

# NEW ZEALAND DATA SHEET

## PEG-INTRON<sup>®</sup> REDIPEN<sup>®</sup> INJECTOR

### NAME OF DRUG

Peginterferon alfa-2b

### DESCRIPTION

Peginterferon alfa-2b is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

PEG-Intron Redipen Injector is a single use disposable injection pen. The PEG-INTRON Powder for Injection and solvent are contained in separate compartments of a two-chamber cartridge inside the Redipen Injector.

PEG-INTRON Redipen Injector is available in 5 different strengths:

- 50, 80, 100, 120 or 150 µg of peginterferon alfa-2b.

PEG-INTRON Powder for Injection also contains dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80 as excipients. The solvent provided for parenteral use is sterile Water for Injections. When reconstituted as recommended, each Redipen Injector is capable of delivering the labelled dose in 0.5 mL of PEG-INTRON solution (see DOSAGE AND ADMINISTRATION for the five dosage settings on the PEG-INTRON Redipen Injector).

### PHARMACOLOGY

*In vitro* and *in vivo* studies suggest that the biological activity of peginterferon alfa-2b is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and

such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Intron A<sup>®</sup> (recombinant interferon alfa-2b) also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of Intron A is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

## Pharmacokinetics

Peginterferon alfa-2b is a well characterised polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of peginterferon alfa-2b is prolonged compared with that of interferon alfa-2b. Peginterferon alfa-2b has a potential to depegylate to free interferon alfa-2b. The biologic activity of pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

Peginterferon alfa-2b  $C_{max}$  and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 L/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean peginterferon alfa-2b elimination half-life is approximately 40 hours, with apparent clearance of 22.0 mL/hr.kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30%) of peginterferon alfa-2b apparent clearance.

Renal function: Renal clearance appears to account for 30% of total clearance of peginterferon alfa-2b. In a single dose study (1.0 µg/kg) in patients with impaired renal function,  $C_{max}$ , AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PEG-INTRON Solution for Injection (1 mcg/kg subcutaneously administered every week for four weeks), the clearance of PEG-INTRON is reduced by a mean of 17% in patients with moderate renal impairment (creatinine clearance 30-49 ml/min) and by a mean of 44% in patients with severe renal impairment (creatinine clearance 10-29 ml/min) compared to subjects with normal renal function. Clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving haemodialysis. The dose of PEG-INTRON for monotherapy should be reduced in patients with moderate or severe renal impairment (See DOSAGE AND ADMINISTRATION: Use in Renal Impairment).

Hepatic function: The pharmacokinetics of PEG-INTRON has not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PEG-INTRON in a single dose study using a subcutaneous dose of 1 µg/kg were assessed. However, the number

of subjects aged  $\geq 65$  yrs in this study was small to detect differences between the age groups. As renal function is often reduced in elderly patients which may affect the elimination of PEG-INTRON, caution should be exercised in the use of PEG-INTRON for this patient group.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PEG-INTRON is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PEG-INTRON in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PEG-INTRON 0.5  $\mu\text{g}/\text{kg}$  is 1.1%.

## Clinical Trials

The results of a large multi-centre randomised, Phase III clinical trial demonstrated efficacy and safety of PEG-INTRON for the treatment of chronic hepatitis C. The objectives of this trial in 1,219 previously untreated patients were to assess the safety and efficacy of 48 weeks of treatment with 3 doses of PEG-INTRON (0.5, 1.0 and 1.5  $\mu\text{g}/\text{kg}$  administered once weekly subcutaneously) vs Intron A (interferon alfa-2b, 3 MIU administered subcutaneously three times a week). Eligible patients for the trial had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) ( $>100$  copies/mL), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, as well as abnormal serum ALT. Subjects with pre-existing severe psychiatric condition or a history of severe psychiatric disorder were excluded.

The primary measures of efficacy in the clinical trial were loss of HCV-RNA ( $<100$  copies/mL) (virologic) and normalisation of ALT (biochemical) 6 months after completing 1 year of treatment.

Using the virologic assessment, all doses of PEG-INTRON in the clinical trial were statistically superior to Intron A (Table 1).

**Table 1 – Proportion of Patients with Sustained Loss of HCV** [Number (%) of Patients]

Response*	A	B	C	D
	PEG-Intron 0.5 $\mu\text{g}/\text{kg}$ Once Weekly N=315	PEG-Intron 1.0 $\mu\text{g}/\text{kg}$ Once Weekly N=297	PEG-Intron 1.5 $\mu\text{g}/\text{kg}$ Once Weekly N=304	Intron A 3 MIU Three Times a Week N=303
<b>Sustained Response 6 Months Post Treatment</b>	57 (18%)	73 (25%)	71 (23%)	37 (12%)
<b>p Values**</b>	A vs D 0.042	B vs D <0.001	C vs D <0.001	

\*Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/mL (National Genetics Institute, Culver City, CA)

\*\*Chi-square Test

HCV genotype 1 infection and high pre-treatment HCV level (>2 million copies/mL) are well-recognised predictors of a poor response to interferon therapy. When considered by the subgroups of HCV genotype and viral load, the response rate with all dose regimens of PEG-INTRON remains superior to Intron A.

The Quality of Life was less affected by the 0.5 µg/kg dose of PEG-INTRON than by either the 1.0 µg/kg dose once weekly or the 3 million IU of Intron A three times a week.

## INDICATIONS

PEG-INTRON is indicated for the treatment of chronic hepatitis C in patients who have received no prior interferon therapy. Patients must be 18 years of age or older and have compensated liver disease.

The optimal treatment for chronic hepatitis C is considered to be the administration of the combination of interferon alfa-2b with ribavirin (See Contraindications)

## CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Hypersensitivity to any interferon
- Autoimmune hepatitis or a history of autoimmune disease
- Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication
- Creatinine clearance < 50 mL/min
- Decompensated liver disease
- When used in combination with ribavirin, patients with (creatinine clearance < 50 mL/min)
- Men whose female partners are pregnant must not be treated with PEG-INTRON when used in combination with ribavirin

## PRECAUTIONS

Discontinue treatment with PEG-INTRON in patients with signs of liver decompensation.

**Cardiovascular:** As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PEG-INTRON therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PEG-INTRON therapy.

**Acute hypersensitivity:** Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PEG-INTRON, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

**Fever:** While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

**Hydration:** Adequate hydration must be maintained in patients undergoing therapy with PEG-INTRON since hypotension related to fluid depletion has been seen in some patients treated with alfa interferons. Fluid replacement may be necessary.

**Metabolic disturbances:** Hypertriglyceridaemia and aggravation of hypertriglyceridaemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

**Ocular changes:** Ophthalmological disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alfa interferons (see ADVERSE REACTIONS). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Because these ocular events may occur in conjunction with other disease states, periodic visual examinations during PEG-INTRON therapy are recommended in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PEG-INTRON should be considered in patients who develop new or worsening ophthalmologic disorders.

**Pulmonary changes:** Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alfa treated patients. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with alfa interferon. Any patient developing fever, cough, dyspnoea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely. If appropriate, discontinue PEG-INTRON.

**Psychiatric and Central Nervous System (CNS):** Patients with pre-existing severe psychiatric condition or a history of severe psychiatric disorder should not be treated with PEG-INTRON. Severe CNS effects, particularly depression, homicidal ideation, suicidal ideation and attempted suicide have been observed in some patients during PEG-INTRON therapy. Other CNS effects including aggressive behaviour, sometimes directed towards others, psychosis including hallucinations, confusion and alteration of mental status, have been observed with alfa interferon. More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses of interferon alfa-2b. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of PEG-INTRON. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored by the prescribing physician during treatment and in the 6 month follow-up period. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in

mind by the prescribing physician. If symptoms persist or worsen, or suicidal ideation or aggressive behaviour towards others is identified, it is recommended that PEG-INTRON Therapy be discontinued, and the patient followed with psychiatric intervention as appropriate.

**Thyroid changes:** Infrequently, patients treated for chronic hepatitis C with interferon alfa have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PEG-INTRON may be continued if TSH levels can be maintained in the normal range by medication.

**Organ transplantation:** The safety and efficacy of PEG-INTRON Injection for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alfa therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported but a causal association with interferon alfa therapy has not been established.

**HIV/HCV Coinfection:** Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone may increase the risk in this patient subset.

**Other:** Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease and sarcoidosis, use of PEG-INTRON in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

The development of auto-antibodies has been reported during treatment with alfa interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

**Laboratory tests:** Standard haematological tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and at weeks 2 and 4 of therapy, and periodically during treatment with PEG-INTRON. Acceptable baseline values that may be considered as a guideline are:

- Platelets  $\geq 100 \times 10^9/L$
- Neutrophil count  $\geq 1.5 \times 10^9/L$
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

#### Use in Renal Impairment

It is recommended that renal function be evaluated in all patients prior to initiation of PEG-INTRON. Patients with moderate renal impairment should be closely monitored and, should have their dose of PEG-INTRON reduced if medically appropriate. If serum creatinine rises to  $> 0.02$  g/L, PEG-INTRON must be discontinued.

### Use in Hepatic Impairment

The safety and efficacy of PEG-INTRON therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PEG-INTRON must not be used for these patients.

### Use in the Elderly ( $\geq 65$ years of age)

As renal function is often reduced in elderly patients which may affect the elimination of PEG-INTRON, caution should be exercised in the use of PEG-INTRON for this patient group (see PRECAUTIONS, Use in Renal Impairment).

### Use in Children

PEG-INTRON is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

### Carcinogenicity, Mutagenicity, Impairment of Fertility

Reproductive studies with peginterferon alfa-2b have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. Peginterferon alfa-2b is likely to also cause this effect. In studies on interferon use in non-human primates, abnormalities of the menstrual cycle have been observed. Decreased serum oestradiol and progesterone concentrations have been reported in women treated with human leucocyte interferon. Effects on fertility have not been determined by animal studies with either peginterferon alfa-2b or interferon alfa-2b.

Carcinogenicity studies with peginterferon alfa-2b or interferon alfa-2b have not been performed. Genotoxicity of peginterferon alfa-2b was evaluated in assays for gene mutations (Ames test) and chromosomal damage (human lymphocytes *in vitro* and mouse micronucleus assay *in vivo*) and was negative in both assays.

### Use in Pregnancy (Category B3)

Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (Rhesus monkeys) at 90 and 180 times the recommended subcutaneous dose of 3 million International Units (IU)/m<sup>2</sup> three times weekly (TIW). Abortion was observed in all dose groups (7.5, 15 and 30 MIU/kg, every other day), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended maximum dose equivalent for humans). Therefore, PEG-INTRON is recommended for use in fertile women only when they are using effective contraception during the treatment period. There are no adequate data on the use of interferon alfa-2b in pregnant women. PEG-INTRON is not recommended for use during pregnancy.

### Use during Lactation

It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse events from PEG-INTRON in nursing infants, a decision must be made whether to discontinue the treatment or discontinue nursing, taking into account the importance of the medicinal product to the mother.

## Driving and Operating Machinery

Patients who develop fatigue, somnolence or confusion during treatment with PEG Intron are cautioned to avoid driving or operating machinery.

## Concomitant Therapy and Drug Interactions

Results of a pharmacokinetic interaction study with a single dose of PEG-INTRON demonstrated no effect on the activity of cytochrome P450 (CYP) 1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. The literature, however, reports up to a 50% reduction in clearance of CYP 1A2 substrates (e.g. theophylline) when administered with other forms of interferon alfa and therefore caution should be exercised when PEG-INTRON Injection is used with medications metabolised by CYP 1A2.

Caution should be used when administering interferon alfa-2b with medications metabolized by CYP2C8/9 and CYP2D6, especially those with narrow therapeutic indices.

Patients co-infected with Human Immunodeficiency Virus (HIV) and are receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding treatment with PEG-INTRON and ribavirin to HAART.

No pharmacokinetic interactions were noted between PEG-INTRON and ribavirin in a multiple-dose pharmacokinetic study.

## **ADVERSE REACTIONS**

The safety of PEG-INTRON was determined in a clinical trial in 1,219 previously untreated patients with chronic hepatitis C (see Clinical Trials). In the trial, 916 patients received PEG Intron at one of three dose regimens (0.5 µg/kg: 315; 1.0 µg/kg: 297; 1.5 µg/kg: 304) and 303 patients received Intron A (interferon alfa-2b) as a control.

Most undesirable effects were mild or moderate in severity and not treatment limiting. The majority of patients reported headache and myalgia. The most commonly reported adverse effects (≥ 10% of patients) are presented in Table 2 for the PEG-INTRON 0.5 µg/kg and 1.0 µg/kg and Intron A treatment groups.

<b>Table 2</b>	Adverse events reported very commonly in clinical trials (≥ 10 % of patients)		
	PEG-INTRON 0.5 µg/kg once weekly N=315	PEG-INTRON 1.0 µg/kg once weekly N=297	Intron A 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %

Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Impaired Concentration	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported effects ( $\geq 2\%$  of patients) were pruritus, dry skin, malaise, increased sweating, right upper quadrant pain, neutropenia, rash, vomiting, dry mouth, emotional lability, nervousness, dyspnoea, anaemia, leucopenia, viral infection somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paraesthesia, coughing, agitation, sinusitis, hypertonia, hyperaesthesia, blurred vision, confusion, flatulence, decreased libido, erythema, eye pain, apathy, hypoaesthesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder, hearing impairment/loss.

In patients treated with PEG-INTRON in clinical trials, severe psychiatric events were uncommon; life-threatening psychiatric events occurred infrequently. These events included suicide, suicidal ideation, aggressive behaviour, sometime directed towards others, and psychosis including hallucinations.

Following the marketing of PEG-INTRON Injection, rhabdomyolysis, myositis, renal insufficiency and renal failure have been reported rarely. Rarely reported events during PEG-INTRON therapy include seizures, pancreatitis, hypertriglyceridaemia, arrhythmia, diabetes, peripheral neuropathy.

Other ophthalmologic disorders that have been reported rarely with alfa interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see PRECAUTIONS).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents. Cardiomyopathy that may be reversible upon discontinuation of interferon alfa, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cardiac ischaemia, cerebrovascular ischemia, cerebrovascular haemorrhage, encephalopathy (see PRECAUTIONS), ulcerative and ischaemic colitis, myocardial infarction sarcoidosis or exacerbation of sarcoidosis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, injection site necrosis have been reported.

Granulocytopenia ( $< 0.75 \times 10^9/L$ ) occurred in 4% and 7%, and thrombocytopenia ( $< 70 \times 10^9/L$ ) in 1% and 3%, respectively, in patients receiving 0.5 or 1.0  $\mu\text{g}/\text{kg}$  of PEG-INTRON.

Very rarely, alpha interferons, including Peg-Intron may be associated with aplastic anaemia or pure red cell aplasia.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura, rheumatoid arthritis, SLE, vasculitis, Vogt-Koyanagi-Harada syndrome.

Cases of acute hypersensitivity reactions, including anaphylaxis, urticaria, angioedema have been reported.

Other adverse events reported with PegIntron alone or in combination with ribavirin include: chest pain, asthenic conditions (including asthenia, malaise and fatigue), abdominal pain, hypothyroidism, hyperthyroidism, hypertriglyceridemia, anxiety, emotional lability, irritability, dyspnea, cough, pruritus, rash, dry skin, migraine headache, homicidal ideation, peripheral neuropathy, facial palsy, paraesthesia, dehydration, hypertension, hypotension, palpitations, fungal infection, bacterial infection including sepsis, diabetes, diabetic ketoacidosis.

## **DOSAGE AND ADMINISTRATION**

PEG-INTRON treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PEG-INTRON monotherapy is administered subcutaneously at a dose of 0.5  $\mu\text{g}/\text{kg}$  once weekly for at least 6 months. A dose of 1.0  $\mu\text{g}/\text{kg}$  once weekly may be considered for some patients based on hepatitis C genotype 1 at baseline.

In all patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e. 1 year of treatment. In patients who fail to show loss of HCV-RNA at 6 months, treatment with PEG-INTRON should be discontinued.

The dose is to be administered subcutaneously on the same day of each week. The patient may self-administer the dose at the discretion of the physician. When self-administration is recommended, the patient should be advised to vary the injection site each time the injection is administered.

### **DOSE MODIFICATION:**

If an adverse reaction develops during the course of treatment, modify the dosage of PEG-INTRON to one-half the recommended dose once weekly until the adverse event abates. If persistent or recurrent intolerance develops despite adequate dosage adjustment, discontinue treatment with PEG-INTRON.

<b>Laboratory values</b>	<b>Reduce PEG-INTRON REDIPEN to one-half dose if:</b>	<b>Discontinue PEG-INTRON REDIPEN if:</b>
Neutrophils	< 0.75 x 10 <sup>9</sup> /l	< 0.5 x 10 <sup>9</sup> /l
Platelets	< 50 x 10 <sup>9</sup> /l	< 25 x 10 <sup>9</sup> /l

Use in renal impairment: In patients with moderate renal dysfunction (creatinine clearance 30-50mL/min), the starting dose of PEG-INTRON should be reduced by 25%. Patients with severe renal dysfunction (creatinine clearance 10-29 mL/min), including those on haemodialysis, should have the starting dose of PEG-INTRON reduced by 50%. If renal function decreases during treatment PEG-INTRON therapy should be discontinued.

**Combination Therapy:** See the PEGATRON Data Sheet.

Directions for use, handling and disposal of PEG-INTRON Redipen Injector

**Preparation and Administration:** *Please refer to enclosed package insert for detailed instructions on the use of the PEG-INTRON Redipen Injector.* Some important points to note are:

1. In each Redipen Injector there is a two-chamber cartridge containing powder of peginterferon alfa-2b (at strength of 50µg, 80µg, 100µg, 120µg or 150µg) and sterile water for injection in separate compartments for single use. The powder is reconstituted with the sterile water just before use. A small volume is lost during preparation of PEG-INTRON for injection when dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PEG-INTRON powder to ensure delivery of the labelled dose in 0.5mL of PEG-INTRON, solution for Injection.
2. Each PEG-INTRON Redipen Injector has five dosage settings and is capable of delivering one of the five different doses:

**Table 3**

<b>Strength</b>	<b>Actual Dose (µg) for each Dosage Setting (mL)</b>				
	<b>0.3 mL</b>	<b>0.35 mL</b>	<b>0.4 mL</b>	<b>0.45 mL</b>	<b>0.5 mL</b>
<b>50 µg</b>	30 µg	35 µg	40 µg	45 µg	50 µg
<b>80 µg</b>	48 µg	56 µg	64 µg	72 µg	80 µg

<b>100 µg</b>	60 µg	70 µg	80 µg	90 µg	100 µg
<b>120 µg</b>	72 µg	84 µg	96 µg	108 µg	120 µg
<b>150 µg</b>	90 µg	105 µg	120 µg	135 µg	150 µg

3. PEG-INTRON should be administered subcutaneously after reconstituting the powder as instructed attaching the injection needle provided in the packaging and setting the prescribed dose. **A complete and illustrated set of instructions is provided in the enclosed package insert.**
4. Remove the PEG-INTRON Redipen Injector from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).
5. Only use the needle supplied with the PEG-INTRON Redipen Injector. The use of other needles may result in the wrong dose being delivered and/or cause the pen to not operate properly.
6. As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discoloration is present.
7. The reconstituted PEG-INTRON solution contains no antimicrobial agent and is for use in a single patient on one occasion only. Discard any unused solution. PEG-INTRON Injection must not be mixed with other medicinal injectable products
8. Once the prescribed dose is administered, discard the PEG-INTRON Redipen Injector with any unused solution safely in a sharps container. The PEG-INTRON Redipen Injector is for use in a single patient on one occasion only and **MUST NOT BE SHARED.**

**Stability of the reconstituted solution:** The chemical and physical in-use stability for the reconstituted solution has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, the reconstituted product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2°C to 8°C.

## OVERDOSAGE

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PEG-INTRON.

## PRESENTATION

PEG-INTRON Redipen Injector is a single use disposable injection pen and is available in the following strengths:

50, 80, 100, 120 and 150 µg of peginterferon alfa-2b and solvent (sterile Water for Injections). Also, one injection needle and two cleansing swabs are provided for use with each PEG-INTRON Redipen Injector.

Store at 2°C to 8°C. (Refrigerate. Do not freeze.)

## **SPONSOR**

Merck Sharp & Dohme (NZ) Ltd  
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Tel: 0800 500 673

## **MEDICINES CLASSIFICATION**

Prescription Only Medicine

## **DATE OF PREPARATION**

20 January 2011