

# New Zealand Datasheet

## Name of Medicine

IMUKIN®

Recombinant human interferon gamma-1b [rbe]

## Presentation

Vials containing  $2 \times 10^6$  IU (100 mcg) recombinant interferon gamma-1b (rbe) in 0.5mL.

## Uses

### Actions

IMUKIN (interferon gamma-1b [rbe]), a biologic response modifier, is a single-chain polypeptide containing 140 amino acids. Production of IMUKIN is achieved by fermentation of a genetically engineered *Escherichia coli* bacterium containing the DNA which encodes for the human protein. Purification of the product is achieved by conventional column chromatography. IMUKIN is a highly purified sterile solution consisting of non-covalent dimers of two identical 16,465 Dalton monomers, with a specific activity of 20 million IU/mg.

Interferons are a family of functionally-related proteins synthesised by eukaryotic cells in response to viruses and a variety of natural and synthetic stimuli. Early studies suggest that interferon gamma increases macrophage cytotoxicity by enhancing the respiratory burst via generation of toxic oxygen metabolites capable of mediating the killing of intracellular micro-organisms. It increases HLA-DR expression on macrophages and augments Fc receptor expression which results in increased antibody-dependent cell-mediated cytotoxicity.

In a placebo-controlled clinical trial in patients with Chronic Granulomatous Disease, IMUKIN was shown to reduce the frequency of serious infections during the trial period of 12 months. The overwhelming majority of these patients were also receiving prophylactic antimicrobial therapy.

Data on the safety and efficacy of IMUKIN in 37 CGD patients under the age of 3 years was pooled from 4 uncontrolled post-marketing studies and 2 sequential post-marketing surveillance studies. The rate of serious infections per patient-year in this uncontrolled group was similar to the rate observed in the IMUKIN treatment groups in controlled trials.

In 6 of the 10 patients receiving IMUKIN therapy before age one year 2-fold to 25-fold elevations from baseline of AST and/or ALT were observed. These elevations occurred as early as 7 days after starting treatment. Treatment with IMUKIN was interrupted in all 6 of these patients and was restarted at a reduced dosage in 4. Liver transaminase values returned to baseline in all patients and transaminase elevation recurred in one patient upon IMUKIN rechallenge.

In severe, malignant osteopetrosis (inherited disorder characterised by an osteoclast defect leading to bone overgrowth and deficient phagocyte oxidative metabolism), a treatment-related enhancement of superoxide production by phagocytes was observed in situ.

In a controlled randomised study in 16 patients with severe, malignant osteopetrosis, IMUKIN in combination with calcitriol was shown to reduce the frequency of serious infections versus calcitriol alone. In an analysis which combined data from two clinical studies, 19 of 24 patients treated with IMUKIN in combination with or without calcitriol for at least 6 months had reduced trabecular bone

volume compared to baseline. The clinical relevance of this observed decrease in IMUKIN patients versus a control group could not be established.

## **Pharmacokinetics**

### Absorption

Following subcutaneous single dose administration of 0.05 mg/m<sup>2</sup> of IMUKIN in healthy male subjects, a mean peak plasma concentration (C<sub>max</sub>) of 631 ng/mL (CV = 33.82%) was observed after a mean time (t<sub>max</sub>) of 8 hours (CV = 23.99%), being the mean area under the curve (AUC<sub>0-∞</sub>) 8.3 ng\*h/mL. Similar times of maximum plasma levels have been reported in male and female tumour patients (6.3 ± 2.0 hours, mean ± S.D.) after the s.c. administration of doses in the range of 0.1 - 0.5 mg/m<sup>2</sup>. I.m. administration showed peak plasma concentrations after about 4 hours. The apparent fraction of drug absorbed after i.m. or s.c. injection was greater than 89%. A dose proportionality has been demonstrated after i.v. and i.m. administration for doses ranging from 0.1 mg/m<sup>2</sup> to 2.5 mg/m<sup>2</sup> and after s.c. administration from 0.1 mg/m<sup>2</sup> to 0.5 mg/m<sup>2</sup>.

### Distribution

The volume of distribution at the steady state after bolus i.v. or s.c. administration ranged from 10.9 to 46.69 L. In healthy male subjects, there was no accumulation of IMUKIN after 12 consecutive daily injections of 0.1 mg/m<sup>2</sup>. The mean value of the MRT after s.c. administration in the range of 0.1 - 0.5 mg/m<sup>2</sup> is 10.95 h (S.D. ± 2.40 h).

### Metabolism and elimination

The metabolism of the cloned interferons falls within the natural handling of proteins. Interferon gamma was not detected in the urine of healthy male subjects following administration of 0.1 mg/m<sup>2</sup> via i.v., i.m. or s.c. routes. *In vitro* hepatic and renal perfusion studies demonstrate that the liver and kidneys are capable of clearing IMUKIN from perfusate. Preclinical studies in nephrectomised animals demonstrated a reduction in the clearance of interferon gamma from blood; however prior nephrectomy did not prevent elimination. The mean value of the apparent clearance following s.c. single dose administration in the range of 0.1 - 0.5 mg/m<sup>2</sup> was 287 mL/min (S.D. ± 148 mL/min).

## **Indications**

IMUKIN is indicated as an adjunct for reduction of the frequency of serious infections in patients with Chronic Granulomatous Disease (CGD).

The benefits of IMUKIN have been most marked in children with CGD although IMUKIN may be used in adult patients.

## **Dosage and Administration**

The recommended dosage of IMUKIN for injection for the treatment of patients with CGD is 50 µg /m<sup>2</sup> three times a week, for patients whose body surface area is greater than 0.5m<sup>2</sup>, and 1.5 µg/kg/dose for patients whose body surface area is equal to or less than 0.5m<sup>2</sup>.

The actually drawn volume must be controlled before injection. Injections should be administered subcutaneously, preferably in the evening. The optimum sites of injection are the right and the left deltoid region and anterior thigh. IMUKIN can be administered by a physician, nurse, family member or patient who is trained in the administration of subcutaneous injections.

The formulation does not contain a preservative. Once opened, the content of a vial should be used immediately. The unused portion of any vial should be discarded.

Treatment with IMUKIN should continue in the event of infectious complications related to CGD. In the event of other intercurrent illness, the treating physician should decide if and for how long IMUKIN should be discontinued. If severe reactions occur, therapy should be discontinued until the reaction

abates.

Although the most beneficial dose of IMUKIN has not yet been established, higher doses than that referred to above are not recommended, as neither the safety nor efficacy has been established for higher or lower doses. If severe reactions occur, the dose should be modified (50% reduction), or therapy discontinued until adverse reactions abate.

## **Contraindications**

IMUKIN is contraindicated in patients who develop or have known acute hypersensitivity to interferon gamma, known hypersensitivity to closely-related interferons or to any other component of the product.

## **Warnings and Precautions**

Patients with pre-existing cardiac disease may experience an acute, self-limited exacerbation of their cardiac condition at doses of 250 µg/m<sup>2</sup>/day or higher, as observed in early clinical trials, although no direct cardiotoxic effect has been demonstrated

Caution should be exercised when treating patients with known seizure disorders and / or compromised central nervous system function.

Reversible neutropenia and thrombocytopenia that can be severe and may be dose related have been observed during IMUKIN therapy. Caution should be exercised when administering IMUKIN® to patients with myelosuppression.

Caution should be observed in patients with hepatic insufficiency. Elevations of AST and/or ALT have been observed during IMUKIN therapy, as early as 7 days after starting therapy. The incidence appeared to be higher in patients less than 1 year of age compared to older children. The transaminases elevations were reversible with reduction in dosage or interruption of IMUKIN treatment.

Simultaneous administration of interferon gamma with other heterologous serum protein preparations or immunological preparations (e.g. vaccines) should be avoided due to the risk of an unexpected, or amplified immune response.

Patients with serious liver disease and patients with severe renal insufficiency should be treated with caution since the possibility of interferon gamma accumulation exists in these patients.

Patients being treated with IMUKIN and their parents should be informed regarding the potential benefits and risks associated with treatment. If home use is considered to be desirable by the physician, instructions on appropriate use should be given.

In addition to tests normally required for monitoring patients with CGD, patients should have the following tests performed before beginning IMUKIN therapy and at appropriate periods during treatment: haematological tests, including complete blood counts, differential and platelet counts; blood chemistries, including renal and liver function tests; urinalysis.

More than 900 patients treated with IMUKIN in single-agent clinical trials have been tested for the presence of antibody to interferon gamma by a sensitive radioimmunoprecipitation assay which detects neutralising as well as non-neutralising antibody. In only one patient the performed assay was positive. None the less, subsequent samples were negative. Interferon gamma 1b, the active ingredient of IMUKIN, is an exogenous protein, which may lead to the occurrence of antibodies during the course of treatment.

## **Use in Pregnancy**

An increased incidence of abortions has been observed in pregnant primates, which received the drug in doses approximately 100 times higher than that recommended for human use. For lower doses there is no evidence of maternal toxicity, embryotoxicity, fetotoxicity or teratogenicity in preclinical studies.

IMUKIN should therefore be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

## **Use during Lactation**

It is not known whether IMUKIN is excreted in human milk: therefore breast feeding is not recommended.

## **Fertility**

Studies investigating the effect of IFN-gamma on human fertility have shown conflicting results. Based on the information available it can not be excluded that the presence of higher levels of IFN-gamma may impair male fertility and that in certain cases of female infertility increased levels of IFN-gamma may have played a role. In younger patients, the long-term effect on fertility is also not known.

## **Effects on Ability to Drive and Use Machines**

No studies on the effect on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as fatigue, convulsion, confusional state, disorientation or hallucination during treatment. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience any of these events, they should avoid potentially hazardous tasks such as driving or operating machinery.

Even when given at the recommended dosage of 50 µg/m<sup>2</sup> by subcutaneous injection, IMUKIN may affect the ability to drive a vehicle or to operate machinery. This effect may be enhanced by alcohol.

## **Adverse Effects**

The clinical and laboratory toxicity associated with multiple dose IMUKIN therapy is dose, route and schedule-dependent.

The most common adverse experiences occurring with IMUKIN therapy include constitutional symptoms such as fever, headache, chills, myalgia or fatigue which may decrease in severity as treatment continues. Paracetamol may also be used to ameliorate these effects.

### Blood and lymphatic system disorders

- neutropenia
- thrombocytopenia

### Metabolism and nutrition disorders

- hyponatraemia\*
- hypoglycaemia\*
- hypertriglyceridaemia\*

### Psychiatric disorders

- depression
- confusional state\*
- disorientation\*
- hallucination\*

### Nervous system disorders

- convulsion\*
- Parkinsonian gait\*
- Parkinsonian rest tremor\*
- gait disturbance\*

#### Cardiac disorders

- cardiac failure\*
- myocardial infarction\*
- tachyarrhythmia\*
- atrioventricular block\*

#### Vascular disorders

- transient ischaemic attack\*
- deep vein thrombosis\*
- pulmonary embolism\*
- hypotension\*
- syncope\*

#### Respiratory, thoracic and mediastinal disorders

- interstitial lung disease\*
- bronchospasm\*
- tachypnoea\*

#### Gastrointestinal disorders

- diarrhoea
- vomiting
- nausea
- pancreatitis (including fatal outcome)\*
- gastrointestinal haemorrhage\*
- abdominal pain

#### Hepatobiliary disorders

- hepatic enzymes increased
- hepatic failure\*

#### Skin and subcutaneous disorders

- rash
- (exacerbation of) dermatomyositis\*

#### Musculoskeletal and connective tissue disorders

- myalgia
- arthralgia
- systemic lupus erythematosus\*
- back pain

#### Renal and urinary disorders

- (reversible) renal failure\*
- proteinuria

#### General disorders and administration site conditions

- fever

- headache
- chills
- fatigue
- injection site pain
- chest discomfort\*

#### Investigations

- autoantibody positive\*

\*These adverse reactions were seen in clinical trials of conditions other than the registered indications CGD and osteopetrosis and usually at higher doses than recommended

## Interactions

There is no evidence that IMUKIN reduces the efficacy of antibiotics or glucocorticoids in CGD patients

Drug interactions seen with IMUKIN are similar to those seen with other interferons in animal experiments.

It is theoretically possible that hepatotoxic and / or nephrotoxic drugs might have effects on the clearance of IMUKIN. Also the effects of anti-inflammatory drugs, NSAID's, theophylline, immunosuppressive and cytostatic drugs on the acute cellular effects of IMUKIN and its therapeutic effects in CGD patients when such drugs are used concomitantly in chronic conditions are not known. Theoretically, the concomitant administration of heterologous serum protein preparations or immunological preparations (e.g. vaccines) may increase the immunogenicity of IMUKIN.

IMUKIN potentially can alter the half-lives of simultaneously administered drugs which are metabolised by the cytochrome P-450 system.

Concurrent use of drugs having neurotoxic (including effects on the central nervous system), haemotoxic, myelosuppressive and cardiotoxic effects may increase the toxicity of interferons in these systems.

IMUKIN should not be mixed with other drugs in the same syringe.

## Overdosage

IMUKIN has been administered at higher doses (>100 mcg/m<sup>2</sup>) to patients with advanced malignancies by the intravenous or intramuscular route.

Patients with pre-existing cardiac disease may experience an acute, self-limited exacerbation of their cardiac condition at doses of 250 mcg/m<sup>2</sup>/day or higher, as observed in early clinical trials, although no direct cardiotoxic effect has been demonstrated.

Central nervous system adverse reactions including decreased mental status, gait disturbance and dizziness have been observed, particularly in cancer patients receiving doses greater than 100 mcg/m<sup>2</sup>/day. These abnormalities were reversible within a few days upon dose reduction or discontinuation of therapy.

Reversible neutropenia and elevation of hepatic enzymes and of triglycerides and thrombocytopenia have also been observed.

## Pharmaceutical Precautions

The formulation does not contain a preservative. Once opened, the content of a vial should be used immediately. The unused portion of any vial should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Vials of IMUKIN must be stored in a refrigerator (2 - 8°C), but must not be frozen and must not be shaken vigorously.

An unopened vial of IMUKIN should not be left at room temperature for a total time exceeding 12 hours prior to use.

## Medicine Classification

Prescription Medicine

## Package Quantities

Packs of 6 x 100 mcg /0.5ml vials

## Further Information

IMUKIN is a registered trademark.

## Excipients

Mannitol, sodium succinate hexahydrate, succinic acid, polysorbate 20, water for injection.

## Toxicology

IMUKIN did not induce overt signs of acute toxicity in 3 animal models treated parenterally with doses up to 28 mg/kg. Furthermore, no evidence of definitive irritative, haemolytic or mutagenic potential was observed.

In multidose studies of 2 to 13 weeks duration, the 0.25 mg/kg and 0.75 mg/kg doses respectively were found to be the NOAELs (No Observed Adverse Event Levels) in rats following i.v. or i.m. administration. In squirrel monkeys, daily i.v. doses as high as 1.5 mg/kg were without toxic effect over a 2-week period, and a s.c. dose of 0.15 mg/kg was the NOAEL in a 10-day study in cynomolgus monkeys. In contrast, a 4-week study employing an HSA formulation in cynomolgus monkeys produced haematological, biochemical and histopathological changes after i.v. doses of more than 0.15 mg/kg, with mortality occurring at the 1.5 mg/kg dose level. These latter findings do not represent major safety concerns since the effects appeared to be dose-related, occurring at multiples of approx. 100 to 1000 times the intended clinical dose. Furthermore, since clinical experience to date has not revealed any similar toxicity findings, these results may be related to species sensitivity or formulation differences.

No indication of teratogenic potential was observed in segment II studies conducted in rats or rabbits. No evidence of maternal, foetal or developmental toxicity was observed in a segment III study in rats; the NOAEL was 0.67 mg/kg/day. A single segment I study conducted in rats showed that IMUKIN® is free of adverse effects on fertility and general reproduction.

An increased incidence of abortions has been observed in pregnant primates who received the drug in doses 100 times higher than the recommended human dose. Reversible irregular menstrual cycles were observed in primates receiving 0.03 mg/kg/day or greater, for two consecutive menstrual cycles, whereas doses of 0.003 mg/kg/day were free of any adverse effects on the reproductive indices.

Carcinogenic studies have not been performed, as antibody formation in the animals against the human protein preclude any evaluation in such experiments.

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