Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Mar. 69 p. (Technology appraisal guidance; no. 308).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis), only if:

- Further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose or
- Cyclophosphamide is contraindicated or not tolerated or
- The person has not completed their family and treatment with cyclophosphamide may materially affect their fertility or the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months or
- The person has had uroepithelial malignancy

People currently receiving treatment initiated within the National Health Service (NHS) with rituximab that is not recommended for them by the National Institute for Health and Care Excellence (NICE) in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Internal Medicine

Nephrology

Rheumatology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

Target Population

Patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Interventions and Practices Considered

Rituximab in combination with glucocorticoids

Major Outcomes Considered

- Clinical effectiveness
  - Mortality
  - Remission rate and duration of remission
  - Number and severity of relapses
  - Change in renal function
  - Cumulative dose of immunosuppressants
  - Adverse effects of treatment
  - Health-related quality of life

- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches and Study Selection

Searches

The manufacturer's search methods and electronic strategies were appraised by the ERG group. The ERG sought clarification from the manufacturer where weaknesses in the manufacturer's search methods were considered to impact the performance of the search and may thus potentially lead to the omission of studies.

The manufacturer's searches for direct clinical evidence were adequately reported and strategies were explained. The manufacturer clearly acknowledges cyclophosphamide (CYC) as the most relevant comparator in the induction of remission; however, separate searches were not conducted by the manufacturer for other evidence that could have been used to inform indirect comparisons against other drugs. Separate adverse events searches were not conducted for either rituximab (RTX) or CYC.

The sensitivity of the search strategies in the submission was open to question due to i) omission of free-text synonyms for "rtx" in all search strategies, i.e., "rituximab" or "mabthera", "rituxan" and "rituxin"; ii) omission of the subject heading "Vasculitis". These limitations were raised in the ERG clarification letter and the manufacturer re-ran searches and produced responses which are described below.

The manufacturer searched the minimum required databases. Searches for ongoing or completed and unpublished trials – using sources such as ClinicalTrials.gov, metaRegister of Controlled Trials, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) – were not reported. In addition, the ERG suggests that the manufacturer should have searched relevant society websites such as the European Vasculitis Society (EUVAS) and specialist conference abstracts, such as those associated with the International Vasculitis & ANCA Workshop.

The ERG considered that the language restriction to English only publications was too restrictive. It is not clear whether relevant foreign language publications may have been missed.

Translation of the strategies from Medline and EMBASE to the Cochrane Library was not consistently applied; intervention terms were omitted in the Cochrane Library search. The manufacturer acknowledged and rectified this in their Clarification Response letter.

Four search priority requests were made by the ERG to the manufacturer in the clarification letter:

1. To review and conduct searches for direct evidence using synonyms such as rituximab, "Rituxan" or "Mabthera" and including a broader subject heading "Vasculitis". Revision and re-run of searches by the manufacturer identified a further 35 records but the manufacturer stated that these were all related to trials that had already been found by the initial search. Hence the manufacturer stated that no new publications were identified that were relevant for consideration within this appraisal.
2. To search within clinical trials registers for completed and unpublished trials. The manufacturer reported that they had searched ClinicalTrials.gov and WHO ICTRP, and found 17 studies. However, the manufacturer reported that with the exception of RAVE and

RITUXVAS, these studies were found to be either unpublished, not involving the licence population, not yet initiated, or, in one case, the study was withdrawn prior to enrolment.

3. To carry out separate adverse events searches for both RTX and CYC. According to the manufacturer, safety information for RTX were acquired from the United States (US) and European Union (EU) regulatory dossier. The ERG noted that a direct search for adverse event data would have been preferable and provided suggested search strategies to the manufacturer. The manufacturer ran these search strategies and identified 2,284 papers on RTX and 8,485 on CYC. Given the large number of records to sift and the short time scales, the number of studies relevant to the decision problem was not determined by the manufacturer.
4. To carry out indirect comparator searches for CYC compared to other drugs that would be used in sequence such as methotrexate (MTX) or mycophenolate mofetil (MMF). The manufacturer did not conduct separate indirect comparison searches and re-stated their belief that the evidence base for the additional comparators is not within the scope of the appraisal as they do not reflect the population concerned. The ERG designed and carried out searches for trials comparing CYC and MMF (see Appendix 1 of the ERG report [see the "Availability of Companion Documents" field]) in combination with a sensitive randomised controlled trial (RCT) filter and identified 715 records. The ERG found two studies that appeared relevant for the decision problem set out for this appraisal. In their clarification response the manufacturer acknowledged the MYCYC trial, comparing MMF to CYC, but stated that the results of this study were not yet published. However, the ERG searched and found one published conference abstract reporting early results from this trial.

Study Selection

The process of study selection was neither described nor evaluated within the MS (e.g., citations screened independently by more than one reviewer). The PRISMA diagram presented in the original submission was inadequate as a record of the search and selection process, but this has been updated adequately in response to a request of the ERG. Details of all studies excluded at full paper stage were provided and the reason for exclusion was given.

Inclusion Criteria

The reported criteria for the effectiveness review are detailed in the box below.

Box. Inclusion and Exclusion Criteria Reported by the Manufacturer

Inclusion Criteria Published papers or abstracts which evaluated the following: • RTX had to be the major focus of the paper, in order to eliminate papers which mentioned RTX as part of a discussion of treatments for rheumatoid arthritis • AAV had to be a major focus of the paper, in order to eliminate papers covering the use of RTX in other autoimmune diseases • Patient population should consist of those patients who were receiving RTX for induction of remission (or treatment of flare), i.e., not maintenance data, to be consistent with the proposed RTX licence • Correct dosage of RTX 375 mg/m^2 body surface area once weekly for 4 weeks • Clinical trial data • Documents relating to humans	
Exclusion Criteria Published papers or abstracts which evaluated the following were excluded:	**Rationale/Justification**
Any papers providing a review, update or commentary on data published elsewhere Any papers which only mentioned RTX within a discussion of treatments for AAV or other auto-immune diseases, animal studies or in vitro research	To ensure no duplication of results/data No data in these papers Only human data relevant to decision problem
Case reports Studies where there were data for fewer than 20 patients Post hoc subgroup analyses	Not statistically robust analyses
Papers covering Churg-Strauss syndrome paediatric studies	Not in the licence, i.e., induction of remission only using 4 x 375 mg/m^2 dose of RTX for adults with generalised, "severe" AAV

Incorrect dosage of RTX Maintenance of remission only	only

AAV, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; RTX, rituximab

See Section 4 of the original ERG (see the "Availability of Companion Documents" field) report for additional details.

Cost-effectiveness

ERG Comment on Manufacturer's Review of Cost-effectiveness Evidence

The manufacturer conducted a systematic review with the objective of identifying studies that addressed the cost-effectiveness of one or more interventions for patients with either granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). The manufacturer undertook systematic searches across the following electronic databases and research registers:

- Medline
- Medline In-Process
- EMBASE
- EMBASE Alerts
- Econlit
- National Health Service Economic Evaluation Database (NHS EED)

Articles were excluded if they were not related to humans, not written in the English language, or the patient population was inappropriate (≤18 years old). Articles were also excluded if they reported on the cost-effectiveness of treating co-morbidities potentially associated with MPA or GPA. There was no restriction in the search strategy with respect to intervention and comparators.

Articles were included if they reported a measure relevant to cost-effectiveness, for example:

- Incremental cost per quality-adjusted life-year (QALY) gained
- Cost of being in remission/not being in remission
- Cost of disease relapse compared with not having a relapse
- Direct and indirect costs of treating GPA or MPA in any currency and at any geographical location

Articles were also included if they used a decision model to estimate the cost-effectiveness of any intervention for MPA or GPA. A total of 159 records were identified, however ultimately all were excluded. Thus, the systematic review did not identify any studies that reported on the cost-effectiveness of treatment for MPA or GPA.

In addition, the manufacturer conducted systematic reviews in an attempt to identify studies investigating health-related quality of life (HRQoL) and resource use in patients with GPA or MPA, but reported that no relevant studies were found.

The manufacturer's reporting of search strategies for finding cost-effectiveness, HRQoL and resource use evidence was adequate. The minimum required sources were searched. Study design filters were applied by the manufacturer. As described in the clinical effectiveness review critique of the manufacturer's searches (see Section 4.1.1 in the ERG report [see the "Availability of Companion Documents" field]), the sensitivity of the economic evaluation search strategies could have been improved by the inclusion of free-text synonyms for "rtx" in all search strategies, i.e., "rituximab" or "mabthera", "rituxan" and "rituxin" and the subject heading "Vasculitis". The ERG considered that the language restriction to English only publications was too restrictive and it is not clear whether relevant foreign language publications have been missed. Translation of the search strategies from Medline and EMBASE to other databases was not consistently applied; intervention terms were omitted in the NHS EED and EconLit searches.

See Section 5.1 of the ERG report for more information on cost-effectiveness methods (see the "Availability of Companion Documents" field).

Number of Source Documents

Clinical Effectiveness

The systematic review identified 2 relevant, published randomised controlled trials (RCTs) comparing rituximab (RTX) with cyclophosphamide (CYC) for anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) (RAVE and RITUXVA).

Cost-effectiveness

A total of 159 records were identified; however, ultimately all were excluded.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Data Extraction

All key efficacy and safety data appear to have been extracted accurately from the two principal studies; however, the process of data extraction was neither described nor evaluated within the manufacturer's submission (MS) (e.g., using double data extraction or verification). Only the most basic study characteristics were extracted from the identified non-randomised controlled trial (RCT) efficacy studies. Consequently, the submission made no use of data from studies other than RAVE and RITUXVAS in the analysis or to illuminate or facilitate the interpretation of the efficacy or safety data from these two principal trials.

Quality Assessment

The quality assessment consisted of the critical appraisal of the RAVE and RITUXVAS trials using standard RCT criteria. RAVE was both a superiority and non-inferiority trial, depending on analysis and outcome, but only criteria assessing superiority were applied. This was corrected at the request of the ERG. RITUXVAS was a superiority trial and was appraised as such. The submission found that the RCTs had a low risk of bias across all criteria. The submission did not report a high risk of bias on any criteria, but considered criteria on blinding to be "Not applicable" to the RITUXVAS trial as it was "open-label". This is not an appropriate judgement because the open-label nature of the trial renders it at high risk of performance and detection bias, i.e., patients and outcome assessors are aware of the treatment received and their judgments might be altered as a result.

The ERG applied a combination of the Cochrane risk of bias tool to appraise risk of bias within each trial, as well as the non-inferiority trial extension of the CONSORT statement for the RAVE trial. The findings of this appraisal are provided in Appendix 2 of the ERG report and were generally consistent with the reported assessment in the MS, except for the high risk of performance and detection bias in the RITUXVAS trial as noted above. Refer to Section 4.1 of the ERG report for additional critique of the quality assessment (see the "Availability of Companion Documents" field).

Evidence Synthesis

The submission did not include an evidence synthesis. The principal RCTs were not combined in a meta-analysis because of clinical heterogeneity (slightly different populations, different interventions and different regimens for the comparators). The manufacturer did not perform a narrative synthesis either. The Results section of the MS consisted of the reproduction and description of the published findings of the trials, including the presentation of multiple published sub-group analyses. Despite the presentation of non-RCT evidence and studies of adverse events, no use was

made of any evidence other than from the two key trials. The manufacturer justified this by claiming that the data were "problematic for providing robust conclusions".

Refer to Section 4 of the ERG report for additional information on clinical effectiveness (see the "Availability of Companion Documents" field).

Cost-effectiveness

Description of the Manufacturer's Economic Model

Model Scope

The model presented by the manufacturer estimates the incremental costs and health effects of a treatment sequence beginning with rituximab (RTX) compared to a treatment sequence that begins with cyclophosphamide (CYC). The sequence that begins with CYC is assumed to represent the "standard of care" whereas the RTX sequence represents a pathway of care deemed by the manufacturer to be realistic based upon expert opinion. Cost-effectiveness is presented in terms of the incremental cost per quality-adjusted life year (QALY) gained from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a lifetime time horizon. In practice, only NHS costs are included. Three populations can be evaluated within the model: (1) treatment naïve, (2) recurrent disease and (3) all patients. The "all patients" population (which forms the manufacturer's base case analysis) is made up of "treatment naïve" and "recurrent disease" patients; however, the structure of the model and the parameter values used for the different populations means that the "all patients" analysis does not represent an average of the "treatment naïve" and "recurrent disease" populations. The manufacturer's model only considers the use of RTX as an induction therapy for these populations – maintenance therapy or the use of RTX following an initial relapse observed in the model is not considered. While the model allows a subgroup analysis of a "recurrent disease" population – that is, patients who have previously been treated but have relapsed – patients who relapse within the model are not permitted to receive RTX, even if they enter the model as "treatment naïve" patients.

In line with current methodological guidance, all costs and health outcomes are discounted at an annual rate of 3.5%. The model was programmed in Microsoft Excel® with an additional macro written using Visual Basic for Applications (VBA) to perform probabilistic sensitivity analysis (PSA).

The manufacturer's submission lacked some clarity regarding the disease and treatment pathway assumed within the economic model, and regarding the values assumed for some key parameters. In order to ensure clarity regarding the manufacturer's modelling methods, assumptions and the data that underpin the model, Sections 5.2.2, 5.2.3 and 5.2.4 of the ERG report provide a detailed description of the submitted model. This description has been produced by the ERG through a detailed scrutiny of the submitted model, the MS report and subsequent clarification response.

Model Structure

A conceptual form of the model implemented by the manufacturer is presented in Figure 1 of the ERG report, as produced by the ERG. This illustrates the disease pathway and the associated treatment sequence for the RTX and CYC groups.

Refer to Section 5 of the ERG report for more information on cost-effectiveness analysis (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service

(NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on the Evidence for Cost-effectiveness

Availability and Nature of Evidence

The Committee observed that the manufacturer's approach was generally in line with the National Institute for Health and Care Excellence (NICE) reference case, but that the manufacturer's decision problem did not match the final NICE scope in all areas (notably excluding some comparators and end points). The Committee concluded that the outlined economic analysis was acceptable for assessing the cost effectiveness of rituximab in treating anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee identified several reasons for uncertainty in the results of the manufacturer's updated economic models submitted in response to the first consultation. The reasons included: not all treatment sequences were modelled, no incremental analyses were reported, not all costs and consequences were included, there were concerns about the way relapse rates were calculated, there were errors in the model, and there was uncertainty about utility values. The Committee then considered the manufacturer's weighted-average threshold analysis submitted in response to the second consultation. It was aware that another Committee had agreed to consider a whole-population weighted-incremental cost-effectiveness ratio (ICER) analysis in Omalizumab for treating severe persistent allergic asthma (see the National Guideline Clearinghouse summary of the NICE guideline Omalizumab for treating severe persistent allergic asthma [review of technology appraisal guidance 133 and 201]), but the circumstances were different to the current appraisal. The Committee recalled that NICE's Guide to the methods of technology appraisal states that estimates of clinical and cost-effectiveness should be provided separately for each relevant subgroup of patients. The Committee concluded that the manufacturer's models submitted in response to the first consultation, and the manufacturer's weighted-average threshold analysis submitted in response to the second consultation did not provide a suitable basis for decision-making.

Some of the Committee's concerns had been resolved in the Evidence Review Group's (ERG) exploratory analyses. Accordingly, the Committee was able to identify the most plausible ICER for people who can have cyclophosphamide.

For people who cannot have cyclophosphamide, the Committee considered the manufacturer's original and updated analyses, and the ERG's exploratory and illustrative analyses. The Committee agreed that, for people who cannot have cyclophosphamide, there was a lack of consensus

about the appropriate comparator treatment. The Committee concluded there was substantial uncertainty about the cost-effectiveness of rituximab for people who cannot have cyclophosphamide, but on balance the ICER was likely to be lower than £30,000 per quality-adjusted life year (QALY) gained.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee noted that, in the manufacturer's updated models, the utility value in the uncontrolled disease health state was based on extrapolation from the utility values in the remission and non-remission health states. It concluded that that the revised utility value in the uncontrolled disease health state was more plausible than the value in the original model, but was still a source of some uncertainty.

The Committee noted that the economic model did not include disutilities for cyclophosphamide's cumulative long-term toxicity or the costs of managing long-term toxicity. It agreed that these issues added some uncertainty to the cost-effectiveness estimates.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

The Committee agreed that rituximab was cost-effective for adults with ANCA-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis), only if:

- Further cyclophosphamide treatment would exceed the maximum cumulative dose (25 g) of cyclophosphamide; or
- The person cannot have cyclophosphamide (as specified in Section 4.8 of the original guideline document).

What Are the Key Drivers of Cost-effectiveness?

The Committee was aware from the ERG's exploratory analyses based on the manufacturer's original model that the ICER substantially increased when the number of outpatient appointments was reduced. The Committee also noted that the ICERs presented by the manufacturer and the ERG were sensitive to changes in treatment sequence.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The Committee agreed that the most plausible ICER on which to base its decision for people who can have cyclophosphamide was £12,100 per QALY gained, provided by the comparison of 2 courses of cyclophosphamide followed by 1 course of rituximab with 2 courses of cyclophosphamide.

The Committee concluded there was substantial uncertainty about the cost-effectiveness of rituximab for people who cannot have cyclophosphamide, but on balance the ICER was likely to be lower than £30,000 per QALY gained.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of rituximab and a review of this submission by the Evidence Review Group. For clinical effectiveness, two randomised controlled trials were the main source of evidence. For cost-effectiveness, the manufacturer's economic model was considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

Potential Harms

The summary of product characteristics lists the following adverse events occurring at an incidence of 10% or greater in patients receiving rituximab to treat granulomatosis with polyangiitis and microscopic polyangiitis: diarrhoea, peripheral oedema, muscle spasms, arthralgia, back pain, dizziness, tremor, insomnia, cough, dyspnoea, epistaxis and hypertension.

For full details of adverse reactions, see the summary of product characteristics.

Contraindications

Contraindications

For full details of contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of

its date of publication.

- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and the doctor responsible for their care thinks that rituximab is the right treatment, it should be available for use, in line with NICE's recommendations.
- NICE has developed a costing statement explaining the resource impact of this guidance to help organisations put this guidance into practice (see the "Availability of Companion Documents" field).

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Mar. 69 p. (Technology appraisal guidance; no. 308).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Mar

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Gary McVeigh (*Chair*), Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital; Dr Brian Shine (*Vice Chair*), Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford; Dr Andrew Black, General Practitioner, Mortimer Medical Practice, Herefordshire; Professor David Bowen, Consultant Haematologist, Leeds Teaching Hospitals NHS Trust; Dr Matthew Bradley, Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline; Dr Ian Campbell, Honorary Consultant Physician, Llandough Hospital, Cardiff; Dr Ian Davidson, Lecturer in Rehabilitation, University of Manchester; John Dervan, Lay Member; Professor Simon Dixon, Professor of Health Economics, University of Sheffield; Dr Martin Duerden, Assistant Medical Director, Betsi Cadwaladr, University Health Board, North Wales; Dr Alexander Dyker, Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle; Christopher Earl, Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital; Gillian Ells, Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald; Dr Susan Griffin, Research Fellow, Centre for Health Economics, University of York; Professor Carol Haigh, Professor in Nursing, Manchester Metropolitan University; Professor John Henderson, Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children; Dr Paul Hepple, General Practitioner, Muirhouse Medical Group; Professor Peter Jones, Emeritus Professor of Statistics, Keele University; Professor Steven Julious, Professor in Medical Statistics, University of Sheffield; Dr Tim Kinnaird, Lead Interventional Cardiologist, University Hospital of Wales, Cardiff; Terrance Lewis, Lay Member; Warren Linley, Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University; Professor Jonathan Michaels, Professor of Clinical Decision Science, University of Sheffield; Malcolm Oswald, Lay Member; Professor Femi Oyebode, Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health; Dr John Radford, Director of Public Health, Rotherham Primary Care Trust and MBC; Dr Lindsay Smith, General Practitioner, Westlake Surgery; Dr Murray Smith, Associate Professor in Social Research in Medicines and Health, University of Nottingham; Paddy Storrie, Lay Member; Dr Alison Talbot-Smith, Consultant in Public Health, Herefordshire Clinical Commissioning Group; Charles Waddicor, Formerly Chief Executive, NHS Berkshire West

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis. Costing statement.

London (UK): National Institute for Health and Care Excellence (NICE); 2014 Mar. 1 p. (Technology appraisal guidance; no. 308). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Care Excellence (NICE) Web site .

- Latimer N, Carroll C, Wong R, Tappenden P, Venning MC, Luqmani R. Rituximab in combination with corticosteroids for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis. A single technology appraisal. Sheffield (UK): School of Health and Related Research (ScHARR), The University of Sheffield; 2013. 151 p. Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis. Information for the public: Technology appraisals. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Mar. (Technology appraisal guidance; no. 308). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site .

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