

## Prescribing Information

# Zevalin®

### 1. Name of the Medicinal Product

Zevalin 1.6 mg/ml, Kit for radiopharmaceutical preparation for infusion.

### 2. Qualitative and Quantitative Composition

Ibritumomab tiuxetan\* 1.6 mg per ml

One vial contains 3.2 mg of ibritumomab tiuxetan

\*produced by a genetically engineered Chinese Hamster Ovary (CHO) cell line conjugated to the chelating agent MX-DTPA

Zevalin is supplied as a kit for the preparation of yttrium-90 radiolabelled ibritumomab tiuxetan. The final formulation after radiolabeling contains 2.08 mg ibritumomab tiuxetan in a total volume of 10 ml.

For a full list of excipients, see section 6.1.

### 3. Pharmaceutical Form

Kit for radiopharmaceutical preparation for infusion.

Clear, colorless solution.

### 4. Clinical Particulars

#### 4.1. Therapeutic Indications

The <sup>90</sup>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.

The <sup>90</sup>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

<sup>90</sup>Y]-radiolabelled Zevalin should only be handled and administered by qualified personnel with appropriate authorization for the use and manipulation of radionuclides within a designated clinical setting. Its preparation, use, transfer, storage and disposal are subject to the regulations and/or appropriate authorization. Infusions should be administered under the close supervision of an experienced physician with full resuscitation facilities immediately available (for radiopharmaceutical precautions see also sections 4.4 and 6.6).

Zevalin should be used following pre-treatment with rituximab.

Refer to the product information of rituximab for detailed guidance on its use.

The prepared infusion solution must be given as a slow intravenous administration over 10 minutes.

Do not use as an intravenous bolus.

The <sup>90</sup>Y]-radiolabelled Zevalin solution must be prepared according to section 6.6: “Instructions for use and handling and disposal”.

Before administration to the patient, the percent radioincorporation of the prepared <sup>90</sup>Y]-radiolabelled Zevalin must be checked according to the procedure outlined in section 6.6.

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

The recommended radioactivity for patients receiving Zevalin as monotherapy is:

- patients with 150,000 platelets per mm<sup>3</sup> and more: 15 MBq [<sup>90</sup>Y]-radiolabelled Zevalin per kg body weight up to a maximum of 1200 MBq.
- patients with fewer than 150,000 but more than 100,000 platelets per mm<sup>3</sup>: 11 MBq [<sup>90</sup>Y]-radiolabelled Zevalin per kg body weight up to a maximum of 1200 MBq.

The recommended radioactivity for patients receiving Zevalin as consolidation after remission induction is:

- patients with 150,000 platelets per mm<sup>3</sup> and more: 15 MBq [<sup>90</sup>Y]-radiolabelled Zevalin per kg body weight up to a maximum of 1200 MBq.
- patients with fewer than 150,000 platelets per mm<sup>3</sup> should not receive Zevalin consolidation treatment.

<sup>90</sup>Y]-radiolabelled 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. Flush the line with at least 10 ml of sodium chloride 9 mg/ml (0.9%) solution after the infusion of <sup>90</sup>Y]-radiolabelled Zevalin.

Treatment consists of two intravenous administrations of rituximab and one administration of <sup>90</sup>Y]-radiolabelled Zevalin in the following order:

**Day 1:** an intravenous infusion of rituximab.

Rituximab infusion dose schedule: 250 mg/m<sup>2</sup> of rituximab.

**Day 7, 8 or 9:** an intravenous infusion of rituximab shortly before the administration of <sup>90</sup>Y]-radiolabelled Zevalin.

Rituximab infusion dose schedule: 250 mg/m<sup>2</sup> of rituximab.

<sup>90</sup>Y]-radiolabelled Zevalin infusion: 10 minute intravenous infusion of [<sup>90</sup>Y]-radiolabelled Zevalin is given up to a maximum dose of 1200 MBq. If the average radiochemical purity is less than 95%, the preparation should not be administered.

- Repeated use

Data on the re-treatment of patients with <sup>90</sup>Y]-radiolabelled Zevalin are not available.

- Children

There is no experience in children and adolescents below 18 years of age.

#### 4.3. Contraindications

Hypersensitivity to ibritumomab tiuxetan, to yttrium chloride, to rituximab, to other murine proteins or to any of the excipients.

Pregnancy and lactation.

#### 4.4. Special Warnings and Special Precautions for Use

Because the Zevalin therapeutic regimen includes the use of rituximab, see also the prescribing information of rituximab.

Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides. This radiopharmaceutical may be received, used and administered only by authorized persons in designated settings. Its receipt, storage, use, transfer, and disposal are subject to the regulations and/or appropriate licenses of the local competent official organizations. Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

In most patients Zevalin administration results in severe and prolonged cytopenia which is generally reversible.

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 hematological toxicity may be increased when Zevalin is administered shortly (<4 months) after fludarabine containing regimens.

<sup>90</sup>Y]-radiolabelled Zevalin should not be administered to patients who are likely to develop life-threatening hematological toxicity signs. Patients receiving Zevalin as consolidation should have recovered from induction chemotherapy and have achieved a neutrophil count > 1,500/mm<sup>3</sup> and a platelet count > 150,000/mm<sup>3</sup> before Zevalin administration.

Zevalin should not be administered in the patients mentioned below as safety and efficacy has not been established:

- patients in whom more than 25% of the bone marrow has been infiltrated by lymphoma cells
- patients who have received prior external beam radiation involving more than 25% of active bone marrow
- patients receiving Zevalin as monotherapy with platelet count <100,000/mm<sup>3</sup> and patients receiving Zevalin as consolidation after remission induction with platelet count <150,000/mm<sup>3</sup>
- patients with neutrophil count <1,500/mm<sup>3</sup>
- patients who have received prior bone marrow transplant or stem cell support
- children and adolescents under 18 years of age

Patients should not receive growth factor treatment such as G-CSF for 2 weeks prior to Zevalin treatment as well as for 2 weeks following completion of the regimen because of the potential sensitivity of rapidly dividing myeloid cells to radiation.

Special caution is required with respect to bone marrow depletion.

Severe mucocutaneous reactions including Stevens-Johnson Syndrome with fatal outcome, have rarely been reported

in association with the Zevalin therapeutic regimen, which includes rituximab and radiolabelled Zevalin.

The onset of the reactions varied from days to months. Patients experiencing a mucocutaneous reaction should not receive any further component of the Zevalin regimen.

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

Severe infusion reactions may occur during or following rituximab infusion, which may be associated with chest pain, cardiogenic shock, myocardial infarction, pulmonary edema, ventricular fibrillation, apnea, bronchospasm, dyspnea, hypoxia, angioneurotic edema, flushing, hypotension, ARDS, and lung infiltration. Infusion-related reactions due to Zevalin are less common and less severe.

Anaphylactic and other hypersensitivity reactions following Zevalin administration have been reported in less than 1% of patients following the intravenous administration of proteins to patients. Medicinal products 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 administration of rituximab and radiolabelled Zevalin.

After use of Zevalin, patients should generally be tested for HAMA before any further treatment with mouse derived proteins.

Long-term animal studies on the effect on fertility and reproductive function have not been performed. Due to the nature of the compound, females of child-bearing potential, as well as males, should use effective contraceptive measures during treatment with Zevalin and for 12 months afterwards.

The safety of immunization with any vaccine, particularly live viral vaccines, following therapy with Zevalin has not been studied. The ability to generate a primary or anamnestic humoral response to any vaccine has also not been studied.

No data are available on patients with CNS-lymphoma as those patients were not included in clinical studies.

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 should be immediately terminated and restarted in another vein.

#### 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.

#### 4.6. Pregnancy and Lactation

Animal reproduction studies were not conducted with ibritumomab tiuxetan. Since IgG is known to pass the placenta and because of the concomitant use of radiation, Zevalin must not be used during pregnancy. Pregnancy must be excluded before the start of treatment in women. Females of child-bearing potential as well as males should use effective contraceptive methods during treatment with Zevalin and for 12 months afterwards. When it is necessary to administer Zevalin to women of child-bearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise and alternative therapies which do not involve ionizing radiation should be then considered.

It is not known whether ibritumomab tiuxetan is excreted in human milk. Because human IgG is excreted in human milk and because the potential for absorption and immunosuppression in the infant is unknown, women must discontinue breast-feeding.

#### 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

The radiation dose resulting from therapeutic exposure may result in secondary malignancies and in development of hereditary defects. It is necessary to ensure that the risks of the radiation are less than from the disease itself.

The majority of patients may be expected to experience adverse reactions.

The frequencies of the adverse reactions reported below (very common ≥1/10; common ≥1/100 <1/10; uncommon ≥1/1,000 <1/100; rare ≥1/10,000 <1/1,000; very rare <1/10,000) are based on clinical trial data. Adverse drug reactions deriving from post-marketing experience are described separately. The adverse drug reactions are at least possibly related to the Zevalin therapeutic regimen which includes rituximab and radiolabelled Zevalin.

##### Anaphylactic reactions and hypersensitivity

Anaphylactic and other hypersensitivity reactions have been reported in fewer than 1% of patients following the intravenous administration of proteins to patients. Medicinal products 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 administration of Zevalin.

##### Hematological adverse reactions

Hematological toxicity has been very commonly observed in clinical trials, and is dose-limiting. 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 were 20 days and 35 days for Grade 3 or 4 thrombocytopenia and 20 days and 28 days for Grade 3 or 4 neutropenia.

##### Infections

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.

##### Secondary malignancies

Myelodysplasia / Acute Myeloid Leukemia (AML) has been reported in five out of 211 patients assigned to treatment with Zevalin. The risk of developing secondary myelodysplasia or leukaemia following therapy with alkylating agents is well known. Since all of these patients were pre-treated with alkylating agents, available results provide insufficient data on whether Zevalin contributes to an increased risk of myelodysplasia, or on the extent of risk.

<b>System Organ Class (MedDRA)</b>	<b>Very common (≥1/10)</b>	<b>Common (≥1/100, &lt;1/10)</b>	<b>Uncommon (≥1/1,000, &lt;1/100)</b>	<b>Rare (≥1/10,000, &lt;1/1,000)</b>
<b>Infections and Infestations</b>		Infection*, Sepsis*, Pneumonia*, Urinary tract infection, Oral moniliasis		
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>		Tumour pain, Myelodysplastic syndrome/ Acute myeloid leukemia*		Meningioma
<b>Blood and Lymphatic System Disorders</b>	Thrombocytopenia, Leukocytopenia, Neutropenia, Anemia*	Febrile neutropenia, Pancytopenia*, Lymphocytopenia		
<b>Immune System Disorders</b>		Hypersensitivity reaction		
<b>Metabolism and Nutrition Disorders</b>		Anorexia		
<b>Psychiatric Disorders</b>		Anxiety, Insomnia		
<b>Nervous System Disorders</b>		Dizziness, Headache		
<b>Cardiac Disorders</b>			Tachycardia	
<b>Vascular Disorders</b>		Hemorrhage while thrombocytopenic*		Intracranial hemorrhage while thrombocytopenic*
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		Cough, Rhinitis		
<b>Gastrointestinal Disorders</b>	Nausea	Vomiting, Abdominal pain, Diarrhea, Dyspepsia, Throat irritation, Constipation		
<b>Skin and Subcutaneous Tissue Disorders</b>		Pruritus, Rash		
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>		Arthralgia, Myalgia, Back pain, Neck pain		
<b>General Disorders and Administration Site Conditions</b>	Asthenia, Pyrexia, Rigors	Pain, Flu syndrome, Malaise, Peripheral Edema, Sweating increased		
* fatal outcome has been observed either in clinical trials or in post-marketing experience.				

##### Incidence of adverse reactions by System Organ Class

The table below reports adverse reactions by MedDRA System Organ Class:

In total, infections of any cause occurred very commonly but are listed in the table under the specifically reported term.

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 9.1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Disease progression is the natural evolution of the underlying disease.

In the study with 204 patients receiving Zevalin as consolidation following first-line remission induction, infections were observed more frequently than as described in the below table (very common).

In addition, the following adverse drug reactions were observed in this study:

- MedDRA SOC General disorders and administration site conditions: fatigue (very common)
- MedDRA SOC Vascular disorders: petechia (very common), hypertension (common), hypotension (common)
- MedDRA SOC Reproductive system and breast disorders: amenorrhea (common)

##### Post-marketing experience

##### *MedDRA SOC Skin and subcutaneous tissue disorders*

Mucocutaneous reaction, including Stevens-Johnson Syndrome with fatal outcome has been rarely reported in post-marketing experience.

##### *MedDRA SOC General disorders and administration site conditions*

Isolated reports of extravasation with subsequent infusion site reaction, like dermatitis, desquamation and site ulcer have been received.

Isolated reports have been received showing that Zevalin-associated radiation might cause damage to lymphoma-surrounding tissue and complications due to lymphoma swelling.

Because the Zevalin therapeutic regimen includes the use of rituximab, see also the prescribing information of rituximab.

#### 4.9. Overdose

Overdose as high as 19.2 MBq/kg of <sup>90</sup>Y]-radiolabelled Zevalin occurred in clinical trials. Expected hematological toxicity was observed, comprising 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 <sup>90</sup>Y]-radiolabelled Zevalin overdosage. Treatment consists of discontinuation of Zevalin and supportive therapy, which may include growth factors. If available, autologous stem cell support should be administered to manage hematological toxicity.

For accidental administration of the pure radio-pharmaceutical precursor product yttrium-90, refer to the product information of yttrium-90.

## 5. Pharmacological Properties

### 5.1. Pharmacodynamic Properties

Pharmacotherapeutic group:

Various therapeutic radiopharmaceuticals

ATC code: V10XX02.

Ibritumomab tiuxetan is a recombinant murine IgG<sub>1</sub> 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 internalize on antibody binding. 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.

<sup>90</sup>Y]-radiolabelled Zevalin binds specifically to B-cells, including CD20-expressing 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.

Rituximab pre-treatment is necessary to clear circulating B-cells, enabling Zevalin to deliver radiation more specifically to the lymphomas. Rituximab is administered in a reduced dose when compared with the approved monotherapy.

Treatment with <sup>90</sup>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 count of B-cells were within normal range within 9 months after treatment.

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 section 4.2). The efficacy and toxicity of a variation of the Zevalin therapeutic regimen employing a reduced activity of <sup>90</sup>Y]-Zevalin 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<sup>3</sup>).

**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 to treatment with rituximab. The trial was conducted in 143 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<sup>2</sup> weekly times 4 doses. The primary efficacy endpoint of the study was to determine the ORR using the IWRC (see Table 1). 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 1.**  
**Summary of Efficacy Data<sup>1</sup>**

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

<sup>1</sup> IWRC: International workshop response criteria

<sup>2</sup> CRu: Unconfirmed complete response

<sup>3</sup> Estimated with observed range

<sup>4</sup> Duration of response: Interval from the onset of response to disease progression

<sup>5</sup> "+" indicates an ongoing response

<sup>6</sup> 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<sup>3</sup>). 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; platelet count <100,000 cells/mm<sup>3</sup>; or neutrophil count <1,500 cells/mm<sup>3</sup>. In this study, a modification of the Zevalin therapeutic regimen with a lower [<sup>90</sup>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 hematologic toxicity (see section 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-positive grade 1 or 2 follicular lymphoma; stage III or IV at diagnosis; normal peripheral blood cell count; <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<sup>2</sup> 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. With a median follow-up of 2.9 years, the median progression free survival (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 IV infusions of 250 mg/m<sup>2</sup> rituximab followed by intravenous injections of 15 MBq/kg of [<sup>90</sup>Y]-radiolabelled Zevalin, the median serum effective half-life of [<sup>90</sup>Y]-radiolabelled Zevalin was 28 h.

As yttrium-90 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 yttrium-90 occurs in a radius of 5 mm around the isotope.

## 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 [<sup>90</sup>Y]- or [<sup>111</sup>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 (see sections 4.4 and 4.6).

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

## 5.4. Radiation 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 ( $\chi_{90}$ ) by yttrium-90 in tissue is 5 mm.

Analyses of estimated radiation absorbed dose were carried out using quantitative imaging with the gamma-emitter [<sup>111</sup>In]-radiolabelled Zevalin, blood sampling, and the MIRDOSE3 software program. The imaging dose of [<sup>111</sup>In]-radiolabelled Zevalin was always given immediately following an infusion with rituximab at 250 mg/m<sup>2</sup> to deplete peripheral CD20+ cells and to optimize biodistribution. Following administration of [<sup>111</sup>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 [<sup>111</sup>In]-radiolabelled Zevalin, the estimated radiation dosimetry for individual organs following administration of [<sup>90</sup>Y]-radiolabelled Zevalin at activities of 15 MBq/kg and 11 MBq/kg was calculated according to Medical Internal Radiation Dosimetry (MIRD) (Table 2). The estimated radiation-absorbed doses to normal organs were substantially below recognized upper safety limits. Individual patient dosimetry results were not predictive for [<sup>90</sup>Y]-radiolabelled Zevalin toxicity.

**Table 2.**  
**Estimated Radiation Absorbed Doses From [<sup>90</sup>Y]-Zevalin**

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

<sup>1</sup> Organ region of interest

<sup>2</sup> Sacrum region of interest

<sup>3</sup> Whole body region of interest

## 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:

Human albumin solution

Sodium chloride

Disodium phosphate dodecahydrate

Sodium hydroxide

Potassium dihydrogen phosphate

Potassium chloride

Pentetic acid

Hydrochloric acid, diluted

Water for injections

### 6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products.

No incompatibilities have been observed between Zevalin and infusion sets.

### 6.3. Shelf-life

4 years.

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

### 6.4. Special Precautions for Storage

Store at 2°C - 8°C (in a refrigerator).

Do not freeze.

Store in the original package in order to protect from light.

After radiolabelling: Store at 2°C - 8°C (in a refrigerator) and protect from light.

Storage should be in accordance with national regulations for radioactive materials.

### 6.5. Nature and Contents of Container

2 ml of solution of ibritumomab tiuxetan in a vial (type I glass) with a rubber stopper (teflon-lined bromobutyl).

2 ml of solution of sodium acetate solution in a vial (type I glass) with a rubber stopper (teflon-lined bromobutyl).

10 ml of formulation buffer in a vial (type I glass) with a rubber stopper (teflon-lined bromobutyl).

10 ml empty reaction vial (type I glass) with a rubber stopper (teflon-lined bromobutyl).

Pack size of 1 kit

### 6.6. Instructions for Use and Handling and Disposal

#### • Preparation

Read complete directions thoroughly before starting the preparation procedure.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and during the determination of radiochemical purity of [<sup>90</sup>Y]-radiolabelled Zevalin.

#### • Radiation protection

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

#### • Disposal

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

#### 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

Radiochemical 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 [<sup>90</sup>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 five-minute incubation period, add the formulation buffer to the reaction vial terminating incubation.

Immediately prior to this addition withdraw an equal volume of air from the reaction vial in order to normalise pressure. Gently add the formulation buffer down the side of the reaction vial. Do not foam, shake, or agitate the mixture.

#### Step 5: Assay the [<sup>90</sup>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 [<sup>90</sup>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 radio-incorporation

The radioincorporation assay for radiochemical purity, is performed by Instant Thin Layer Chromatography (ITLC) and should 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 silica gel (SG) plates Art. No. 61885, Gelman Sciences, Ann Arbor, Michigan, USA or equivalent; dimensions: 0.5 cm x 6 cm, origin: 1.4 cm, cut line: 3.5 cm, solvent front: 5.4 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 0.9% sodium chloride solution to developing chamber assuring the liquid will not touch the 1.4 cm origin mark on the ITLC strip.
- 2) Using a 1 ml insulin syringe with a 25- to 26-G needle, place a hanging drop (7-10 µl) of [<sup>90</sup>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 [<sup>90</sup>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 should 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 = 
$$\frac{\text{net CPM bottom half} \times 100}{\text{net CPM top half} + \text{net CPM bottom half}}$$
- 7) If the average radiochemical purity is less than 95%, the preparation should not be administered.

#### Manufacturer:

Bayer Schering Pharma AG, Berlin, Germany

#### Registration Holder:

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