Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imunovir 500 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Inosine Acedoben Dimepranol.

Excipients: each tablet contains 67mg wheat starch.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White to off-white oblong tablets with a faint amine odour, engraved with a score-line on one side and 'DN' on the other.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Imunovir 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) As an adjunct to podophyllin or carbon dioxide laser in treatment of patients with 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 4 g, (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:
100 mg/kg of body weight daily, up to a maximum of 3-4 g, 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:

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

Imunovir 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) Imunovir 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 humans to uric acid. It is *not* due to a fundamental drug-induced alteration of enzyme or renal clearance function. Therefore, Imunovir 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.

In some people acute hypersensitivity reactions (urticarial, angioedema, anaphylaxis) may occur. Treatment with Imunovir should be withdrawn in these cases. Imunovir contains wheat starch. Suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine

4.5 Interaction with other medicinal products and other forms of interactions

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

Isoprinosine may be administered after but not concomitantly with immunosuppressive agents, as there may be a pharmacokinetic influence on the desired therapeutic effects.

Concomitant use with AZT increases AZT nucleotide formation through multiple mechanisms involving increased plasma AZT bioavailability and increased intracellular phosphorylation in human blood monocytes.

As a result Imunovir increases the effect of AZT.

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 Imunovir is excreted in human milk. Therefore, Imunovir 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 Imunovir is unlikely to produce a debilitating effect on the ability to drive or use a machine. *(See also section 4.8, Undesirable Effects.)*

4.8 Undesirable effects

During treatment with Isoprinosine, the only consistently observed drug-related side effects in adults as well as paediatric population 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.

Very common	≥1/10
Common	≥1/100, <1/100
Uncommon	≥1/1,000, <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000,
Not Known	Cannon be estimated from the available data

System Organ Class	Frequency	Adverse Reaction
Immune system disorders:	Not known	Angioedema, Hypersensitivity, Urticaria, Anaphylactic reaction
Psychiatric disorders	Uncommon	Nervousness
Nervous system disorders	Common	Headache, Vertigo
	Uncommon	Somnolence, Insomnia
	Not Known	Dizziness
Gastrointestinal disorders:	Common	Vomiting, Nausea, Epigastric discomfort
	Uncommon	Diarrhoea, Constipation
	Not Known	Abdominal pain upper
Hepatobiliary disorders	Not known	Liver dysfunction, Cholestasis
Skin and subcutaneous tissue disorders	Common	Rash, Pruritus
	Not Known	Erythema
Musculosleltal and connective tissue disorders	Common	Arthralgia
Renal and urinary disorders	Uncommon	Polyuria
General disorders and administration site conditions	Common	Fatigue, Malaise
Investigations	Very Common	Blood uric acid increased, Urine uric acid increased
	Common	Blood urea increased, Transaminases increased, Blood alkaline phosphate increased

Reporting of suspected adverse reactions
Final SmPC CRN 2103315 MAH Change NPL to KoRa
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:

Ireland
Preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option.
FREEPOST, Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace, Dublin 2,
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
E-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

There has been no experience of overdosage with Imunovir. 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

Imunovir 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 Imunovir 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.

Imunovir 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 Dimepranol Acedoben 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.

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

5.2 Pharmacokinetic properties

Each moiety of the drug exhibits separate pharmacological properties

Absorption: When administered orally in man, Imunovir is rapidly and completely absorbed (≥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 was found in the following tissues in order of decreasing specific activity when drug was administered to monkeys: kidneys, lung, liver, heart, spleen, testes, pancreas, brain and skeletal muscle

Metabolism: In human subjects following a 1 g oral dose of Imunovir, the following plasma levels were found for DIP and PAcBA, respectively: 3.7 microgram/ml (2 hours) and 9.4 microgram/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 + 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 > 90% of the expected value from solution. The recovery of the DIP moiety and its metabolite was >76%. The plasma AUC was >88% for DIP and > 77% for PAcBA.

5.3 Preclinical safety data

Imunovir 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 LD_{50} 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 (100 mg/kg/day) *(See also item 4.6 for usage recommendations in pregnancy)*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Wheat starch
Mannitol (E421)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

100 (5 x 20) tablets in transparent, colourless PVC/PVDC blister packs sealed with aluminium foil.

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.

7 MARKETING AUTHORISATION HOLDER

Kora Corporation Limited trading as Kora Healthcare
20 Harcourt Street
Dublin 2
D02 H364
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1748/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 November 1983

Date of last renewal: 3 November 2008

10 DATE OF REVISION OF THE TEXT

May 2022