1. Introduction
Radioimmunotherapy is a new form of therapy that uses monoclonal antibodies in the treatment of patients with non-Hodgkin’s lymphoma (NHL). In this form of therapy, the monoclonal antibodies are labelled with a radionuclide. The monoclonal antibodies carry the radionuclide highly selectively to the malignant cells. The beta radiation the radionuclide emits then destroys the malignant cell the antibody has bound to, and malignant cells in the vicinity. In the latter situation, a non-radiolabelled antibody cannot be sufficiently effective due to poor circulation in the tumour or due to the tumour size.

One of the reasons why radioimmunotherapy is a good option for the treatment of follicular NHL is the fact that lymphoma cells are sensitive to radiation. The disease is often in an advanced stage (III/IV), in which total body irradiation is not an option. Radioimmunotherapy carries the advantage that it allows radiation to be targeted specifically, while limiting exposure of healthy tissue.

Zevalin® consists of the monoclonal CD20-directed mouse antibody ibritumomab in conjunction with the chelator tiuxetan, to which $^{90}$Y (a pure beta emitter) is attached. The chelator promotes stable binding of the $^{90}$Y to the antibody ibritumomab. The labelled product obtained is referred to as $^{90}$Y-Zevalin®. (In the literature, the name Zevalin® is used to refer to both unlabelled ibritumomab tiuxetan and the labelled product $^{90}$Y-Zevalin®).

Rituximab (Mabthera®) is a CD-20-directed, chimeric (mouse/human) monoclonal antibody on the surface of malignant and normal B lymphocytes. Treatment with rituximab leads to a response in approximately 50% of patients with relapsed NHL with a duration of response of approximately 12 months. Recent randomised research into rituximab combined with cyclophosphamide, vincristine and prednisolone (R-CVP) versus CVP as first-line treatment of follicular NHL showed that the R-CVP combination is superior to CVP. This led to the authorisation of R-CVP as first-line treatment for follicular NHL in 2004. Based on the positive results of the HOVON 39 study, rituximab was also authorised in July 2006 as maintenance treatment in patients with relapsed or refractory follicular NHL responding to induction chemotherapy, optionally in combination with rituximab.

2. Methodology
This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications
$^{90}$Y-Zevalin® has been authorised since January 2004 for the treatment of adult patients with relapsed or refractory CD20+ follicular B-cell non-Hodgkin’s lymphoma (NHL) after...
According to the Dutch haematological consensus, the current treatment strategy for follicular Non-Hodgkin’s Lymphoma (NHL) (stages III and IV, revised in 2006) is as follows:

1. **1st line:** R-CVP (rituximab [MabThera®] in combination with cyclophosphamide, vincristine and prednisolone) with or without maintenance treatment with rituximab. Chlorambucil (Leukeran®), optionally combined with rituximab, is used in older patients.
2. **2nd line:** FR (fludarabine phosphate [Fludara®] in combination with rituximab) or R-CHOP (rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone).
3. **3rd line:** autologous/allogeneic stem cell transplantation or ²⁹⁰Y-Zevalin®

If a good response is not achieved or if relapse occurs within 6 months of 1st line treatment with RCVP, 2nd line treatment with FR or R-CHOP is omitted. ²⁹⁰Y-Zevalin® then becomes the 2nd line treatment.

**Contraindications**
- Hypersensitivity to ibritumomab tiuxetan, to yttrium chloride, to other mouse proteins or to one of the excipients.
- Pregnancy and breast-feeding. Pregnancy should be ruled out prior to administration. Ibritumomab is an IgG monoclonal antibody. Human IgG is known to cross the placenta and to be excreted in human milk.

**Special warnings and precautions**
²⁹⁰Y-Zevalin® may not be administered to patients with a risk of life-threatening haematological toxicity.
²⁹⁰Y-Zevalin® may not be administered to the patients listed below as the safety and efficacy have not been established:
- patients with more than 25% bone marrow involvement
- patients with a history of external radiotherapy to more than 25% of the active bone marrow
- patients with <100x10⁹/l thrombocytes or <1,5x10⁹/l neutrophil granulocytes
- patients with a history of bone marrow transplantation or stem cell support
- children and adolescents younger than 18 years

Patients who have received therapeutic Zevalin® mouse proteins, should be tested for human anti-mouse antibodies (HAMA). Patients who have developed HAMA may have allergic or hypersensitivity reactions during their treatment with Zevalin® or other mouse proteins.

After Zevalin® usage, patients should always be tested for HAMA prior to each following treatment with mouse proteins.

**4. Relation to other therapy**
A randomised study in patients with NHL showed ²⁹⁰Y-Zevalin® to be more effective than non-radiolabelled rituximab, specifically 80% versus 56% (p=0,002) in overall response (OR) and 30% versus 16% (p=0,04) in complete response (CR). The OR in a sub-analysis of the patients with follicular NHL was 86% versus 55% (p < 0,001). The time to disease
progression in patients with follicular NHL was 15.0 months in the \(^{90}\)Y-Zevalin\(^{\text{R}}\) group and 10.2 months in the rituximab group. The subgroup of patients achieving a complete response (CR) or complete response unconfirmed (CRu) showed a time to disease progression of 24.7 months versus 13.2 months in favour of \(^{90}\)Y-Zevalin\(^{\text{R}}\). The quality of life also significantly improved in patients to whom \(^{90}\)Y-Zevalin\(^{\text{R}}\) was administered (week 12 compared to baseline; p=0.001). This was not the case in the rituximab group. A study in patients with rituximab-refractory follicular NHL showed that 74% of the patients still achieved a good response to \(^{90}\)Y-Zevalin\(^{\text{R}}\) treatment (even complete response in 15% of the patients).

\(^{90}\)Y-Zevalin\(^{\text{R}}\) can induce long-term remission, which can last more than 5 years. It is also important to note that \(^{90}\)Y-Zevalin\(^{\text{R}}\) therapy given at a point will not be less effective or be associated with more side-effect.

5. Medical information necessary for planning
- Relevant medical history
- Prior mouse protein therapies
- Thrombocyte count
- Neutrophil granulocyte count
- Patient weight
- Percentage bone marrow involvement

6. Radiopharmaceutical
Tracer: \(^{90}\)Y-Zevalin\(^{\text{R}}\) (\(^{90}\)Y-ibritumomab tiuxetan)
Nuclide: yttrium-90 (supplied as \(^{90}\)Y chloride)
Recommended dosage:
- Patients with a thrombocyte count of 150x10\(^{9}\)/l or over: 15 MBq \(^{90}\)Y-radiolabelled Zevalin\(^{\text{R}}\) per kg body weight up to a maximum of 1200 MBq
- Patients with a thrombocyte count between 100x10\(^{9}\)/l and 150x10\(^{9}\)/l: 11 MBq/kg body weight up to a maximum of 1200 MBq
Administration: intravenous

Requirements for carrying out the treatment
This therapy requires a special licence under the Nuclear Energy Act. The \(^{90}\)Y-chloride dosage is 1850 MBq per patient. Labelling takes place in a laminar flow hood. Appropriate Perspex shielding should be used for the vials and syringes containing the beta emitter \(^{90}\)Y (1 cm thickness).
Requirements for labelling and testing the radiochemical purity include:
- Shielding
- Dose calibrator
- ITLC strips
- Beta or gamma counter

A crash cart (emergency cart) should be available for the adequate treatment of possible anaphylactic reactions or other allergic reactions to \(^{90}\)Y-Zevalin\(^{\text{R}}\). The crash cart should, for
instance, contain: adrenaline, antihistamines and corticosteroids. Various departments are involved in radioimmunotherapy in general and therefore also in the eventual treatment of patients with $^{90}\text{Y}$-Zevalin®. It is extremely important that the various departments involved (Haematology, Pharmacy and Nuclear Medicine) are fully aligned when patients are treated with $^{90}\text{Y}$-Zevalin®.

7. Radiation safety

Radiation dose to staff and patient relatives

The radiation dose during the labelling procedure is low. The mean radiation dose to the hands is 0,60 mSv (range 0,50-0,80 mSv) and the mean radiation dose to the body is <0,1 mSv. The median radiation dose 1 metre away from the patient, immediately after the administration of $^{90}\text{Y}$-Zevalin® is 2,95 μSv/h (2,4-3,9 μSv/h). In the first 7 days after treatment, the median deep dose equivalent radiation exposure to the family members in closest contact with the patient is 0,035 mSv (0,014-0,079 mSv), which is less than normal background radiation. Standard general measures therefore suffice to prevent contact with body fluids.

Please note

The radionuclide $^{90}\text{Y}$ is a pure beta emitter. Admission to a clinic for treatment in isolation is therefore not required. Only 7,3%-3,2% of the administered dose of radioactivity is excreted via the kidneys in the urine in the first 7 days. The half-life of $^{90}\text{Y}$ is 64,1 h.

Patients should adhere to the following guidelines for a week after administration of $^{90}\text{Y}$-Zevalin® to prevent exposing others to radiation.

- toilets should be flushed twice after each use
- urine that has spilled alongside the toilet or on the lid of the toilet seat should be wiped with toilet paper/tissue and flushed
- patients should wash their hands thoroughly with soap and water immediately after using the toilet
- when patients accidentally cut themselves they should rinse away any blood
- men should urinate sitting down
- condoms should be used during sexual intercourse

NB: Adequate contraception should be used for one year after treatment.

Please consult the Dutch ‘Aanbevelingen inzake het werken met therapeutische doses radionucliden’ for more general safety measures. VROM/SZW/NVNG 2005’.

8. Patient preparation /essentials for procedure

a) Administration

The procedure comprises two rituximab pre-treatments (on days 1 and 8) to eliminate circulating B-lymphocytes (B cells), enabling $^{90}\text{Y}$-Zevalin® to emit its radiation more specifically to the CD20+ lymphoma cells; Rituximab pretreatment improves $^{90}\text{Y}$-Zevalin® biodistribution. Rituximab is administered at a lower dose than in unlabelled monotherapy, specifically at the 250 mg/m² dosage. The radiolabelled Zevalin® is administered intravenously over 10 min on day 8, as soon as possible, specifically within 4 h of the second rituximab administration (not as a bolus), after which the patient may return home after a short physical exam (mostly within 1 h of administration). The $^{90}\text{Y}$-Zevalin® solution
should be slowly administered intravenously by a specialist in nuclear medicine (1 ml per min over 10 min) using a Perspex-shielded syringe. This can be done immediately after the rituximab infusion has finished. Administration should occur through a 0.20 or 0.22 micron low protein binding membrane filter. Rituximab may not pass through the filter. When the solution of \(^{90}\)Y-Zevalin\(^{\text{R}}\) is administered by hand (1 ml per min), physiological saline should be passed through the filter after every 1 ml volume of \(^{90}\)Y-Zevalin\(^{\text{R}}\) has been administered (to flush the filter and the line). For this purpose, an infusion bag of physiological saline (0.9% NaCl) should also be attached via an infusion line to the 3-way cock.

After administration of \(^{90}\)Y-Zevalin\(^{\text{R}}\), the line should be flushed with 10 ml of physiological saline. The treatment therefore comprises 2 intravenous administrations of rituximab (under the supervision of the haematologist) and 1 administration of \(^{90}\)Y-Zevalin\(^{\text{R}}\) (by the specialist in nuclear medicine) in this order:

- On day 1: intravenous infusion of rituximab. Dosage: 250 mg/m\(^2\).
- On day 8 (day 7 or 9 is also acceptable): intravenous infusion of rituximab shortly followed by administration of \(^{90}\)Y-Zevalin\(^{\text{R}}\). Dosage: 250 mg/m\(^2\).

Infusion of \(^{90}\)Y-Zevalin\(^{\text{R}}\): An infusion of \(^{90}\)Y-Zevalin\(^{\text{R}}\) is administered over 10 minutes to a maximum dose of 1200 MBq.

b) Dosimetry

Dosimetry studies of \(^{111}\)In-Zevalin\(^{\text{R}}\) in patients treated in four clinical studies have shown that the estimated absorbed radiation dose to normal organs were considerably lower than the established safety limits. The dosimetry results of individual patients did not predict the toxicity of the \(^{90}\)Y-Zevalin\(^{\text{R}}\) treatment for the authorised therapeutic indication. This is why routine dosimetry measurements are not recommended.

c) Essentials for procedure

This therapy requires a special licence under the Nuclear Energy Act. The \(^{90}\)Y-chloride dosage is 1850 MBq per patient. Labelling takes place in a laminar flow hood. Appropriate Perspex shielding should be used for the vials and syringes containing the beta emitter \(^{90}\)Y (1 cm thickness).

Requirements for labelling and testing of radiochemical purity include:

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d) Side-effects

The Zevalin\(^{\text{R}}\) treatment regimen consists of the administration of rituximab and \(^{90}\)Y-Zevalin\(^{\text{R}}\); the side-effects of both should therefore be considered. In the SmPC ("Summary of Product Characteristics" of Zevalin\(^{\text{R}}\), the scientific package leaflet), the side-effects and their frequency during clinical studies are listed as very common (≥10%),
common (≥1-10%), uncommon (≥1/1.000 to <1/100) and rare (≥1/10.000 to <1/1.000).
The causality was not considered. The tables do not distinguish between the side-effects caused by \(^{90}\text{Y}\)-Zevalin\(^{\text{R}}\) and the side-effects caused by rituximab. An integrated analysis of the side-effects in 349 patients treated with Zevalin\(^{\text{R}}\) in several trials has also been published. The paragraphs below provide a short overview of the side-effects that can be attributed mainly to rituximab and those that can be attributed to \(^{90}\text{Y}\)-Zevalin\(^{\text{R}}\).

e) Infusion-related side-effects
Infusion-related side-effects (fever, chills, etc), mainly mild to moderate in severity (grade 1 and 2), are common and relate mainly to rituximab (250 mg/m\(^2\)) administrations on day 1 and day 8. Side-effects may require the speed of the rituximab infusion to be adjusted resulting in the infusion time exceeding 5 h. The infusion-related side-effects of rituximab are generally much less severe during the infusion on day 8. The rituximab infusion on day 8 therefore generally takes less time (2-3 h). Infusion-related side-effects during the 10 min \(^{90}\text{Y}\)-Zevalin\(^{\text{R}}\) administration are rare but not impossible and less severe due to the lower ibritumomab dose (< 2 mg) compared to rituximab (250 mg/m\(^2\)). Please also refer to the rituximab SmPC (Summary of Product Characteristics, scientific package leaflet) for the side-effects caused by rituximab administration and the measures to be taken in their event, further information on the premedication required, etc.

Rituximab is administered under the supervision of a haematologist.

f) Anaphylactic reactions and other hypersensitivity reactions
Anaphylactic and other hypersensitivity reactions have been reported in fewer than 1% of patients who received intravenous protein administration. Medicines for the treatment of hypersensitivity reactions, e.g. adrenaline, antihistamines and corticosteroids should be available for immediate use in the event of an allergic reaction during Zevalin\(^{\text{R}}\) administration.

g) Haematological toxicity
Mild to severe thrombocytopaenia and neutropaenia are very common, in particular during the first 12 weeks after \(^{90}\text{Y}\)-Zevalin\(^{\text{R}}\) administration (nadir 4-6 weeks after injection) and are almost always reversible. Grade 3 (53% of patients) or 4 (10%) thrombocytopaenia was reported with a median recovery time of 23 days; grade 3 (30%) or 4 (30%) neutropaenia with a median recovery time of 28 days. Anaemia is also very common (>10% of patients). The decrease in Hb recovers more quickly than the low thrombocyte and neutrophil granulocyte counts.

h) Infections
Hospitalisation due to an infection is common (7% of patients).

i) Secondary malignancies
Five patients (1%) in the integrated toxicity study were reported to have myelodysplastic syndrome (MDS, n=2), acute myeloid leukaemia (AML, n=2) or AML after MDS (n=1). All patients had had prior (alkylating) chemotherapy. More data (in particular long-term data) are needed for a definitive conclusion.

j) Mucocutaneous reactions
Mucocutaneous reactions, including Stevens-Johnson syndrome with a fatal outcome, have rarely been reported (frequency: >1/10.000 and <1/1000). The mucocutaneous reactions reported occurred after the Zevalin\(^{\text{R}}\) infusion. We could not ascertain whether the rare mucocutaneous reactions should be attributed specifically to rituximab or to \(^{90}\text{Y}\)-Zevalin\(^{\text{R}}\).
Others
Zevalin® can influence the ability to drive or use machines, as dizziness is a very common side-effect (8%).

9. Follow-up
The haematologist provides follow-up care in the outpatients’ department. Weekly blood tests should be performed, in particular a full blood count with differential. Particular attention should be paid to the thrombocyte count. If the thrombocyte count declines to < 30 x 10^9/l, blood tests are recommended 3x/week until the thrombocyte count is over 30 x 10^9/l (after which weekly blood tests should be continued until week 12 after administration of ^90Y-Zevalin®). Thrombocyte transfusions should be given if necessary. In the Netherlands, the thrombocyte level to trigger this decision differs per hospital and is often between 10 x 10^9/l and 20 x 10^9/l.

10. Literature
- EU “Summary of Product Characteristics rituximab” (SmPC, wetenschappelijke bijluiertekst) 6 juli 2006.
- EU “Summary of Product Characteristics Zevalin” (SmPC, wetenschappelijke bijluiertekst) 15 november 2005.
- Gordon LI, Witzig T, Molina A et al. Yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy

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