NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA174; Rituximab for the first line treatment of chronic lymphocytic leukaemia, TA193; Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia, and TA202; Ofatumumab for the treatment of refractory chronic lymphocytic leukaemia

The guidance was issued on the following dates:

TA174 – July 2009

TA193 – July 2010

TA202 – October 2010

The review date for TA174 and TA193 is December 2010.

TA174 and TA193 were considered for review in December 2010 and October 2012. Both times the consideration of a review was deferred until the publication of the MO20927 trial: NICE "…will consult on our plans for TA174 and TA193 within 6 months of the publication of MO20927."

The review date for TA202 is September 2013.

1. Recommendation

TA174 and TA193 should be moved to the static list.

That we consult on this proposal.

A decision on whether to review TA202 will be deferred until publication of data from randomised controlled trials of ofatumumab in combination with chemotherapy versus chemotherapy alone (NCT00824265 and NCT01313689). A consultation will take place within 6 months of the publication of NCT01313689.

2. Original remit(s)

TA174: to appraise the clinical and cost effectiveness of rituximab within its licensed indication for the first line treatment of chronic lymphocytic leukaemia.

TA193: to appraise the clinical and cost effectiveness of rituximab within its licensed indication for the treatment of relapsed/refractory chronic lymphocytic leukaemia.

TA202: to appraise the clinical and cost effectiveness of ofatumumab within its licensed indication for the treatment of refractory chronic lymphocytic leukaemia.

3. Current guidance

TA174:

1.1 Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide is considered appropriate.

1.2 Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

TA193:

1.1 Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with relapsed or refractory chronic lymphocytic leukaemia except when the condition:

- is refractory to fludarabine (that is, it has not responded to fludarabine or has relapsed within 6 months of treatment) or
- has previously been treated with rituximab, unless:
  - in the context of a clinical trial, at a dose lower than the dose currently licensed for chronic lymphocytic leukaemia or
  - in the context of a clinical trial, in combination with chemotherapy other than fludarabine and cyclophosphamide.

1.2 Rituximab in combination with fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia that has previously been treated with rituximab, unless rituximab has been given as specified in section 1.1.

1.3 Rituximab in combination with chemotherapy other than fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia.

1.4 People with chronic lymphocytic leukaemia that is refractory to fludarabine (as defined in section 1.1), who are currently receiving rituximab in combination with fludarabine and cyclophosphamide should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

1.5 People with chronic lymphocytic leukaemia that has previously been treated with rituximab other than as specified in section 1.1, who are currently receiving rituximab in combination with fludarabine and cyclophosphamide and people who are currently receiving rituximab in combination with other chemotherapy regimens that is not in the context of research, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

TA202:

1.1 Ofatumumab is not recommended for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab.

1.2 People currently receiving ofatumumab for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab should have the option to continue treatment until they and their clinician consider it appropriate to stop.

4. Rationale[1]

TA174 – previously untreated chronic lymphocytic leukaemia

TA174 does not recommend rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide. Data are now available in abstract form from a three arm study comparing obinutuzumab (another anti-CD20 agent) plus chlorambucil with rituximab plus chlorambucil and chlorambucil alone. Consideration was given to updating TA174 as a multiple technology appraisal with newer drugs for the same indication (obinutuzumab and an extension of the indication for ofatuzumab), but following consultation on the draft scopes it has been decided that the appraisals of obinutuzumab and ofatumumab for previously untreated chronic lymphocytic leukaemia should proceed as single technology appraisals. Therefore it was not considered appropriate to review TA174 at the present time. Consideration may be given to updating TA174 when the single technology appraisals are considered for review. In the meantime TA174 can be moved to the static list.

TA193 and TA202 – relapsed or refractory chronic lymphocytic leukaemia

TA193 recommended rituximab only in certain circumstances, or in the context of research outside of those circumstances. No new evidence that would change these recommendations has been found.

TA202 did not recommend ofatumumab for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab[2]. Most of the clinical evidence for this appraisal came from a single-arm study and therefore the estimation of clinical benefit was highly uncertain. There are two ongoing randomised clinical studies in refractory chronic lymphocytic leukaemia comparing ofatumumab plus chemotherapy with chemotherapy alone. The results of these studies would provide a more robust estimate of clinical effectiveness than was available for TA202. One of the studies is in fludarabine-refractory chronic

[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

[2] The marketing authorisation for MabCampath (alemtuzumab) was withdrawn for commercial reasons last year but it remains available to patients with chronic lymphocytic leukaemia through patient access programmes (see http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2012/08/WC500130945.pdf)

lymphocytic leukaemia and is therefore particularly relevant to TA202. TA202 should be considered for review when the results of this study are available.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

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 November 2007 (TAs 174 and 193) and April 2009 (TA202) 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

The manufacturer of rituximab has not made any changes to the current marketing authorisations or indicated that they are planning to extend the current marketing authorisations. It does not appear that any relevant new interventions or comparators have come to market since the original guidance was issued although there are new interventions in development, including a possible extension of the indications of ofatumumab to include first-line use.

The manufacturer noted that a single-arm phase II study is currently underway (MO20927) to evaluate the safety and response rate of rituximab plus chlorambucil in previously untreated patients with CD20-positive B-cell chronic lymphocytic leukaemia. They also specified that the MO20927 trial has been superseded by the BO21004 trial, which is a three armed RCT which evaluates the use of obinutuzumab plus chlorambucil versus rituximab plus chlorambucil versus chlorambucil alone as a first line treatment in a population with chronic lymphocytic leukaemia and co-existing medical conditions. It is a randomised study and therefore provides more robust data than MO20927. The results of stage I of the study (which aimed to demonstrate that chlorambucil plus an anti-CD20 monoclonal antibody is superior to chlorambucil monotherapy, stage II will compare the two monoclonal antibodies) have been published in abstract form. The study found that chemoimmunotherapy with obinutuzumab plus chlorambucil or rituximab plus chlorambucil statistically significantly prolongs progression free survival compared with chlorambucil alone.

Two ongoing trials of ofatumumab for the treatment of relapsed or refractory chronic lymphocytic leukaemia were identified:,ofatumumab in combination with fludarabine and cyclophosphamide compared with fludarabine-cyclophosphamide for relapsed chronic lymphocytic leukaemia (NCT00824265) and ofatumumab therapy versus physicians' choice in patients with bulky fludarabine-refractory chronic lymphocytic leukaemia (NCT01313689). These studies are expected to be completed in early 2014.

Literature searches identified a number of new studies which have been published since the original guidance, of which 11 were not relevant: 1 (Zagaokina 2010) evaluated rituximab as a second line chemotherapy treatment but it was not clear if it was in people with relapsed/refractory chronic lymphocytic leukaemia, 4 were case series or narrative reviews (Casak 2011, Dungarwalla 2008, Lepretre 2010, Weirda 2010), 1 was a pharmacokinetic study (Li 2012), 4 were reviews of studies identified in TA174 or TA193 or TA202 (Hallek 2010, Lemery 2010, Molika 2011, Robak 2010), and 1 was an economic evaluation study from a US perspective (Hornberger 2012).

New systematic reviews and meta-analysis (N=3)

.A Cochrane review (Bauer 2012) evaluated the effectiveness of rituximab, ofatumumab and other monoclonal anti-CD20 antibodies as first-line treatment for chronic lymphocytic leukaemia. Five relevant RCTs were identified of which 2 were published as abstracts only, and therefore were not included. Three RCTs (N = 1421) assessed the efficacy of monoclonal anti-CD20 antibodies (rituximab) plus chemotherapy compared to chemotherapy alone. The meta-analysis of these 3 trials found patients receiving chemotherapy plus rituximab benefit in terms of overall survival as well as progression-free survival compared to those with chemotherapy alone.

A systematic review and network meta-analysis (Cheng, 2012) of 5 RCTs evaluated the effect of rituximab in combination with fludarabine and cyclophosphamide on progression free survival in people with treatment naïve chronic lymphocytic leukaemia. The study found the combination of these three treatments resulted as statistically significantly longer period of progression free survival.

A systematic review and network meta-analysis (Terasawa 2013) of 25 RCTs evaluated the effect of rituximab in combination with fludarabine on progression free survival in people with treatment-naïve chronic lymphocytic leukaemia. The study found that rituximab in combination with fludarabine resulted in a statistically significantly longer period of progression free survival than chlorambucil and bendamustine, but no statistically significant differences between chemotherapy regimens were identified.

Studies in older patient populations (N=1)

In TA174 the evidence of clinical effectiveness for rituximab was based mainly on a single unpublished randomised controlled trial (the CLL-8 trial) The Committee heard from the clinical expert that the trial population was younger and fitter than the population of people with chronic lymphocytic leukaemia seen in routine practice within the NHS in England and Wales. One study (Woyach 2013) evaluated the effectiveness of rituximab in combination with fludarabine compared with chlorambucil, fludarabine, fludarabine with consolidation alemtuzumab, and FR with consolidation alemtuzumab in patients aged 70 years and older. The study results found that rituximab is an effacious treatment regardless of patient age. The risk of disease progression decreased 40% for patients younger than 70 years treated with fludarabine compared to chlorambucil, but did not decrease among patients over 70 years. In contrast, the addition of rituximab to fludarabine decreased the risk of progression by 44% relative to fludarabine alone (hazard ratio = 0.56; 95%

confidence interval 0.43 to 0.74) and did not have a differential effect on progression-free survival by age group (P = 0.55)

Studies evaluating the effectiveness of rituximab in the longer term (N=1)

Woyach (2011) utilised data from the CALGB9712 study, which was included as supporting evidence in the ERG report for TA174. The study included people with chronic lymphocytic leukaemia who were chemotherapy naive. The study evaluated the long term (medium follow-up 117 months) effect of rituximab in combination with fludarabine compared with fludarabine monotherapy in terms of progression-free survival, overall survival, impact of genomic features, and risk of therapy-related myeloid neoplasm. The study found there was a greater overall survival and progression-free survival with fludarabine plus rituximab compared with fludarabine monotherapy.

8. Implementation

Two submissions from Implementation (TA174/TA193, and TA202) are included in Appendix 3. Since the original guidance the published, it appears that NICE guidance is being adhered to and current practice has not significantly changed.

9. Equality issues

TA174: The Committee noted there was a group of patients for whom a regimen of fludarabine in combination with cyclophosphamide was not suitable, and who might therefore be treated with rituximab in combination with chlorambucil. This group would be expected to include a high proportion of people with poor performance status or comorbidities. However the Committee noted that a negative recommendation for rituximab in combination with chlorambucil did not appear to have an impact on any group protected by the equalities legislation. It is not obvious that there is a clear correlation between the comorbidity factors which rendered this patient group unsuitable for certain chemotherapies and 'disability' as defined in the Disability Discrimination Act 1995. The Committee could not be satisfied that a negative recommendation of rituximab in combination with chlorambucil represented less favourable treatment or loss of benefit, given the lack of clear evidence as to the relative clinical effectiveness of rituximab in combination with chlorambucil in this particular patient group.

TA193 and TA202: No equalities issues were raised in the original guidance

GE paper sign off: Janet Robertson, 11th December 2013

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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 within 6 months of the publication of NCT01313689	NICE will reconsider whether a review is necessary at the specified date.	Yes for TA202
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

Options	Consequence	Selected – 'Yes/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
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 for TA174 and TA193

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

TA29 Fludarabine for the treatment of B-cell chronic lymphocytic leukaemia. Issued September 2001. Review decision (approx. August 2005, as undated): *"deferred to allow the results of the current MRC trial CLL4 to inform the review."* The results of CLL4 appear to be in the process of publication..

TA119 Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia. Issued February 2007. Review decision May 2010: transfer to static.

TA216 Bendamustine for the treatment of chronic lymphocytic leukaemia. Issued February 2011. Review date: December 2013.

Referred - QSs and CGs

Haematological malignancies (in the core library of topics, not in progress, and no date is given).

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
TA174: Rituximab is licensed for the first-line treatment of people with chronic lymphocytic leukaemia in combination with chemotherapy. Rituximab is administered intravenously, once every 4 weeks for a total of six cycles; a complete course of treatment with rituximab lasts 24 weeks. Dosing is calculated according to body surface area, with an initial dose of 375 mg/m^2 followed by 500 mg/m^2 for all subsequent doses. Six cycles of rituximab equate to a total dose of 2875 mg/m^2. Rituximab is available in 100 mg (10 ml) and 500 mg (50 ml) vials. The cost of a 100 mg vial is £174.63, and of a 500 mg vial is £873.15 (excluding VAT; 'British national formulary' [BNF] edition 57). For a person with a body surface area of 1.93 m2, the cost of rituximab for the first dose is £1397 and for subsequent doses £1746 including wastage of excess rituximab. The total cost of rituximab is £10,128 per course	The indication for TA174 is the same, as is the cost.

Indication considered in original appraisal	Proposed indication (for this appraisal)
TA193: Rituximab is licensed for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Dosing is calculated according to body surface area, with an initial dose of 375 mg/m^2 followed by 500 mg/m^2 for all subsequent doses. Six cycles of rituximab equate to a total dose of 2875 mg/m^2. Rituximab is administered intravenously, once every 4 weeks for a total of six cycles; a complete course of treatment with rituximab lasts 24 weeks.	The indication for TA193 is the same, as is the cost.
TA202: Ofatumumab has a conditional marketing authorisation for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab. Ofatumumab is delivered by intravenous infusion. The recommended dose is 300 mg of ofatumumab for the first infusion and 2000 mg of ofatumumab for subsequent infusions. The infusion schedule is eight consecutive weekly infusions, followed 4–5 weeks later by four consecutive monthly infusions (that is, every 4 weeks). Ofatumumab is currently available in 100 mg (5 ml) vials. The cost of ofatumumab is £182.00 per 100 mg vial, excluding VAT (Monthly Index of Medical Specialities [MIMS], August 2010).	The indication for TA202 is the same (apart from now not being conditional), as is the cost.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Obinutuzumab (with chlorambucil, 1st line) (Roche).	Phase III. [redacted]
Ofatumumab in combination with chlorambucil, 1st line (GlaxoSmithKline).	Phase III. [redacted]

Registered and unpublished trials

Trial name and registration number	Details
An open-label study to characterize the safety and response rate of MabThera (rituximab) plus chlorambucil in previously untreated patients with CD20-positive B-cell chronic lymphocytic leukemia. NCT00532129 *(also known as MO20927.)*	Phase II, non-randomised, completed. Enrolment: 100 Primary study completion date: April 2012. *Preliminary results are available on the Roche website.*
Prospective study of efficacy and safety of RFC (rituximab, fludarabine, cyclophosphamide) regimen as a first-line therapy in patients with B-cell chronic lymphocytic leukemia and favorable somatic status. NCT01271010	Phase IV, non-randomised, currently recruiting. Estimated enrolment: 200 Primary study completion date: July 2017.
Prospective randomized study to compare efficacy and safety of RFC-lite (rituximab, fludarabine, cyclophosphamide) regimen with LR (rituximab, chlorambucil) as a first-line therapy in patients with B-cell chronic lymphocytic leukemia and unfavorable somatic status. NCT01283386	Phase IV, non-randomised, currently recruiting. Estimated enrolment: 200 Primary study completion date: July 2017.
A randomized, open label study to assess the effect of maintenance treatment with MabThera vs no treatment, after induction with MabThera, cladribine and cyclophosphamide on progression-free survival in previously untreated patients with progressive B-CLL. The trial conducted with PALG Sites. NCT00718549	Phase III, ongoing not recruiting. Estimated enrolment: 128 Primary study completion date: July 2017.
Open-label, multicenter, randomized, comparative, phase III study to evaluate the efficacy and safety of FCR vs. FC Alone in previously treated patients with CD20 positive B-cell CLL. NCT00090051	Phase III, completed. Enrolment: 552 Primary study completion date: July 2008. Study completion date: May 2012. *Preliminary results are available on the ClinicalTrials.gov website.*

Trial name and registration number	Details
Single-agent rituximab as maintenance treatment versus observation after combined induction immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) in patients older than 65 years with previously untreated B-cell chronic lymphocytic leukemia (B-CLL): a phase III Intergroup trial of the GOELAMS and the FCGCLL/WM groups. NCT00645606	Phase III, currently recruiting. Estimated enrolment: 542 Primary study completion date: July 2017.
Phase III trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) versus bendamustine and rituximab (BR) in patients with previously untreated chronic lymphocytic leukaemia. NCT00769522	Phase III, ongoing not recruiting. Estimated enrolment: 564 Primary study completion date: July 2011. Estimated study completion date: January 2018.
A phase III Intergroup CLL study of asymptomatic patients with untreated chronic lymphocytic leukemia randomized to early intervention versus observation with later treatment in the high risk genetic subset with IGVH unmutated disease. NCT00513747	Phase III, ongoing not recruiting. Estimated enrolment: 84 Primary study completion date: December 2033.
International, multicentre, randomized phase III study of rituximab as maintenance treatment versus observation alone in patients with chronic lymphocytic leukemia NCT01118234	Phase III, currently recruiting. Estimated enrolment: 256 Primary study completion date: December 2015.
A randomized study to assess the effect on response rate of MabThera (Rituximab) added to a standard chemotherapy, bendamustine or chlorambucil, in patients with chronic lymphocytic leukemia. NCT01056510	Phase IV, currently recruiting. Estimated enrolment: 600 Primary study completion date: May 2014.
An open-label, multi-center, three arm randomized study to investigate the safety and efficacy on progression-free survival of RO5072759 + chlorambucil (GClb) compared to rituximab + chlorambucil (RClb) or chlorambucil (Clb) alone in previously untreated CLL patients with comorbidities. NCT01010061 *(also known as BO21004)*	Phase III, ongoing not recruiting. Estimated enrolment: 787 Primary study completion date: 2021.

Trial name and registration number	Details
A phase 3, randomized, controlled study evaluating the efficacy and safety of GS-1101 (CAL-101) in combination with ofatumumab for previously treated chronic lymphocytic leukemia. NCT01659021	Phase III, currently recruiting. Estimated enrolment: 210 Primary study completion date: December 2014.
A randomized, multicenter, open-label, phase 3 study of the Bruton's Tyrosine Kinase (BTK) inhibitor ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. NCT01578707	Phase III, ongoing not recruiting. Estimated enrolment: 350 Primary study completion date: July 2015.
A phase 3 study to evaluate the efficacy and safety of dinaciclib or ofatumumab in subjects with refractory chronic lymphocytic leukemia. NCT01580228	Phase III, currently recruiting. Estimated enrolment: 466 Primary study completion date: April 2016.
A randomised investigation of alternative ofatumumab-containing regimens in less fit patients with CLL NCT01678430	Phase III, currently recruiting. Estimated enrolment: 670 Primary study completion date: 2017.
A phase III, open label, randomized, multicenter trial of ofatumumab added to chlorambucil versus chlorambucil monotherapy in previously untreated patients with chronic lymphocytic leukemia. NCT00748189	Phase III, ongoing not recruiting. Estimated enrolment: 447 Primary study completion date: March 2013.
A phase III, open label, randomized trial of ofatumumab added to fludarabine-cyclophosphamide vs. fludarabine-cyclophosphamide combination in subjects with relapsed chronic lymphocytic leukemia. NCT00824265	Phase III, currently recruiting. Estimated enrolment: 352 Primary study completion date: January 2014.

Trial name and registration number	Details
An open label, multicenter study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine-refractory chronic lymphocytic leukaemia (CLL). NCT01313689 *"The purpose of this study is to confirm the clinical benefit observed in the pivotal registration study, Hx-CD20-406. The Committee for Medicinal Products for Human Use (CHMP) required that a randomized study be conducted in CLL patients with bulky fludarabine-refractory disease as a specific obligation for grant of conditional approval for ARZERRA™ in the European Union (EU). This study will compare ofatumumab with the physicians' choice of therapy."*	Phase III, currently recruiting. Estimated enrolment: 120 Primary study completion date: March 2014.
A phase III, open label, randomized, multicenter trial of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia (CLL) who have responded to induction therapy. NCT01039376	Phase III, currently recruiting. Estimated enrolment: 532 Primary study completion date: May 2017.
A randomised investigation of alternative ofatumumab containing regimens in less fit patients with chronic lymphoid leukemia (CLL) (RIAltO) ISRCTN09988575	Phase III, ongoing. Estimated enrolment: 670 Primary study completion date: December 2015.

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Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No. 174 Rituximab for the first line treatment of chronic lymphocytic leukaemia and No. 193 Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia

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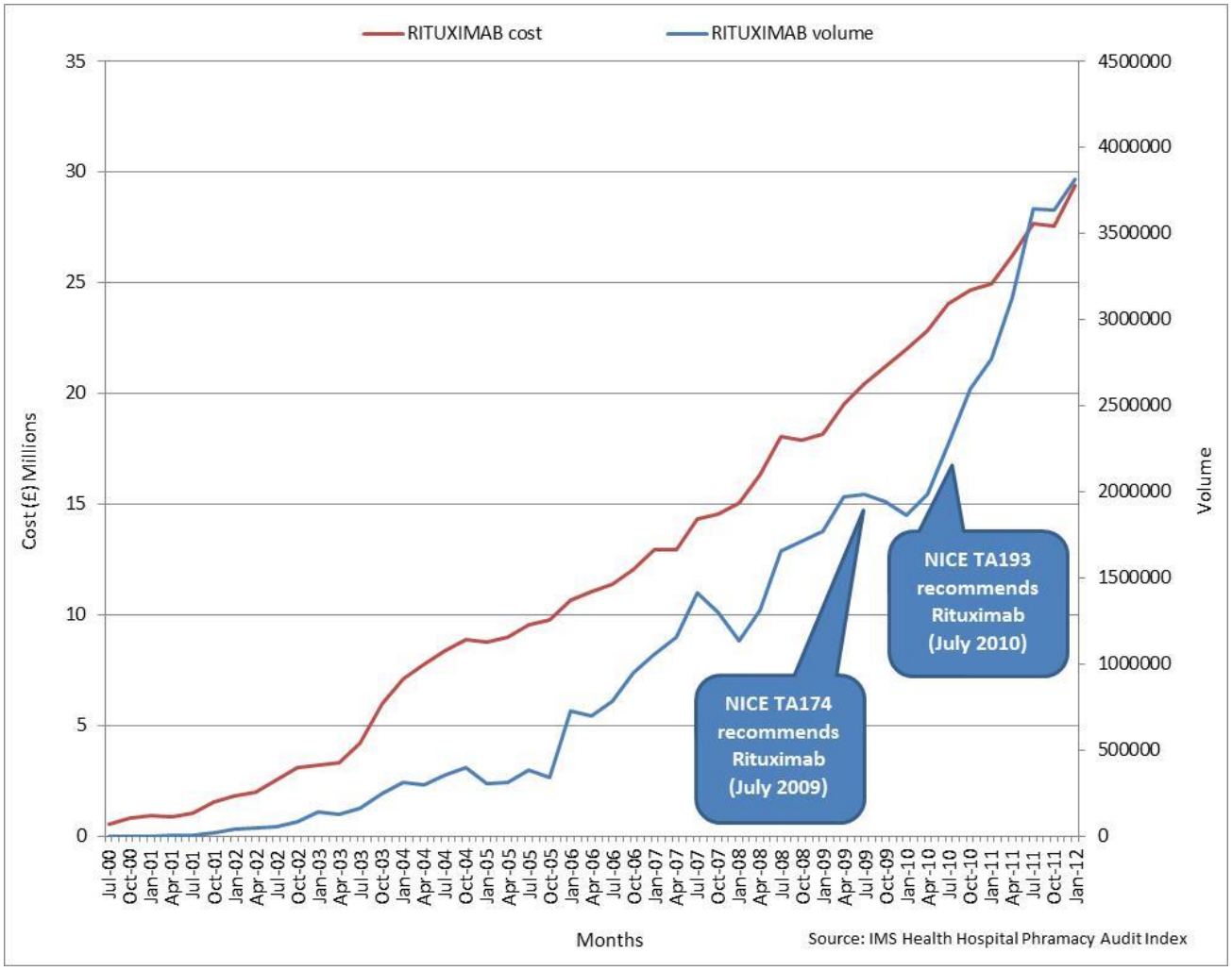
Appendix A: Healthcare activity data definitions 20

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 in hospitals in England between July 2000 and January 2012. Please note these data need to be treated with caution as there is more than one indication for rituximab.

Figure 1 Cost and volume of Rituximab prescribed and dispensed in hospitals in England.



2. Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

2.1 Richards, M. (2010) Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to

measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

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.

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No. 202 Ofatumumab for the treatment of refractory chronic lymphocytic leukaemia

Please contact Rebecca Braithwaite regarding any queries
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4. Routine healthcare activity data

4.1. ePACT data

- No data available.

4.2. Hospital Pharmacy Audit Index data

- No data available.

5. Implementation studies from published literature

- Information is taken from the uptake database (ERNIE) website.
- Nothing to add.

6. Qualitative input from the field team

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

Nothing to add.