FRONT SIDE

PHARMACEUTICAL PARTICULARS

List of excipients
Povidone K-25, Potato Starch, Magnesium Stearate.

Incompatibilities
Not Applicable

Shelf life
24 months

Packaging information
Aluminum/PVC/PE/PVDC blisters in carton box.

Package contains 10, 20, 30, 50 or 60 tablets.

Storage and handling Instructions
Store below 30°C, protected from light.

PATIENT COUNSELING INFORMATION

What is Inosine Pranobex and what it is used for?
Inosine Pranobex is an immunostimulant and antiviral drug indicated in the management of:

- Mild to moderate COVID-19 patients.
- Influenza and other acute viral respiratory infections
- Mucocutaneous infections due to herpes simplex virus (type I and/or type II)
- Genital warts as adjunctive therapy to podophyllin or carbon dioxide laser
- Subacute sclerosing panencephalitis (SSPE)

What you need to know before you use Inosine Pranobex?
Before starting treatment with Inosine Pranobex your doctor will ask you, about your own medical history, if necessary he may perform physical examination and advice lab investigations.

In what conditions, you should not use Inosine Pranobex?
You should not take Inosine Pranobex if you have a history of gout (accumulation of uric acid in smaller joints), hyperuricaemia (increased in blood uric acid level), urolithiasis (kidney stone), or to patients with impaired kidney function.

What is the dosage of Inosine Pranobex?
Inosine Pranobex is to be taken as directed by your treating physician.

In what conditions, you should stop using Inosine Pranobex and see a doctor immediately?
You should stop using Inosine Pranobex -

1. If your serum and urine uric acid level start increasing above normal level.
2. If you start experiencing any allergic reaction.

What medicines you should not take along with Inosine Pranobex?
You should not take xanthine oxidase inhibitors drugs (drugs reducing production of uric acid), uricosuric agents (drugs which increase excretion of uric acid), diuretics (drugs which helps to excrete excess amount of water from body) immunosuppressive drugs (drugs which suppresses immune system) and zidovudine.

What are the possible side effects of Inosine Pranobex?
The possible side effects of Inosine Pranobex are, increased in blood and urine uric acid level, increased blood urea level, increased blood transaminases level, increased blood alkaline phosphate, fatigue, malaise (illness), arthralgia (joint pain), rash (red, bumpy, scaly or itchy patches of skin), pruritus (itching), vomiting, nausea, epigastric discomfort (stomach discomfort), headache, vertigo (a sensation of whirling and loss of balance), Somnolence (excessive sleepiness), Insomnia (trouble falling asleep), Nervousness, Diarrhoea, Constipation, Polyuria (excessive urination), Angioedema, Hypersensitivity (swelling of the area beneath the skin), Urticaria (round, red welts on the skin that itch), Anaphylactic reaction (A severe, potentially life-threatening allergic reaction), Dizziness (lightheadedness), upper Abdominal pain, Erythema (superficial reddening of the skin).

If any adverse events occurred please report to following

- Email: drugsafety@themismedicare.com
- Link to download form - https://www.themismedicare.com/adverse-events/

DETAILS OF MANUFACTURER

Manufactured in India by:

THEMIS MEDICARE

THEMIS MEDICARE LIMITED
Sector 6A, Plot No. 16, 17 & 18,
IIE, SIDCUL, Haridwar-249 403,
Uttarakhand, India.

PP21VEXP0003

VIRALEX

Inosine Pranobex 500 mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains
Inosine Pranobex ..... 500 mg
Excipients ..... Q.S.

DOSAGE FORM AND STRENGTH

Oral Tablet, 500 mg

CLINICAL PARTICULARS

Therapeutic indication
Viralex (Inosine Pranobex 500 mg tablets) is indicated in the management of:

- Mild to moderate COVID-19 patients.
- Influenza and other acute viral respiratory infections
- Mucocutaneous infections due to herpes simplex virus (type I and/or type II)
- Genital warts as adjunctive therapy to podophyllin or carbon dioxide laser
- Subacute sclerosing panencephalitis (SSPE)

Posology and method of administration

Posology

Adults and the Elderly:
The recommended dosage is 50 mg/kg bd wt/day, rounded to the nearest multiple of 500 mg (usually 3 g/day, up to a maximum of 4 g/day), administered orally in 3-4 divided doses during waking hours.

The recommended duration of therapy is for 10 days.

Method of administration
For oral use.

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

Contraindications

- Hypersensitivity to the active substance.
- Acute gout or elevated blood uric acid blood levels.

Special warnings and precautions for use

a. Inosine Pranobex 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, Inosine Pranobex 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. In the case of long term treatment (3 months or longer), the serum and/or 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 (urticaria, angioedema, anaphylaxis and anaphylactic shock) may occur. Treatment with Inosine Pranobex should be withdrawn in these cases.

Drugs interactions
The drug should be used with caution with xanthine oxidase inhibitors (e.g. allopurinol) or uricosuric agents, including diuretics (e.g. hydrochlorothiazide, chlorthalidone, indapamide) and loop diuretics (furosemide, torasemide, ethacrynic acid)..

Inosine Pranobex 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 zidovudine (AZT) increases AZT nucleotide formation through multiple mechanisms involving increased plasma AZT bioavailability and increased intracellular phosphorylation in human blood monocytes.

As a result Inosine Pranobex increases the effect of AZT.

Use in special populations (such as pregnant women, lactating women)
Controlled trials monitoring foetal risk and impairment of fertility in humans are not available. It is not known if Inosine Pranobex is excreted in human milk. Therefore, Inosine Pranobex should not be administered during pregnancy or lactation unless the physician decides the benefits outweigh the potential risk.

Although animal tests have shown no teratogenic effect, the use of Inosine Pranobex in women where pregnancy is suspected or confirmed should be avoided.

Effects on ability to drive and use machines
Inosine Pranobex has no or negligible influence on the ability to drive and use machines.

230 mm

180 mm

BACK SIDE

Undesirable effects
Frequency convention –
very common : ≥1/10;
Common : ≥1/100, <1/10;
Uncommon : ≥1/1,000, <1/100;
Rare : ≥1/10,000, <1/1,000;
Very rare : <1/10,000, including isolated reports;
Not Known : Cannot 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 (Drowsiness), Insomnia
	Not Known	Dizziness
Gastrointestinal disorders:	Common	Vomiting, Nausea, Epigastric discomfort, Epigastric pain
	Uncommon	Diarrhoea, Constipation
	Not known	Abdominal pain upper
Skin and subcutaneous tissue disorders	Common	Rash, Pruritus (Itching)
	Not known	Erythema
Musculoskeletal 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
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:
- Email: drugsafety@themismedicare.com
- Link to download form - https://www.themismedicare.com/adverse-events/

Overdose
There has been no experience of overdose with Inosine Pranobex. 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.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action
The broad spectrum antiviral activity of Inosine Pranobex *in vivo* is due to its immunomodulating effect. It positively impacts host's immune system, by enhancing T-cell lymphocyte proliferation and activity of natural killer cells, increasing levels of pro-inflammatory cytokines, and thereby restoring deficient responses in immunosuppressed patients. It has been shown that it can affect viral RNA levels and hence inhibit growth of several viruses.

Pharmacodynamic properties
Pharmacotherapeutic group: Other antivirals, ATC code: J05AX05

Inosine Pranobex 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 Inosine Pranobex 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.

Inosine Pranobex increases cytokine IL-1 production and enhances IL-2 production, up regulating 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 dimeparanol 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) which take part in emitting signals via specific T cells receptor (TcR) that results in a nearly threefold increase in density.

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

In vitro, Inosine Pranobex exhibits inhibitory activity on the replication of herpes virus type 1 (HSV-1).

Pharmacokinetic properties
Each moiety of the drug exhibits separate pharmacological properties.

Absorption: When administered orally in man, Inosine Pranobex 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 Inosine Pranobex, the following plasma levels were found for DIP and PAcBA, respectively: 3.7µg/ml (2 hours) and 9.4µg/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.

NONCLINICAL PROPERTIES

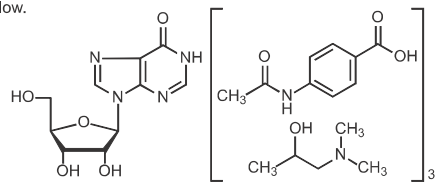
Animal Toxicology/ Pharmacology
Inosine pranobex showed a low toxicity profile in multivariate acute, subacute and chronic toxicology in mice, rats, dogs, cats and monkeys in doses up to 1500mg/kg/day and produced the lowest acute oral LD_{50} at 50 times the maximum therapeutic dosage level of 100mg/kg/day.

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 Use in special populations (such as pregnant women, lactating women) for usage recommendations in pregnancy).*

DESCRIPTION
Inosine Pranobex (BAN), also known as Inosine Acedoben Dimepranol (INN), Methisoprinol or Isoprinosine, is a synthetic purine derivative with immunomodulatory and antiviral properties. It is a synthetic compound of p-acetamidobenzoic acid salt of N,N dimethylamino-2-propanol [DIP. PAcBA] and β-inosine in a 3:1 molar ratio. The molecular formula of Inosine Pranobex is $C_{52}H_{78}N_{10}O_{17}$; its molecular weight is 1115.2 g/mol and its structural formula is given below.



230 mm

180 mm

Specification Box

Market : Export (General Export) | Item : Insert | New Item Code : PP21VEXP0003

Product Name : Viralex **(Tablets)** | Ref, Code : PP21VEXP0001

Material : 60 GSM Maplitho Paper | Artist : Jayshree

Size : 180 x 230 mm (LxH), Folding Size : 45 x 57.5 mm (2Vx2H), **Front & Back Side** | Varnish : NA

Location : Haridwar | TP : NA

Item Code : NA | Date : 15.09.2022, 19.09.2022

Color : Black

Prepared by	Reviewed and Approved By						
Packaging Development	Head Packaging Development	Clinical / Medical Affairs (If applicable)	Regulatory Affairs	Research and Development (If applicable)	Manufacturing Location		Corporate Quality Assurance
					Head Production	Head Quality Assurance	
19.09.2022 Sign / Date	19.09.2022 Sign / Date	20.09.2022 Sign / Date	20.09.2022 Sign / Date	NA Sign / Date	# Sign / Date	# Sign / Date	SAMEER SARJERAO JADHAV Digitally signed by SAMEER SARJERAO JADHAV Date: 2022.09.26 09:25:55 +05'30' Sign / Date

Reason for change : New Development for General Export Registration.

Path : D \ Themis \ DRA \ General Export \ Viralex Tablet

NA - Not Applicable # - Refer attached plant artwork