ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zevalin is supplied as a kit for the preparation of yttrium-90 radiolabelled ibritumomab tiuxetan. The kit contains one ibritumomab tiuxetan vial, one sodium acetate vial, one formulation buffer vial, and one empty reaction vial. The radionuclide is not part of the kit.

One ibritumomab tiuxetan vial contains 3.2 mg ibritumomab tiuxetan* in 2 ml solution (1.6 mg per ml).
*murine IgG_1 monoclonal antibody produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line and conjugated to the chelating agent MX-DTPA.

The final formulation after radiolabelling contains 2.08 mg ibritumomab tiuxetan [^{90}Y] in a total volume of 10 ml.

Excipients

This medicinal product can contain up to 28 mg sodium per dose, depending on the radioactivity concentration. To be taken into consideration by patients on a controlled sodium diet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparations for infusion.

Ibritumomab tiuxetan vial: Clear colourless solution.
Sodium acetate vial: Clear colourless solution.
Formulation buffer vial: Clear yellow to amber coloured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zevalin is indicated in adults.

[^{90}Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. The benefit of Zevalin following rituximab in combination with chemotherapy has not been established.

[^{90}Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).

4.2 Posology and method of administration

[^{90}Y]-radiolabelled Zevalin must only be received, handled and administered by qualified personnel and must be prepared in accordance with both radiation safety and pharmaceutical quality requirements (for more details see also sections 4.4, 6.6 and 12).

Posology
Zevalin must be used following pretreatment with rituximab. Please refer to the Summary of Product Characteristics of rituximab for detailed guidance on its use.
The treatment regimen consists of two intravenous administrations of rituximab and one administration of [^{90}Y]-radiolabelled Zevalin solution in the following order:

Day 1: intravenous infusion of 250 mg/m^2 rituximab.

Day 7 or 8 or 9:

- intravenous infusion of 250 mg/m^2 rituximab shortly (within 4 hours) before administration of [^{90}Y]-radiolabelled Zevalin solution.

- 10-minute intravenous infusion of [^{90}Y]-radiolabelled Zevalin solution.

Repeated use: Data on the re-treatment of patients with Zevalin are not available.

The recommended radioactivity dose of [^{90}Y]-radiolabelled Zevalin solution is:

Treatment of rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL):

- patients with ≥ 150,000 platelets/mm^3: 15 MBq/kg body weight.
- patients with 100,000-150,000 platelets/mm^3: 11 MBq/kg

The maximum dose must not exceed 1200 MBq.

Repeated use: Data on the re-treatment of patients with [90Y]-radiolabeled Zevalin are not available.

Consolidation therapy after remission induction in previously untreated patients with follicular lymphoma

- patients with ≥ 150,000 platelets/mm³: 15 MBq/kg up to a maximum of 1200 MBq
- for patients with less than 150,000 platelets per mm³ see section '4.4'

Repeated use: Data on the re-treatment of patients with [90Y]-radiolabelled Zevalin are not available.

Special populations

Paediatric population

Zevalin is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

Older people

Limited data in elderly patients (aged ≥ 65 years) are available. No overall differences in safety or efficacy were observed between these patients and younger patients.

Patients with hepatic impairment
The safety and efficacy have not been studied in patients with hepatic impairment.

Patients with renal impairment
The safety and efficacy have not been studied in patients with renal impairment.

Method of administration

The [^{90}Y]-radiolabelled Zevalin solution must be prepared according to section 12.
Before administration to the patient, the percent radioincorporation of the prepared [^{90}Y]-radiolabelled Zevalin must be checked according to the procedure outlined in section 12.
If the average radiochemical purity is less than 95%, the preparation must not be administered.

The prepared solution must be given as a slow intravenous infusion over 10 minutes.
The infusion must not be administered as an intravenous bolus.

Zevalin may be infused directly by stopping the flow from an infusion bag and administering it directly into the line. A 0.2 or 0.22 micron low protein-binding filter must be on line between the patient and the infusion port. The line must be flushed with at least 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection after the infusion of Zevalin.

4.3 Contraindications

- Hypersensitivity to ibritumomab tiuxetan, to yttrium chloride, or to any of the excipients listed in section 6.1.

- Hypersensitivity to rituximab or to other murine-derived proteins.

- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Since the Zevalin regimen includes rituximab, see also the Summary of Product Characteristics of rituximab.

[^{90}Y]-radiolabelled Zevalin solution must only be received, handled and administered by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides within a designated clinical setting. Its receipt, preparation, use, transfer, storage, and disposal are subject to the regulations and/or appropriate authorisation/licences of the local competent official organisations.
Radiopharmaceuticals must be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions must be taken, complying with the requirements of Good Manufacturing Practice of pharmaceuticals.
Infusions must be administered under the close supervision of an experienced physician with full resuscitation facilities immediately available (for radiopharmaceutical precautions see also sections ‘4.2 and 12’).

[^{90}Y]-radiolabelled Zevalin solution must not be administered to patients who are likely to develop life-threatening haematological toxicity signs.

Zevalin must not be administered in patients mentioned below, as safety and efficacy have not been established:
- > 25% of the bone marrow infiltrated by lymphoma cells
- prior external beam radiation affecting more than 25% of active bone marrow

- platelet counts <100,000/mm^3 (monotherapy) and <150,000/mm^3 (consolidation treatment)
- neutrophil counts < 1,500/mm^3
- prior bone marrow transplant or stem cell support

- *Haematological toxicity*

Special caution is required with respect to bone marrow depletion. In most patients, administration of Zevalin (after pretreatment with rituximab) results in severe and prolonged cytopenia which is generally reversible (see section 4.8). Therefore, complete blood cell and platelet counts must be monitored following Zevalin treatment weekly until levels recover or as clinically indicated. The risk of haematological toxicity may be increased after prior therapy with fludarabine containing regimens (for details see section 4.5).

- *Treatment with growth factors*

Patients must not receive growth factor treatment such as G-CSF for 3 weeks prior to Zevalin administration as well as for 2 weeks following completion of the treatment in order to assess the adequate bone marrow reserve correctly and because of the potential sensitivity of rapidly dividing myeloid cells to radiation (see also section 4.5).

- *Human anti-murine antibodies*

Patients who had received murine-derived proteins before Zevalin treatment must be tested for human anti-murine antibodies (HAMA). Patients who have developed HAMAs may have allergic or hypersensitivity reactions when treated with Zevalin or other murine-derived proteins.

After use of Zevalin, patients must generally be tested for HAMA before any further treatment with murine-derived proteins.

- *Infusion reactions*

Infusion reactions may occur during or following Zevalin administration after pretreatment with Rituximab. Signs and symptoms of infusion reactions may include dizziness, cough, nausea, vomiting, rash, pruritus, tachycardia, asthenia, pyrexia and rigors (see section 4.8). In case of a potential severe infusion reaction treatment must be stopped immediately.

- *Hypersensitivity*

Hypersensitivity reactions following Zevalin administration are commonly observed. Severe hypersensitivity reactions including anaphylaxis occur in < 1 % of patients (see also section 4.8). In case of hypersensitivity reactions, Zevalin infusion must be stopped immediately. Medicinal products for the treatment of hypersensitivity reactions, e.g. adrenaline, antihistamines and corticosteroids, must be available for immediate use in the event of an allergic reaction during administration of rituximab or Zevalin.

- *Severe mucocutaneous reactions*

Severe mucocutaneous reactions, including Stevens-Johnson Syndrome, some with fatal outcome, have been reported in association with Zevalin after pretreatment with rituximab. The onset of the reactions varied from days to months. In patients experiencing a severe mucocutaneous reaction treatment must be discontinued.

- *Contraception*

Long-term animal studies on the effect on fertility and reproductive function have not been performed. There is a potential risk that ionizing radiation by [^{90}Y]-radiolabelled Zevalin could cause toxic effects on female and male gonads. Due to the nature of the compound, women of child-bearing potential, as well as males, must use effective contraceptive methods during and up to 12 months after treatment with Zevalin (see also section 4.6 and 5.2).

- *Immunization*

The safety and efficacy of immunization with any vaccine, particularly live viral vaccines, following therapy with Zevalin have not been studied. Due to the potential risk of developing viral infections it is not recommended to administer live viral vaccines to patients who have recently received Zevalin (see section 4.5). A potentially limited ability to generate a primary or anamnestic humoral response to any vaccine following Zevalin treatment has to be taken into consideration.

- *NHL with CNS involvement*

No data are available on patients with CNS-lymphoma as those patients were not included in clinical studies. The use of Zevalin is therefore not recommended in NHL patients with CNS involvement.

- *Extravasation*

Close monitoring for evidence of extravasation during the injection of Zevalin is required in order to avoid radiation-associated tissue damage. If any signs or symptoms of extravasation have occurred, the infusion must be immediately terminated and restarted in another vein.

- *Secondary malignancies*

The use of Zevalin is associated with an increased risk of secondary malignancies, including acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS), (see also section 4.8).

- *Excipients*

The final [^{90}Y]-radiolabelled Zevalin solution contains up to 28 mg sodium per dose, depending on the radioactivity concentration. Patients on a controlled sodium diet must take this into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known interactions with other medicinal products. No interaction studies have been performed.

Growth factor treatment such as G-CSF must not be given to patients for 3 weeks prior to Zevalin administration as well as for 2 weeks following completion of the treatment (see also section 4.4).

In a clinical trial in which Zevalin was administered as consolidation after prior first line chemotherapy, a higher frequency of severe and prolonged neutropenia and thrombocytopenia was observed in patients who had received Zevalin within 4 months after a combination chemotherapy of fludarabine with mitoxantrone and/or cyclophosphamide compared to those patients who had received any other chemotherapy. Hence the risk of haematological toxicity may be increased when Zevalin is administered shortly (< 4 months) after fludarabine-containing regimens (see also section 4.4).

The safety and efficacy of immunization with any vaccine, particularly live viral vaccines, following therapy with Zevalin have not been studied (see also section 'Special warnings and precautions for use').

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies were not conducted with ibritumomab tiuxetan. Since IgGs are known to cross the placenta, and because of the significant risk associated with radiation, Zevalin is contraindicated during pregnancy (see section 4.3).

Pregnancy must be excluded before the start of treatment in women.

Any woman who has missed a period must be assumed to be pregnant until proven otherwise and alternative therapies which do not involve ionising radiation must be then considered.

Women of childbearing potential as well as males must use effective contraceptive methods during and up to 12 months after treatment with Zevalin.

Breast-feeding
Although it is not known whether ibritumomab tiuxetan is excreted in human milk, maternal IgGs are known to be excreted in human milk. Therefore, women must discontinue breast-feeding, as the potential for absorption and immunosuppression in the infant is unknown. Zevalin must be used following pretreatment with rituximab for which breast-feeding is not recommended during treatment and up to 12 months following treatment (please refer to the Summary of Product Characteristics of rituximab for detailed guidance on its use).

Fertility
No animal studies have been performed to determine the effects of Zevalin on fertility in males or females. There is a potential risk that ionizing radiation by [^{90}Y]-radiolabelled Zevalin could cause toxic effects on female and male gonads (see sections ‘4.4 and 5.2). Patients should be advised that fertility may be affected and that male patients may wish to consider semen cryopreservation.

4.7 Effects on ability to drive and use machines

Zevalin could affect the ability to drive and to use machines, as dizziness has been reported as a common side effect.

4.8 Undesirable effects

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. In all cases it is necessary to ensure that the risks of the radiation are less than from the disease itself.
Since Zevalin is used after pretreatment with rituximab (for details see section 4.2), see also the prescribing information of rituximab.

The overall safety profile of Zevalin after pretreatment with rituximab is based on data from 349 patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin’s lymphoma studied in five clinical trials, on data from a study with 204 patients receiving Zevalin as consolidation therapy after first-line remission induction, and from post-marketing surveillance.

The most frequently observed adverse drug reactions in patients receiving Zevalin after pretreatment with rituximab are thrombocytopenia, leukocytopenia, neutropenia, anaemia, infections, pyrexia, nausea, asthenia, rigors, petechiae, and fatigue.

The most serious adverse drug reactions in patients receiving Zevalin after pretreatment with rituximab are:

- Severe and prolonged cytopenias (see also ‘Special warnings and precautions for use’)
- Infections
- Haemorrhage while thrombocytopenic
- Severe mucocutaneous reactions (see also ‘Special warnings and precautions for use’)
- Myelodysplastic syndrome / acute myeloid leukaemia

Fatal outcomes have been reported for each of the following serious adverse drug reactions. These reports originated either from clinical trials or from postmarking experience.

- Infection
- Sepsis
- Pneumonia
- Myelodysplastic syndrome / Acute myeloid leukaemia
- Anaemia
- Pancytopenia
- Haemorrhage while thrombocytopenic
- Intracranial haemorrhage while thrombocytopenic
- Mucocutaneous reactions, including Stevens-Johnson Syndrome

The frequencies of the adverse drug reactions which were considered to be at least possibly related to Zevalin after pretreatment with rituximab are represented in the table below. These adverse drug reactions are based upon 349 patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma studied in 5 clinical trials. In addition, the adverse drug reactions marked with ** were observed in the study with 204 patients receiving Zevalin as consolidation therapy after first-line remission induction where indicated. The adverse drug reactions identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

Adverse reactions listed below are classified according to frequency and System Organ Class (MedDRA).

Frequency groupings are defined according to the following convention:
(very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100, rare: ≥ 1/10,000 to <1/1,000; very rare: <1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in clinical trials or during post-marketing surveillance in patients treated with Zevalin after pretreatment with rituximab

System Organ Class (MedDRA)	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations	Infection*	Sepsis*, Pneumonia*, Urinary tract infection, Oral candidiasis			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Tumour pain, Myelodysplastic syndrome/Acute myeloid leukaemia*, **		Meningioma	
Blood and lymphatic system disorders	Thrombocytopenia, Leukocytopenia, Neutropenia, Anaemia*	Febrile neutropenia, Pancytopenia*, Lymphocytopenia			
Immune system disorders		Hypersensitivity reaction			
Metabolism and nutrition disorders		Anorexia			

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Not known
Psychiatric disorders		Anxiety, Insomnia			
Nervous system disorders		Dizziness, Headache			
Cardiac disorders			Tachycardia		
Vascular disorders	Petechiae**	Haemorrhage while thrombocytopenic* Hypertension** Hypotension**		Intracranial haemorrhage while thrombocyto-penic*	
Respiratory, thoracic, and mediastinal disorders		Cough, Rhinitis			
Gastrointestinal disorders	Nausea	Vomiting, Abdominal pain, Diarrhoea, Dyspepsia, Throat irritation, Constipation			
Reproductive system and breast disorders		Amenorrhea**			
Skin and subcutaneous tissue disorders		Rash, Pruritus			Mucocutaneous reaction (including Stevens Johnson Syndrome) *
Musculoskeletal and connective tissue disorders		Arthralgia, Myalgia, Back pain, Neck pain			
General disorders and administration site conditions	Asthenia, Pyrexia, Rigors Fatigue**	Pain, Flu-like symptoms, Malaise, Peripheral oedema, Sweating increased			Extravasation with subsequent infusion site reactions, Damage to lymphoma-surrounding tissue and complications due to lymphoma swelling

** fatal outcome has been observed*
*** has been observed in a study with 204 patients receiving Zevalin as consolidation after first-line remission induction*

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

- Blood and lymphatic system disorders
  Haematological toxicity has been very commonly observed in clinical trials, and is dose-limiting (see also section 'Special warnings and precautions for use').
  Median time to blood platelet and granulocyte nadirs were around 60 days after start of treatment. In clinical trials with the indication of relapsed and refractory NHL, grade 3 or 4 thrombocytopenia was reported with median times to recovery of 13 and 21 days and grade 3 or 4 neutropenia with median times to recovery of 8 and 14 days. Following Zevalin as consolidation

after first line remission induction the median times to recovery was 20 days and 35 days for grade 3 or 4 thrombocytopenia and 20 days and 28 days for grade 3 or 4 neutropenia.

- Infections and infestations
  - Data from 349 patients with relapsed or refractory low-grade, follicular lymphoma, or transformed non-Hodgkin's lymphoma studied in five trials:
    During the first 13 weeks after treatment with Zevalin**,** patients very commonly developed infections. Grade 3 and grade 4 infections were reported commonly. During follow-up, infections occurred commonly. Of these, grade 3 was common, grade 4 uncommon.

  - Data from 204 patients receiving Zevalin as consolidation therapy after first line remission induction:
    Infections were very commonly observed.

  Infections may be bacterial, fungal, viral including reactivation of latent viruses.

- General disorders and administration site conditions
  Reports of extravasation with subsequent infusion site reactions including e.g. infusion site dermatitis, infusion site desquamation, and infusion site ulcer have been received.
  Zevalin-associated radiation might cause damage to lymphoma-surrounding tissue and complications due to lymphoma swelling

- Immune system disorders
  Data from 349 patients with relapsed or refractory low-grade, follicular lymphoma, or transformed non-Hodgkin's lymphoma studied in five trials:
  Hypersensitivity reactions following Zevalin administration are commonly observed. Severe (Grade 3/4) hypersensitivity reactions including anaphylaxis occur in less than 1% of patients (see also section 'Special warnings and precautions for use').

- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
  - Secondary malignancies

Refractory or relapsed NHL:
Myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML) has been reported in eleven out of 211 patients with relapsed or refractory NHL assigned to treatment with Zevalin in four studies.

Consolidation therapy:
From the final analysis at around 7.5 years of a study investigating the efficacy and safety of Zevalin consolidation in patients with advanced-stage follicular lymphoma responding to first-line chemotherapy (Study 4, Section 5.1) of the 204 patients receiving Y-90 Zevalin following first line chemotherapy, 26 (12.7%) patients in the Zevalin arm developed a second primary malignancy compared to 14 (6.8%) of patients in the control arm. Seven patients (3.4%, 7/204) were diagnosed with MDS/AML after receiving Zevalin, compared to one patient (0.5%, 1/205) in the control arm, with a median follow-up of 7.3 years. Deaths due to second primary malignancy included 8 (3.9%) patients in the Zevalin arm compared to 3 (1.5%) patients in the control arm. Deaths due to MDS/AML included five (2.5%) patients in the Zevalin arm compared to no patients in the control arm.
The risk of developing secondary myelodysplasia or leukaemia following therapy with alkylating agents is well known.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions afterauthorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Doses up to 19.2 MBq/kg of Zevalin have been administered in clinical trials. Expected haematological toxicity was observed, including grade 3 or 4. Patients recovered from these toxicity signs, and overdoses were not associated with serious or fatal outcome.

There is no known specific antidote for [^{90}Y]-radiolabelled Zevalin overdosage. Treatment consists of discontinuation of Zevalin and supportive therapy, which may include growth factors. If available, autologous stem cell support must be administered to manage haematological toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Various therapeutic radiopharmaceuticals, ATC code: V10XX02

Mechanism of action

Ibritumomab tiuxetan is a recombinant murine IgG_1 kappa monoclonal antibody specific for the B-cell antigen CD20. Ibritumomab tiuxetan targets the antigen CD20 which is located on the surface of malignant and normal B-lymphocytes. During B-cell maturation, CD20 is first expressed in the midstage of B-lymphoblast (pre-B-cell), and is lost during the final stage of B-cell maturation to plasma cells. It is not shed from the cell surface and does not internalise on antibody binding.

[^{90}Y]-radiolabelled ibritumomab tiuxetan binds specifically to CD20-expressing B-cells, including malignant cells. The isotope yttrium-90 is a pure β-emitter and has a mean path length of about 5 mm. This results in the ability to kill both targeted and neighbouring cells.

The conjugated antibody has an apparent affinity constant for the CD20 antigen of approximately 17 nM. The binding pattern is very restricted, with no cross-reactivity to other leukocytes or to other types of human tissue.
Rituximab pretreatment is necessary to clear circulating B-cells, enabling ibritumomab tiuxetan [^{90}Y] to deliver radiation more specifically to the lymphoma B-cells. Rituximab is administered in a reduced dose when compared with the approved monotherapy.

Pharmacodynamic effects

Treatment with [^{90}Y]-radiolabelled Zevalin also leads to depletion of normal CD20+ B-cells. Pharmacodynamic analysis demonstrated that this was a temporary effect; recovery of normal B-cells began within 6 months and median counts of B-cells were within normal range within 9 months after treatment.

Clinical efficacy and safety

The safety and efficacy of the Zevalin therapeutic regimen were evaluated in two multi-center trials enrolling a total of 197 subjects. The Zevalin therapeutic regimen was administered in two steps (see 4.2). The efficacy and safety of a variation of the Zevalin therapeutic regimen employing a reduced dose of ibritumomab tiuxetan [^{90}Y] was further defined in a third study enrolling a total of 30 patients who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3).

Study 1 was a single-arm study of 54 patients with relapsed follicular lymphoma refractory to rituximab treatment. Patients were considered refractory if their last prior treatment with rituximab did not result in a complete or partial response, or if time to disease progression (TTP) was

< 6 months. The primary efficacy endpoint of the study was the overall response rate (ORR) using the International Workshop Response Criteria (IWRC). Secondary efficacy endpoints included time to disease progression (TTP) and duration of response (DR). In a secondary analysis comparing objective response to the Zevalin therapeutic regimen with that observed with the most recent treatment with rituximab, the median duration of response following the Zevalin therapeutic regimen was 6 vs. 4 months. Table 1 summarizes efficacy data from this study.

Study 2 was a randomized, controlled, multicenter study comparing the Zevalin therapeutic regimen versus treatment with rituximab. The trial was conducted in 143 rituximab-naïve patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL. A total of 73 patients received the Zevalin therapeutic regimen, and 70 patients received rituximab given as an intravenous infusion at 375 mg/m^2 weekly times 4 doses. The primary efficacy endpoint of the study was to determine the ORR using the IWRC (see Table 2). The ORR was significantly higher (80% vs. 56%, p = 0.002) for patients treated with the Zevalin therapeutic regimen. The secondary endpoints, duration of response and time to progression, were not significantly different between the two treatment arms.

Table 2.Summary of Efficacy Data in patients with relapsed/refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL

	Study 1	**Study 2**	
	Zevalin therapeutic regimen N = 54	**Zevalin therapeutic regimen N = 73**	**Rituximab N = 70**
Overall Response Rate (%)	74	80	56
Complete Response Rate (%)	15	30	16
CRu Rate[2] (%)	0	4	4
Median DR[3,4] (Months) [Range[5]]	6.4 [0.5-24.9+]	13.9 [1.0-30.1+]	11.8 [1.2-24.5]
Median TTP[3,6] (Months) [Range[5]]	6.8 [1.1-25.9+]	11.2 [0.8-31.5+]	10.1 [0.7-26.1]

[1]IWRC: International Workshop response criteria
[2]CRu: Unconfirmed complete response
[3]Estimated with observed range.
[4]Duration of response: interval from the onset of response to disease progression.
[5]"+" indicates an ongoing response.
[6]Time to Disease Progression: interval from the first infusion to disease progression.

Study 3 was a single arm study of 30 patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3). Excluded from the study were patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were considered to have impaired bone marrow reserve if they had any of the following: prior myeloablative therapy with stem cell support; prior external beam radiation to >25% of active marrow; a platelet count <100,000 cells/mm^3; or neutrophil count <1,500 cells/mm^3. In this study, a modification of the Zevalin therapeutic regimen with a lower [^{90}Y]-Zevalin activity per body weight (11 MBq/kg) was used. Objective, durable clinical responses were observed

[67% ORR (95% CI: 48-85%), 11.8 months median DR (range: 4-17 months)] and resulted in a greater incidence of haematologic toxicity (see 4.8) than in Studies 1 and 2.

Study 4 investigated the efficacy and safety of Zevalin consolidation in patients with advanced-stage follicular lymphoma responding to first-line chemotherapy. Major inclusion criteria were: CD20+ grade 1 or 2 follicular lymphoma; stage III or IV at diagnosis; normal peripheral blood cell counts; < 25% bone marrow involvement; age ≥ 18 yrs; and complete response (CR/Cru) or partial response (PR) after first-line chemotherapy determined by physical examination, CT scans and bone marrow biopsy. After completing induction therapy, patients were randomized to receive either Zevalin (250 mg/m^2 rituximab on day -7 and on day 0 followed on day 0 by Zevalin 15 MBq/kg body weight; maximal dose 1200 MBq; [n=208]) or no further treatment (control; n=206). Induction therapies included CVP n=106, CHOP (-like) n=188, fludarabine combinations n=22, chlorambucil n=39 and rituximab-chemotherapy combinations n=59. Median progression free survival (PFS) was calculated at a median follow-up of 2.9 years. PFS increased from 13.5 months (control) to 37 months (Zevalin; p<0.0001; HR 0.465). For patient subgroups in PR or CR after induction, median PFS was 6.3 vs 29.7 months (p<0.0001; HR 0.304) and 29.9 vs 54.6 months (p=0.015; HR 0.613), respectively. After Zevalin consolidation, 77% of patients in PR after induction therapy converted to CR. Patients whose response status changed after Zevalin from PR to CR showed a significantly longer median progression free survival time (986 days) compared to those patients who remained in PR (median progression free survival time of 460 days, p=0.0004). In total, 87% of patients were in CR(u); 76% in CR and 11% in CRu.

5.2 Pharmacokinetic properties

In patients given intravenous infusions of 250 mg/m^2 rituximab followed by intravenous injections of 15 MBq/kg of [^{90}Y]-radiolabelled Zevalin, the median serum effective half-life of ibritumomab tiuxetan [^{90}Y] was 28 h.

As ^{90}Y forms a stable complex with ibritumomab tiuxetan, the biodistribution of the radiolabel follows the biodistribution of the antibody. Irradiation by the emitted beta particles from ^{90}Y occurs in a radius of 5 mm around the isotope.

In clinical studies, the [^{90}Y]-radiolabelled Zevalin after pretreatment with rituximab results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There is a potential risk that [^{90}Y]-radiolabelled Zevalin after pretreatment with rituximab could cause toxic effects on the male and female gonads (see sections 4.4 and 4.6).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single and repeated dose toxicity.
The human radiation dose estimates derived from biodistribution studies in mice with [^{90}Y]- or [^{111}In]-radiolabelled ibritumomab tiuxetan predicted acceptable radiation to normal human tissue with limited levels of skeleton and bone marrow radiation. The linker chelate tiuxetan forms a stable complex with the radioisotopes yttrium-90 and indium-111 and only negligible degradation due to radiolysis is expected.

The single and repeated dose toxicity studies of the non-radioactive compound in cynomolgus monkeys did not indicate any other risk than the expected B-cell depletion arising from the use of ibritumomab tiuxetan alone or in combination with rituximab. Studies on reproductive and developmental toxicity have not been performed.

Studies on the mutagenic and carcinogenic potential of Zevalin have not been performed. Due to the exposure to ionising radiation derived from the radiolabel, a risk of mutagenic and carcinogenic effects has to be taken into account.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ibritumomab tiuxetan vial:
Sodium chloride
Water for injections

Sodium acetate vial:
Sodium acetate
Water for injections

Formulation buffer vial:
Disodium phosphate dodecahydrate
Human albumin solution
Hydrochloric acid, diluted (for pH adjustment)
Pentetic acid
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

No incompatibilities have been observed between Zevalin and infusion sets.

6.3 Shelf life

66 months.

After radiolabelling, an immediate use is recommended. Chemical and physical in-use stability has been demonstrated for 8 hours at 2°C - 8°C and protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store the vials in the original package in order to protect from light.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

For storage conditions of the radiolabelled product, see section 6.3.

6.5 Nature and contents of container

Zevalin is supplied as a kit for the preparation of yttrium-90 (^{90}Y) radiolabelled ibritumomab tiuxetan.

Zevalin contains 1 of each of the following:

Ibritumomab tiuxetan vial: type I glass vial with a rubber stopper (teflon-lined bromobutyl) containing 2 ml solution.
Sodium acetate vial: type I glass vial with a rubber stopper (teflon-lined bromobutyl) containing 2 ml solution.
Formulation buffer vial: type I glass vial with a rubber stopper (teflon-lined bromobutyl) containing 10 ml solution.
Reaction vial: type I glass vial with a rubber stopper (teflon-lined bromobutyl)

Pack size of 1 kit.

6.6 Special precautions for disposal and other handling

General warning
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or approporiate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Contents of the kit are intended only for use in the preparation of yttrium-90 radiolabelled ibritumomab tiuxetan and are not to be administered directly to the patient without first undergoing the preparative procedure.

For instructions on extemporary preparation of the medicinal product before administration,see section 12.

If at any time in the preparation of this product the integrity of the containers is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before extemporary preparation is not radioactive. However, after Yttrium-90 is added, adequate shielding of the final preparation must be maintained.

Any unused medicinal product or waste material must be disposed of in accordance with local requirements. Contaminated materials must be disposed of as radioactive waste by the authorised route.

7. MARKETING AUTHORISATION HOLDER

Ceft Biopharma s.r.o.
Trtinova 260/1
Cakovice, 196 00 Praha 9
Czech Republic

8. MARKETING AUTHORISATION NUMBER

EU/1/03/264/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2004
Date of latest renewal: 16 January 2009

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

Yttrium-90 decays by the emission of high-energy beta particles, with a physical half-life of 64.1 hours (2.67 days). The product of radioactive decay is stable zirconium-90. The path length of beta emission (χ_{90}) by yttrium-90 in tissue is 5 mm.

Analyses of estimated radiation absorbed dose were carried out using quantitative imaging with the gamma-emitter [^{111}In]-radiolabelled Zevalin**,** blood sampling, and the MIRDOSE3 software program. The imaging dose of [^{111}In]-radiolabelled Zevalin was always given immediately following an infusion with rituximab at 250 mg/m² to deplete peripheral CD20+ cells and to optimise bio-distribution. Following administration of [^{111}In]-radiolabelled Zevalin**,** whole body scans were performed at up to eight time-points, acquiring both anterior and posterior images. Blood samples, used to calculate residence times for red marrow, were drawn up to eight time-points.

Based upon dosimetry studies with [^{111}In]-radiolabelled Zevalin, the estimated radiation dosimetry for individual organs following administration of [^{90}Y]-radiolabelled Zevalin at activities of 15 MBq/kg and 11 MBq/kg was calculated according to Medical Internal Radiation Dosimetry (MIRD) (Table 3). The estimated radiation-absorbed doses to normal organs were substantially below recognised upper safety limits. Individual patient dosimetry results were not predictive for [^{90}Y]-radiolabelled Zevalin toxicity.

Table 3.
Estimated Radiation Absorbed Doses From [^{90}Y]-Zevalin

Organ	[^{90}Y]-Zevalin mGy/MBq	
	Median	**Range**
Spleen[1]	9.4	1.8 - 20.0
Liver[1]	4.8	2.9 - 8.1
Lower Large Intestinal Wall[1]	4.7	3.1 – 8.2
Upper Large Intestinal Wall[1]	3.6	2.0 – 6.7
Heart Wall[1]	2.9	1.5 - 3.2
Lungs[1]	2.0	1.2 - 3.4
Testes[1]	1.5	1.0 – 4.3
Small Intestine[1]	1.4	0.8 – 2.1
Red Marrow[2]	1.3	0.6 - 1.8
Urinary Bladder Wall[3]	0.9	0.7 - 1.3
Bone Surfaces[2]	0.9	0.5 - 1.2
Ovaries[3]	0.4	0.3 - 0.5
Uterus[3]	0.4	0.3 - 0.5
Adrenals[3]	0.3	0.2 - 0.5
Brain[3]	0.3	0.2 - 0.5
Breasts[3]	0.3	0.2 - 0.5
Gallbladder Wall[3]	0.3	0.2 - 0.5
Muscle[3]	0.3	0.2 - 0.5
Pancreas[3]	0.3	0.2 - 0.5
Skin[3]	0.3	0.2 - 0.5
Stomach[3]	0.3	0.2 - 0.5
Thymus[3]	0.3	0.2 - 0.5
Thyroid[3]	0.3	0.2 - 0.5
Kidneys[1]	0.1	0.0 - 0.3
Total Body[3]	0.5	0.4- 0.7

[1] Organ region of interest
[2] Sacrum region of interest
[3] Whole body region of interest

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Read complete directions thoroughly before starting the preparation procedure.

Proper aseptic technique and precautions for handling radioactive materials must be employed.

Waterproof gloves must be utilised in the preparation and during the determination of radiochemical purity of [^{90}Y]-radiolabelled Zevalin.

Radiation protection precaution in accordance with local regulations must be taken, since administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc..

Characteristics of yttrium-90

- The following minimum yttrium-90 characteristics are recommended:

Radioactivity concentration at time of use	1.67 to 3.34 GBq/ml
Total extractable activity to deliver at time of use	≥ 1.48 GBq corresponding to 0.44 ml to 0.89 ml of yttrium-90 solution
HCl concentration	0.035-0.045 M
Chloride identification	Positive
Yttrium identification	Positive
Radiochemical purity of the yttrium-90 chloride solution	≥ 95% of free ionic yttrium-90
Bacterial endotoxins	≤150 EU/ml
Sterility	No growth
Radionuclidic purity strontium-90 content	≤ 0.74 MBq strontium-90 / 37 GBq yttrium-90
Metal impurities	
Total metals*	≤ 50 ppm
Individual metals*	≤ 10 ppm each

* Metals to be included need to be based on the specific manufacturing process. Control of these metals can be achieved either through process validation or release test.

- Additional testing that might be required for suitability assessment:

Process-specific impurities:

Total organic carbon (e.g. organic chelators)	Below limit of quantitation*
Process residuals (e.g. ammonia, nitrate)	Below limit of quantitation*
Total Alpha impurities	Below limit of quantitation*
Total other Beta impurities (non-strontium-90)	Below limit of quantitation*

Total Gamma impurities	Below limit of quantitation*

* Needs to be included as release test or controlled through process validation if above limit of quantitation

Directions for radio-labelling of Zevalin with yttrium-90:

Sterile, pyrogen-free yttrium-90 chloride of the above specified quality must be used for the preparation of [^{90}Y]-radiolabelled Zevalin.

Before radiolabelling, bring refrigerated Zevalin cold kit to room temperature 25°C.

Clean the rubber stopper of all cold kit vials and the yttrium-90 chloride vial with a suitable alcohol swab and allow to air dry.

Place cold kit reaction vial in a suitable dispensing shield (plastic enclosed in lead).

Step 1: Transfer sodium acetate solution to the reaction vial

Using a 1-ml sterile syringe, transfer sodium acetate solution to reaction vial. The volume of sodium acetate solution added is equivalent to 1.2 times the volume of yttrium-90 chloride to be transferred in step 2.

Step 2: Transfer yttrium-90 chloride to the reaction vial

Aseptically transfer 1500 MBq of yttrium-90 chloride with a 1 ml sterile syringe to the reaction vial containing the sodium acetate solution transferred in step 1. Mix completely by coating the entire inner surface of the reaction vial. Mix by inversion, rolling the container, avoid foaming or agitating the solution.

Step 3: Transfer ibritumomab tiuxetan solution to the reaction vial

Using a 2-3 ml sterile syringe, transfer 1.3 ml ibritumomab tiuxetan solution to the reaction vial. Mix completely by coating the entire inner surface of the reaction vial. Mix by inversion, rolling the container, avoid foaming or agitating the solution.

Incubate the yttrium-90 chloride/acetate/ibritumomab tiuxetan solution at room temperature for five minutes. Labelling time longer than six minutes or shorter than four minutes will result in inadequate radioincorporation.

Step 4: Add the formulation buffer to the reaction vial

Using a 10-ml syringe with a large bore needle (18-20 G), draw formulation buffer that will result in a combined total volume of 10 ml.

After the 5-minute incubation period, withdraw from the reaction vial the same volume of air as the formulation buffer to be added in order to normalise pressure and immediately thereafter gently add the formulation buffer down the side of the reaction vial to terminate incubation. Do not foam, shake, or agitate the mixture.

Step 5: Assay the [^{90}Y]-radiolabelled Zevalin solution for its specific radioactivity

Radiochemical purity of the radiolabelled preparation applies as long as more than 95% of yttrium-90 is incorporated into the monoclonal antibody.

Before administration to the patient, the percent radioincorporation of the prepared [^{90}Y]-radiolabelled Zevalin must be checked according to the procedure outlined below.

Caution: Patient dose not to exceed 1200 MBq.

Instructions for determining the percent radioincorporation

The radioincorporation assay for radiochemical purity, is performed by Instant Thin Layer Chromatography (ITLC) and must be carried out according to the following procedure.

Required materials not supplied in the Zevalin kit:

- Developing chamber for chromatography
- Mobile phase: sodium chloride 9 mg/ml (0.9%) solution, bacteriostatic-free
- ITLC strips (e.g. ITLC TEC-Control Chromatography Strips, Biodex, Shirley, New York, USA, Art. Nr. 150-772 or equivalent, dimensions: approximately 0.5-1 cm x 6 cm)
- Scintillation vials
- Liquid scintillation cocktail (e.g. Ultima Gold, catalog No. 6013329, Packard Instruments, USA or equivalent)

Assay procedure:

1.) Add approximately 0.8 ml sodium chloride 9 mg/ml (0.9%) solution to developing chamber assuring the liquid will not touch the 1.4 cm origin mark on the ITCL strip.

2.) Using a 1 ml insulin syringe with a 25- to 26-G needle, place a hanging drop (7-10 µl) of [^{90}Y]-radiolabelled Zevalin onto the ITLC strip at its origin. Spot one strip at a time and run three ITLC strips. It may be necessary to perform a dilution (1:100) before application of the [^{90}Y]-radiolabelled Zevalin to the ITLC strips.

3.) Place ITLC strip in the developing chamber and allow the solvent front to migrate past the 5.4 cm mark.

4.) Remove ITLC strip and cut in half at the 3.5 cm cut line. Place each half into separate scintillation vials to which 5 ml LSC cocktail must be added (e.g. Ultima Gold, catalog No. 6013329, Packard Instruments, USA or equivalent). Count each vial in a beta counter or in an appropriate counter for one minute (CPM), record net counts, corrected for background.

5.) Calculate the average Radiochemical Purity (RCP) as follows:

6.) Average % RCP = $\frac{\text{net CPM bottom half}}{\text{net CPM top half + net CPM bottom half}} \times 100$

7.) If the average radiochemical purity is less than 95%, the preparation must not be administered.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONIDTIONS AND REQUIRMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance
Biogen IDEC, Inc.
14 Cambridge Center
Cambridge, MA 02142
USA

Name and address of the manufacturer responsible for batch release
CIS bio international
RN 306- Saclay
B.P. 32
91192 Gif-sur-Yvette Cedex
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.1 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation Application and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significang change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations for infusion
Ibritumomab tiuxetan [^{90}Y]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 3.2 mg ibritumomab tiuxetan* to be diluted in 2 ml solution (1.6 mg per ml).

*recombinant murine IgG_1 monoclonal antibody produced by DNA technology in a Chinese hamster ovary (CHO) cell line and conjugated to the chelating agent MX-DTPA.

3. LIST OF EXCIPIENTS

Ibritumomab tiuxetan vial:
Sodium chloride
Water for injections

Sodium acetate vial:
Sodium acetate
Water for injections

Formulation buffer vial:
Human albumin solution
Sodium chloride
Disodium phosphate dodecahydrate
Sodium hydroxide
Potassium dihydrogen phosphate
Potassium chloride
Pentetic acid
Hydrochloric acid, diluted
Water for injections

Please see the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Kit for radiopharmaceutical preparations for infusion.

One ibritumomab tiuxetan vial.

2 ml of sodium acetate solution

10 ml of formulation buffer

Empty reaction vial (10 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Must be administered by authorised personnel only.

8. EXPIRY DATE

EXP

After radiolabelling, immediate use is recommended. Chemical and physical in-use stability has been demonstrated for 8 hours at 2°C - 8°C and protected from light.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store the vials in the original container in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material must be disposed of in accordance with local requirements.
Contaminated materials must be disposed of as radioactive waste by the authorised route.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ceft Biopharma s.r.o.
Trtinova 260/1
Cakovice, 196 00 Praha 9
Czech Republic

12. MARKETING AUTHORISATION NUMBER

EU/1/03/264/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

IBRITUMOMAB TIUXETAN SOLUTION VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations
Ibritumomab tiuxetan solution
Intravenous infusion, after preparation.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3.2 mg/2 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SODIUM ACETATE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations
Sodium acetate solution
Intravenous infusion, after preparation.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

FORMULATION BUFFER SOLUTION VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations
Formulation buffer solution
Intravenous infusion, after preparation.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
REACTION VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations
Reaction vial
Intravenous infusion, after preparation.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Empty

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations for infusion
Ibritumomab tiuxetan [^{90}Y]

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. WHAT ZEVALIN IS AND WHAT IT IS USED FOR

This medicine is a radiopharmaceutical product for therapy only.

Zevalin is a kit for the preparation of the active substance ibritumomab tiuxetan [^{90}Y], a monoclonal antibody labelled with the radioactive substance yttrium-90 (^{90}Y). Zevalin attaches to a protein (CD20) on the surface of certain white blood cells (B-cells) and kills them by irradiation.

Zevalin is used to treat patients suffering from specific subgroups of B-cell non-Hodgkin's lymphoma (CD20+ indolent or transformed B-cell NHL) if an earlier rituximab, another monoclonal antibody, treatment has not worked, or has stopped working (refractory or relapsed disease).

Zevalin is also used in previously untreated patients with follicular lymphoma. It is used as a **consolidation** therapy to improve the reduction in the number of lymphoma cells (remission) achieved with the initial chemotherapy regimen.

The use of Zevalin does involve exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN ZEVALIN

You must not be given Zevalin:
- if you are **allergic** (hypersensitive) to any of the following:
  - ibritumomab tiuxetan, yttrium chloride or to any of the other ingredients of Zevalin (listed in section 6 'What Zevalin contains')
  - rituximab or other murine-derived proteins
- if you are pregnant or breast-feeding (see also section "pregnancy and breast feeding").

Take special care with Zevalin

In the following cases, Zevalin use is not recommended since its safety and efficacy have not been established:

- **more than a quarter** of your bone marrow contains malignant abnormal cells.
- **If you have had external beam radiation** (a type of radiotherapy) to more than a quarter of your bone marrow.
- **If you receive Zevalin alone and the number of your blood platelets is fewer than 100,000/mm^3**
- **If the number of your blood platelets is fewer than 150,000/mm^3 after chemotherapy**
- **If the number of your white blood cells is fewer than 1,500/mm^3**
- **If you have had a bone marrow transplant or have received blood stem cells** in the past.

If you have been treated with other proteins (especially mouse-derived) before Zevalin treatment, you may be more likely to have an allergic reaction. You may, therefore, need to be tested for special antibodies.

In addition, Zevalin is not recommended for the use in patients with non-Hodgkin's lymphoma involving the brain and/or spinal cord as those patients were not included in clinical studies.

Children
Zevalin is not recommended for use in children below age 18 since safety and efficacy have not been established.

Elderly patients
Limited data in elderly patients (aged 65 years or over) are available. No overall differences in safety or efficacy were observed between these patients and younger patients.

Other medicines and Zevalin
Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription.
In particular, your doctor will need to interrupt treatment with growth factors such as filgrastim for a period of three weeks before giving you Zevalin to two weeks after Zevalin treatment.
If you are given Zevalin less than 4 months after chemotherapy containing the active substance fludarabine, you may have a higher risk of having a reduced number of blood cells.
Please tell your doctor that you were given Zevalin if you are due for vaccination after using it.

Pregnancy and breast-feeding
Zevalin must not be used during pregnancy. Your doctor will perform tests to exclude pregnancy before you start the treatment. Women of child-bearing potential and male patients must use reliable contraception during treatment with Zevalin and for up to one year after stopping treatment.
There is a potential risk that ionizing radiation by Zevalin could harm your ovaries and testicles. Please ask your doctor how this may affect you, especially if you are planning on having children in the future.

Women must not breast-feed during treatment and for 12 months following the treatment.

Driving and using machines
Zevalin can affect your ability to drive and use machines, as dizziness is a common side effect. Please be cautious until you are sure you are not affected.

Zevalin contains sodium
This medicine contains up to 28 mg sodium per dose, depending on the radioactivity concentration. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE ZEVALIN

There are strict laws on the use, handling and disposal of radiopharmaceutical products. Zevalin will only be used in special controlled areas. This product will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this product and will keep you informed of their actions.

The dose of Zevalin depends on your body weight, blood platelet counts and what Zevalin is being used for (indication). The maximum dose must not exceed 1200 MBq ('megabecquerel', a unit to measure radioactivity).

Zevalin is used with another medicine containing the active substance rituximab.

You will be given a total of 3 infusions in the course of two visits to a medical facility, 7 to 9 days apart.

- On day 1 you will be given one rituximab infusion
- On day 7, 8, or 9 you will be given one rituximab infusion, followed by one Zevalin infusion shortly afterwards (within 4 hours).

The recommended dose is:

For consolidation therapy in patients with follicular lymphoma
- The usual dose is 15 MBq/kg body weight.

For therapy of patients with relapsed or refractory Non-Hodgkin's lymphoma not responding to rituximab
- The usual dose is 11 or 15 MBq per kg body weight, depending on your blood platelet count.

Preparation of Zevalin
Zevalin is not used directly, but must be prepared by your healthcare professional first. The kit allows the coupling of antibody ibritumomab tiuxetan with the radioactive isotope yttrium ^{90}Y (radiolabelling).

How Zevalin is given
Zevalin is given by intravenous infusion (drip into a vein) usually lasting about 10 minutes.

After you are given Zevalin
The amount of radiation that your body will be exposed to due to Zevalin is smaller than with radiotherapy. Most radioactivity will decay within the body, but a small part will be eliminated through your urine. Therefore, for one week after the Zevalin infusion you must wash your hands thoroughly each time after urinating.

After treatment your doctor will perform regular blood tests to check your platelet and white cell counts. These usually decrease around two months after start of treatment.

If your doctor plans to treat you with some other antibody after treatment with Zevalin, you will need to be tested for special antibodies. Your doctor will tell you if this applies to you.

If you have received more Zevalin than you should
Your doctor will treat you, as appropriate, if you have any particular ill effects. This may include discontinuation of Zevalin therapy and treatment with growth factors or your own stem cells.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zevalin can cause side effects, although not everybody gets them.

Tell your doctor **immediately** if you notice symptoms of any of the following:

- **infection:** fever, chills
- **blood poisoning (sepsis):** fever and chills, changes in mental status, rapid breathing, increased heart rate, decreased urine output, low blood pressure, shock, problems with bleeding or clotting
- **infections of the lung (pneumonia):** breathing difficulties
- **Low counts of blood cells:** unusual bruising, more bleeding then usual after injury, fever, or if you feel unusually tired or breathless
- **severe mucous membrane reactions,** which may occur days or months after Zevalin and/or rituximab administration. Your doctor will immediately stop the treatment.
- **extravasation** (leakage of the infusion to the surrounding tissue): pain, burning sensation, stinging or another reaction at the infusion site during administration. Your doctor will immediately stop the infusion and restart it using another vein.
- **allergic** (*hypersensitivity*) **reactions/infusion reactions**: symptoms for allergic reactions/ infusion reactions may be skin reactions, breathing difficulties, swelling, itching, flushing, chills, dizziness (as potential sign for low blood pressure). Depending on the kind/severity of reaction your doctor will decide if treatment must be stopped immediately.

The side effects marked with an asterisk (*) have led to death in some cases, either in clinical trials or during the marketing of the product.

The side effects marked with two asterisks (**) were observed additionally under consolidation therapy.

Very common side effects (may effect more than 1 in 10 people)

- decreased number of blood platelets, white and red blood cells (*thrombocytopenia, leukocytopenia, neutropenia, anaemia*)*
- feeling sick *(nausea)*
- weakness, fever, chills *(rigor)*
- infection*
- tiredness**
- red pinpoint spots under the skin (*petechia*)**

Common side effects (may effect up to 1 in 10 people)

- blood poisoning (*sepsis*)*; infection of the lungs *(pneumonia)**; urinary tract infection, fungal infections in the mouth such as oral thrush (*oral candidiasis*)
- other blood related cancers (*myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML)*) *, **; tumour pain
- fever with decrease in the number of specific white blood cells *(febrile neutropenia);* decreased counts of all blood cells *(pancytopenia)**; decreased number of lymphocytes *(lymphocytopenia)*
- allergic (*hypersensitivity*) reactions
- severe loss of appetite *(anorexia)*
- feeling anxious (*anxiety)*; trouble sleeping (*insomnia*)
- dizziness; headache,
- bleeding due to decreased blood platelet counts*,
- cough; runny nose
- vomiting, stomach (*abdominal*) pain; diarrhoea; indigestion; throat irritation; constipation

- rash; itching (*pruritus*)
- joint pain (*arthralgia*) aching muscles (*myalgia*); back pain; neck pain
- pain; flu-like symptoms; generally feeling unwell (*malaise*), swelling caused by build-up of fluid in the arms and legs and other tissues (*peripheral oedema*); increased sweating
- high blood pressure (*hypertension*)**
- low blood pressure (*hypotension*)**
- absence of menstruation (amenorrhea)**

Uncommon side effects: (may effect up to 1 in 100 people)
- rapid heart beat (*tachycardia*),

Rare side effects: (may effect up to 1 in 1,000 people)
- benign brain tumour (*meningioma*),
- bleeding in the head due to decreased blood platelet counts*,

Side effects for which frequency is not known:
- reaction of the skin and mucous membranes (including *Stevens-Johnson Syndrome*)*
- leakage of the infusion to the surrounding tissue (*extravasation*), causing skin inflammation *(infusion site dermatitis)* and shedding (*infusion site desquamation*) or injection site ulcers
- tissue damage around tumours of the lymph system and complications due to swelling of such tumours

Reporting of side effects
If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine**.**

5. HOW TO STORE ZEVALIN

Keep this medicine out of the sight and reach of children.

Do not use Zevalin after the expiry date which is stated on the pack.

This medicine will be stored by a healthcare professional.
Store in a refrigerator (2°C - 8°C). Do not freeze.
Store the vials in the original package in order to protect from light.
Storage must be in accordance with national regulations for radioactive materials.

After radiolabelling, an immediate use is recommended. Stability has been demonstrated for 8 hours at 2°C - 8°C and protected from light.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Zevalin contains

- The active substance is ibritumomab tiuxetan. Each vial contains 3.2 mg ibritumomab tiuxetan in 2 ml solution (1.6 mg per ml).
- The other ingredients are:
  - *ibritumomab tiuxetan vial*: sodium chloride, water for injections
  - *sodium acetate vial*: sodium acetate, water for injections

- *formulation buffer vial*: human albumin solution, sodium chloride, disodium phosphate dodecahydrate, sodium hydroxide, potassium dihydrogen phosphate, potassium chloride, pentetic acid, hydrochloric acid (diluted) for pH adjustment, water for injections

The final formulation after radiolabelling contains 2.08 mg [^{90}Y] ibritumomab tiuxetan in a total volume of 10 ml.

What Zevalin looks like and contents of the pack
Zevalin is a kit for radiopharmaceutical preparation for infusion, containing:
- One ibritumomab tiuxetan glass vial, with 2 ml clear, colourless solution.
- One sodium acetate glass vial, with 2 ml clear, colourless solution.
- One formulation buffer glass vial, with 10 ml clear, yellow to amber coloured solution.
- One reaction glass vial (empty)

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Czech Republic

Manufacturer
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.