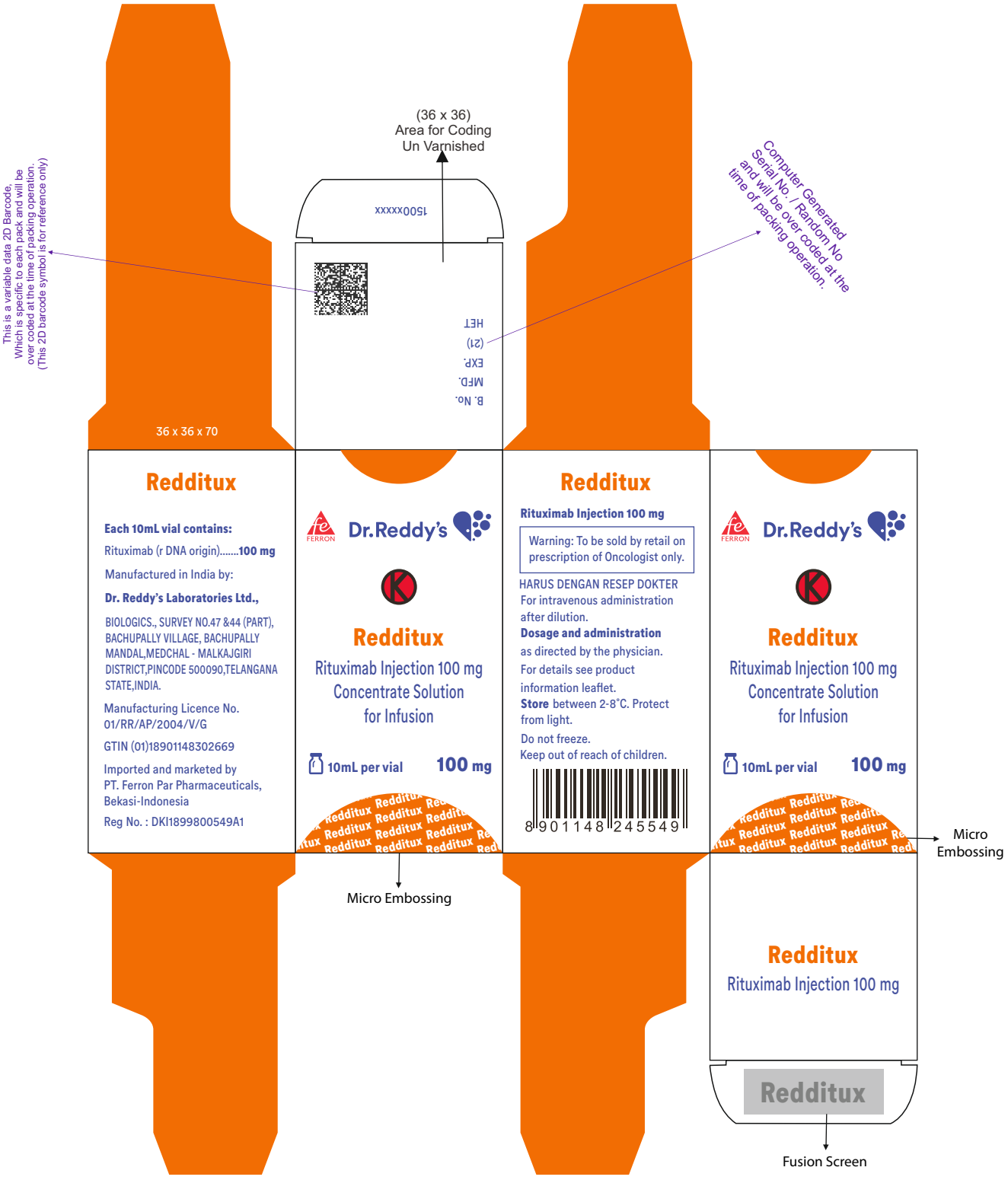


PANTONE CODES	
	2091
	Orange 021 C
	032
	185 C
	Black C

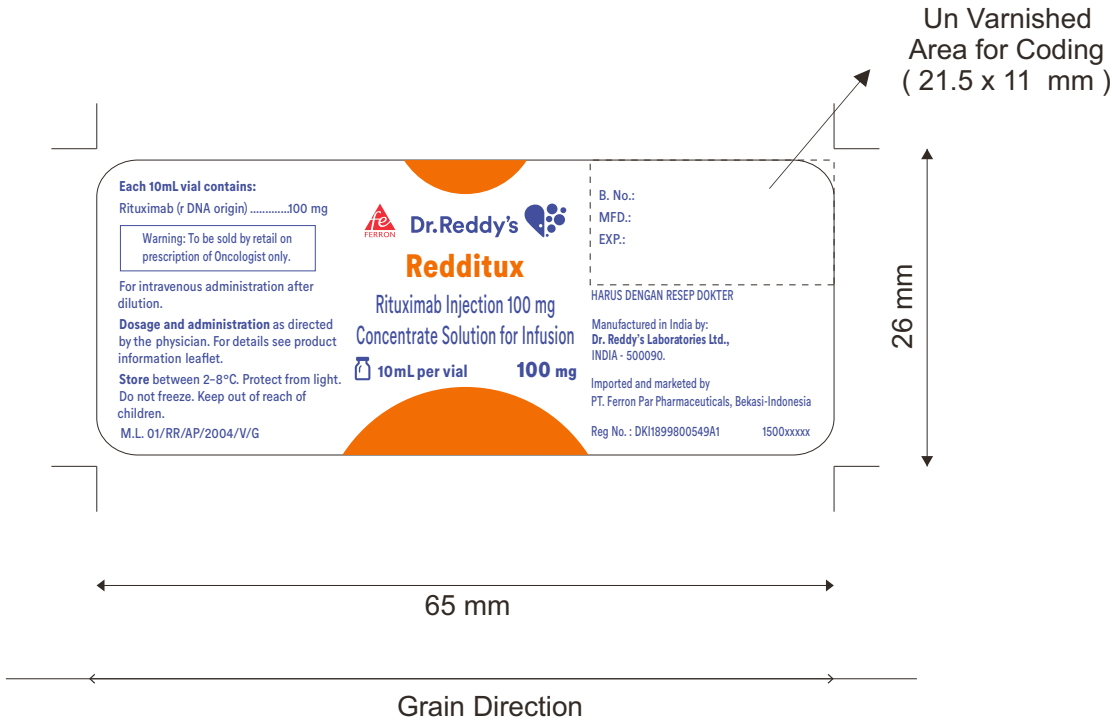
UNIQUE designers

Version No: 00

Date: 31.08.2023

Change History:
New Artwork (31.08.2023)

DISETUJUI OLEH BPOM : 20 Februari 2025 ID: EREG100240VR12500006



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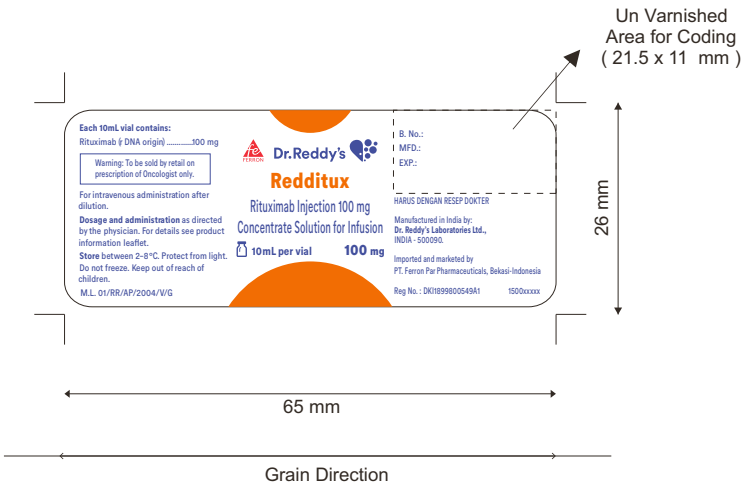

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UNIQUE designers	PANTONE CODES
	2091
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DISETUJUI OLEH BPOM : 20 Februari 2025 ID: EREG100240VR12500006

FERRON

Dr.Reddy's

REDDITUX
(Rituximab)

1. NAME OF THE MEDICINAL PRODUCT
Redditux 10mg/ml concentrate for solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Redditux	Redditux
Each 10 ml, vial contains Rituximab (r- DNA origin) 100 mg	Each 50 ml, vial contains Rituximab (r- DNA origin) 500 mg

Active substance: Rituximab (r-DNA origin)

Rituximab is a genetically engineered mouse-human chimeric monoclonal antibody representing a glycosylated immunoglobulin that contains murine light and heavy chain variable regions and human IgG1 constant region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatographies, including specific viral inactivation and removal procedures.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear to opalescent, colourless to yellowish liquid.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Non-Hodgkin's lymphoma (NHL)
Redditux is indicated for the treatment of patients with relapsed or chemoresistant low-grade or follicular, CD 20-positive, B-cell non-Hodgkin's lymphomas.
Redditux is indicated for treatment of patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy.
Redditux is indicated for patients with follicular lymphoma as maintenance treatment after induction therapy.
Redditux is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.
Chronic lymphocytic leukaemia (CLL)
Redditux in combination with fludarabine and cyclophosphamide is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
General
The prepared Redditux solution should be administered as an IV infusion through a dedicated line. Do not administer the prepared infusion solutions as an IV push or bolus.
Redditux infusions should be administered in an environment where full resuscitation facility are immediately available, and under the close supervision of an experienced physician.
Patients should be closely monitored for the onset of cytokine release syndrome (see section *Special warning and precaution for use*). Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumor lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis.
Mild or moderate infusion-related reactions (section *Undesirable effects*) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.
Standard dosage
Low-grade or Follicular Non-Hodgkin's Lymphoma:
Intravenous formulations
Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be administered before each infusion of Redditux.
Premedication with glucocorticoids should be considered if rituximab is not given in combination with steroid-containing chemotherapy.
Redditux should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m² body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after IV administration of the glucocorticoid component of CHOP. Safety and efficacy of rituximab have not been established in combination with other chemotherapies.
Dosage adjustments during treatment
No dose reductions of Redditux are recommended. When Redditux is given in combination with CHOP or CVP chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.
First infusion:
The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
Subsequent IV infusions:
Subsequent doses of Redditux can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.
Chronic lymphocytic leukaemia
Intravenous Formulations only
Premedication consisting of an analgesic / anti-pyretic (e.g. paracetamol) and an antihistaminic drug (e.g. Diphenhydramine) should always be administered before each infusion of Redditux.
Premedication with glucocorticoids should also be considered, particularly if Redditux IV is not given in combination with steroid-containing chemotherapy.
Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10⁹/L it is recommended to administer prednisone/prednisolone 100 mg intravenously shortly before infusion with rituximab to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.
The recommended dosage of Redditux in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m² body surface area administered on day 1 of the first treatment cycle followed by 500 mg/m² body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after Redditux infusion.
Dosage adjustments during treatment
No dose reductions of Redditux are recommended. When Redditux is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.
First infusion:
The recommended initial infusion rate is 50 mg/hr; subsequently after the first 30 minutes, it the rate can be escalated in 50 mg/hr increments every 30 minutes infusion, to a maximum of 400 mg/hr.
Subsequent infusions :
Subsequent infusion of Redditux can be started at a rate of of 100 mg/hr, and increased by 100 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
Special Dosage Instructions
Children and adolescents
Rituximab is not recommended for use in children due to lack of data on safety and efficacy.
Elderly
No dose adjustment is required in elderly patients (aged >65 years).

4.3 Contraindications
Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Hypersensitivity to the active substance or to any of the excipients or to murine proteins.
Active, severe infections (see section special warnings and precautions for use).
Patients in a severely immunocompromised state

4.4 Special warnings and precautions for use
Progressive Multifocal Leukoencephalopathy
All patients treated with Rituximab for granulomatosis with polyangiitis and microscopic polyangiitis must be given the patient alert card with each infusion. The alert card contains important safety information for patients regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML).
Use of rituximab may be associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). Very rare cases of fatal PML have been reported following use of rituximab. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a Neurologist should be considered as clinically indicated.
If any doubt exists, further evaluation, including MRI scan preferably with contrast, CSF testing for JC Viral DNA and repeat neurological assessments, should be considered.
The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.
If a patient develops PML the dosing of rituximab must be permanently discontinued.
Following resumption of the immune system in immunocompromised patients with PML, stabilization or improved outcome has been seen. It remains unknown if early detection of PML and suspension of rituximab therapy may lead to similar stabilization or improved outcome.
Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Infusion related reactions
Rituximab is associated with infusion related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.
This set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of Rituximab and can be observed with both formulations.
Severe infusion related reactions with fatal outcome have been reported during post-marketing use of the rituximab intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first Rituximab IV infusion. They were characterized by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms.
Patients with a high tumour burden or with a high number (≥25 x 10⁹/l) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10⁹/L.
Severe cytokine release syndrome is characterized by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of **tumour lysis syndrome** such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated Lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. Severe, including fatal, renal toxicity can occur after rituximab administered in patients with NHL. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests itself within one or two hours of initiating

the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section posology and method of administration) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.
Infusion related adverse reactions of all kinds have been observed in 77% of patients treated with rituximab (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients) see section undesirable effects. These symptoms are usually reversible with interruption of rituximab infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required.
Please see cytokine release syndrome above for severe reactions.
Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of rituximab. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.
Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.
Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the rituximab infusion.
Cardiac disorders
Angina pectoris or cardiac arrhythmias such as atrial flutter and fibrillation heart failure and/or myocardial infarction have occurred in patients treated with rituximab. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.
Haematological studies
Although rituximab is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10⁹/l and/or platelet counts < 75 x 10⁹/l as clinical experience in this population is limited. Rituximab has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.
Regular full blood counts, including neutrophil and platelet counts, should be performed during rituximab therapy.
Infections
Serious infections, including fatalities, can occur during therapy with rituximab (see section undesirable effects). Rituximab should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section Contraindications).
Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infections (see section undesirable effects).
Cases of hepatitis B reactivation have been reported in subjects receiving rituximab including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that rituximab treatment may also worsen the outcome of primary hepatitis B infections. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.
Very rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported during post-marketing use of Rituximab in NHL and CLL (see section undesirable effects). The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.
Immunizations
The safety of immunization with live viral vaccines, following rituximab therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with rituximab may receive non-live vaccinations. However with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received rituximab monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for ×2-fold increase in antibody titer). For CLL patients Similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.
Mean pre-therapeutic antibody titers against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with rituximab.
Skin reactions
Severe mucocutaneous such as Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens - Johnson syndrome, some with fatal outcome, have been reported (see section undesirable effects). In case of such an event, treatment should be permanently discontinued.

4.5 Interaction with other medicinal products and other forms of interaction
Currently, there are limited data on possible drug interactions with rituximab.
In CLL patients, co-administration with rituximab did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of rituximab.
Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituximab is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue Rituximab in patients with a rising serum creatinine or oliguria
Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

4.6 Fertility, Pregnancy and lactation
Pregnancy
IgG immunoglobulins are known to cross the placental barrier. B cell levels in human neonates following maternal exposure to rituximab have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk.
Contraception in males and females
Due to the long retention time of Rituximab in B cell depleted patients, women in childbearing potential should use effective contraceptive methods during and for 12 months following treatment with Rituximab.
Lactation
Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with rituximab and for 12 months following rituximab treatment.
Fertility
Animal studies did not reveal deleterious effects of rituximab on reproductive organs.

4.7 Effects on ability to drive and use machines
No studies on the effects of rituximab on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that rituximab would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
The overall safety profile of rituximab in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with rituximab monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.
The most frequently observed adverse drug reactions (ADRs) in patients receiving rituximab were infusion-related reactions, which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of rituximab.
Infectious events (predominantly bacterial and viral) occurred in approximately 30-65 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trial in patients with CLL.
The most frequent reported or observed serious adverse drug reactions were:
- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), see section special warnings and precautions for use.
- Infections, see section special warnings and precautions for use.
- Cardiovascular events, see section special warnings and precautions for use.

Other serious ADRs reported include hepatitis B reactivation and PML (see section special warnings and precautions for use).
The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised in the tables below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as 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) and very rare (<1/10,000). The ADRs identified only post-marketing surveillance, and for which a frequency could not be estimated, are listed under "unknown".
Table 1: ADRs reported in clinical trials or during post-marketing surveillance in patients with NHL and CLL disease treated with rituximab monotherapy/maintenance or in combination with chemotherapy

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Unknown [4]
Infections and infestations	bacterial infections, viral infections, [a]bronchitis	sepsis, [b]pneumonia, [c]febrile infection, [d]herpes zoster, [e]respiratory tract infection, fungal infections, infections of unknown aetiology, [f]acute bronchitis, [g]sinusitis, hepatitis B [1]		serious viral infection,[2] pneumocystis jiroveci	PML	
Blood and lymphatic system disorders	neutropenia, leucopenia, [h]febrile neutropenia, [i]thrombocytopenia, anaemia	[j]panicytopenia, [k]thrombocytopenia, alopecia	Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		Transient increase in serum IgM levels [3]	Late neutropenia[3]
Immune system disorders	infusion related reactions [4], angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome [4], cytokine release syndrome [4], serum sickness,	Infusion – related acute reversible thrombocytopenia [4]
Metabolism and nutrition disorders	hyperglycaemia, decreased [l]appetite [4]	anorexia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness			
Nervous system disorders	Headache	Peripheral neuropathy, paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		facial nerve palsy [3]	Cranial neuropathy, loss of other senses [3]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss [3]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss [3]

FERRON

Dr.Reddy's

REDDITUX
(Rituximab)

Baca seluruh isi leaflet dengan cermat sebelum Anda menggunakan obat ini.
- Simpan leaflet ini, mungkin suatu saat Anda perlu membacanya kembali.
- Apabila Anda memiliki pertanyaan mengenai penggunaan obat ini, tanyakan pada dokter atau apoteker.
- Obat ini hanya diperuntukkan untuk Anda. Tidak boleh memberikan obat ini pada orang lain karena akan membahayakan, meskipun orang tersebut memiliki gejala yang sama seperti Anda.
- Apabila muncul efek samping, segera hubungi dokter atau apoteker. Termasuk efek samping yang tidak tercantum di dalam leaflet.

Apakah Redditux itu?
Redditux mengandung antibodi (rituximab) yang merupakan suatu jenis protein. *Rituximab* berikatan di permukaan suatu tipe sel darah putih, yaitu limfosit B. Saat *rituximab* berikatan dengan permukaan sel, akan menyebabkan kematian sel.

Apakah kegunaannya Redditux?
Redditux dapat digunakan untuk pengobatan dari 2 kondisi yang berbeda. Dokter Anda mungkin akan meresepkan Redditux untuk pengobatan:
- *Non-Hodgkin's lymphoma (NHL)*
  Non-Hodgkin's lymphoma adalah penyakit pada sistem limfatik. Limfosit B dikaitkan sebagai penyebab dari gejala yang Anda rasakan.
  Redditux dapat digunakan secara tunggal maupun kombinasi dengan obat lain sesuai dengan resep dokter untuk mendorong penyembuhan penyakit Anda. Redditux dapat digunakan secara kontinu (terapi pemeliharaan) selama 2 tahun pada pasien yang responsif terhadap terapi.
- *Chronic lymphocytic leukemia*
  Chronic lymphocytic leukemia (CLL) merupakan bentuk paling umum dari leukemia pada orang dewasa. CLL mempengaruhi limfosit khusus, yaitu sel B, yang berasal dari sumsum tulang belakang dan kemudian berkembang di node limfa. Pasien dengan CLL memiliki banyak limfosit yang abnormal, yang terakumulasi terutama pada sumsum tulang belakang dan darah. Penyebaran dari limfosit abnormal inilah yang menyebabkan timbulnya gejala yang Anda rasakan. Redditux yang dikombinasikan dengan kemoterapi akan menghancurkan sel tersebut dan secara bertahap akan dihilangkan dari tubuh melalui proses biologi.

Bagaimana menggunakan Redditux?
Redditux merupakan infus (drip) yang diberikan secara langsung ke pembuluh darah vena. Saat pemberian Redditux Anda akan dipantau oleh tenaga kesehatan profesional jika Anda mengalami efek samping selama pemberian infus. Sebelum pemberian infus, Anda akan diberikan obat-obatan untuk mencegah atau mengurangi kemungkinan reaksi yang ditimbulkan oleh Redditux.
- **Jika Anda sedang diterapi untuk NHL**
  Jika Anda diterapi dengan Redditux saja, Anda akan menerima infus setiap minggu dengan total 4 infus (hari ke-1, 8, 15 dan 22), sehingga lama pengobatan paling tidak selama 22 hari. Pengulangan terapi dengan Redditux mungkin dilakukan. Jika Anda diterapi dengan Redditux dalam kombinasi dengan obat lain, Anda akan menerima infus Redditux pada hari yang bersamaan dengan obat lainnya, yang biasanya diberikan 8 kali dalam interval waktu setiap 3 minggu. Jika Anda memberikan respon terhadap terapi maka Anda akan menerima infus Redditux sebagai terapi kontinu (terapi pemeliharaan). Anda akan menerima satu infus Redditux setiap 3 bulan sekali dalam waktu 2 tahun. Dokter Anda akan menyesuaikan jumlah infus, bergantung pada penyakit Anda.
- **Jika Anda sedang diterapi untuk CLL**
  Saat Anda sarapi dengan Redditux dalam kombinasi dengan kemoterapi, Anda akan menerima infus Redditux pada hari ke-1 siklus pertama kemudian hari pertama pada setiap siklus selama total 6 siklus. Setiap siklus memiliki durasi 28 hari. Kemoterapi harus diberikan setelah infus Redditux. Dokter Anda akan memutuskan apakah Anda harus menerima terapi tambahan secara bersamaan.

Bagaimanakah jika Anda lupa menggunakan Redditux?
- Dokter atau perawat Anda akan memberikan instruksi saat pemberian obat, sehingga tidak mungkin terlewat pemberian obat yang sudah direspkan. Namun, apabila Anda berpikir Anda melewatkan pemberian obat, beritahu dokter atau apoteker Anda sesegera mungkin. Jika Anda ragu akan apa yang harus Anda lakukan, bertanyalah pada dokter Anda.

Beberapa hal yang perlu diperhatikan bila menggunakan Redditux:
Sebelum menggunakan Redditux
Anda tidak boleh menggunakan Redditux bila:
- Anda memiliki riwayat alergi terhadap *rituximab*, kandungan protein serupa atau komponen lain yang terkandung dalam lanzan.
- Anda memiliki infeksi aktif yang berat. Jika Anda tidak yakin, Anda harus memberitahukan dokter Anda yang akan memberikan informasi terkait hal tersebut.

Beritahukan dokter Anda sebelum menggunakan Redditux bila:
- Anda sedang mengalami infeksi hepatitis atau pernah mendenta hepatitis. Pada beberapa kasus, pasien yang memiliki hepatitis B dapat terserang hepatitis kembali, yang dapat berakibat fatal (sangat jarang terjadi). Pasien dengan riwayat infeksi hepatitis B harus melakukan pemeriksaan gejala hepatitis B aktif dengan hati-hati.
- Anda mengonsumsi obat-obatan untuk menurunkan tekanan darah tinggi. Anda mungkin akan diminta untuk tidak mengonsumsi obat tersebut 12 jam sebelum melakukan infus Redditux. Beberapa orang mengalami penurunan tekanan darah selama infus.
- Anda memiliki riwayat penyakit jantung (seperti angina, palpitasi atau gagal jantung) atau riwayat masalah pernapasan. Dokter Anda mungkin akan memberikan perhatian khusus kepada Anda selama penggunaan Redditux (dalam kasus di atas).

Perhatian khusus menggunakan Redditux
- Beritahukan dokter Anda bila Anda mengonsumsi atau sebelumnya pernah mengonsumsi obat yang dapat mempengaruhi sistem imun, seperti kemoterapi atau obat-obatan penurun daya tahan tubuh.
- Bila Anda memerlukan vaksinasi dalam waktu dekat, termasuk vaksin yang dibutuhkan untuk bepergian ke negara lain. Beberapa vaksin tidak boleh diberikan pada waktu yang bersamaan atau dalam beberapa bulan setelah pemberian Redditux. Dokter Anda akan melakukan pengecekan apakah Anda perlu mendapatkan vaksin sebelum pemberian Redditux.

Sampai saat ini, belum ada informasi yang cukup mengenai penggunaan Redditux pada anak-anak dan remaja; jika Anda di bawah umur 18 tahun, Anda atau orangtua/penanggungjawab Anda harus melakukan konsultasi kepada dokter apakah Redditux merupakan terapi yang tepat.

Menggunakan obat lain
Sebelum memulai terapi, pastikan dokter Anda mengetahui obat-obatan yang sedang Anda konsumsi atau yang baru-baru ini Anda konsumsi (termasuk yang Anda beli sendiri dari apotek, supermarket atau toko obat). Hal ini sangat penting karena jika menggunakan lebih dari satu obat pada saat yang bersamaan karena dapat menguatkan atau melemahkan efek obat-obat tersebut. Redditux sebaiknya tidak digunakan bersama obat lain kecuali dokter Anda memberitahukan bahwa obat tersebut aman digunakan.
Kehamilan dan menyusui
Anda harus memberitahukan dokter Anda jika Anda sedang hamil, jika Anda berpikir Anda hamil atau jika Anda sedang merencanakan kehamilan. Hal ini karena Redditux merupakan antibodi dan dapat melewati masuk plasenta serta dapat mempengaruhi bayi Anda.
Jika Anda wanita yang berpotensi untuk hamil, Anda harus menggunakan metode kontrasepsi yang efektif dalam mengontrol kehamilan selama dan sampai 12 bulan setelah terapi terakhir dengan Redditux.
Redditux juga dapat terkandung dalam air susu ibu dan Anda tidak boleh menyusui bayi Anda selama terapi serta selama 12 bulan setelah terapi terakhir dengan Redditux.
Mengemudi dan menggoperasikan mesin
Tidak diketahui bagaimana Redditux mempengaruhi kemampuan Anda dalam mengemudi kendaraan maupun menggoperasikan mesin.

Apa saja efek yang tidak diinginkan yang mungkin terjadi?
Seperti semua obat-obatan, Redditux dapat menimbulkan efek samping, meski tidak terjadi pada semua orang. Umumnya, efek samping Redditux bersifat ringan sampai sedang tapi bisa menjadi serius dan memutuhkan pengobatan. Beberapa dari reaksi berikut dapat menjadi fatal namun jarang terjadi.
Reaksi setelah infus
Selama atau dalam 2 jam pertama setelah pemberian infus pertama, Anda dapat mengalami demam, menggigil dan gemetar. Beberapa pasien ada yang mengalami meliputi, gatal, nyeri, lelah, sakit kepala, kesulitan bernapas, pembengkakan lidah atau tenggorokan, hidung meran atau gatal, muntah, kemerahan atau jantung berdebar. Jika ada memiliki riwayat sakit jantung atau angina, reaksi ini dapat memburuk.

Beritahukan kepada petugas yang memberikan infus dengan segera jika Anda mengalami gejala di atas, sehingga dapat dikurangi kecepatan infusnya atau dihentikan sejenak. Anda mungkin membutuhkan terapi tambahan seperti antihistamin atau *paracetamol*. Saat gejala tersebut hilang atau membaik, infus dapat dilanjutkan. Reaksi ini kecil kemungkinannya untuk terjadi kembali setelah infus kedua.
Infeksi
Beritahukan dokter Anda jika setelah terapi Redditux Anda mengalami gejala infeksi, seperti demam, batuk, radang tenggorokan, terasa sakit atau panas saat buang air kecil, atau mulai merasa lemah atau tidak sehat. Anda dapat lebih mudah mengalami infeksi setelah terapi Redditux. Sering kali merupakan gejala flu, namun ada beberapa kasus terjadi infeksi saluran kemih atau pneumonia. Beberapa pasien yang menggunakan Redditux sangat jarang mengalami infeksi otak yang serius, yang dapat menjadi fatal.

Beritahukan dokter Anda dengan segera jika Anda mengalami hilang ingatan, kesulitan berpikir, kesulitan berjalan atau kehilangan penglihatan.

Efek samping lainnya
Efek samping yang sangat umum terjadi terkait Redditux (dilaporkan pada lebih dari 1 dari 10 pasien) meliputi:
- Infeksi seperti pneumonia (bakteri) atau herpes (virus) atau inflamasi pada saluran bronkus (bronkitis)
- Jumlah sel darah putih yang rendah, dengan atau tanpa demam, penurunan jumlah keping darah dalam darah
- Reaksi alergi sebelah infus, sakit punggung, sakit pada rahang
- Mual, peningkatan kadar gula dalam darah, penurunan natrau makan
- Ruam kulit, gatal, botak di kulit kepala, demam, menggigil, kekemahan fisik, sakit kepala, batuk.
- Penurunan daya tahan tubuh (penurunan kadar IgG)

Cardiac disorders		* myocardial infarction [1,and 2], arrhythmia, * atrial fibrillation, tachycardia, * cardiac disorder	* left ventricular failure, * supraventricular tachycardia, * ventricular tachycardia, * angina, * myocardial ischaemia, bradycardia,	severe cardiac events [1and 2]	heart failure [1and 2]	
Vascular disorders		Phlebitis, hypertension, orthostatic hypotension, hypotension			Vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders	cough	Bronchospasm[4], Respiratory disease, Chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease [3]	Respiratory failure [4],	Lung infiltration
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, constipation, stomatitis, gastritis	dysphagia, stomatitis, dyspepsia, anorexia, throat irritation	Abdominal enlargement		gastro - intestinal perforation [5]	
Skin and subcutaneous tissue disorders	pruritus, rash, * alopecia	urticaria, sweating, night sweats, * skin disorder, nail disorder			severe bullous skin reactions, toxic epidermal necrolysis (Lyell's Syndrome) [1], severes Johnson syndrome	
Musculoskeletal , connective tissue and bone disorders	back pain pain in jaw	hypertonia, myalgia, arthralgia, neck pain, pain,				
Renal and urinary disorders					renal failure [1]	
General disorders and administration site conditions	fever , chills, asthenia, headache, * fatigue, pain	tumour pain, flushing, malaise, cold syndrome, * shivering, * multi -organ failure *, mucosal inflammation, nausea	Infusion site pain			
Investigations	decreased IgG levels, white blood cell count decrease, neutrophil count decrease, weight decrease, platelet count decrease					

*For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with ** where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported*

[1] Includes reactivation and primary infections; frequency based on R- ITC regimen in relapsed/refractory CLL

[2] see also section infection below

[3] see also section haematologic adverse reactions below

[4] see also section infusion -related reactions below. Rarely fatal cases reported

[5] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of rituximab therapy

[6] observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion -via/ -tea/ reactions

[7] includes fatal cases

[8] Frequency not known (cannot be estimated from the available data)

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the rituximab arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia.

Infusion-related reactions

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation and pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac events (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, acute respiratory distress syndrome, ventricular fibrillation, cardiogenic shock and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is <1 % of patients by the eighth cycle of rituximab containing treatment.

Infections

Rituximab induces B-cell depletion in about 70-80 % of patients, but was associated with decreased serum immunoglobulins only in a minority of patients.

Localized candida infections as well as Herpes zoster was reported at a higher incidence in the rituximab-containing arm of randomized studies. Severe infections were reported in about 4 % of patients treated with rituximab monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during rituximab maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2- year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials and cases of hepatitis B reactivation, have been reported, the majority of which were in subjects receiving rituximab in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2 % in R-FC vs. 0 % FC. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Haematologic Adverse Reactions

In clinical trials with rituximab monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2 %, anaemia in 1.1 % and thrombocytopenia in 1.7 % of the patients. During rituximab maintenance treatment for up to 2 years, leucopenia (5 % vs. 2 %, grade 3/4) and neutropenia (10 % vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1 % grade 3/4 %) and was not different between treatment arms. In studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88 % vs. CHOP 79 %, R-FC 23 % vs. FC 12 %), neutropenia (R-CVP 24 % vs. CVP 14 %; R-CHOP 97 % vs. CHOP 86 %, R-FC 30 % vs. FC 19 % in previously untreated CLL), pancytopenia (R-FC 3 % vs. FC 1 % in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below 1x1090, between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below 1x1090, later than 42 days after last dose in patients with no previous prolonged neutropenia) prior to day 42(following treatment with rituximab plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of rituximab were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC: 83% vs. FC 71%). In the relapsed/refractory CLL study, grade 3/4 thrombocytopenias was reported in 11 % of patients in the R-FC group compared to 9 % of patients in the FC group.

In studies of Rituximab in patients with Waldestrom's macroglobuminaemia, transient increase in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level with 4 months.

Cardiovascular adverse reactions

Cardiovascular reactions during clinical trials with rituximab monotherapy were reported in 18.8 % of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with rituximab and observation. Cardiac events were reported at a higher incidence in patients treated with rituximab and first relapse (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3 % of patients treated with rituximab compared to <1 % on observation. In studies evaluating rituximab in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9 %) as compared to the CHOP group (3 patients, 1.5 %). All of these arrhythmias either occurred in the context of a rituximab infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4 % R-FC, 3 % FC) and in the relapsed/refractory study (4 % R-FC, 4 % FC).

Respiratory system

Cases of interstitial lung disease, some with fatal outcome have been reported.

Neurologic events

During the treatment period, four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5 %) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4 % R-FC, 4 % FC) and in the relapsed/refractory study (3 % RFC, 3 % FC).

Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, , hypertension, immunosuppressive therapy and/or chemotherapy.

Gastrointestinal Disorders

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Rituximab in combination with chemotherapy.In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1-77) days in patients with NHL. Evaluate

if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

IgG levels

In the clinical trial evaluating rituximab maintenance treatment, median IgG levels were below the lower limit of normal (LLN) (<7 g/L) after induction treatment in both the observation and the rituximab groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the rituximab group. The proportion of patients with IgG levels below the LLN was about 60 % in the rituximab group throughout the 2 year treatment period, while it decreased in the observation group (36 % after 2 years).

A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with rituximab, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

Skin and subcutaneous tissue disorders:

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of Rituximab exposure. Discontinue Rituximab in patients who experience a severe mucocutaneous reaction. The safety of readministration of Rituximab to patients with severe mucocutaneous reactions has not been determined.

Patient subpopulations -Rituximab monotherapy

Elderly patients (≥ 65 years):

The incidence of ADRs of all grades and grade 3/4 ADR was similar in elderly patients compared to younger patients (<65 years).

Bulky disease:

There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6 % vs. 15.4 %). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment

The percentage of patients reporting ADRs upon re-treatment with further courses of rituximab was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs).

Patient subpopulations - Rituximab combination therapy

Elderly patients (≥ 65 years):

The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (<65 years), with previously untreated or relapsed/refractory CLL.

Post-marketing experience

Non-Hodgkin's Lymphoma

The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and largely data derived from spontaneous reports.

Additional cases of severe infusion-related reactions have been reported during post-marketing use of rituximab.

As part of the continuing post-marketing surveillance of rituximab safety, the following severe adverse reactions have been observed: -

Cardiovascular system: Severe cardiac events, including heart failure and myocardial infarction have been observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and mostly associated with infusion related reactions. Vasculitis, predominantly cutaneous, such as leukocytoclastic vasculitis, has been reported very rarely.

Respiratory system: Respiratory failure/insufficiency, pulmonary infiltrates in the context of infusion related reactions. Pulmonary infiltrates outside of infusion related reactions and interstinal pneumonitis have been reported rarely.

Skin and Appendages: Severe bullous skin reactions including fatal cases of toxic epidermal necrolysis have been reported rarely.

Nervous system: Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy such as severe vision loss, loss of other senses, facial nerve palsy occurred at various times up to several months after completion of rituximab therapy.

Body as a whole: Serum-sickness like reactions have been reported rarely.

Infections and infestations:

Cases of Hepatitis-B reactivation have been reported, the majority of which were in subjects receiving rituximab in combination with cytotoxic chemotherapy. Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab treatment. The majority of the patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Examples of these serious viral infections are infection caused by the herpes viruses (cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy (PML) and Hepatitis C virus.

Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of the patients were HIV positive.

Gastro intestinal system: Gastro intestinal perforation, in some cases leading to death, has been observed in patients receiving rituximab in combination with chemotherapy or non-Hodgkin's lymphoma.

Laboratory Abnormalities

Non-Hodgkin's Lymphoma

Blood and lymphatic system

Neutropenia: Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of rituximab.

4.9 Overdose

Limited experience with doses higher than the approved dose of intravenous rituximab formulation is available from clinical trials in humans. The highest intravenous dose of rituximab tested in humans to date is 5000 mg (2250 mg/m2), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

Patients who experience overdose should have immediate interruption of their infusion and be closely monitored. .

In the post-marketing setting five cases of rituximab overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: monoclonal antibodies, ATC code: L01X C02

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes'.The antigen is expressed on >90 % of all B cell non-Hodgkin's Lymphomas (NHLs)[1]. CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro- B cells, normal plasma cells or other normal tissue[1,2]. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and thus, does not compete for antibody binding[2].

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity` (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B-lymphocytes has also been demonstrated to induce cell death via apoptosis[3].

Peripheral B cell counts declined below normal following completion of the first dose of rituximab. In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy).

5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m^2), the typical population estimates of nonspecific clearance (CL), specific clearance (CL$_2$) likely contributed by B-cells or tumour burden, and central compartment volume of distribution (V$_1$) were 0.14 l/day, 0.59 l/day, and 2.7 l, respectively. The

estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19- positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL$_2$ of rituximab in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL$_2$. However, a large component of inter-individual variability remained for CL$_2$ after correction for CD19-positive cell counts and tumour lesion size. V$_1$ varied by body surface area (BSA) and CHOP therapy. This variability in V$_1$ (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m^2 at weekly intervals for 4 doses to 203 patients with NHL have to rituximab, yielded a mean C$_{max}$ following the fourth infusion of 486 µg/ml (range, 77.5 to 996.6 µg/ml). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.

Upon administration of rituximab at a dose of 375 mg/m^2 as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C$_{max}$ increased with each successive infusion, spanning from a mean of 243 µg/ml (range, 16 – 582 µg/ml) after the first infusion to 550 µg/ml (range, 171 – 977 µg/ml) after the eighth infusion.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Chronic lymphocytic leukaemia

Rituximab was administered as an IV infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C$_{max}$ (N=15) was 408 µg/ml (range, 97 – 764 µg/ml) after the fifth 500 mg/ m^2 infusion and the mean terminal half-life was 32 days (range, 14 – 62 days).

5.3 Preclinical safety data

Rituximab has shown to be highly-specific to the CD20 antigen on B cells. Toxicity studies reported with rituximab in cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B cells in peripheral blood and in lymphoid tissue.

Developmental toxicity studies with rituximab have been performed in cynomolgus monkeys at dosages up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses was observed, which persisted post natally and was accompanied by a decrease in IgG level in the newborn animals affected. B cell counts returned to normal in these animals within 6 months of birth and did not compromise the reaction to immunization.

Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. No long-term animal studies have been performed to establish the carcinogenic potential of rituximab.

Specific studies to determine the effects of rituximab on fertility have not been performed. In general toxicity studies in cynomolgus monkeys no deleterious effects on reproductive organs in males or females were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate

Polysorbate 80

Sodium chloride

Water for injection

6.2 Incompatibilities

No incompatibilities between rituximab and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

6.3 Shelf life

36 months.

The prepared infusion solution of Reditux is physically and chemically stable for 24 hours at 2–8°C and subsequently 12 hours at room temperature (25°C).

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store vials in a refrigerator (2-8°C). Keep the vial in the carton in order to protect from light.

Do not freeze. Keep out of reach of children.

6.5 Nature and contents of container

Clear Type I glass vials with butyl rubber stopper containing 100 mg of rituximab in 10 ml (10 mg/ml) and 500 mg of rituximab in 50 ml (10 mg/ml), packs of 1 vial each.

6.6 Special precautions for disposal

Reditux is provided in sterile, preservative-free, non-pyrogenic, single use vials.

Aseptically withdraw the necessary amount of Reditux, and dilute to a calculated concentration of 1 to 4 mg/ml rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/ml (0.9 %) solution for injection or 5 % D-Glucose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

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

7. MANUFACTURED BY

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PT. Ferron Par Pharmaceuticals

Bekasi - Indonesia

8. MARKETING AUTHORISATION NUMBER(S)

DKI18998005494A1

9. Date of Revision of the Text

April 2016

HARUS DENGAN RESEP DOKTER

ON MEDICAL PRESCRIPTION ONLY

Efek samping yang umum terjadi terkait Reditux (dilaporkan pada lebih dari 1 dari 100 pasien) meliputi:

- Infeksi seperti sepsis dan pneumonia (bakteri), herpes dan hepatitis B (virus) atau kandida (jamur), inflamasi saluran bronkus dan sinus, atau infeksi umum lainnya
- Jumlah sel darah merah, sel darah putih dan keping darah yang rendah
- Reaksi alergi (hipersensitivitas)
- Penurunan berat badan, kelebihan cairan pada wajah dan tubuh, peningkatan kadar enzim dalam darah [LDH (lactate dehydrogenase)],
- penurunan kadar kalsium.
- Sensasi abnormal pada kulit, seperti mati rasa, kesemutan, seperti tertusuk, panas, sensasi merayap pada kulit, penurunan respon terhadap sentuhan. Perasaan gelisah, sulit tidur, kemerahan pada wajah dan memar di kulit sebagai konsekuensi dari pelebaran pembuluh darah, pusing, rasa cemas
- Peningkatan produksi air mata, gangguan sekresi dan pengeluaran, peradangan pada mata (konjungtivitis)
- Telinga berdenyut, nyeri telinga
- Penyakit jantung (serangan jantung, detak jantung tidak teratur, detak jantung meningkat secara abnormal)
- Tekanan darah rendah atau tinggi, penurunan tekanan darah karena postur tidak benar
- Peradangan, paru-paru sesak dan/atau iritasi, serak dan/atau sinus, napas pendek, pengambilan oksigen dalam organ tubuh tertalu kecil, batuk
- Muntah, diare, nyeri perut, tenggorokan dan mulut iritasi dan/atau luka, kesulitan menelan, sembelit, gangguan pencernaan, Gangguan makan; penurunan jumlah makanan yang dikonsumsi dengan konsekuensi kehilangan berat badan yang berbahaya.
- Gangguan kulit, sensasi terbakar pada kulit, gatal, peningkatan produksi keringat, berkeringat di malam hari
- Gangguan otot dan jaringan ikat, peningkatan pengencangan otot yang abnormal, nyeri, nyeri sendi, nyeri leher dan punggung
- Gangguan umum, nyeri tumor, muncul tanda kemerahan pada wajah dan area lainnya di kulit, ketidakmyamanan umum atau rasa tidak nyaman, sindrom flu, kelelahan, gemetar, berbagai organ tidak berfungsi

Efek samping yang tidak umum terkait Reditux (dilaporkan pada lebih dari 1 dari 1000 pasien) meliputi:

- Pembekuan darah tidak normal, penurunan produksi sel darah, penurunan sel darah merah autoimun, node limfa membesar/membengkak
- Kehilangan mood dan kehilangan ketertarikan dan kesenangan dalam aktivitas biasa, gugup
- Perubahan indera pengecap
- Penyakit jantung (serangan jantung, detak jantung meningkat secara abnormal, detak jantung melemah, detak jantung tidak teratur, nyeri dada) peradangan, iritasi dan/atau sesak pada paru-paru, asma, napas pendek
- Pembengkakan pada perut
- Nyeri pada tempat injeksi

Bagaimana cara menyimpan Redditux?

Jauhkan dari pandangan dan jangkauan anak-anak. Jangan gunakan Redditux setelah tanggal kedaluwarsa seperti yang tercetak pada dus. Tanggal kedaluwarsa adalah hari terakhir pada bulan tersebut.

Simpan dalam lemari pendingin (2-8°C). Simpan vial dalam dus untuk melindungi dari cahaya. Jangan dibekukan. Obat tidak boleh dibuang ke pembuangan air atau pembuangan limbah rumah tangga. Tanyakan apoteker Anda tentang bagaimana membuang obat yang tidak lagi diperlukan. Langkah-langkah ini akan membantu melindungi lingkungan.

Informasi lainnya

Kandungan Redditux

- Bahan aktif dalam Reditux adalah *rituximab*. Setiap vial mengandung rituximab 100 mg dan 500 mg (10 mg/ml).
- Bahan tambahan lainnya adalah natrium sitrat, *polysorbate 80*, natrium klorida dan air pro injeksi.

Seperti apa Redditux dan kandungannya

Redditux merupakan larutan jernih, tidak berwarna, dan berbentuk konsentrat untuk larutan untuk infus.

Kemasan dan nomor registrasi:

Redditux 100: Kotak, 1 vial x 100 mg/10 ml. DKI18998005494A1

Redditux 500: Kotak, 1 vial x 500 mg/50 ml. DKI18998005494A1

HARUS DENGAN RESEP DOKTER

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Tanggal revisi

Mei 2018