1. **NAME OF THE MEDICINAL PRODUCT**

Immukine 2 x $10^6$ IU (0.1 mg) solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial (0.5 ml) contains 2 x $10^6$ 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**

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

Immukine 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**

Immukine is for subcutaneous use. The recommended dosage of Immukine for the treatment of patients with CGD or severe, malignant osteopetrosis is 50 mcg / m$^2$ for patients whose body surface area is greater than 0.5 m$^2$ and 1.5 mcg / kg / dose for patients whose body surface area is equal to or less than 0.5 m$^2$. 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 Immukine 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 / m$^2$. 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.
4.4 Special warnings and precautions for use

The use of Immukine 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 Immukine 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 Immukine 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 Immukine therapy. Caution should be exercised when administering Immukine 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 Immukine 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 Immukine 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.

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. Immukine does not reduce the efficacy of antibiotics or glucocorticoids in CGD or severe, malignant osteopetrosis patients.

Drug interactions seen with Immukine 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 Immukine. Also the effects of anti-inflammatory drugs, NSAIDs, theophylline, immunosuppressive and cytostatic drugs on the acute cellular effects of Immukine 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 Immukine (see section 4.4).

Immukine 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 Immukine. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Immukine 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 Immukine 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100);

rare (≥ 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.

4.9 Overdose

Immukine has been administered at higher doses (>100 mcg / m²) 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 mcg / m² / 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 mcg / m² / 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, Immukine was shown to reduce the frequency of serious infections during the trial period of 12 months by 77 % in patients treated with Immukine 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 Immukine 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 Immukine 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, Immukine 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 Immukine 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 Immukine treated patients versus a control group could not be established.

### 5.2 Pharmacokinetic properties

Immukine is rapidly cleared after intravenous administration and slowly and well absorbed after intramuscular or subcutaneous administration.

With the recommended dosage regimen of subcutaneous administration of 0.05 mg / m$^2$ Immukine, the mean elimination half-lives were 4.9 hours and the mean residence time was 2.5 hours. Time to reach maximum plasma concentration ranged from 4 to 14 hours with a mean of 8 hours.

Interferon gamma-1b was not detected in the urine of healthy male subjects following administration of 100 mcg / m$^2$ by intramuscular or subcutaneous injection.

### 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

Immukine 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 Immukine must not be shaken vigorously. Parenteral drug 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. MARKETING AUTHORISATION HOLDER

[Please enter nationally - National name and address will be entered after finalization of the wording] e.g.:

Boehringer Ingelheim International GmbH
D-55216 Ingelheim am Rhein
Germany (Country name in the language of the text)
Tel: optional
Fax: optional
Email: optional

8. MARKETING AUTHORISATION NUMBER(S)

[Please enter nationally - National MA number will be entered after finalization of the wording]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Please enter nationally - Date of first national authorization/renewal will be entered after finalization of the wording]
10. DATE OF REVISION OF THE TEXT
-Please enter nationally – Date of revision of the text will be entered after finalization of the wording}
LABELLING
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**FOLDING BOX**

1. **NAME OF THE MEDICINAL PRODUCT**

   Immukine 2 x $10^6$ IU (0.1 mg) solution for injection
   Recombinant human interferon gamma-1b

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each vial (0.5 ml) contains 2 x $10^6$ IU (0.1 mg) recombinant human interferon gamma-1b.

3. **LIST OF EXCIPIENTS**

   Also contains D-mannitol, disodium succinate hexahydrate, polysorbate 20, succinic acid, water for injections.
   Please see leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Solution for injection
   One Pack contains 1, 3, 5, 6, 12 vial(s).

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Subcutaneous injection. Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

   Do not shake vigorously.

8. **EXPIRY DATE**

   EXP:
   Once opened the content of a vial should be used immediately. The unused portion of any vial should be discarded.

9. **SPECIAL STORAGE CONDITIONS**

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

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
[To be completed nationally e.g.:]
Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein, Germany

12. MARKETING AUTHORISATION NUMBER(S)
[To be completed nationally]

13. BATCH NUMBER
Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY
Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>NOT APPLICABLE</em></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

3. **EXPIRY DATE**

4. **BATCH NUMBER**

5. **OTHER**
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Immukine $2 \times 10^6$ IU (0.1 mg) solution for injection
Recombinant human interferon gamma-1b

2. METHOD OF ADMINISTRATION

Subcutaneous injection

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml vial

6. OTHER

Store in a refrigerator ($2^\circ$C – $8^\circ$C). Do not freeze.
IMMUKINE contains a substance called recombinant human interferon gamma-1b. Interferons are so-called immunomodulators. These are small proteins that can stimulate the body’s immune system defences. They protect against micro-organisms (e.g. bacteria, viruses and fungi) that can cause disease.

IMMUKINE is for use by patients with chronic granulomatous disease (CGD). CGD is a defect in the metabolism of neutrophils, a type of white blood cell. These normally kill invading bacteria or fungi. The defect with CGD makes neutrophils less able to prevent infections.

IMMUKINE is used to reduce the number of serious infections that may occur with this disease.

IMMUKINE is also used in patients with severe, progressive marble bone disease (osteopetrosis). This is an inherited defect in bone cells, which leads to excessive, abnormal bone growth. It also affects the bone marrow and the blood cells that are usually formed in it. As a result, patients with osteopetrosis are also at risk of serious infections.

2. BEFORE YOU USE IMMUKINE

Do NOT use IMMUKINE

- if you are allergic (hypersensitive) to interferon gamma or to other related interferons or any of the other ingredients of IMMUKINE (please refer to section 6 for further ingredients).

Ask your doctor or pharmacist if you are unsure about whether you are allergic to interferons.

Take special care with IMMUKINE

- if you have heart disease, because higher than usual doses can make your heart condition worse (see section 3 for dosage information)
- if you have seizure disorder and/or compromised central nervous system function
- if your liver does not function as effectively as normal (hepatic insufficiency)
- if your kidneys do not function as effectively as normal (renal insufficiency)
- if your bone marrow does not produce as many blood cells as normal (myelosuppression)
Consult your doctor if one of the warnings above applies to you now or if it did in the past.
You should avoid using IMMUKINE at the same time as other types of protein-based medicines. You should also avoid taking IMMUKINE at the same time as you are given a vaccine. If you have any questions about this, ask your doctor.
You should continue to have the tests used in the management of CGD and severe, progressive osteopetrosis. Your blood count, urine, kidney and liver function should be carefully checked, both before and during the treatment.
High interferon gamma-1b levels in the body may possibly harm the fertility of men and women.

Using other medicines
You may also require antibiotics to treat infections that still occur while you are taking IMMUKINE for the treatment of CGD. There is no evidence that Immukine affects the efficacy of antibiotics or corticosteroids, commonly used medications in CGD and severe, malignant osteopetrosis patients. Medicines that affect the liver or the kidneys may affect the excretion of IMMUKINE from the body. It is possible that IMMUKINE might prolong the activity of other medicines that are broken down and removed from the body by the liver.

If you use IMMUKINE at the same time as medicines or vaccines that have effects upon the heart, blood, bone marrow, nervous system or immune system, the risk of side effects may be increased.

Please tell your doctor or pharmacist if you are taking or have recently taken or regularly take any medicines, including medicines obtained without a prescription.

Fertility, pregnancy and breast feeding
Based on the information available, effects on fertility are not known but cannot be excluded. You should not use IMMUKINE during pregnancy, unless your doctor thinks it is essential. You are recommended not to breast-feed while using IMMUKINE.

Ask your doctor or pharmacist for advice before using any medicine.

Driving and using machines
IMMUKINE can cause fatigue, fits (seizures), confusion, disorientation or distorted or imaginary sensations (hallucinations). These side effects can reduce the ability to respond and can thus have a negative effect upon the ability to drive and use machines. Do not drive or use machines if you realize reduced responsiveness.

Important information about some of the ingredients of Immukine
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5ml vial, i.e. it is ‘sodium-free’. This may be important for people with high blood pressure and others wishing to maintain a low sodium diet.

3. HOW TO USE IMMUKINE
IMMUKINE is for injection under the skin (subcutaneous use) and can be administered by a doctor or nurse. You or a family member could also administer IMMUKINE. You or your family member should be trained by a doctor or nurse in giving this type of injection.

The recommended dosage of Immukine for the treatment of patients with CGD or severe, malignant osteopetrosis is 50mcg/m² for patients whose body surface area is greater than 0.5 m² and 1.5 mcg/kg for patients whose body surface area is equal to or less than 0.5 m².

Your doctor will decide how much Immukine you need to take to treat CGD or severe, progressive osteopetrosis.

Always use IMMUKINE as your doctor has told you. Check with your doctor or pharmacist if you are not sure how to use IMMUKINE or if you need any other advice.
You should inject (or should have injected) under your skin the exact amount of IMMUKINE your doctor has told you that you need. You should give the injections three times per week (for example, Monday, Wednesday and Friday), preferably in the evening. The recommended injection sites are the upper arm or the top of the thigh.

- Always check the amount of IMMUKINE solution before giving the injection.
- Do not use IMMUKINE if you can see small particles or discolouration of the solution.
- Do not mix IMMUKINE with other medicines.
- Do not strongly shake IMMUKINE vials.

If you use more IMMUKINE than you should
Immediately consult your doctor if you have administered more IMMUKINE than your doctor has told you.

Symptoms after having administered too much IMMUKINE can include the following:
- central nervous system side effects such as difficulty in thinking, difficulty in walking, and dizziness
- if you have heart disease, this may get worse for a short time.
- blood disorders can occur during treatment with IMMUKINE. These include:
  - temporary changes in the number of some blood cells
  - increases in blood levels of certain substances (liver enzymes and triglycerides)
  These changes can be detected by your doctor with a blood test.

These symptoms resolve with reduction in dose or with discontinuing IMMUKINE.

If you forget to use IMMUKINE
Have your injections at the times your doctor has recommended. If you forget to take a dose, do not inject a double dose to make up for it. You can still administer it on the same or following day. Contact your doctor if you think you have gone too long without taking a dose.

If you stop using IMMUKINE
Please inform your doctor if you stop using IMMUKINE.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, IMMUKINE can cause side effects, although not everybody gets them. The risk of side effects occurring depends on the dose and the dosing schedule you have been given.

The most common side effects are flu-like symptoms such as fever, headache, cold chills, and fatigue. These may become less severe over time as the treatment is continued. Some of these symptoms can be reduced by administering IMMUKINE just before going to sleep. A medicine such as paracetamol can be used to reduce some of these side effects.

Some people who take IMMUKINE may develop short-term skin problems, such as a temporary skin rash, spotty skin rash, the sudden formation of blisters on the skin, and reddening of the skin at the injection site.
However, these are rarely severe enough to stop treatment with IMMUKINE.

The side effects listed below are grouped by how likely they are to happen.

Very common side effects (more than 1 in 10 patients treated) are:
- fever
- headache
- chills
- pain at the injection site
- vomiting
- nausea (feeling sick)
- diarrhoea
- fatigue
- raised levels of liver enzymes
- rash

**Common side effects (less than 1 in 10 patients treated) are:**
- muscle pain
- joint aching or pain
- back pain
- stomach pain
- depression

**Not known (cannot be estimated from the available data):**
- shortage of white blood cells (neutropenia)
- shortage of blood platelets (thrombocytopenia) which might be associated with bruises and a tendency towards bleeding.
- Proteins in the urine

Side effects have also been seen in patients with conditions other than CGD or malignant osteopetrosis. These events have not been seen in clinical trials involving CGD or osteopetrosis. The following side effects have been reported in clinical trials with patients suffering from other diseases/conditions than CGD or osteopetrosis. Often the doses used in these studies were higher than the recommended dose for CGD and osteopetrosis. For this reason it is not possible to say accurately how often they occurred.

**Not known (cannot be estimated from the available data):**
- low blood levels of sodium which can cause tiredness and confusion, muscle twitching, fits or coma (hyponatraemia)
- high levels of a sugar called glucose (hyperglycaemia)
- fatty acids called triglycerides (hypertriglyceridaemia) in the blood

The following nervous system disorders have been observed:
- confusion
- disorientation
- effects on ability to walk such as Parkinsonian gait
- trembling
- fits (seizures)
- distorted or imaginary sensations (hallucinations)

The following heart disorders have also been seen to occur:
- additional and irregular heart beats
- disturbance in the heart rate, such as faster or slower heart rate
- heart problems which can cause shortness of breath or ankle swelling (heart failure)
- heart attack

The following blood system disorders have been reported:
- low blood pressure
- fainting
- mild, temporary stroke (transient ischemic attack)
- blood clot or blockage of a lung artery (deep venous thrombosis and pulmonary embolism); Symptoms can include shortness of breath

The following respiratory disorders have occurred:
- rapid breathing
- chest tightness (bronchospasm or interstitial lung disease).
- bleeding in the digestive system
- inflammation of the pancreas, which can lead to death
- damage to the liver that affects its function (liver failure)
- damage to the kidneys that affect their function but can be treated effectively (reversible kidney failure)
- pains in the chest
- worsening of a skin condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- development of the long-term disease called systemic lupus erythematosus (i.e. the patient’s own immune system attacks various parts of the body)
- autoimmune reaction (Autoantibody response)

If any of the side effects get serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE IMMUKINE

Keep out of the reach and sight of children.

Do not use IMMUKINE after the expiry date which is stated on the carton and vial, after `Do not use after` or `EXP`. The expiry date refers to the last day of that month.

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

IMMUKINE solution for injection vials are for single use only. IMMUKINE contains no preservatives. Once opened, you should use the contents of a vial immediately. Dispose of any unused contents of the vial.

Do not use IMMUKINE if you notice particles or discolouration in it before use.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What IMMUKINE contains

Each vial (0.5 ml) contains 2 x 10^6 IU (0.1 mg) recombinant human interferon gamma-1b. This is a substance produced using E. coli bacteria modified by gene technology.

The other ingredients are D-mannitol, disodium succinate hexahydrate, polysorbate 20, succinic acid and water for injections.

What IMMUKINE looks like and contents of the pack

IMMUKINE is a clear, colourless solution for injection. IMMUKINE is available in 3 ml vials containing 0.5 ml solution for injection.

Pack sizes: 1, 3, 5, 6 and 12 vials(s) in one folding box.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

To be completed nationally

Manufacturer
Boehringer Ingelheim RCV GmbH & Co KG
Dr. Boehringer-Gasse 5-11
1121 Vienna
Austria
Tel: +43 1 80 105-0
Fax: +43 1 804 08 23

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria: Imukin®
Belgium: Immukine®
Bulgaria: -
Cyprus: Imukin®
Czech Republic: -
Denmark: Imukin®
Estonia: -
Finland: Imukin®
France: Imukin®
Germany: Imukin®
Greece: Imukin®
Hungary: Imukin®
Iceland: -
Ireland: Immukin®
Italy: Imukin®
Latvia: -
Liechtenstein: -
Lithuania: -
Luxembourg: Immukine®
Malta: Immukin®
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Norway: Imukin®
Poland: -
Portugal: Imukin®
Romania: -
Slovakia: -
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