IMUKIN

(recombinant human interferon gamma-1b [rbe])

NAME OF THE MEDICINE

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 the human protein. Purification of the product is achieved by conventional column chromatography.

DESCRIPTION

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. Excipients include mannitol, sodium succinate, succinic acid, polysorbate 20 and water for injections.

PHARMACOLOGY

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. However, the mechanism of action of Imukin in Chronic Granulomatous Disease (CGD) remains unknown.

Pharmacokinetics

Absorption

Imukin is rapidly cleared after intravenous administration. It is slowly cleared after intramuscular or subcutaneous administration although it is well absorbed. The mean elimination half-lives were 38 minutes, 2.9 hours and 5.9 hours after administration of a single 2 x 10^6 IU (100μg)/m^2 injection by intravenous, intramuscular and subcutaneous routes respectively. Following subcutaneous single dose administration of 0.05 mg/m² of Imukin in healthy male subjects, a mean peak plasma concentration (C_{max}) of 631 pg/mL (CV = 33.82%) was observed after a mean time (t_{max}) of 8 hours (CV = 28.20%), being the mean area under the curve ($AUC_{0-\infty}$) 8.3 ng*h/mL. Similar times of maximum plasma levels have been reported in male and female patients with lymphoma, plasmacytoma or solid tumours (6.3 ± 2.0 hours, mean ± S.D.) after the subcutaneous administration of doses in the range of 0.1 - 0.5 mg/m². Intramuscular administration showed peak plasma concentrations after about 4 hours. The apparent fraction of drug absorbed after intramuscular or subcutaneous injection was greater than 89%. A dose-proportionality has been demonstrated after intravenous and intramuscular administration for doses ranging from 0.1 mg/m² to 2.5 mg/m² and after subcutaneous administration from 0.1 mg/m² to 0.5 mg/m^2.

Distribution

The initial volume of distribution following intravenous administration of Imukin was 12.4 L. In another study, the volume of distribution after administration of a subcutaneous dose was 47.93 L (S.D. ± 25.55 L). In healthy male subjects, there was no accumulation of Imukin after 12 consecutive daily injections of 0.1 mg/m². The mean value of the MRT after subcutaneous administration in the range of 0.1 - 0.5 mg/m² 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^2 via intravenous, intramuscular or subcutaneous routes. The mean value of the apparent clearance following subcutaneous single dose administration in the range of 0.1 - 0.5 mg/m² was 287 mL/min (S.D. ± 148 mL/min).

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.

CLINICAL TRIALS

In a placebo-controlled clinical trial in patients with CGD, Imukin was shown to reduce the frequency of serious infections during the trial period of 12 months. The majority of these patients were also receiving prophylactic antimicrobial therapy. The data generated in this trial on superoxide production and staphylococcal killing by phagocytes did not confirm the proposed immunomodulatory effects. However, the clinical endpoints clearly established the benefit of Imukin therapy and suggest that broader anti-infective mechanisms beyond just oxidative pathways may exist.

Data on the safety and efficacy of Imukin in 37 CGD patients under the age of 3 years were 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 aspartate aminotransferase (AST) and/or alanine aminotransferase (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 elevations recurred in one patient upon Imukin rechallenge.

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.

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 component of the product.

PRECAUTIONS

Imukin should be used with caution in patients with pre-existing cardiac disease, including symptoms of ischaemia, congestive heart failure or arrhythmia. No direct cardiotoxic effect has been demonstrated but it is possible that acute and transient "flu-like" or constitutional symptoms such as fever and chills frequently associated with Imukin administration at doses of 5×10^6 IU (250μg)/m^2/day or higher may exacerbate pre-existing cardiac conditions.

Caution should be exercised when treating patients with known seizure disorders and/or compromised central nervous system function. Central nervous system reactions including decreased mental status, gait disturbance and dizziness have been observed, particularly in patients receiving doses greater than 5×10^6 IU (250μg)/m^2/day. Most of these abnormalities were mild and reversible within a few days upon dose reduction or discontinuation of therapy.

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

Caution should be observed in patients with hepatic insufficiency (see Effect on laboratory tests).

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.

Use of Imukin should be restricted to physicians experienced in the management of patients with CGD.

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.

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. 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. All assays performed to date have been negative, with the exception of one patient, whose subsequent samples were negative. However, since the interferon gamma present in Imukin is not identical to the corresponding endogenous interferon, it would be prudent to monitor patients periodically for the presence of antibodies against Imukin.

The stopper of the glass vial with IMUKIN contains natural rubber (a derivative of latex) which may cause allergic reactions.

Use in Pregnancy (Category B3)

The developmental toxicity of Imukin has not been fully and adequately investigated in species known to be responsive to this product. Imukin has shown an increased incidence of abortions in primates dosed subcutaneously with approximately 3.6×10^6 IU (180μg)/m^2 but failed to demonstrate teratogenic activity for Imukin. There are no adequate and well controlled studies in pregnant women. Imukin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. In addition, studies evaluating

recombinant murine interferon gamma in pregnant mice revealed increased incidences of uterine bleeding and abortifacient activity and decreased neonatal viability at maternally toxic doses. The clinical significance of this latter observation with recombinant murine interferon gamma tested in an homologous system is uncertain.

Use in Lactation

It is not known whether Imukin is excreted in human milk. Breast-feeding is not recommended because of unknown risk to the newborn.

Carcinogenicity

Imukin has not been tested for its carcinogenic potential.

Genotoxicity

The Ames test revealed no evidence of mutagenic potential and a micronucleus assay showed no evidence of chromosomal damage.

Effects on Fertility

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

Female cynomolgus monkeys exhibited irregular menstrual cycles or absence of cyclicity when treated with daily subcutaneous doses above approximately 7.2×10^6 IU ($360\mu g$)/m^2. No studies have been performed assessing any potential effects of Imukin on male fertility in primates.

Effect 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 1×10^6 IU ($50\mu g$)/m^2 by subcutaneous injection, Imukin may affect reactions such that the ability to drive a vehicle or to operate machinery is impaired. This effect may be enhanced by alcohol.

Effect on laboratory tests

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 transaminase elevations were reversible with reduction in dosage or interruption of Imukin treatment.

INTERACTIONS WITH OTHER MEDICINES

Simultaneous administration of interferon gamma with other heterologous serum protein preparations or immunological preparations (eg vaccines) should be avoided because of the risk of unexpected amplified immune response.

Caution should be exercised in concomitant administration of Imukin with other myelosuppressive drugs.

Imukin does not reduce 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, NSAIDs, 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.

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 or cardiotoxic effects may increase the toxicity of interferons in these systems.

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

ADVERSE EFFECTS

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

Serious adverse reactions have not been observed in patients receiving the recommended dose of Imukin, 1 x 10^6 IU (50μg)/m^2 by subcutaneous injection.

The most common adverse experiences occurring with Imukin therapy are constitutional symptoms such as fever, headache, chills, myalgia or fatigue which may decrease in severity as treatment continues. Some of these symptoms can be minimised by bedtime administration. Paracetamol may also be used to ameliorate these effects. Anorexia and weight loss have been observed in clinical trials at a similar incidence to placebo.

The following definitions apply to the frequency terminology used hereafter: very common (≥1/10); common (≥1/100 - <1/10); uncommon (≥1/1,000 - <1/100); rare (≥1/10,000 - <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

<u>Blood and lymphatic system disorders</u>

Frequency not known:	neutropenia
	thrombocytopenia

<u>Metabolism and nutrition disorders</u>

Frequency not known:	hyponatraemia*
	hypoglycaemia*
	hypertriglyceridaemia*

Psychiatric disorders	
Common:	depression
Frequency not known:	confusional state*
	disorientation*
	hallucination*
Nervous system disorders	
Frequency not known:	convulsion*
	Parkinsonian gait*
	Parkinsonian rest tremor*
	gait disturbance*
Cardiac disorders	
Frequency not known:	cardiac failure*
	myocardial infarction*
	tachyarrhythmia*
	atrioventricular block*
Vascular disorders	
Frequency not known:	transient ischaemic attack*
	deep vein thrombosis*
	pulmonary embolism*
	hypotension*
	syncope*
Respiratory, thoracic and mediastinal disorders	
Frequency not known:	interstitial lung disease*
	bronchospasm*
	tachypnoea*
Gastrointestinal disorders	
Very common:	diarrhoea
	vomiting
	nausea
Common:	abdominal pain
Frequency not known:	pancreatitis (including fatal outcome)*
	gastrointestinal haemorrhage*
Hepatobiliary disorders	
Very common:	hepatic enzymes increased
Frequency not known:	hepatic failure*

Skin and subcutaneous tissue disorders

Very common:	rash
Frequency not known:	(exacerbation of) dermatomyositis*

Musculoskeletal and connective tissue disorders

Common:	myalgia
	arthralgia
	back pain
Frequency not known:	systemic lupus erythematosus*

Renal and urinary disorders

Frequency not known:	(reversible) renal failure*
	proteinuria

General disorders and administration site conditions

Very common:	fever
	headache
	chills
	fatigue
	injection site pain
Frequency not known:	chest discomfort*

Investigations

Frequency not known:	autoantibody positive*

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

DOSAGE AND ADMINISTRATION

The recommended dosage of Imukin for injection for the treatment of patients with CGD is 1 x 10^6 IU (50μg)/m^2 for patients whose body surface area is greater than 0.5m^2, and 3 x 10^4 IU (1.5μg)/kg/dose for patients whose body surface area is equal to or less than 0.5m^2.

Care should be taken to ensure accurate adjustment of the volume of solution drawn into the syringe prior to injection. Injections should be administered subcutaneously three times weekly (for example, Monday, Wednesday, Friday). 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 once they are trained in the administration of subcutaneous injections.

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.

There are limited data available to adequately characterise the patient population most likely to benefit from Imukin. However, there is some evidence to suggest that Imukin may be most effective in the young, in those with X-linked disease and in those with a history of more serious prior infection. In adult patients, a significant difference between Imukin and placebo has not been demonstrated.

Higher doses are not recommended. The optimum dose of Imukin has not been established. Safety and efficacy have not been established for Imukin given in doses greater or less than the recommended dose of 1 x 10^6 IU (50μg)/m^2 three times weekly.

Available data indicate that Imukin is well tolerated and patients continue to benefit through 12 months of therapy. It is not known how long treatment with Imukin should continue since the safety and efficacy of a longer duration of treatment are unknown.

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Imukin has been administered at higher doses (>2 x 10^6 IU [100μg]/m^2) to patients with advanced malignancies by the intravenous or intramuscular route.

Central nervous system adverse reactions including decreased mental status, gait disturbance and dizziness have been observed, particularly in cancer patients receiving doses greater than 2 x 10^6 IU (100μg)/m^2/day. These abnormalities were reversible within a few days upon dose reduction or discontinuation of therapy. Reversible neutropenia, elevation of hepatic enzymes, raised triglycerides and thrombocytopenia have also been observed.

In patients with pre-existing cardiac disease, including symptoms of ischaemia, congestive heart failure or arrhythmia, no direct cardiotoxic effect has been demonstrated, but at very high doses (5 X 10^6 IU [250μg]/m^2/day or higher), it is possible that acute, self-limited constitutional toxicities may exacerbate pre-existing cardiac conditions.

PRESENTATION AND STORAGE CONDITIONS

Vials containing 2 x 10^6 IU (100μg) interferon gamma-1b (rbe) per 0.5mL.

Packs of 6 vials.

The formulation does not contain a preservative. Once opened, the contents of a vial should be used immediately. Each vial is for use in one patient on one occasion only. The unused portion of any vial should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Vials of Imukin must be placed in a refrigerator (2 - 8°C), but must not be frozen or shaken vigorously.

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

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

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POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

DATE OF FIRST INCLUSION IN AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

Approved by the Therapeutic Goods Administration (TGA) on 8 April 1994

DATE OF MOST RECENT AMENDMENT

24 July 2013