

Re-Submission

ibritumomab tiuxetan (Zevalin®)

No. (171/05)

Schering Health Care Ltd

8 June 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a re-submission

ibritumomab tiuxetan (Zevalin®) is not recommended for use within NHS Scotland for the preparation of a radiopharmaceutical incorporating Yttrium 90 [⁹⁰Y] for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL) following the incorporation of Yttrium 90. It should be used following pre-treatment with rituximab.

Dosing information

In patients with a platelet count $\geq 150,000$ cells/ml:

Day 1: Rituximab infusion $250\text{mg}/\text{m}^2$

Day 7, 8 or 9: Rituximab infusion $250\text{mg}/\text{m}^2$ shortly before infusion of [^{90}Y] ibritumomab tiuxetan 15MBq [^{90}Y] per kg body weight to a maximum of 1200 MBq .

In patients with a platelet count $>100,000 <150,000$ cells/ml, the recommended regimen is as above, but the dose of [^{90}Y] ibritumomab tiuxetan should be reduced to 11MBq [^{90}Y] per kg body weight up to a maximum of 1200 MBq .

Additional information:

The kit supplied does not include ^{90}Y , which must be supplied by the end-user. The radiolabelled product must be handled and administered by qualified personnel and its preparation, use, transfer, storage and disposal are subject to the regulations and/or appropriate authorisation. Before administration to the patient the end product must be tested for radiochemical purity and if this is less than 95% it should not be administered.

[^{90}Y] emits beta radiation and is associated with a lower environmental risk and less stringent safety precautions than radio-pharmaceuticals which are sources of gamma radiation.

Rituximab should be administered in a hospital environment where full resuscitation facilities are available.

Product availability date

March 2005

Summary of evidence on comparative efficacy

The study most relevant to the licensed indication was a single-arm open-label phase II trial involving 54 heavily pre-treated patients with follicular NHL refractory to rituximab who received [^{90}Y] ibritumomab tiuxetan ([^{90}Y] IT) and rituximab. A Phase III study compared [^{90}Y] IT and rituximab with rituximab alone. Patients were excluded from this study if they had previously been exposed to rituximab and recruitment was not restricted to patients with follicular disease, though they formed the majority (113/143, 79%). Both studies specified a baseline platelet count $\geq 150,000$ cells/ml and used the licensed dose regimen for such patients. In the comparative study, patients in the control arm received four once-weekly doses of rituximab $375\text{mg}/\text{m}^2$, as specified in the Summary of Product Characteristics for rituximab monotherapy.

Another open-label study investigated the use of [⁹⁰Y] IT with rituximab in patients with relapsed or refractory indolent follicular or transformed NHL and mild thrombocytopenia (defined as 100,000-149,000 platelets/ml), at the reduced dose specified in the Summary of Product Characteristics for such patients. Patients were excluded if they had received anti-CD20 therapy such as rituximab.

The primary efficacy end-point in all trials was overall response rate (ORR) comprising the proportion of patients achieving protocol-defined complete or partial responses.

In the treatment of rituximab-refractory patients in the first study, the ORR was 74% (40 of 54 patients). Fifteen percent of patients had complete responses (CR) and 59% had a partial response (PR).

In the comparative study, the ORR was 58/73 patients (80%, 95%CI 68%, 88%) receiving [⁹⁰Y] IT with rituximab and 39/70 patients (56%, 95%CI 43%, 67%) on rituximab alone ($p=0.002$ for the difference). CR rates were 30% for patients receiving [⁹⁰Y] IT with rituximab and 16% for rituximab monotherapy and PR was 45% and 36% respectively. In a sub-group of patients with follicular disease ($n=113$), the ORR were 86% and 55% respectively ($p=0.001$).

In the study recruiting patients with mild thrombocytopenia, the ORR was 25/30 (83%; 95% CI 64, 94) and comprised 37% with CR, 6.7% with unconfirmed CR and 40% with a PR.

In the three pivotal trials, the published sources give response rates according to recently published International Workshop (IW) criteria. The EPAR also gives response rates, according to protocol-defined criteria, which are consistently lower, e.g. 59% ORR in rituximab relapsed or refractory patients receiving [⁹⁰Y] IT compared with 74% by IW criteria.

On an intention-to-treat basis, the median time to progression of disease (TTP) was in the range 7 to 12.6 months across the three main studies and duration of response (DR) was between 6 and 18.5 months. In the comparative trial there was no significant difference between [⁹⁰Y] IT with rituximab and rituximab alone for either TTP or DR. TTP was longer in responders than in the overall analysis in two studies (range 9 to 13 months).

Follicular disease was pre-specified in the first study. In the remaining two studies, there was sub-group analysis for patients with follicular disease. In the comparative study, median TTP was 13 months in patients treated with [⁹⁰Y] IT compared with 10 months with rituximab alone. Median DR was 18 and 12 months respectively. In patients with mild thrombocytopenia median TTP was 11 months.

In a quality of life assessment in the comparative study, there was a significant improvement from baseline in patients treated with [⁹⁰Y] IT but not with rituximab alone. With a median 44 months follow-up of the cohort from the comparative study, there were non-significant trends towards longer TTP, DR and TTNT in patients treated with [⁹⁰Y]IT and rituximab versus rituximab alone, particularly in patients with follicular NHL. Median DR with [⁹⁰Y]IT approached 2 years, and ongoing responses of over 5 years have been achieved.

Summary of evidence on comparative safety

In the comparative trial, the overall incidence of non-haematological adverse events was similar between [⁹⁰Y] IT with rituximab and rituximab alone, although [⁹⁰Y] IT with rituximab was associated with higher incidence of grade 1 / 2 cough, bronchospasm, dyspnoea, nausea, vomiting and anorexia. All haematological adverse events were more frequent and severe in the [⁹⁰Y] IT with rituximab group, although these were transient and reversible and the regimen was generally well-tolerated. Infection occurred in 30/73 (41%) of patients receiving [⁹⁰Y] IT with rituximab compared with 13/70 (19%) with rituximab alone, and the associated rates of hospitalisation for infection or febrile neutropenia were 7% and 1% of treated patients respectively.

Summary of clinical effectiveness issues

The licence for rituximab currently includes its use in previously untreated patients in combination with chemotherapy; however it had previously been restricted to patients who are chemoresistant or in their second or subsequent relapse after chemotherapy i.e. third- and last-line therapy. This raises the possibility that patients could be classed as rituximab relapsed or refractory following first-line treatment whereas, in the pivotal trials, the study populations were predominantly heavily pre-treated and refractory to chemotherapy, i.e. with end-stage disease.

It is uncertain whether the results of these trials would be applicable to patients relapsed or refractory following first-line use of rituximab. Patients in the pivotal trials were excluded if their bone marrow involvement was 25% or more.

Summary of comparative health economic evidence

The manufacturer presented cost-utility estimates through a mixed analysis, incorporating a review of individual patients' casenotes coupled with a Markov model for those whose casenotes were censored. The analysis adopted monthly cycles and a fifteen-year time horizon. This compared treatment with ibritumomab tiuxetan with a conventional care arm which was composed of a range of other treatments including chemotherapy, radiotherapy and stem cell transplant.

For the ibritumomab tiuxetan arm the model drew clinical effectiveness data from the licensing trial. Since this trial was a phase II single arm trial no comparative data on active comparators were available for the patient group under consideration. For conventional care the manufacturer used data from a case review of 46 Canadian patients, of whom 17 matched the inclusion criteria of the licensing trial and were used as the basis for the comparison.

Quality of life values were drawn from an EQ-5D survey of 24 NHS consultants and specialist oncology nurses. Drug costs were based upon the BNF, though the costs of ibritumomab tiuxetan were supplied by the manufacturer. The proportion of patients receiving comparator treatments was drawn from the Canadian data, with UK unit costs being applied from the literature and NHS reference costs.

The manufacturer estimated that treatment with ibritumomab tiuxetan would on average cost an additional £8,535 per patient over the fifteen-year time horizon and result in an additional 0.38 QALYs, to give an average cost effectiveness of £22,445 per QALY. Curtailing the time horizon to five years worsened the estimate of cost effectiveness to £25,589 per QALY.

Limited data were presented within the submission regarding the clinical parameters of the model. Clarification by the manufacturer indicated that the Markov model element derived the transition probabilities from the casenote review, and extrapolated using these. This differentiated transition probabilities by treatment arm, the likelihood for moving from progressive disease to palliation being assumed to be considerably worse for the conventional care arm than for the ibritumomab tiuxetan arm. Equalising the transition probabilities between the two arms of the model increased the cost per QALY to £31000. The quality of life value derived for progressive disease was also very low and additional sensitivity analysis provided by the manufacturer indicated that adjusting this value caused further increases in the cost per QALY. The effect on the QALY of the combined effect of these two weaknesses is not known. Therefore, the manufacturer has not presented a sufficiently robust economic analysis to gain acceptance by SMC

Summary of patient and public involvement

Patient Interest Group Submission: Leukaemia Care.
Patient Interest Group Submission: Lymphoma Association.

Additional information: guidelines and protocols

National Institute for Health and Clinical Excellence (NICE). Guidance on the use of rituximab for recurrent or refractory Stage III or IV follicular non-Hodgkin's lymphoma. March 2002.

Following a Single Technology Appraisal, in September 2006 NICE recommended rituximab as an option for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy.

Additional information: previous SMC advice

On 8th April 2005, following a full submission, the Scottish Medicines Consortium (SMC) advised that ibritumomab tiuxetan (Zevalin®) is not recommended for use within NHS Scotland for the preparation of a radiopharmaceutical incorporating Yttrium 90 [90Y] for the treatment of adult patients with rituximab-relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma. No economic information was submitted to allow an assessment of its cost effectiveness.

On 13th December 2004 following a full submission, the Scottish Medicines Consortium (SMC) accepted rituximab for use within NHS Scotland for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy.

On 10th November 2006 SMC following a full submission, accepted rituximab for restricted use within NHS Scotland as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab.

Additional information: comparators

None - The product is co-administered with rituximab (MabThera, Roche) at a reduced dose compared with rituximab monotherapy.

Additional information: costs

Drug acquisition costs for a single treatment, including [⁹⁰Y] provided by Schering, were provided as follows:

Zevalin [®] kit	£7,250
Ytracis [®] [⁹⁰ Y]	£1,360
Rituximab*	£1,746
Total	£10,356

*Dose of 250mg/m² on days 1 and 8 (assumes average patient of 1.8m²):
Total of x2 500mg vials at £873 each.

The SPC does not support repeated treatment.

Additional information: budget impact

The gross cost of ibritumomab tiuxetan was estimated by the manufacturer to be £253k in year 1, of which £186k appear to be the direct drug costs associated with ibritumomab tiuxetan. These are anticipated to rise to £596k and £425k respectively by year 5. This is based upon a patient population of 18 in year 1, rising to 41 by year 5.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 10 May 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Witzig, T. E., Flinn, I. W., et al: Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncology*, 20; 15: 3262-3269, 2002.

Witzig, T. E., Gordon, L. I., et al: Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncology*, 20; 10: 2453-2463, 2002.

Wiseman, G. A., Gordon, L. I. Et al: Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin's lymphoma and mild thrombocytopenia: a phase II multicenter trial. *Blood*, 99; 12: 4336-4342, 2002.

Gordon, L. I., Witzig, T. et al: Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated Bcell lymphoma. *Clinical Lymphoma*, 5; 2: 98-101, 2004.