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 IgG1 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 [90Y] 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.

[90Y]-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.

[90Y]-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

[90Y]-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 [90Y]-radiolabelled Zevalin solution in the following order:

Day 1: intravenous infusion of 250 mg/m2 rituximab.

Day 7 or 8 or 9:

- intravenous infusion of 250 mg/m2 rituximab shortly (within 4 hours) before administration of [90Y]-radiolabelled Zevalin solution.
- 10 minute intravenous infusion of [90Y]-radiolabelled Zevalin solution.

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

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

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

- patients with ≥ 150,000 platelets/mm3: 15 MBq/kg body weight.
- patients with 100,000-150,000 platelets/mm3: 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 [90Y]-radiolabelled Zevalin solution must be prepared according to section 12.

Before administration to the patient, the percent radioincorporation of the prepared [90Y] 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.

[90Y]-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').

[90Y]-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/mm3 (monotherapy) and <150,000/mm3 (consolidation treatment)
- neutrophil counts < 1,500/mm3
- 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 [90Y]-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 [90Y]-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 [90Y]-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			
Psychiatric disorders		Anxiety, Insomnia			

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Not known
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			

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Not known
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 [90Y]-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 IgG1 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.

[90Y]-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 [90Y] 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 [90Y]-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 [90Y] 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/mm3).

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/m2 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	Zevalin therapeutic	Rituximab

	regimen N = 54	regimen N = 73	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/mm3). 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/mm3; or neutrophil count <1,500 cells/mm3. In this study, a modification of the Zevalin therapeutic regimen with a lower [90Y]-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/m2 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/m2 rituximab followed by intravenous injections of 15 MBq/kg of [90Y]-radiolabelled Zevalin, the median serum effective half-life of ibritumomab tiuxetan [90Y] was 28 h.

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

In clinical studies, the [90Y]-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 [90Y]-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 [90Y]- or [111In] 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 (90Y) 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

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(S)

PLGB 53745/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/01/2021

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 (χ90) by yttrium-90 in tissue is 5 mm.

Analyses of estimated radiation absorbed dose were carried out using quantitative imaging with the gamma-emitter [111In]-radiolabelled Zevalin, blood sampling, and the MIRDOSE3 software program. The imaging dose of [111In]-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 [111In]-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 [111In]-radiolabelled Zevalin, the estimated radiation dosimetry for individual organs following administration of [90Y]-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 [90Y]-radiolabelled Zevalin toxicity.

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

	[^{90}Y]-Zevalin mGy/MBq	
Organ	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

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

Organ	[^{90}Y]-Zevalin mGy/MBq	
	Median	Range
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 [90Y]-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 [90Y]-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 [90Y]-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 [90Y] 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 [90Y]-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 [90Y]-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 = $\frac{\text{net CPM bottom half}}{} \times 100$

net CPM top half + net CPM bottom half

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.