Scottish Medicines Consortium

ibritumomab tiuxetan (Zevalin®) No. (171/05)
Schering Health Care Ltd

8 April 2005

The Scottish Medicines Consortium (SMC) 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 full submission

Ibritumomab tiuxetan (Zevalin®) is not recommended for use within NHS Scotland for the preparation of a radiopharmaceutical incorporating Yttrium 90 [^{90}Y] 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.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Ibritumomab tiuxetan
(Zevalin®)

Licensed indication under review

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 under review

In patients with a platelet count ≥150,000 cells/ml:

Day 1: Rituximab infusion 250mg/m^2

Day 8: Rituximab infusion 250mg/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.

UK launch date

March 2005

Comparator medications

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

Cost per treatment period and relevant comparators

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

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

*Dose of 250mg/m^2 on days 1 and 8 (assumes average patient of 2m^2):
Total of x2 500mg vials at £873 each.

The Summary of Product Characteristics does not support repeated treatment.

Summary of evidence on comparative efficacy

The study most relevant to the licensed indication was a single-arm phase II trial involving 54 heavily pre-treated patients with follicular NHL refractory to rituximab and chemotherapy 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 ≥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 375mg/m^2, as specified in the summary of product characteristics for rituximab monotherapy.

Another open-label study investigated the use of [^{90}Y] 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.

Primary endpoints

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). In the comparative study, the ORR was 80% (58/73) in patients receiving [^{90}Y] IT with rituximab and 56% (39/70) with rituximab alone (p=0.002 for the difference). In the study recruiting patients with mild thrombocytopenia, the ORR was 83% (25/30).

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 [^{90}Y] IT compared with 74% by IW criteria.

Secondary endpoints, sub-group analysis and uncontrolled trials

In the treatment of rituximab refractory patients, where the ORR was 74%; 15% of patients had complete responses (CR) and 59% had partial response (PR).

In the comparative study, CR rates were 30% for patients receiving [^{90}Y] IT with rituximab and and 16% for rituximab monotherapy. ORR was 80% and 56% respectively (p=0.002) and PR was 45% and 36%. In a sub-group of patients with follicular disease (n=113), the ORR were 86% and 55% respectively (p<0.001).

In patients with mild thrombocytopenia, the ORR of 83% comprised 37% with CR, 6.7% with unconfirmed CR and 40% PR.

On an intention-to-treat basis, the median time to progression of disease (TPP) was in the range 7 to 11 months across the three main studies and duration of response (DR) was between 6 and 14 months. In the comparative trial there was no significant difference between [^{90}Y] IT with rituximab and rituximab alone for either of those measures. 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 [^{90}Y] 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 [^{90}Y] 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 [^{90}Y]IT and rituximab versus rituximab alone, particularly in patients with follicular NHL. Median DR with [^{90}Y]IT approached 2 years, and ongoing responses of over 5 years have been achieved.

Overall response rates and duration of response in studies of [^{90}Y] IT with rituximab in patients with CD20-positive B-cell Non-Hodgkins Lymphoma

Response	Rituximab-refractory pts with follicular disease	[^{90}Y] IT with rituximab vs rituximab alone, rituximab-naïve patients		Mild thrombocytopenia, anti-CD20-naïve patients
	[^{90}Y] IT with rituximab	[^{90}Y] IT with rituximab	Rituximab	[^{90}Y] IT with rituximab
	n = 54	n = 73	n = 70	n = 30
OR rate(%)	74	80	56	83
CR rate (%)	15	30	16	37
CRu rate (%)	0	4	4	6.7
PR (%)	59	45	36	40
Median DR (months) [range]	6.4 [0.5 – 24.9+]	14.2 [0.9-28.9]	12.1 [2.1-24.5+]	11.5 [1.0 – 53.9]
Median TTP (months) [range]	6.8 [1.1-25.9+]	11.2 [0.8 – 31.5+]	10.1 [0.7-26.1]	9.4 [1.7 – 54.8+]

OR= Overall response **CR**= Complete response **CRu**= Unconfirmed CR **PR**= Partial response
DR= Duration of response **TTP**= Time to Progression of disease

Summary of evidence on comparative safety

In the comparative trial, the overall incidence of non-haematological adverse events was similar between [^{90}Y] IT with rituximab and rituximab alone, although [^{90}Y] 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 [^{90}Y] IT with rituximab group, although these were transient and reversible and it was generally well-tolerated. Infection occurred in 30/73 (41%) of patients receiving [^{90}Y] 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 has recently been extended to include its use in previously untreated patients in combination with chemotherapy, whereas it had previously been restricted to patients who are chemoresistant or in their second or subsequent relapse after chemotherapy ie third- and last-line therapy. This raises the possibility that patients could be classed as rituximab relapsed or refractory following first-line treatment. 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

No health economic evaluation was submitted.

Budget impact

The manufacturer estimates that 35 patients will receive the drug in year 1, rising to 41 in year 5. The additional drug cost according to their calculations will be £385k in year 1 rising to £451k in year 5. Any savings will be in terms of reduced hospital admissions but these have not been quantified.

Guidelines and protocols

National Institute for Clinical Excellence. *Guidance on the use of rituximab for recurrent or refractory Stage III or IV follicular non-Hodgkin's lymphoma. March 2002.* Note that this precedes extension of the licence for rituximab to allow first-line use.

Following the change of licence, the Scottish Medicines Consortium accepted rituximab for use within Scotland for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy. (SMC 135/04, 13 December 2004).

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.

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 11 March, 2005.

Drug prices are those available at the time of SMC assessment.

References

Those shaded grey are additional to those 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 B-cell lymphoma. Clinical Lymphoma, 5; 2: 98-101, 2004.

A: Summary of Product Characteristics. Zevalin 1.6 mg/ml, Kit for radiopharmaceutical preparation for infusion. Schering AG, Berlin. 16 January 2004.

B: EPAR Scientific discussion. Zevalan. European Medicines Agency 2005.

C: Summary of Product Characteristics. Mabthera 500 mg. Roche, Welwyn Garden City. 5 August 2004.