

# New Zealand Datasheet

## Name of Medicine

IMUNOVIR

Inosine dimepranol acedoben (inosine pranobex)

## Presentation

500mg Tablet: Biconvex, circular, white tablet marked NPT on one face and having a breakline on the other.

## Uses

### Actions

The immunomodulatory properties of IMUNOVIR have been established in a number of pre-clinical studies. *In-vitro* studies in animals and *in-vivo* studies utilising human peripheral blood monocytes have demonstrated the ability of IMUNOVIR to promote T-cell differentiation, to enhance NK cell activity and T-helper cell function, to induce the acquisition of various T-cell subset markers, to potentiate the proliferative response of lymphocytes to various plant mitogens, and to enhance the production of the lymphokines, interleukin 1 (IL-1) and interleukin 2 (IL-2), and the receptors for IL-2.

Either its thymomimetic action or its influence on IL-1 and IL-2 production which in turn enhance NK T-lymphocyte activity, may be responsible for the immunorestorative properties of IMUNOVIR in patients with prodromal AIDS, chronic generalised lymphadenopathy (PGL) or AIDS-related complex (ARC).

The characteristics of Acquired Immunodeficiency Syndrome (AIDS) suggest that a central defect in the cellular immune response is the critical focus of the disease. The implication of the putative etiologic agent, human T-cell lymphotropic virus (HTLV-111), by its frequent isolation from patients or the more frequent presence of anti HTLV-111 antibodies in patients' sera strongly suggests such a central defect, since the virus readily attacks and destroys the T-helper/inducer cell subset. This action of the virus could easily explain many other aberrations in immune function or alterations in the numbers of certain recognisable cells of the immune system observed in AIDS (i.e. lymphopenia, reduced T-cell number, reduced T-helper/inducer number, reduced cytotoxic T lymphocytes, reduced natural killer cell number and function, reduced production of interferon, IL-1 and IL-2).

Prodromal AIDS (PGL and ARC) has been linked epidemiologically and etiologically to AIDS and is characterised by the presence of HTLV-111 antibodies, chronic generalised lymphadenopathy, fatigue, weight loss, fever and diarrhoea. In general the immunologic abnormalities seen in AIDS patients are also observed, in a less severe form, in patients with prodromal AIDS. Therapy with an agent capable of modulating certain aspects of the immune response is indicated in an attempt to correct the underlying cellular immune defect characteristic of prodromal AIDS and prevent the patient from developing the more serious opportunistic infections and neoplasia which characterise AIDS.

Improvement of the immune response, associated with clinical benefit to the patient and less progression to AIDS, has been established in two clinical trials designed to determine the efficacy of IMUNOVIR in the treatment of prodromal AIDS. The proposed target organ for IMUNOVIR is the bone marrow causing it to produce a

stem cell that can acquire the differentiated characteristics of one or more cell types.

Recently IMUNOVIR, in two large scale multi-centre trials and a number of smaller trials, has been shown to improve the survival probability of, and delay the progress in development of clinical symptoms of patients' suffering from subacute sclerosing panencephalitis (SSPE). The fundamental pathogenesis of SSPE is not adequately understood although several mechanisms have been proposed to explain the clinical silent persistence of the measles or measles-like virus that, after a long incubation period, produces an overt disease that has a generally ingravescent course.

Such proposed mechanisms include: (1) the presence of blocking factors (immune complexes) in serum and cerebrospinal fluid inhibiting immune function, (2) antibody mediated antigenic modulation of target cells rendering them immune to host cell-mediated lysis, (3) alteration in the antigenic expression of the M polypeptide resulting in an infected cell no longer recognised by host cytotoxic effector cells.

Each of these mechanisms has an immunologic basis and these are several possible explanations for the therapeutic success of IMUNOVIR in SSPE. These are: (1) cells suppressing antibody production are generated resulting in diminished levels of "blocking factors" and/or the expression of antigen on target cells permitting their detection and destruction by normal immunologic effector mechanisms, (2) the stimulation of a clone(s) of cells with inductive and/or effector functions directed at the modified M polypeptides. Unfortunately a more comprehensive understanding of the mechanism of action of IMUNOVIR in SSPE must await further clarification of the exact pathogenesis of this disease.

### **Pharmacokinetics**

IMUNOVIR is a molecular complex of inosine and the salt N, N-dimethyl-amino-2-propanol (DIP), p-acetoamidobezoate (PACBA) in a 1:3 molar ratio.

Human pharmacokinetic studies of orally administered IMUNOVIR from both solution and tablet reveal rapid absorption with peak plasma levels of 8mcg/mL (PACBA) and 4mcg/mL (DIP) 1 hour following administration of 1 gram of IMUNOVIR. These plasma concentrations are approximately equimolar (45 and 38 millimolar, respectively). PACBA has a half-life of 50 minutes, while DIP is more slowly eliminated with a half-life of 3.5 hours.

PACBA is excreted in urine only 30-40% as the original compound and 66-70% as its primary metabolite, the O-acyl glucuronide. DIP is excreted approximately 56% unchanged and 44% as its metabolite, the N-oxide. The purine moiety of IMUNOVIR, is metabolised to hypoxanthine, xanthine, and uric acid, all of which are normal endogenous purine metabolites. At steady-state administration of doses from 3-6 grams of IMUNOVIR per day, the increase of daily uric acid excretion in urine over pre-medicine levels indicates absorption of at least 30-70% of the inosine moiety.

### **Indications**

IMUNOVIR is indicated for the enhancement of the immune response in patients with persistent generalised lymphadenopathy at risk of developing Acquired Immunodeficiency Syndrome (AIDS).

Three double-blind placebo-controlled clinical trials designed to establish the immuno-enhancing effect in immunodepressed male homosexuals at risk of developing AIDS were carried out in 157 patients. Data on 132 patients completing 28 days of treatment (70 drug and 62 placebo) and 86 patients (45 drug and 41 placebo) completing 90 days of follow-up examination were analysed for the primary

immunologic variables (NK cell activity, total T-lymphocytes and total T-helper cells). The data from the three studies were pooled and the medicine and placebo groups were compared.

The pretreatment baseline levels indicated that the three study groups enrolled at 9 different centres were immunologically homogeneous. Treatment for 28 days with IMUNOVIR resulted in marked and sustained improvement in all three cell-mediated immunity measurements. NK cell activity showed a significantly greater increase in medicine treated than in placebo treated patients after 14 days of treatment which persisted up to two months after cessation of treatment. An increase was observed in total T-lymphocytes which was significantly greater in medicine treated patients than in those receiving placebo on day 14. A T-helper lymphocyte increase was also found, which was significantly greater in the medicine treated group on day 14 and on day 28 than in the respective placebo group increases.

The progression of at risk patients to CDC defined AIDS was slower in the medicine treated group. After seven months follow-up, six placebo treated patients had developed fully blown AIDS.

IMUNOVIR is also indicated for the long term treatment of SSPE with the intention of improving the probability of survival and delaying progress of clinical symptomatology. Two major multicentre studies have been performed, the first in the US involving 74 patients, the second in Japan involving 151 cases.

In the first study 74 patients treated with IMUNOVIR were compared with two groups of untreated patients derived from each of the United States and Lebanese registries by life-table analysis. At each of the post-onset intervals statistically significant differences ( $P < 0.001$ ) existed between the treated group and each of the control groups. Overall, an individual patient presenting with the clinical symptoms of SSPE has a 62% probability of long term survival (> 8 years) if provided with IMUNOVIR therapy, but only a 2-8% probability if given the traditional forms of treatment. When considering disease progression, beyond 8 years post onset 32% of treated patients will be expected to be a pre-stage IV clinical condition as opposed to 5-10% of untreated individuals.

The second study compared the progress of 89 patients treated with IMUNOVIR with 62 untreated patients over a ten year period. This study showed similar results in that the probability of survival was significantly greater and the progression of the development of clinical symptoms significantly slower in the IMUNOVIR treated group when all possible bias was accounted for.

## **Dosage and Administration**

IMUNOVIR is to be administered orally. For patients with persistent generalised lymphadenopathy 3000mg/day (6 tablets) for 28 days is recommended. The course is to be repeated according to the results of immune function studies. The dosage for children is usually 50mg/kg/day. The recommended dosage for SSPE is 100mg/kg/day in divided doses.

## **Contraindications**

There are no known contraindications for IMUNOVIR.

## **Warnings and Precautions**

Because the purine moiety of IMUNOVIR is rapidly catabolised to uric acid, resulting in elevations of serum and urinary uric acid, IMUNOVIR should be used with caution in patients with a history of gout, urolithiasis, nephrolithiasis, or renal dysfunction.

Uricosuric agents may be administered to patients with severely elevated serum uric acid levels.

Specific studies on the effects of IMUNOVIR on animal reproduction have been performed and were consistently negative. Well controlled trials concerning foetal risk and impairment of fertility in humans are not available. Care should, therefore, be taken in using IMUNOVIR in pregnant women and women of child bearing age, and the risks involved should be well assessed.

## **Adverse Reactions**

The only consistently reported adverse reaction association with administration of IMUNOVIR in either of the two recognised indications is a mild, dose-related increase in serum uric acid. This increase is transient, with uric acid returning to baseline levels upon cessation of treatment.

Tolerance studies have shown mean serum uric acid levels increasing from 5.7 - 6.3mg% after one week at 1g/day, to 6.6mg% after one week at 3g/day, and to 7.2mg% after one week at 4g/day. With administration of IMUNOVIR at 4g/day, 2 of 20 subjects had urinary uric acid levels greater than 1.5g/24 hour, a level that has been associated with the eventual formation of urinary uric acid stones. With doses of 8g/day, 5 of 20 subjects had urine uric acid levels greater than 1.5g/24 hours. Both serum and urine uric acid levels returned to normal when IMUNOVIR was discontinued.

Typically, the anticipated increase in serum uric acid was noted in 21 male pre-AIDS patients receiving IMUNOVIR at a dose of 3g/day for 28 days. Only 4 patients had serum uric acid levels exceeding the upper normal limit of 8.5mg/dl. The mean serum uric acid level in these patients reached a maximum of 6.6mg/dl on the 7th day of treatment. At day 28 of treatment, the value was 6.1mg/dl. At the next follow-up measurement (60 days post-medicine) the serum uric acid had returned to pre-treatment level (5.0mg/dl).

In tolerance studies in which 22 female volunteers received 6g/day IMUNOVIR, the mean elevation in serum uric acid was only 0.9mg/dl. The pre-treatment mean serum uric acid level was approximately 1mg/dl lower in the female volunteers than in male subjects. The highest serum uric acid level observed was 7.4mg/dl in one subject, representing an elevation of 2.3mg/dl. It is evident from this study that problems related to elevated serum uric acid would be highly unlikely in female subjects.

In two double-blind placebo-controlled studies in patients with prolonged generalised lymphadenopathy, a total of 5 adverse reactions believed to be medicine-related were reported among 97 evaluable patients receiving 3g/day of IMUNOVIR for 28 days. These included 4 cases of nausea, and one case of cold-like reaction (sinusitis). Occasionally reports of nausea, abdominal discomfort or vomiting have been noted. Nervousness, insomnia, fatigue or sleeplessness, vertigo and headache have occasionally been noted. Two reports of exacerbation of allergic rash associated with prior treatment with amoxicillin have been received from foreign studies.

Clinical chemistry, haematology and urinalysis from a number of clinical trials suggest no consistent pattern of drug toxicity. There is some evidence that doses of 8g/day may produce hepatotoxicity but no such effects have been observed at the dose of 3g/day recommended in the treatment of AIDS, ARC or SSPE.

## **Interactions**

Clinical experience has identified no interactions resulting from topical or systemic administration of other medicines with IMUNOVIR.

IMUNOVIR was shown to be compatible with a wide range of medicines in a long-term study in patients with amyotrophic lateral sclerosis. Concurrent administration of numerous other therapeutic medicines during the 4 year study demonstrated the IMUNOVIR did not potentiate toxicity, interfere with medicine absorption, or induce additive pharmacological actions.

## **Overdosage**

An overdosage with IMUNOVIR has not been reported and seems unlikely due to the high oral LD50 (greater than 5000mg/day) reported in mouse, rat, guinea pig and cat. An anticipated symptom of overdose would be severe gastric disturbance.

In the event of an overdose, monitoring of potentially elevated urine and serum uric acid levels and the administration of uricosuric agents if necessary would be recommended.

## **Pharmaceutical Precautions**

Tablets should be stored in amber bottles protected from light and moisture.

## **Medicine Classification**

Prescription Medicine.

## **Package Quantities**

100 Tablets.

## **Further Information**

IMUNOVIR is a molecular complex of inosine and the acetamidobenzoic acid salt (PACBA) of N,N-dimethyl-amino-2-propanol (DIP) in a 1:3 molar ratio. It is a white crystalline powder which decomposes above 150°C, has a bitter taste, a UV absorption maximum at 259nm in neutral aqueous solution and is 25% w/v soluble in water. The medicine has a molecular weight of 1115.26.

Inosine, a component of IMUNOVIR, is a naturally occurring substance found in the metabolic pathway of purines and in varying, but small, amounts in cells and tissue fluids of a wide variety of species.

The PACBA moiety is chemically related to p-aminobenzoic acid, a naturally occurring metabolite in human tissue. The DIP moiety is a novel substance chemically and pharmacologically.

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## **Date of Preparation**

6 October 1990.