 2 and 7, overall response (participants who achieved a complete response, unconfirmed complete response, or partial response) at completion of treatment, and safety (including administration-related reactions, and adverse reactions occurring within 24 hours of treatment regarding as being related to rituximab). Secondary efficacy endpoints were analysed in the intention-to-treat population. The safety population included all participants who received at least 1 dose of intravenous or subcutaneous rituximab.

Table 1 Summary of stage 1 analysis of the SABRINA trial (Davies et al. 2014)

	Rituximab IV 375 mg/m² BSA per cycle	Rituximab SC 1400 mg per cycle	Analysis
Randomised	n=64	n=63	
Per protocol	n=48	n=54	
Primary outcome: geometric mean rituximab C_{trough} at induction cycle7	83.13 micrograms/ ml	134.58 micrograms/ ml	Geometric mean ratio 1.62, 90% CI 1.36 to 1.94. The lower limit of the 90% CI exceeded the pre-specified margin of 0.8; therefore rituximab SC was shown to be non- inferior to rituximab IV for this outcome
Selected secondary outcomes:			

Geometric mean AUC at induction cycle 7	2734 micrograms per day/ml (n=58)	3779 micrograms per day/ml (n=55)	Geometric mean ratio 1.38, 90% CI 1.24 to 1.53
Overall response (complete, unconfirmed complete, or partial response) at the end of induction treatment according to investigator assessment ^a	84% (54/64)	90% (57/63)	None reported. The trial was not <u>powered</u> to detect differences between the groups
Safety^b	n=65	n=62	
Participants experiencing any treatment-related adverse events	46% (30/65)	73% (45/62)	None reported
Participants experiencing administration-related adverse events	32% (21/65)	50% (31/62)	None reported
Participants experiencing serious adverse events	22% (14/65)	23% (14/62)	None reported
Participants experiencing neutropenia	35% (23/65)	35% (22/62)	None reported
Participants experiencing nausea	23% (15/65)	29% (18/62)	None reported
Participants experiencing constipation	26% (17/65)	23% (14/62)	None reported

Abbreviations: AUC, area under the concentration time curve; BSA, body surface area; CI, confidence interval; IV, intravenous; SC, subcutaneous

^a Efficacy outcomes were assessed in the intention-to-treat population (all randomised participants).

^b Safety outcomes were assessed in the safety population (all participants who received at least 1 dose of intravenous or subcutaneous rituximab).

Time and motion study ([Rule et al. 2014](#))

- Design: prospective, observational, time and motion study conducted alongside a phase III, randomised, open-label, multinational study (still recruiting) assessing rituximab subcutaneous injection as induction and maintenance therapy in people with relapsed or refractory indolent non-Hodgkin's lymphoma. The time and motion study was conducted in 3 centres in the UK (Plymouth, London, and Oxford).
- Population: adults aged 18 years and over with histologically confirmed CD20-positive indolent non-Hodgkin's lymphoma who had received and relapsed or been refractory to 1 or more adequate treatments prior to enrolment.
- Intervention and comparison: people in the subcutaneous rituximab group received induction therapy with 1 dose of intravenous rituximab followed by 7 cycles of subcutaneous rituximab plus chemotherapy. People in the intravenous rituximab group received induction therapy with 8 cycles of intravenous rituximab. Induction therapy cycles lasted 21–28 days in both groups. Following induction therapy, people received ongoing maintenance therapy with the same formulation as in the induction phase every 8 weeks for 2 years. No information was provided in the paper on the dose used for either intravenous or subcutaneous rituximab. Generally, only monotherapy administration of rituximab as maintenance therapy was observed during the time and motion study to avoid the introduction of bias caused by administration of other chemotherapy agents, infusion reactions following the first dose of rituximab, and delays caused by complications of therapy. However, for subcutaneous rituximab, collection of data during induction therapy with rituximab (followed by same day chemotherapy) was also allowed.

- Outcomes: steps in the processes for subcutaneous and intravenous administration of rituximab were identified and differences between the processes used as variables. The 5 endpoints assessed were healthcare professional time for pre-specified tasks associated with administration of the intravenous infusion or subcutaneous injection; quantity of consumables used per pre-specified task (results not reported); and participant times in the treatment room, treatment chair and hospital. Costs associated with each task were calculated by multiplying the time taken to perform the task by the corresponding cost per hour for the particular healthcare professional involved. Time was measured by using a stopwatch to calculate health care professional time, and using the time of day in hours and minutes to measure the participant time in the treatment chair and treatment room. The study was not sufficiently powered to detect statistical differences between the intravenous and subcutaneous rituximab groups. Thirty one treatment room observations and 20 drug preparation area observations were recorded for subcutaneous rituximab and 38 treatment room observations and 13 drug preparation area observations were recorded for intravenous rituximab.

Table 2 Summary of time and motion study (Rule et al. 2014)

	Intravenous rituximab	Subcutaneous rituximab	Analysis
Treatment room observations	n=38	n=31	
Drug preparation room observations	n=13	n=20	
Outcome 1: mean active healthcare professional time ^a	223.3 minutes	48.5 minutes	Difference between the groups: 174.8 minutes, 95% CI 172.5 to 177.1 minutes (The study was not powered to detect differences between the groups)

Outcome 2: mean participant time in the treatment bed/chair	238.8 minutes	45.7 minutes	Difference between the groups: 193.1 minutes, 95% CI 177.9 to 206.6 minutes (The study was not powered to detect differences between the groups)
Outcome 3: mean participant time in the treatment room	263.8 minutes	70.0 minutes	Difference between the groups: 193.8 minutes, 95% CI 179.5 to 207.1 minutes (The study was not powered to detect differences between the groups)
Outcome 4: mean participant time in hospital	303.8 minutes	110.0 minutes	Difference between the groups: 193.8 minutes, 95% CI not reported (The study was not powered to detect differences between the groups)
Mean staff costs associated with 1 cycle of rituximab ^a	£146.43	£31.26	Difference between the groups: £115.17, 95% CI £98.95 to £136.93 (The study was not powered to detect differences between the groups)
Abbreviations: <u>CI, confidence interval</u> .			
^a Active healthcare professional time and associated costs assume that the healthcare professional is actively treating the participant for the total duration of the intravenous rituximab infusion time, and the participant undergoing treatment with rituximab is the sole focus of the healthcare professional's attention taking up 100% of their time.			

Clinical effectiveness

Stage 1 of the SABRINA trial reported by [Davies et al. 2014](#) was designed to assess pharmacokinetic non-inferiority of 3-week cycles of fixed-dose subcutaneous rituximab compared with intravenous rituximab.

For the primary outcome (ratio of observed geometric mean C_{trough} between the groups), subcutaneous rituximab was shown to be pharmacokinetically non-inferior to intravenous

rituximab because the lower limit of the 90% CI around the geometric mean ratio exceeded the pre-specified margin of 0.8. The study authors reported that rituximab C_{trough} (and AUC) has been linked with clinical efficacy in studies of the intravenous infusion.

Subgroup analyses by body surface area demonstrated non-inferiority of subcutaneous compared with the intravenous rituximab across a range of body surface areas, although as might be expected, people with a low body surface area demonstrated a higher C_{trough} geometric mean ratio (2.29, 90% CI 1.49 to 3.52) than in the overall per protocol population (1.62, 90% CI 1.36 to 1.94); whereas people with a high body surface area demonstrated a lower C_{trough} geometric mean ratio (1.41, 90% CI 1.14 to 1.75). The authors state that the results of these subgroup analyses should be interpreted with caution due to the small number of participants in each subgroup.

Secondary clinical efficacy outcomes included overall response rate (the percentage of people achieving a complete, unconfirmed complete or partial response to treatment) at the end of induction treatment. In the intention-to-treat population the overall response rate at the end of induction was similar in the 2 groups; however the trial was not powered to detect differences between the groups (see table 1 for more information). No other efficacy results such as progression-free survival or overall survival were reported in the stage 1 analysis.

Time and motion study

In the time and motion study reported by [Rule et al. 2014](#), administration of subcutaneous rituximab was associated with healthcare professional time and cost savings compared with intravenous rituximab. However, the significance of any differences between the groups could not be assessed because the study had insufficient power.

In the base analysis, compared with intravenous rituximab, subcutaneous rituximab was associated with savings in mean healthcare professional time and mean costs per patient (time savings: 174.8 minutes, 95% CI 172.5 to 177.1 minutes; cost savings: £115.17, 95% CI £98.95 to £136.93). This analysis assumed that during administration of intravenous rituximab, the healthcare professional was actively treating the participant for the total duration of the intravenous rituximab infusion time, and the participant undergoing treatment with rituximab was the sole focus of the healthcare professional's attention taking up 100% of their time. In practice this may not be the case and so the authors completed 2 alternative analyses using different scenarios.

The first alternative scenario assumed that the healthcare professional was responsible for 3.5 participants at any one time and therefore the time spent monitoring the intravenous infusion would be reduced. Compared with the base analysis, this scenario led to a reduction in the benefit of subcutaneous rituximab compared with intravenous rituximab in terms of mean healthcare professional time and mean costs saved per patient (time savings: 69.4 minutes, 95% CI 67.1 to 71.7 minutes; cost savings: £41.94, 95% CI £32.92 to £55.43).

The second alternative scenario assumed that only the time during which the healthcare professional was physically present with the participant was active healthcare professional time. Compared with the base analysis, this scenario also led to a reduction in the benefit of subcutaneous rituximab compared with intravenous rituximab in terms of mean healthcare professional time and mean costs saved per patient (time savings: 30.9 minutes, 95% CI 28.5 to 33.2 minutes; cost savings: £15.22, 95% CI £8.39 to 26.46). However, in all analyses, subcutaneous rituximab was associated with savings in terms of healthcare professional time and costs compared with intravenous rituximab.

Subcutaneous rituximab was associated with a reduction in mean patient time spent in the treatment chair or bed, treatment room and hospital overall. The majority of the time saved was mean time spent in the treatment chair or bed (238.8 minutes with intravenous rituximab, compared with 45.7 minutes with subcutaneous rituximab; difference between the groups: 193.1 minutes, 95% CI 177.9 to 206.6 minutes).

Safety and tolerability

In stage 1 of the SABRINA trial reported by [Davies et al. 2014](#), after a median follow-up of 8.74 months in the intravenous rituximab plus chemotherapy group, and 8.84 months in the subcutaneous rituximab plus chemotherapy group, around 90% of participants in each group experienced at least 1 adverse event. In the intravenous rituximab group 3/65 (5%) people discontinued treatment because of an adverse event, 2 of which were regarded as related to treatment. In the subcutaneous rituximab group, 1/62 (2%) people discontinued treatment due to an adverse event, which was not considered to be treatment-related.

Treatment-related adverse events were more common in the subcutaneous rituximab plus chemotherapy group compared with the intravenous rituximab plus chemotherapy group (73% [45/62] and 46% [30/65] respectively: statistical analysis not reported). The most common adverse events were neutropenia, nausea and constipation (see table 1 for more information). The proportion of people who experienced a grade 3 or worse adverse event,

or a serious adverse event, did not differ between the groups (46% [30/65] and 22% [14/65] respectively in the intravenous rituximab plus chemotherapy group, and 47% [29/62] and 23% [14/62] in the subcutaneous rituximab plus chemotherapy group respectively). Subgroup analysis by body surface area did not suggest that those with a low body surface area (and hence higher exposure to rituximab) in the subcutaneous group were at increased risk of adverse events compared with those with a low body surface area in the intravenous group. However these findings were based on small numbers of people in each subgroup and should be interpreted with caution.

Administration-related reactions were more common with subcutaneous rituximab compared with intravenous rituximab (50% [31/62] and 32% [21/65] respectively: statistical analysis not reported). Most administration-related reactions (98% in the intravenous rituximab group and 95% in the subcutaneous rituximab group) were mild-to-moderate (grade 1 or 2). Adverse reactions which occurred in more than 5% of participants in either group included erythema, pruritus, chills, injection site erythema and vomiting.

The geometric mean AUC at induction cycle 7 was around 40% higher in the subcutaneous rituximab group, compared with the intravenous group, highlighting that overall exposure to rituximab was higher in people in the subcutaneous than the intravenous group. The [European Public Assessment Report \(EPAR\) for rituximab](#) states that due to the increased exposure of subcutaneous rituximab, long-term safety issues which potentially could affect overall survival cannot be excluded. It is not known whether increased exposure could affect the incidence of the very rare but serious complications such as progressive multifocal leukoencephalopathy.

The [SPC for rituximab subcutaneous injection](#) states that before starting rituximab subcutaneous injections, people must receive a full dose of rituximab by intravenous infusion, using rituximab intravenous formulation. This is because the highest risk of experiencing an administration-related reaction is generally observed in cycle 1 and beginning treatment with rituximab intravenous infusion allows for management of administration reactions by slowing or stopping the infusion.

The SPC states that, during the development programme, the safety profile of the rituximab subcutaneous injection was comparable to that of the intravenous infusion with the exception of local injection site reactions.

Evidence strengths and limitations

Stage 1 of the SABRINA trial demonstrated pharmacokinetic non-inferiority of subcutaneous rituximab compared with intravenous rituximab in adults with previously untreated CD20-positive follicular lymphoma.

The analysis of the primary pharmacokinetic outcome was based on the per-protocol data set. No sensitivity analyses using alternative data sets were reported. The [European Medicines Agency guideline on Points to consider on switching between superiority and non-inferiority](#) states that non-inferiority studies should be analysed using both the per-protocol and the intention-to-treat data sets. The results of the 2 analyses should be consistent to be considered robust.

The [EPAR for Rituximab](#) states that although overall response rate, and complete response rate are acceptable relevant efficacy endpoints, the most compelling endpoints, progression-free survival and overall survival, are not available at this time. Also, the clinical efficacy outcomes reported in the trial were secondary, not primary endpoints and the size and duration of the study was insufficient to assess differences between the groups in outcomes such as overall response rate and complete response rate.

Stage 1 of the SABRINA trial included only 127 participants. In addition, it was undertaken in 67 centres, each enrolling between 1 and 6 participants, with only 6 centres enrolling more than 3 participants. This may have affected how rigorously and consistently trial outcomes were assessed. The trial was open-label, which could have introduced bias, and was too short-term to assess clinical tumour response. Stage 2 analysis should provide further information on clinical efficacy.

Only people with previously untreated histologically confirmed CD20-positive grade 1, 2 or 3a follicular lymphoma were included in the SABRINA trial, yet the licence includes treating people with CD20-positive diffuse large B cell non-Hodgkin's lymphoma in combination with chemotherapy. The [EPAR for rituximab](#) states that data generated in people with follicular lymphoma can be extrapolated to other non-Hodgkin's lymphoma indications that use the same dose and regimens. It was agreed that extrapolation of the induction efficacy results in follicular lymphoma to CD20-positive large B-cell non-Hodgkin's lymphoma was appropriate.

For indications that require weekly rituximab dosing (such as monotherapy with rituximab in people with stage III–IV follicular lymphoma who are chemoresistant or are in their

second or subsequent relapse after chemotherapy), the [EPAR for rituximab](#) notes that pharmacokinetic modelling suggests that exposure to rituximab is significantly increased with the subcutaneous injection compared with the intravenous infusion. Because comparative safety data for treatment of this population with subcutaneous rituximab at a dose of 1400 mg once weekly is not available, subcutaneous rituximab was not approved for indications requiring weekly use. This information is reflected in the [SPC for rituximab subcutaneous injection](#).

The time and motion study had limitations. It only included a small number of observations limiting the findings, and it was not powered to detect statistical differences between the intravenous and subcutaneous rituximab groups. The processes for preparing and administering rituximab may differ between centres and this could reduce the applicability of the results. Staff involved in the study were unfamiliar with using subcutaneous rituximab and so it may have taken longer to prepare and administer it than when the product is used routinely. In addition, because subcutaneous rituximab was an investigational drug at the time of the study, staff involved in its preparation were generally of a higher grade and more costly than those preparing the intravenous infusion. For intravenous rituximab, only observations of monotherapy maintenance regimens were included, induction therapy with intravenous rituximab plus chemotherapy was excluded. Therefore, it is unclear what the savings with subcutaneous compared with intravenous rituximab would be when used alongside other chemotherapy regimens.

The SABRINA trial was funded and sponsored by F. Hoffman-La Roche. The time and motion study was funded by Roche Products Limited.

Context

Alternative treatments

Rituximab subcutaneous injection provides an alternative route of administration to the intravenous infusion.

Costs of alternative treatments

Drug	Usual dose for non-Hodgkin's lymphoma ^a	Cost per cycle excluding VAT ^b
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Intravenous rituximab	375 mg/m ² body surface area per cycle	Based on a body surface area of 1.86 m ² and assuming wastage: £1222.40
Subcutaneous rituximab	Fixed dose of 1400 mg per cycle	£1344.65
<p>^a Doses taken from the relevant summaries of product characteristics.</p> <p>^b Costs taken from MIMS August 2014, excluding VAT. Costs may vary in different settings because of negotiated procurement discounts. The costs do not include the staff costs and consumables associated with administering intravenous infusions.</p>		

A commercial pricing agreement is in place with NHS England to supply subcutaneous rituximab at a price which provides drug cost savings to NHS England (Roche Products Limited, personal communication, August 2014).

Estimated impact for the NHS

Likely place in therapy

The subcutaneous formulation of rituximab may provide an alternative to intravenous rituximab for treating non-Hodgkin's lymphoma. It offers a quicker, less invasive mode of administration; however, administration-related reactions are more common with the subcutaneous injection compared with the intravenous infusion (50% compared with 32% respectively in stage 1 of SABRINA). Before starting rituximab subcutaneous injections, all patients must have received a full dose of rituximab intravenous infusion to facilitate management of administration reactions.

It should be noted that monotherapy with rituximab subcutaneous injection in people with stage III–IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy cannot be recommended because the safety of the once weekly subcutaneous administration has not been established ([SPC for rituximab subcutaneous injection](#)).

The drug cost of the rituximab subcutaneous injection is higher than the intravenous infusion, although a commercial pricing agreement is currently in place with NHS England to supply subcutaneous rituximab at a price which provides drug cost savings to NHS England (Roche Products Limited, personal communication, August 2014).

Administration of rituximab subcutaneous injection takes approximately 5 minutes, whereas administration of the intravenous infusion can take several hours, particularly if the person experiences infusion-related adverse reactions and the infusion rate needs to be slowed. The time and motion study suggests that the subcutaneous injection offers benefits in terms of healthcare professional time and associated costs saved compared with administration of the intravenous infusion. However, these benefits may not be as great if rituximab is used with other drugs given intravenously.

The patent for intravenous rituximab expired in 2013. Several biosimilar forms of rituximab are in development but information on their lead indications and cost is not available at present (National Institute for Health Research Horizon Scanning Centre, personal communication, August 2014).

Results of stage 2 of the [SABRINA trial](#) (estimated completion date November 2017) and other ongoing trials are awaited to provide further longer-term data on the efficacy and safety of subcutaneous rituximab in non-Hodgkin's lymphoma.

Local decision makers will need to consider the available evidence when making decisions about using subcutaneous rituximab, in the setting of their local care pathways and usual rituximab-containing treatment schedules. The likely benefits of its use will need to be balanced against the increased risk of administration-related reactions, current lack of longer-term efficacy and safety data, and the absence of direct patient-oriented outcomes such as overall survival and quality of life in non-Hodgkin's lymphoma.

Estimated usage

Using non-Hodgkin's lymphoma incidence figures for 2013, the manufacturer of subcutaneous rituximab estimates that 6665 people per year might be treated with subcutaneous rituximab in England. Taking into account the list price for subcutaneous rituximab, and the reduction in staffing costs suggested in the [Rule et al. 2014](#) time and motion study, the manufacturer estimates the following increased drug costs would be associated with treating these 6665 people with subcutaneous rather than intravenous rituximab:

- 8 cycles of induction therapy (n=1915): £153,296
- 8 cycles of therapy for treating diffuse large B cell non-Hodgkin's lymphoma (n=3360): £268,969

- 6 cycles of maintenance therapy (n=1390): £95,374.

(Roche Products Limited, personal communication, July 2014)

Relevance to NICE guidance programmes

Rituximab subcutaneous injection for non-Hodgkin's lymphoma was not considered appropriate for a NICE technology appraisal. NICE is developing a clinical guideline on [Non-Hodgkin's lymphoma](#), expected date of publication August 2016.

NICE has issued several technology appraisals relating to Non-Hodgkin's lymphoma:

- [Rituximab for aggressive non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 65
- [Rituximab for the first-line treatment of stage III–IV follicular lymphoma: review of NICE technology appraisal guidance 110](#), NICE technology appraisal guidance 243
- [Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma](#), NICE technology appraisal guidance 226
- [Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma: Review of technology appraisal guidance 37](#), NICE technology appraisal guidance 137
- [Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma](#), NICE technology appraisal guidance 306.

The following NICE technology appraisals relating to Non-Hodgkin's lymphoma are in development:

- [Bendamustine in combination with rituximab for the first-line treatment of advanced indolent non-Hodgkin's lymphoma](#), expected date of publication to be confirmed.
- [Idelalisib for treating refractory indolent non-Hodgkin's lymphoma](#), expected date of publication May 2015.

NICE is developing the following clinical guideline relating to non-Hodgkin's lymphoma:

- [Non-Hodgkin's lymphoma](#), expected date of publication August 2016.

NICE has published several technology appraisals relating to other licensed indications for intravenous rituximab. NICE has also issued several pieces of guidance including recommendations on the use of intravenous rituximab.

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

Expert advisers

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Declarations of interest

Dr Helen McCarthy has received an unconditional educational grant from Roche to attend the American Society Haematology meeting in December 2012. Dr McCarthy has attended a Roche advisory board for rituximab and GA101 use in chronic lymphocytic leukaemia as a member of the UK chronic lymphocytic leukaemia forum. Dr McCarthy is the principle site investigator for a site that is participating in the MabCUTE study, an ongoing study on subcutaneous rituximab in non-Hodgkin's lymphoma.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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