

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isoprinosine 500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg Inosine Acedoben Dimepranol

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

A round white to off-white uncoated tablet with a bisecting scoreline on one side and 'NPT' on the obverse.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Isoprinosine tablets are indicated:

- a) As an immunomodulator for the management of patients with immunodepression suffering from viral infections such as subacute sclerosing panencephalitis, varicella, herpes simplex Type 1 & 2.
- b) In the management of recurrent herpes simplex Type 1 & 2.
- c) As an adjunct in the treatment of genital warts.

4.2 Posology and method of administration

a) Route of administration: Oral

b) Dosing:

Dosage is determined on the basis of lean body weight of the patient and the severity of the disease. Daily administration should be divided evenly during waking hours. The normal duration of acute treatment is 5-14 days.

Adults and the Elderly:

50mg/kg of body weight daily, up to a maximum of 4g, (usually, 2 tablets x 3-4 times a day).

Children over the age of 1 year:

50mg/kg of body weight daily. (1 tablet per 10 kg up to 20 kgs; thereafter, use adult dose).

SSPE Dosage:

100mg/kg of body weight daily, up to a maximum of 3-4g continuously, with regular monitoring to evaluate patient status and requirement for extended treatment.

Genital Warts Dosage:

3g (2 tablets x 3 times a day) for a total of 14-28 days, as an adjunct to conventional topical or surgical procedures, according to the following schedules:

- a) 14-28 days continuous in “low risk” patients, allowing up to 2 months more with no drug to achieve maximum lesion clearance rate; or
- b) 5 days per week, 1-2 consecutive weeks a month, for 3 months in “high risk*” patients, allowing until end of 3rd month to achieve maximum clearance rate.

* The latest “high risk” profile composite for recurrences or cervical dysplasia for patients with genital HPV infections is similar for other conditions and includes:

- Genital HPV history >2 years or >3 failures of past therapy.
- Immunodepression resulting from:
 - history of recurrent or chronic infections or any other STD.
 - cancer chemotherapy.
 - habitual excess alcohol consumption.
- Poorly controlled diabetes.
- Atopy.
- Long-term use of oral contraceptives (2 years or more).
- Red blood cell (RBC) folate levels at or below 660nmol/L.
- No history of cutaneous childhood warts.
- Multiple vaginal sexual partners or any change in a long-standing partner.
- Frequency of vaginal sex ($\geq 2-6$ times per week).
- Anal sex.
- Age (per additional year after median age of 20 ± 3 years) = 1.1 odds ratio $p = 0.001$ at 95% CI).
- Current smoker, generally, but was found protective in college women of median age of 20 ± 3 years).

To make ingestion easier, the tablets may be crushed and dissolved in a small amount of flavoured liquid at the time of administration.

4.3 Contraindications

Isoprinosine should not be used in those cases where there is a known hypersensitivity to product components or in cases where the patient is presently suffering from gout or elevated uric acid blood levels.

4.4 Special warnings and precautions for use

- a) Isoprinosine may cause a transient elevation of baseline serum and urinary uric acid, usually remaining within the normal range (using 8mg % as the upper limit), particularly in males and in the ageing population of both sexes. The elevation of uric acid levels is due to the catabolic metabolism of the inosine moiety in this product in humansto uric acid. It is not due to a fundamental drug-induced alteration of enzyme or renal clearance function. Therefore, Isoprinosine may be administered with caution in patients with a history of gout, hyperuricaemia, urolithiasis, or to patients with impaired renal function. During treatment, uric acid levels in these patients should be monitored closely.
- b) If administered continuously for 3 months or more, the serum and urine uric acid levels, liver function, blood count and renal functions should be checked on a regular basis in all patients. There is a possibility that ureteric and biliary calculi may occur when patients receive long term treatment.

4.5 Interaction with other medicinal products and other forms of interaction

The drug should be used with caution with xanthine oxidase inhibitors or uricosuric agents, including diuretics.

4.6 Fertility, pregnancy and lactation

Controlled trials monitoring foetal risk and impairment of fertility in humans are not available. It is not known if Isoprinosine is excreted in human milk. Therefore, Isoprinosine should not be administered during pregnancy or lactation unless the physician decides the benefits outweigh the potential risk.

4.7 Effects on ability to drive and use machines

The pharmacodynamic profile of Isoprinosine is unlikely to produce a debilitating effect on the ability to drive or use a machine. (See also *undesirable effects*.)

4.8 Undesirable effects

a) The only consistently observed very common ($\geq 1/10$) drug-related side effect is a transient elevation (usually remaining within normal range) of urine and serum uric acid levels, which usually return to baseline values a few days after the end of treatment.

b) Common ($\geq 1/100$ to $< 1/10$) side effects recorded in $> 1\%$ of clinical studies of 3 months or longer:

<i>Gastrointestinal disorders:</i>	Nausea with or without vomiting, epigastric discomfort
<i>General disorders and administration site conditions</i>	Fatigue or malaise
<i>Investigations</i>	Elevation of transaminases, alkaline phosphatase or blood urea nitrogen (BUN) level
<i>Skin and subcutaneous tissue disorders:</i>	Itching, skin rashes
<i>Nervous system disorders:</i>	Headaches, vertigo,
<i>Musculoskeletal and connective tissue disorders:</i>	Arthralgia

c) Uncommon ($\geq 1/1000$ to $< 1/100$) side effects recorded in $< 1\%$ of clinical studies of 3 months:

<i>Gastrointestinal disorders::</i>	Diarrhoea, constipation
<i>Nervous system disorders::</i>	Drowsiness or insomnia
<i>Psychiatric disorders: Renal and Urinary disorders:</i>	Nervousness Polyuria (increased urine volume).

4.9 Overdose

There has been no experience of overdosage with Isoprinosine. However, serious adverse effects apart from increased levels of uric acid in the body seem unlikely in view of the animal toxicity studies. Treatment should be restricted to symptomatic and supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Isoprinosine is a synthetic purine derivative with immunomodulatory and antiviral properties, which result from an apparent *in vivo* enhancement of host immune responses due to the drug. In clinical studies Isoprinosine has been shown to normalise (to the patient's baseline) a deficient or dysfunctional cell-mediated immunity by evoking a Th1 type response which initiates T lymphocyte maturation and differentiation and potentiation of induced lymphoproliferative responses, in mitogen or antigen-activated cells. Similarly, the drug has been shown to modulate T lymphocyte and natural killer cell cytotoxicity, T8 suppressor and T4 helper cell functions and also to increase the number of IgG and complement surface markers. Isoprinosine increases cytokine IL-1 production and enhances IL-2 production, upregulating the expression of the IL-2 receptor *in vitro*.

It significantly increases endogenous IFN- γ secretion and decreases the IL-4 production *in vivo*. It has also been shown to potentiate neutrophil, monocyte and macrophage chemotaxis and phagocytosis.

In vivo, inosine acedoben dimepranol enhances potentiation of depressed lymphocytic mRNA protein synthesis and translational ability while inhibiting viral RNA synthesis achieved by yet-to-be-clarified degrees of (1) incorporation of inosine-mediated orotic acid into polyribosomes; (2) inhibition of polyadenylic acid attachment to viral messenger RNA and (3) molecular reorganisation of lymphocyte intramembrane plasma particles (IMP) that results in a nearly threefold increase in density.

Isoprinosine inhibits cGMP phosphodiesterase only at high concentrations *in vitro* and at levels not involved in the *in vivo* immunopharmacologic effects.

5.2 Pharmacokinetic properties

Each moiety of the drug exhibits separate pharmacological properties.

Absorption: When administered orally in man, Isoprinosine is rapidly and completely absorbed ($\geq 90\%$) from the gastrointestinal tract and appears in the blood. Similarly, 94-100% of IV values of DIP [N,N-dimethylamino-2-propanol] and PAcBA [p-acetamidobenzoic acid] components are recovered in urine after oral administration in Rhesus monkeys.

Distribution: Radiolabelled material found in the following tissues and in order of decreasing specific activity when drug and its components were administered to monkeys was in kidneys, lung, liver, heart, spleen, testes, pancreas, brain and skeletal muscle.

Metabolism: In human subjects following a 1g radiolabelled oral dose of Isoprinosine, the following plasma levels were found for DIP and PAcBA, respectively: 3.7 micrograms/ml (2 hours) and 9.4 micrograms/ml (1 hour). In human dose tolerance studies, peak post-dose elevation of uric acid levels as a measurement of drug-derived inosine are not linear and can vary $\pm 10\%$ between 1-3 hours.

Excretion: The 24-hour urinary excretion of PAcBA and its major metabolite under steady-state conditions at 4g per day amounted to approximately 85% of the administered dose. 95% of the DIP-derived radioactivity in urine was recovered as unchanged DIP and DIP N-oxide. The elimination half-life is 3.5 hours for DIP and 50 minutes for PAcBA. The major metabolites in humans are the N-oxide for DIP and the o-acylglucuronide for PAcBA.

Because the inosine moiety is degraded by the purine degradation pathway to uric acid, radiolabelled experiments in humans are inappropriate. In animals up to about 70% of the administered inosine can be recovered as urinary uric acid following oral tablet administration and the remainder as the normal metabolites, xanthine and hypoxanthine.

Bioavailability/AUC: Urinary recoveries under steady state conditions of the PAcBA moiety and its metabolite were found to be $\geq 90\%$ of the expected value from solution. The recovery of the DIP moiety and its metabolite was $\geq 76\%$. The plasma AUC was $\geq 88\%$ for DIP and $\geq 77\%$ for PAcBA.

5.3 Preclinical safety data

Isoprinosine showed a low toxicity profile in multivariate acute, subacute and chronic toxicology in mice, rats, dogs, cats and monkeys in doses up to 1500mg/kg/day and produced the lowest acute oral LD₅₀ at 50 times the maximum therapeutic dosage level of 100mg/kg/day.

Long-term toxicology studies in mice and rats have shown no indication of carcinogenic potential.

Standard mutagenicity assays and *in vivo* studies in mice and rats and *in vitro* studies in human peripheral blood lymphocytes revealed no aberrant properties.

No evidence of perinatal toxicity, embryotoxicity, teratogenicity or impaired reproductive function in mice, rats and rabbits could be demonstrated in studies with continuous parental dosing of up to 20 times the maximum therapeutically recommended human dose (100mg/kg/day). (*See also item 4.6 for usage recommendations in pregnancy*).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Pregelatinised Maize (corn) starch
Stearic acid
Magnesium stearate
Microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the container tightly closed.

6.5 Nature and contents of container

24 tablets in amber glass bottles with a white PP wadless screw cap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Newport Pharmaceuticals Limited
Frans Maas House
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Swords
Co. Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 336/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 1983

Date of last renewal: 15 February 2008

10 DATE OF REVISION OF THE TEXT

November 2011