

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Immukin 2 x 10⁶ IU (0.1 mg) solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial (0.5 ml) contains 2 x 10⁶ IU (0.1 mg) recombinant human interferon gamma-1b. Interferon gamma-1b is produced in an *E. coli* expression system.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

A clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Immukin is indicated for the reduction of the frequency of serious infections in patients with chronic granulomatous disease (CGD) (see also section 4.4).

Immukin is indicated for the reduction in frequency of serious infections in patients with severe, malignant osteopetrosis (see also section 4.4 and 5.1).

4.2 Posology and method of administration

Immukin is for subcutaneous use. The recommended dosage of Immukin for the treatment of patients with CGD or severe, malignant osteopetrosis is 50 mcg / m² for patients whose body surface area is greater than 0.5 m² and 1.5 mcg / kg / dose for patients whose body surface area is equal to or less than 0.5 m². The actually drawn volume has to be controlled before injection. Injections should be administered subcutaneously preferably in the evening three times weekly (for example, Monday, Wednesday, Friday). The optimum sites of injection are the right and the left deltoid and anterior thigh. Immukine can be administered by a physician, nurse, family member or patient when trained in the administration of subcutaneous injections.

Although the most beneficial dose of Immukin is not known yet higher doses are not recommended. Safety and efficacy has not been established for Immukine given in doses greater or less than the recommended dose of 50 mcg / m². If severe reactions occur, the dosage should be modified (50 % reduction) or therapy should be discontinued until the adverse reaction abates.

The experience in children is limited (see sections 4.4 and 5.1)

4.3 Contraindications

Hypersensitivity to the active substance (interferon gamma-1b) or known hypersensitivity to closely related interferons or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The use of Immukin does not exclude the need for any additional antimicrobial coverage that might be required for the management of CGD. In the pivotal clinical efficacy study the overwhelming majority of the patients were receiving prophylactic antimicrobial therapy (see section 5.1).

Patients with pre-existing cardiac disease may experience an acute, self-limiting exacerbation of their cardiac condition at doses of 250 mcg / m² / 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.

Patients with serious hepatic insufficiency and patients with severe renal insufficiency should be treated with caution since the possibility of interferon gamma-1b accumulation exists in those patients.

Elevations of AST and /or ALT (up to 25-fold) have been observed during Immukin therapy. The incidence appeared to be higher in patients less than 1 year of age compared to older children with 6 out of 10 developing elevated enzyme levels. In one case this occurred as early as 7 days after starting therapy. Treatment with Immukin was interrupted in all 6 of these patients and restarted at a reduced dosage in 4. Liver transaminase values returned to baseline in all patients and did not recur with rechallenge except in one patient. Caution should be especially observed in patients with hepatic insufficiency.

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

Simultaneous administration of interferon gamma-1b with other heterologous serum protein preparations or immunological preparations (e.g. vaccines) should be avoided because of the risk for unexpected amplified immune response (see section 4.5).

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

Interferon gamma-1b is an exogenous protein, which may lead to the occurrence of antibodies during the course of treatment. Up to now Immukin administered to CGD or severe, malignant osteopetrosis patients in the recommended dose does not seem to be associated with significant risk for the induction of neutralising antibodies to interferon gamma-1b.

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

Based on the information available it cannot be excluded that the presence of higher levels of interferon gamma-1b may impair male and female fertility (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults. Immukin does not reduce the efficacy of antibiotics or glucocorticoids in CGD or severe, malignant osteopetrosis patients.

Drug interactions seen with Immukin 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 Immukin. Also the effects of anti-inflammatory drugs, NSAIDs, theophylline, immunosuppressive and cytostatic drugs on the acute cellular effects of Immukin and its therapeutic effects in CGD or severe, malignant osteopetrosis patients when such drugs are used concomitantly in chronic conditions are not known. The concomitant administration of heterologous serum protein preparations or immunological preparations (e.g. vaccines) may increase the immunogenicity of Immukin (see section 4.4).

Immukin potentially can prolong 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of interferon gamma-1b in pregnant women. Higher levels of endogenous interferon gamma were found in women with recurrent first trimester miscarriage compared to women with normal pregnancy. There is no evidence of any clinical relevance for Immukin.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Immukin should not be used during pregnancy unless vitally indicated.

Lactation

It is not known whether interferon gamma-1b is excreted in human milk. Because of the lack of data on neonatal effects, breastfeeding is not recommended.

Fertility

Based on the information available it cannot be excluded that the presence of higher levels of interferon gamma-1b may impair male and female fertility. Studies in animals have shown an impact on male fertility at dose levels which are considered not relevant for human use (see section 5.3). In younger patients the long-term effect on fertility is also not known.

4.7 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.

4.8 Undesirable effects

a) General Description

The clinical and laboratory toxicity associated with multiple-dose Immukin therapy is dose- and schedule-dependent.

The most common adverse events are flu-like symptoms characterised by fever, headache, chills, myalgia or fatigue.

b) Table of Adverse Reactions

Adverse reactions have been ranked under headings of frequency using the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Not Known: Neutropenia#, thrombocytopenia#

Metabolism and nutrition disorders

Not known: Hyponatraemia*, hypoglycaemia*, hypertriglyceridaemia*

Psychiatric disorders

Common: Depression

Not known: Confusional state*, disorientation*, hallucination*

Nervous system disorders

Not known: Convulsion*, Parkinsonian gait*, Parkinsonian rest tremor*, gait disturbance*

Cardiac disorders

Not known: Cardiac failure*, myocardial infarction*, tachyarrhythmia*, atrioventricular block*

Vascular disorders

Not known: Transient ischemic attack*, deep vein thrombosis*, pulmonary embolism*, hypotension*, syncope*

Respiratory, thoracic and mediastinal disorders

Not known: Interstitial lung disease*, bronchospasm*, tachypnoea*

Gastrointestinal disorders

Very common: Nausea, vomiting, diarrhea

Common: Abdominal pain

Not known: Pancreatitis (including fatal outcome)*, gastrointestinal haemorrhage*

Hepatobiliary disorders

Very common: Hepatic enzymes increased⁺

Not known: Hepatic failure*

Skin and subcutaneous tissue disorders

Very common: Rash

Not known: (exacerbation of) Dermatomyositis*

Musculoskeletal and connective tissue disorders

Common: Myalgia, arthralgia, back pain

Not known: Systemic lupus erythematosus*

Renal and urinary disorders

Not known: (reversible) Renal failure*, proteinuria#

General disorders and administration site conditions

Very common: Fever, headache, chills fatigue, injection site pain

Not known: Chest discomfort*

Investigations

Not known: Autoantibody positive*

Cannot be estimated from the available data

+Frequency higher in placebo group than in verum group

*Undesirable effects seen in clinical trials of conditions other than the registered indications CGD and osteopetrosis. In these trials interferon gamma-1b was usually administered at higher doses than recommended for the registered indications (see also section 4.9)

Since these events have not been seen in clinical trials involving CGD or osteopetrosis but are reported in trials of patients with very diverse indications and health statuses, it is not possible to provide meaningful frequencies.

c) Information Characterising Individual Serious and/or Frequently Occurring Adverse Reactions

The flu-like symptoms may decrease in severity as treatment continues. Some of these symptoms can be minimised by bedtime administration. Acetaminophen (paracetamol) may also be used to ameliorate these effects. Vomiting, nausea, arthralgia and injection site tenderness have been reported in some patients.

Transient cutaneous rashes, e.g. dermatitis, maculopapular rash, pustular and vesicular eruptions, and erythema at injection site have occurred in some patients following injection but have rarely necessitated treatment interruption.

The inclusion of autoantibody production and systemic lupus erythematosus is the result of case reports in the literature. The adverse reaction “confusion” is also in the literature as a case report.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie, E-mail: medsafety@hpra.ie

4.9 Overdose

Immukin has been administered at higher doses ($>100 \text{ mcg} / \text{m}^2$) 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

$100 \text{ mcg} / \text{m}^2 / \text{day}$. These abnormalities were reversible within a few days upon dose reduction or discontinuation of therapy.

Blood disorders including reversible neutropenia and thrombocytopenia as well as the onset of increased hepatic enzymes and of triglycerides have also been observed.

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

Further undesirable effects which may occur as a consequence of overdosing as observed in respective clinical trials in other than the registered indications are outlined in section 4.8 above.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators,
ATC code: L03A B03

Interferons are a family of functionally related proteins synthesised by eukaryotic cells in response to viruses and a variety of natural and synthetic stimuli. The real mechanism of action of interferon gamma-1b in CGD is still unknown. Findings related to superoxide anion production remain unequivocal.

However, it is presumed that interferon gamma-1b 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 128 patients with CGD, Immukin was shown to reduce the frequency of serious infections during the trial period of 12 months by 77 % in patients treated with Immukin compared to 30 % in the placebo group ($p = 0.0006$). The overwhelming majority of these patients were also receiving prophylactic antimicrobial therapy.

Data on the safety and efficacy of Immukin 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 Immukin treatment groups in controlled trials.

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, Immukin 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 Immukin 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 Immukin treated patients versus a control group could not be established.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous single dose administration of 0.05 mg/m^2 of Immukin in healthy male subjects, a mean peak plasma concentration (C_{max}) of 631 pg/mL ($\text{CV} = 33.82\%$) interferon gamma-1b was observed after a mean time (t_{max}) of 8 hours ($\text{CV} = 23.99\%$). The mean area under the curve ($\text{AUC}_{0-\infty}$) was 8.3 ng h/mL . In cancer patients a comparable (dose normalised) exposure is observed and AUC increased dose proportional over the $0.1 - 0.5 \text{ mg/m}^2$ dose range. 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^2 to 2.5 mg/m^2 and after s.c. administration from 0.1 mg/m^2 to 0.5 mg/m^2 .

Distribution

The volume of distribution at the steady state after bolus i.v. or s.c. administration ranged from 10.9 to 47.93 L . In healthy male subjects, there was no accumulation of interferon gamma-1b after 12 consecutive daily injections of 0.1 mg/m^2 . The mean value of the Mean Residence Time (MRT) after s.c. administration in the range of $0.1-0.5 \text{ mg/m}^2$ is 10.95 h ($\text{S.D.} \pm 2.40 \text{ h}$).

Metabolism and elimination

The metabolism of cloned interferons falls within the natural handling of proteins. Interferon gamma-1b was not detected in the urine of healthy male subjects following administration of 0.1 mg/m^2 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 interferon gamma-1b from perfusate. Preclinical studies in nephrectomised animals demonstrated a reduction in the clearance of interferon gamma-1b 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 $0.1-0.5 \text{ mg/m}^2$ was 2.87 L/min ($\text{S.D.} \pm 1.48$).

5.3 Preclinical safety data

Although difficult to interpret, due to species restrictions, non-clinical data reveal no hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction, local tolerance and skin sensitisation.

An increased incidence of abortion has been observed in pregnant non-human primates, which received the drug in doses manifold higher than that recommended for human use.

Interferon gamma caused increased apoptosis in rat uterus and placenta and in human cytotrophoblast cells. Teratogenicity was observed in mice at lower doses than the human dose. No teratogenicity was observed in rats and in primates up to 100 times the human dose.

Administration of very high doses of interferon gamma to juvenile male mice caused reduced epididymal and testes weights, reduced sperm counts, sperm abnormalities and reduced mating performance and fertility. These effects are considered not relevant for human use at the indicated dose levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-Mannitol
Disodium succinate hexahydrate
Polysorbate 20
Succinic acid
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

Immukin is for single use only.

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.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

6.5 Nature and contents of container

3 ml glass vials (Type I borosilicate glass) which are stoppered with grey butyl rubber stoppers with aluminium/polypropylene flip-off type caps.

Pack sizes: 1, 3, 5, 6 and 12 vial(s) in one folding box. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vials of Immukin must not be shaken vigorously.

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

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

7 MARKETING AUTHORISATION HOLDER

Horizon Pharma Ireland Limited
Connaught House
1st Floor
1 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2138/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th January 1993

Date of last renewal: 29th September 2007

10 DATE OF REVISION OF THE TEXT

August 2017