NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA243; Rituximab for the first-line treatment of stage III-IV follicular lymphoma, and TA226; Rituximab for first line maintenance treatment of follicular non-Hodgkin's lymphoma

TA243; Rituximab for the first-line treatment of stage III-IV follicular lymphoma:

This guidance was issued in January 2012.

The review date for this guidance is May 2014.

TA226; Rituximab for first line maintenance treatment of follicular non-Hodgkin's lymphoma:

This guidance was issued in June 2011.

The review date for this guidance is May 2014.

1. Recommendation

The guidance should be transferred to the ‘static guidance list’. That we consult on this proposal.

2. Original remit(s)

TA243; Rituximab for the first-line treatment of stage III-IV follicular lymphoma:

To appraise the clinical and cost effectiveness of rituximab, within its licensed indication, for the first line treatment of stage III-IV follicular lymphoma (review of existing guidance 110).

TA226; Rituximab for first line maintenance treatment of follicular non-Hodgkin's lymphoma:

To appraise the clinical and cost effectiveness of rituximab within its licensed indication, for maintenance treatment following response to first-line chemotherapy for follicular non-Hodgkin’s lymphoma.

3. Current guidance

TA243; Rituximab for the first-line treatment of stage III-IV follicular lymphoma:

1.1 Rituximab, in combination with:

- cyclophosphamide, vincristine and prednisolone (CVP)

- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
- mitoxantrone, chlorambucil and prednisolone (MCP)
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi) **or**
- chlorambucil

is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people.

TA226; Rituximab for first line maintenance treatment of follicular non-Hodgkin's lymphoma:

Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy.

4. Rationale[1]

New evidence available since TA243 and TA226 were published includes a license extension for a subcutaneous (s.c) formulation (granted April 2014), with the same drug acquisition cost as the current intravenous (i.v) formulation and clinical efficacy and safety trial data showing that the s.c formulation was non-inferior to the i.v formulation. In addition, rituximab biosimilars may be available in future, which may affect drug acquisition costs, but it is not expected that cost would increase.

Therefore, none of the new evidence available since the publication of TA243 and TA226 is expected to have an impact on the clinical and cost-effectiveness positive recommendations for rituximab for first line treatment or maintenance of follicular non-Hodgkins lymphoma.

A clinical guideline for non-Hodgkins lymphoma is on-going. This guideline will cross-refer to the recommendations of both technology appraisals TA243 and TA226, however, if during development of the guideline it is decided that the recommendations should be incorporated, then this would be permitted as the guidance would be on the static list.

5. Implications for other guidance producing programmes

The Centre for Clinical Practice is developing a clinical guideline on Non-Hodgkin's Lymphoma (NHL) with anticipated publication early in 2016. This guideline will incorporate TA 65 since it is on static list and will cross refer to related Technology Appraisals TA226 and TA243. There are also links to NHL in the suspected cancer guidance due to be published in May 2015.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from July 2010 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Rituximab has received a license extension in April 2014 for a new subcutaneous formulation. This new formulation is approved for the marketing authorisation covered by Technology appraisal 243 (TA243) and Technology appraisal 226 (TA226). NICE's recommendations for rituximab in TA243 as a treatment option for stage III and IV follicular lymphoma in previously untreated people and for rituximab maintenance in TA226 as a treatment option for follicular non-Hodgkin's lymphoma (NHL) that has responded to first-line therapy with rituximab in combination with chemotherapy are in line with its marketing authorisation.

Since publication of TA243 in January 2012 new interventions have become available to be used in combination with rituximab for first-line treatment of indolent NHL. Bendamustine does not currently have a UK marketing authorisation for the first-line treatment of indolent NHL. It has been studied in combination with rituximab compared with rituximab plus chemotherapy in clinical trials (StiL NHL-2003 and BRIGHT) and it was referred to NICE in January 2011. Following on advice received from the manufacturer, this appraisal will be rescheduled to align with latest regulatory expectations. Bendamustine is available in the NHS through the Cancer Drugs Fund for this indication. It is not expected that the widely availability of bendamustine would impact the recommendations in TA243. If bendamustine becomes available it would be looked at in the proposed technology appraisal for bendamustine in combination with rituximab.

Obinutuzumab does not currently have a UK marketing authorisation for follicular indolent NHL but is being studied in a clinical trial (GALLIUM) in combination with chemotherapy compared with rituximab in combination with chemotherapy, followed by obinutuzumab or rituximab maintenance in people with untreated advanced indolent NHL. The final data collection date for the primary outcome measure in the trial is February 2017.

There are 10 additional clinical trials related to the licensed indication of rituximab covered by TA243. Six out of these 10 trials study rituximab plus different chemotherapy regimens (NCT01476787 and NCT01650701 in combination with lenalidomide, NCT01303887 in combination with fludarabine, NCT00801281 in combination with cyclophosphamide, vincristine, doxorubicin and prednisolone [CHOP] or cyclophosphamide, vincristine and prednisolone [CVP], NCT00006721 and NCT01852435 in combination with CHOP). These trials could add new evidence on new chemotherapy regimens to be used in combination with rituximab in people with previously untreated indolent NHL. All these trials, except for NCT00006721, are ongoing trials with estimated dates of completion ranging from September 2016 to June 2024 and therefore, it is not expected that any of these trials would have an

impact on the recommendations of TA243 at the moment. NCT00006721 studies rituximab plus CHOP (R-CHOP) compared with CHOP and compared with CHOP plus tositumumab. This clinical trial is active and its results show that there was no evidence of a significant improvement in progression-free survival comparing R-CHOP and CHOP plus tositumumab (Press et al. 2013). Two additional trials, SABRINA and NCT01724021, compare rituximab administered intravenously with rituximab administered subcutaneously. Stage 1 results from the SABRINA trial show that the pharmacokinetic profile of subcutaneous rituximab was non-inferior to intravenous rituximab and was not associated with new safety concerns. Stage 2 of the trial is ongoing and will provide data for efficacy and safety of the subcutaneous administration (Davies et al. 2014). The results of this trial support the license extension of rituximab. NCT01724021 investigates patient preferences for subcutaneous rituximab compared with intravenous rituximab. The estimated final data collection date for primary outcome measure is December 2017. The 2 remaining trials (NCT01701232 and EudraCT 2011-002908-33) studied rituximab with or without chemotherapy compared with rituximab biosimilar. Some of these trials also include a maintenance phase with rituximab. It is not expected that the availability of rituximab biosimilar will impact the recommendations in TA243 and TA226.

The clinical effectiveness evidence in TA226 mainly relates to the results of the PRIMA study. Updated results of this trial with a longer follow up have been presented in a conference since the publication of TA226. The results are consistent with the earlier results included in TA226, confirming a sustained benefit of rituximab maintenance therapy after first-line induction treatment with rituximab containing regimens (Salles et al. 2013).

There are 4 additional clinical trials related to the licensed indication of rituximab covered by TA226 that are not expected to impact the recommendations included in this technology appraisal. NCT00227695 compares 2 different regimens of rituximab maintenance: given by a short period of time (every 2 months x 4) and given by a longer period of time (for 5 years or until disease progression, relapse or unacceptable toxicity). The MAINTAIN trial investigates extended maintenance (up to 4 years) with rituximab in people with follicular lymphoma and standard maintenance with rituximab in people with other indolent and mantle cell lymphomas. The marketing authorisation of rituximab states that the maximum period of rituximab maintenance is 2 years and because rituximab can only be appraised within its marketing authorisation, it is not expected that the results from these trials would have an impact on the recommendations in TA226. NCT02063685 investigates whether some patients could benefit from a reduced intensity maintenance treatment with rituximab depending on the response to therapy studying minimal residual disease. The estimated primary outcome collection completion date is July 2016. The HUSOM trial evaluates the benefit of rituximab maintenance in people with advanced follicular lymphoma after induction of response with a rituximab containing regimen. This trial is ongoing and its expected completion date is unknown.

Approximately 70 references were identified in the literature search. None of these publications seem to add new evidence that would have an impact on the recommendations in TA243 and TA226. Most of the studies report results on different chemotherapy regimens in combination with rituximab, adverse effects of

treatment with chemotherapy regimens with or without rituximab or are directly related to the trials mentioned above or the trials included in the submissions for TA243 and TA226. All the identified published economic evaluations were conducted outside the UK or were related to TA243 and TA226.

There has been no change to the acquisition cost of rituximab since the publication of TA243 and TA226. It is expected that the cost of the new subcutaneous formulation of rituximab will be the same as the cost of the current intravenous formulation. Future availability of rituximab biosimilar may affect the cost of rituximab, but it is not expected that this would increase.

In summary, in light of the evidence available it is not expected that this would have an impact on the recommendations of the original guidance of rituximab. It is proposed that, because there is a clinical guideline in development for NHL, the recommendations for rituximab in TA243 and TA226 are incorporated into the ongoing clinical guideline and both appraisals are moved to the static list once the clinical guideline has been published.

Implementation

A submission from Implementation is included in Appendix 3.

Based on the implementation advice received, there has been an increase in prescribing costs and volume for rituximab following the publication of NICE technology appraisals 226 and 243. It is important to note that rituximab has more than the 2 licensed indications covered in this review proposal and therefore, the data on prescribing costs and volume for rituximab should be looked at with caution. The increase on prescribing practices of rituximab seems to adhere to NICE guidance.

8. Equality issues

No equality issues were identified during the scoping process or the appraisal of rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma (TA226). During the appraisal of rituximab for the first-line treatment of stage III–IV follicular lymphoma (TA243), comments were received which suggested that the draft recommendations could disadvantage older patients or those with lower performance status and they suggested that the addition of rituximab to chlorambucil would be of benefit to some of these patients. The Committee discussed the addition of rituximab to chlorambucil in the second committee meeting and the recommendations were amended to include rituximab plus chlorambucil.

GE paper sign off: Frances Sutcliffe, Associate Director, 9 April 2014

Contributors to this paper:

Information Specialist: Sadia Mughal

Technical Lead: Pilar Pinilla-Dominguez

Implementation Analyst: Rebecca Braithwaite

Project Manager: Andrew Kenyon

Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to 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

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Rituximab for aggressive non-Hodgkin's lymphoma. Technology Appraisal TA65. Issued September 2003. Review decision November 2006: guidance to be placed on static list.

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma: Review of technology appraisal guidance 37. Technology Appraisal TA137. Issued: February 2008. Review decision March 2011: guidance to be placed on static list.

Improving outcomes in haemato-oncology cancer. NICE Cancer service guidance (CSGHO). Issued: October 2003.

In progress

Non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma. Clinical Guideline in progress. Date of publication: December 2015.

Bendamustine in combination with rituximab for the first-line treatment of advanced indolent non-Hodgkin's lymphoma. Technology Appraisal in development (ID 434). Date of publication: TBC

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
TA226- Rituximab has a marketing authorisation for the 'treatment of follicular lymphoma patients responding to induction therapy'. TA243- The subject of this review of 'Rituximab for the treatment of follicular lymphoma' (NICE technology appraisal guidance 110) is the wider indication: rituximab for the treatment of previously untreated stage III−IV follicular lymphoma in combination with chemotherapy (not just CVP).	Unchanged

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Rituximab and alemtuzumab (Roche)	Fast infusion formulation for 1st-line use. Licensed in US but not in the UK
Rituximab biosimilar (BI 695500) (Boehringer Ingelheim)	Rituximab and alemtuzumab. Intravenous infusion for first-line use. [redacted]
Rituximab biosimilar (CT-P10) (Sandoz)	Rituximab and alemtuzumab. [redacted]
Rituximab biosimilar (GP2013) (Sandoz)	Rituximab and alemtuzumab. Advances, treatment and maintenance. Intravenous infusion. [redacted]
Rituximab subcutaneous (Roche)	Rituximab and alemtuzumab. Subcutaneous administration. [redacted]
Bendamustine hydrochloride (Napp)	For advanced indolent, mantle cell, first-line with rituximab. Intravenous administration. [redacted]
Lenalidomide (Celgene)	With Rituximab, oral administration. [redacted]
Obinutuzumab (Roche)	For indolent, rituximab refractory. Intravenous infusion administration. [redacted]

Registered and unpublished trials

Trial name and registration number	Details
Combined Rituximab and Lenalidomide Treatment for Untreated Patients With Follicular Lymphoma NCT01476787 (RELEVANCE) Phase 3	The purpose of this study is to evaluate the effect of the combined treatment of lenalidomide and rituximab in controlling the Follicular Lymphoma disease and also increase the length of response compared to the available standard combination chemotherapy treatment for Follicular Lymphoma. Status: Currently recruiting Estimated Enrollment: 1000 Estimated Completion date: June 2024
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 NCT01650701 (RELEVANCE) Phase 3	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 lymohoma the "relevance" trial (Rituximab Lenalidomide Versus Any Chemotherapy)is Being Conducted as Two Companion Studies: RV-FOL-GELARC-0683 (N=750) and RV-FOL-GELARC-0683C (N=250); the Combined Total of 1000 Patients Enrolled in Both Studies Will be Analyzed. Status: Currently recruiting Estimated Enrollment: 1000 Estimated Completion date: June 2024
A Trial Looking at Rituximab and Chemotherapy as a Treatment for Follicular Lymphoma in Elderly Patients NCT01303887 (PACIFICO) Phase 3	The purpose of this study is to determine whether R-FC is more beneficial that R-CVP in the treatment of older patients (aged 60 or over) with Follicular Lymphoma (FL). Status: Recruiting Estimated Enrollment: 680 Estimated Completion date: September 2016

Trial name and registration number	Details
Rituximab in Treating Patients With Follicular Non-Hodgkin's Lymphoma NCT00227695 Phase 3	Comparing Two Schedules of Rituximab Maintenance in Rituximab-Responding Patients With Untreated, Chemotherapy Resistant or Relapsed Follicular Lymphoma: A Randomized Phase III Trial Status: Active, not recruiting Estimated Enrollment: 270 Estimated Completion date: September 2017
Study to Evaluate the Efficacy of Response-adapted Strategy in Follicular Lymphoma NCT02063685 Phase 3	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. Status: Recruiting Estimated Enrollment: 602 Estimated Completion date: July 2019
First-line R-CVP vs R-CHOP Induction Immunochemotherapy for Indolent Lymphoma and R Maintenance. NCT00801281 Phase 3	Evaluation of event free survival (EFS) of patients treated with the study chemotherapy induction program: R-CHOP compared to the standard R-CVP regimen and response rates, time to best response, PFS, OS, neutropenic fever rate, infection rate, change in Ig levels, change in lymphocyte subpopulations counts in previously untreated indolent lymphoma patients in need of systemic treatment. Status: Active, not recruiting Estimated Enrollment: 250 Estimated Completion date: June 2017

Trial name and registration number	Details
Significance of Duration of Maintenance Therapy With Rituximab in Non-Hodgkin Lymphomas NCT00877214 (MAINTAIN) Phase 2 / Phase 3	The purpose of this study is to determine if an extended maintenance therapy with Rituximab in follicular and a maintenance therapy in other indolent and mantle cell lymphomas has advantages compared to a shorter or no maintenance therapy. Status: Recruiting Estimated Enrollment:1134 Estimated Completion date: April 2020
A Study of MabThera (Rituximab) Subcutaneous Vs. MabThera (Rituximab) Intravenous in Patients With Follicular Non-Hodgkin's Lymphoma NCT01200758 Phase 3	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 Status: Active, not recruiting Estimated Enrollment: 410 Estimated Completion date: December 2017
Safety and Efficacy Study of BCD-020 in Therapy of Non-Hodgkin's Lymphoma NCT01701232 Phase 2 / Phase 3	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 Status: Recruiting Estimated Enrollment:134 Estimated Completion date: December 2014

Trial name and registration number	Details
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 Phase 3	This multi-center, open-label, randomized study will evaluate the patient preference with subcutaneous versus intravenous administration of MabThera/Rituxan (rituximab) in patients with CD20+ diffuse large B-cell lymphoma or CD20+ follicular non-Hodgkin's lymphoma. Status: Recruiting Estimated Enrollment: 900 Estimated Completion date: December 2017
S0016 Combination Chemotherapy With Monoclonal Antibody Therapy in Treating Patients With Newly Diagnosed Non-Hodgkin's Lymphoma NCT00006721 Phase 3	A Phase III Trial of CHOP Plus Rituximab vs CHOP Plus Iodine-131-Labeled Monoclonal Anti-B1 Antibody (Tositumomab) for Treatment of Newly Diagnosed Follicular Non-Hodgkin's Lymphomas. Status: Active, not recruiting Estimated Enrollment: 571 Primary Completion date: September 2011
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 Phase 3	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 Status: Recruiting Estimated Enrollment: 600 Estimated Completion date: April 2017

Trial name and registration number	Details
A Study of Obinutuzumab (RO5072759) Plus Chemotherapy in Comparison With MabThera/Rituxan (Rituximab) Plus Chemotherapy Followed by GA101 or MabThera/Rituxan Maintenance in Patients With Untreated Advanced Indolent Non-Hodgkin's Lymphoma (GALLIUM) NCT01332968 Phase 3	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. Status: Recruiting Estimated Enrollment: 1400 Estimated Completion date: March 2017
A multicentre, phase III, open-label, randomised study in patients with advanced follicular lymphoma evaluating the benefit of maintenance therapy with Rituximab (MabThera®) after induction of response with chemotherapy plus Rituximab in comparison with no maintenance therapy EudraCT Number: 2004-001756-36 PRIMA	Status: Ongoing Estimated Enrollment: 640
Hungarian Study of Maintenance after Rituximab Pretreatment. A multicentre, phase III, open-label study evaluating the benefit of a long-term MabThera® (rituximab) maintenance therapy in patients with advanced follicular lymphoma after induction of response (CR(u) or PR) with a MabThera® (rituximab)-containing first line regimen EudraCT Number: 2005-000359-13	Status: Ongoing Estimated Enrollment: 150
A randomized, double-blind, multi-center, multi-national Phase III trial to compare efficacy and safety of BI 695500 plus chemotherapy versus rituximab plus chemotherapy in patients with untreated follicular non-Hodgkin’s lymphoma. EudraCT Number: 2011-002908-33	Status: Ongoing Estimated Enrollment: 530

Additional information

Drug cost:
The cost of Rituximab is unchanged since the publication of TA 226 and TA 243.

Drug safety:
"Cases of severe skin reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) have been very rarely reported in patients with autoimmune diseases". *Direct Healthcare Professional Communication on the association of MabThera® (rituximab) with Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome (April 2013).*

References

1. Press OW, Unger JM, Rimsza LM et al. (2013) Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. *J Clin Oncol*. 31:314-20.

2. Davies A, Merli F, Mihaljevic B et al. (2014) Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study. *Lancet Oncol.* 15(3):343-52.

3. Salles GA, Seymour JF, Feugier P et al. (2013) Updated 6 Year Follow-Up Of The PRIMA Study Confirms The Benefit Of 2-Year Rituximab Maintenance In Follicular Lymphoma Patients Responding To Frontline Immunochemotherapy. *Blood* 122:509.

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No. 226 and 243; Follicular lymphoma - rituximab

Please contact Rebecca Braithwaite regarding any queries
rebecca.braithwaite@nice.org.uk

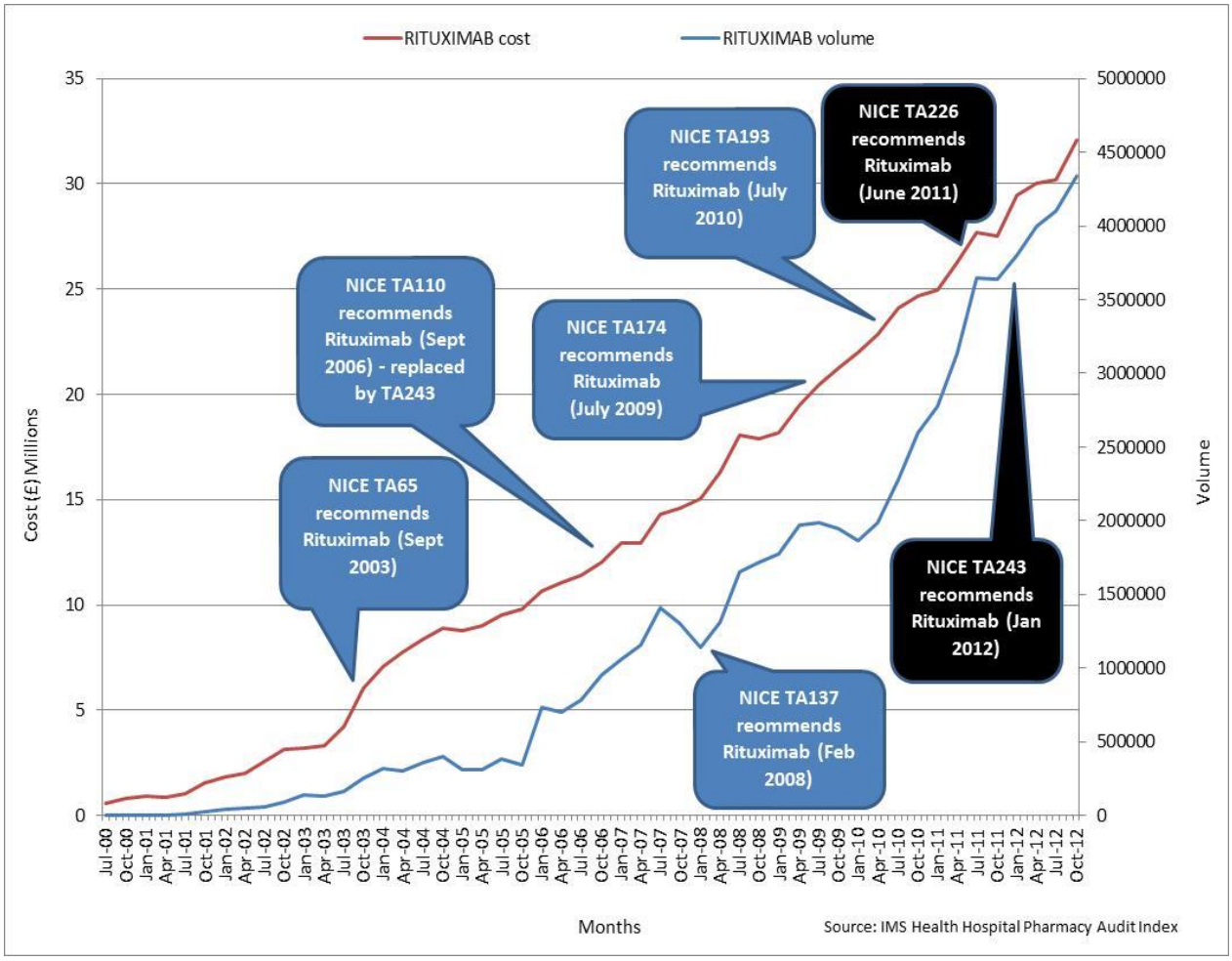
Contents

1. Routine healthcare activity data

1.1. Hospital Pharmacy Audit Index data

This section presents hospital pharmacy audit index data on the net ingredient cost and volume of Rituximab prescribed and dispensed for use in hospitals in England between July 2000 and December 2012. These data need to be treated with caution as rituximab has more than one licensed indication.

Figure 1 Net ingredient cost and volume of Rituximab prescribed and dispensed for use in hospitals in England



2. Implementation studies from published literature

Information is taken from the uptake database website.

Nothing specific to add.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing specific to add.

Appendix A: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.