Antiviral Immunotherapy

Imunovir® 500mg Tablets
Inosine Acedoben Dimepranol
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ANTIVIRAL IMMUNOTHERAPY
Imunovir® 500mg Tablets

Imunovir® tablets contain as an active pharmaceutical ingredient, 500mg Inosine Acedoben Dimepranol (also known as Inosine Pranobex [BAN]), an immunomodulating agent with specific antiviral properties. Imunovir® is an acceptable oral solid dose therapy with a well established safety profile that is indicated for the treatment of:

- 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)

Imunovir® is a Prescription Only Medicine and is available in blister packs of 100 tablets.

| PIP code 100 Tablets: | 001-3987 | Trade Price: | £39.50 |

Imunovir® is marketed worldwide and is known by various trade names in different countries e.g. Delimmun® and Isoprinosine®. The active ingredient is also known in different territories under different names such as Inosine Pranobex (BAN), Inosiplex and Methisoprinol.

Imunovir

Immunomodulation

Inosine Acedoben Dimepranol (IAD) is an immunomodulatory agent that mediates anti-viral properties. IAD supports the immune system through modulation of T-cell proliferation, T-cell function, natural killer cell activity and phagocytosis.

Studies have shown that IAD induced an enhanced lymphocyte transformation response to inactivated HSV antigen in patients with genital herpes (Corey et al 1979). Lomnitzer (1988) demonstrated the in-vitro ability of IAD to enhance the proliferation of peripheral blood mononuclear cells.

IAD has also been shown to elicit a PBMC response coupled with an increase in Interferon activity in patients suffering from SSPE (Gadoth et al 1989). Miglietta et al (1980) showed that IAD brought about an increase in monocyte and neutrophil phagocytosis.
Tsang et al (1985) observed, through *in-vitro* analysis in healthy elderly humans, that the presence of IAD was associated with the restoration of ConA-induced lymphocyte proliferation, natural killer cell activity, neutrophil chemotaxis and IL-2 production to normal or near normal levels in 90%, 85.3%, 84.6% and 71.4% respectively of the subjects studied.

Petrova et al (2010) demonstrated that IAD, administered at a dose of 3g IAD per day for five days repeated weekly for three weeks, was capable of increasing cytokine levels (IFN-γ, IL-10 and TNF-α) in healthy patients at Day 7 and Day 10.

The pivotal role played by the cell-mediated immune system in controlling duration and severity of, and recovery from, viral infection provides the basis for treatment with immunopharmacological agents such as IAD (Miller 1984).

**Genital Herpes**

IAD is one of the treatment options for the treatment of primary genital herpes.

In an 812 patient study Talbot and Menday (1985) found that the clinical response was highly significant in favour of IAD (4g/day for seven days) in patients with both primary lesions irrespective of stage or recurrent episodes when compared to placebo.

In addition the mean reduction in total “symptom score” (based on the pre-treatment and post-treatment evaluation of pain, itching and inflammation on a 4-point scale) was significantly greater in primary cases in the active group (*p*<0.01). The greatest symptomatic relief attributable to IAD was relief of itching and reduction of inflammation. This was particularly apparent for all patients with herpes labialis treated in the prodromal stages.

In a double blind placebo controlled clinical study, IAD was shown to produce a significant reduction in recurrence rate (Figure 1), virus shedding and overall severity of the disease (Miller 1984). Therapy began with an initial dosage of IAD at 3g/day initiated within 24 hours of a recurrence outbreak for
the first 5 days of each recurrence with the dosage reduced to 1g/day on day 6 until the next recurrence occurred at which time the cycle was repeated for 6 months. In the follow-up open phase for another 6 months, all patients received Isoprinosine® at the same treatment schedule as for the first 6 months. Isoprinosine® produced a significant reduction in recurrence rate, virus shedding and overall severity of the disease. A large number of concomitant medications were used with no indications of any drug interaction with Isoprinosine®.

Miller (1984) concluded that IAD has significant therapeutic and epidemiological importance in the management and control of HSV infections.
Byrne et al (1988) in a double blind placebo controlled clinical study further compared episodic therapy (4g IAD per day for 5 days from the first sign of recurrence) to continuous therapy (4g IAD per day for 5 days from the first sign of recurrence followed by a maintenance dose of 1g IAD per day for 1 year) – the final six months was an open label study. Mean recurrence rates remained significantly less than the pre-treatment mean during the follow-up period of 80 to 450 days after cessation of therapy. The results of the study presented in Figure 2 showed that continuous treatment exhibited a statistically significant reduction in the frequency of recurrence of genital herpes infection with the effect persisting for one year.

<table>
<thead>
<tr>
<th></th>
<th>Number of recurrences per month</th>
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<tbody>
<tr>
<td></td>
<td>Episodic treatment</td>
<td>Continuous treatment</td>
</tr>
<tr>
<td></td>
<td>IAD</td>
<td>Placebo</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>0.92</td>
<td>0.77</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.99</td>
<td>0.81</td>
</tr>
<tr>
<td>Changes</td>
<td>0.07</td>
<td>0.04</td>
</tr>
</tbody>
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*p < 0.01 compared with pre-treatment baseline

Figure 2: The effect of IAD on the number of recurrences of genital herpes per month (Adapted from Byrne et al 1988)
In a 12 week double-blind placebo-controlled trial in 39 patients with a high frequency of herpes simplex labialis recurrences (median number of recurrences in the year before the trial was 9.25±2), IAD was shown to affect a greater reduction of recurrences than the placebo group (p<0.02). The dosing regime was 70mg/kg IAD for 7 days which was repeated every four weeks for three cycles (Galli et al 1984).

Genital Warts

IAD through its immunomodulating capability represents a unique oral systemic therapy for the treatment of genital HPV infection.

In a 38 patient randomized placebo-controlled study, Georgala et al (2006) investigated the efficacy and safety of IAD (50mg/kg daily for 12 weeks) as a treatment of cervical condylomata acuminata that was resistant to at least one conventional therapy. Results showed a statistically significant differential between the treatment and placebo groups (p < 0.01) which remained significant when an intention to treat analysis was performed (p < 0.01). Patients that exhibited complete recovery did not experience any recurrence within the 12 month follow-up period.

Davidson-Parker et al (1988) conducted a UK multi-centred, randomised, placebo controlled study in 51 patients suffering from genital warts for at least one year. Results showed that a four week course of IAD (3g per day) improved the clinical response to conventional treatment (primary podophyllin or trichloroacetic acid). Of the 27 patients that attended all of the follow-up visits (2, 4, 8 and 12 weeks post study entry), the conventional therapy supplemented by IAD had a significant effect in eradicating the warts and reducing the extent of lesions compared to conventional treatment alone (Figure 3).

<table>
<thead>
<tr>
<th></th>
<th>Conventional therapy with IAD (14 patients)</th>
<th>Conventional therapy (13 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete eradication of warts</td>
<td>5*</td>
<td>3</td>
</tr>
<tr>
<td>Reduction of number of warts</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Reduction in extent of lesions</td>
<td>11**</td>
<td>5</td>
</tr>
<tr>
<td>General response</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

* p < 0.05 ** p = 0.05

Figure 3: Assessment of the effects on IAD in combination with conventional therapies (Adapted from Davidson-Parker et al 1988)
Sadoul and Beuret (1984) studied the clinical effects of combined IAD/CO₂ laser therapy compared to CO₂ laser therapy alone in 126 patients suffering from cervical condylomata and vulvo-vaginal condylomata that were refractory to multiple treatments (diathermic coagulation, cryotherapy and podophyllin). Results showed that combined IAD/CO₂ laser therapy reduced the clinical failure rate to 6.25% after one treatment compared to 45.16% in the group that received only CO₂ laser therapy. The number of failures was reduced to zero following three treatments with combined IAD/CO₂ laser therapy (Figure 4).

In an open label 60 patient trial Jurisin et al (1986) observed higher rates of healing of genital warts in male patients that received IAD in combination with podophyllin when compared to those patient that received podophyllin alone.

Similarly Kovacs et al (1989) concluded that IAD (3g per day for 4 weeks) in combination with podophyllin compared with podophyllin only resulted in shortened healing times in female patients suffering from condylomatous lesions.

Hicks and Kelly (1997) combined the diverse clinical study data from fourteen clinical trials that evaluated IAD as a drug therapy in the management of genital HPV infections. The meta-analysis of the clinical data from the trials focused on the use of IAD as an adjunct to conventional therapy.

The clinical data shows that the use of IAD in the treatment of genital warts provides a 24-26% additional success rate over the effects of conventional
therapy alone with regard to total lesion clearance and improvement in cellular morphology in surrounding tissue harbouring active HPV-infected cells (Figure 5).

Additionally the meta-analysis of all of the clinical study data revealed that IAD produced a 22-29% greater effect over conventional or control therapy where

- the lesions are single or multiple in site or quantity
- the lesions are situated externally (limited to the perineum and not including perianal warts in either sex) or internally (including vulvovaginal or endocervical sites in females but not urethral meatal warts in males)

![Difference in proportion of successes from baseline when using adjuvant Imunivor®](image)

Baseline control (conventional treatment for genital warts)

Adjuvant use of Imunivor® improves treatment success (measured by the clearance of external genital warts).

In Figure 5, the comparison is with conventional treatment for external genital warts while the bars show the difference achieved by using adjuvant Imunivor® in four trials; 95% confidence intervals are shown (vertical lines).

Pooling the data by meta-analysis (extreme right) gives a clearer and (as the confidence intervals show) a more consistent summary of the individual studies.

Figure 5: The effect of using Imunovir® as an adjunct to conventional therapy (Adapted from Hicks and Kelly 1997)
Subacute Sclerosing Panencephalitis (SSPE)

IAD has been used in many clinical conditions in which sub-acute or chronic viral infections have been associated with a reduced host immune response.

This is classically found in SSPE, in which a reduced immune function, characterised by reduced interferon production, is related to persisting activity of mutated measles virus.

In a 121 patient study the efficacy and safety of oral IAD alone versus combined treatment with oral IAD and intraventricular alpha interferon in patients diagnosed with SSPE was evaluated in a Phase III trial (1997-2002). There were no statistically significant differences between treatment groups on any measure of efficacy. Although there was no significant difference between the treatment groups in rates of clinically defined satisfactory outcomes the observed rates were higher than spontaneous remission rates reported in the literature suggesting that treatment was superior to no treatment. The rate of adverse events was statistically lower in the IAD treatment group when compared to the combination treatment group (Gascon 2003).

In a retrospective study using historical controls involving 59 clinical centres in Japan, Fukuyama et al (1987) concluded that the use of IAD in the treatment of SSPE was useful, with relatively high safety, in that it improved the survival curve of patients with SSPE and caused a delay in the progress of clinical symptoms. The data is entirely consistent with the expected effect of interferon therapy and that the benefits of Isoprinosine® appear independently of interferon therapy and are additive to it.

Fukuyama et al (1987) make the important point that clinical benefits do not appear in every case however IAD was particularly efficacious in the treatment of the slowly progressive form of the disease which accounts for 70% of all SSPE cases.

Ginsberg (1989) in a clinical study comprising 98 prospectively selected patients in USA and Canada showed that the probability of long-term survival
beyond six years was 62% in treated patients compared to 6-26% in the control groups albeit some doubt was raised with respect to the control groups as they were not prospectively randomised.

Horiguchi and Ohya (1995) reported prolonged effectiveness of both neurological symptoms and life expectancy after oral inosiplex and intrathecal interferon therapy. Anlar (1998) studied a combination of subcutaneous interferon-beta and Isoprinosine® according to an open design with stabilization or improvement observed in 3 of the 7 patients. Gokcil (1999) followed up 8 patients treated with intraventricular interferon-alpha in combination with Isoprinosine® or Isoprinosine® alone and noted that all patients receiving combined treatment had survived after 3-4 years of follow up with 3 patients improving or stabilizing.

In an 18 patient study by Gascon et al (1993) that used IAD in combination with α-interferon by intraventricular injection, an improvement in the disability index was found in 3 patients, with the index remaining stable in 5 constituting a response of 44% over a follow-up period of 12 to 40 months. Gascon et al (1993) recommended this combined therapy as treatment of choice in the few cases of SSPE presenting after widespread vaccination policies.

Garg (2002) stated that a combination of oral IAD and intraventricular interferon alfa appears to be the best effective treatment for SSPE albeit patients responding to treatment need to receive it life long. The only effective solution to this disease remains immunisation against measles.
Safety

IAD has been used for almost 40 years receiving its first approval in 1971 in Argentina and its first European approval in Italy in 1979.

Since 1971 approximately 1.45 billion tablets have been prescribed worldwide.

Since 1971 there have been approximately 1500 adverse reactions reported in postmarket surveillance.
References

Immunomodulation

Corey L., Chiang W., Reeves W., Stamm W., Brewer L. and Holmes K. (1979) Effect of Isoprinosine on the cellular immune response in initial genital herpes virus infection. Clinical Research, 27 (1), 41A.


Genital Herpes


Genital Warts


SSPE


Each tablet contains 500mg Inosine Acedoben Dimepranol (INN, also known as inosine pranobex®) which is the p-acetamidobenzoic acid salt of N,N-dimethylamino-2-propanol (DIP-PAcBA) and β-inosine in a 3:1 molar ratio. *British Approved Name (BAN) the non-proprietary designation.

PRESCRIBING INFORMATION: Pharmaceutical Form: White to off-white 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. Therapeutic indications: Imunovir® tablets are indicated in the management of:

a) Mucocutaneous infections due to herpes simplex virus (type I and/or type II)

b) Genital warts as adjunctive therapy to podophyllin or carbon dioxide laser

c) Subacute sclerosing panencephalitis (SSPE)

Posology and method of administration: ORAL ADMINISTRATION. Adults: Mucocutaneous herpes simplex: 1g q.d.s. (4g daily), for 7-14 days. Genital warts: 1g t.d.s. (3g daily), for 14-28 days as adjunctive therapy to podophyllin or carbon dioxide laser. Subacute sclerosing panencephalitis (SSPE): 50-100mg/kg daily, in divided doses every 4 hours. Children: No information is available in children. Elderly: No dosage alterations are necessary in the elderly. Contraindications: There are no known contraindications to therapy with this drug.

Special Warnings and special precautions for use: As the inosine component of Imunovir® is metabolised to uric acid, it should be used with caution in patients with renal impairment, a history of gout or hyperuricaemia.

Interaction with other medicaments and other forms of interaction: None known.

Use in pregnancy and lactation: Although animal tests have shown no teratogenic effect, the use of Imunovir® in women where pregnancy is suspected or confirmed should be avoided.

Undesirable effects: The only consistently observed 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. Side effects recorded in >1% of clinical studies of 3 months or longer and reported infrequently in postmarketing surveillance: Gastrointestinal: Nausea with or without vomiting, epigastric discomfort, Hepatic: Elevation of transaminases, alkaline phosphatase or blood urea nitrogen (BUN) level, Dermatological: Itching, skin rashes, Nervous system: Headaches, vertigo, fatigue or malaise, Other: Arthralgia. Side effects recorded in <1% of clinical studies of 3 months or longer and reported rarely in postmarketing surveillance: Gastrointestinal: Diarrhoea, constipation, Nervous system: Nervousness, drowsiness or insomnia, Genitourinary: Polyuria (increased urine volume). 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.

Legal Category: POM (Prescription only Medicine). Product License Number: PL 39972/0001

Marketing Authorisation Holder: KoRa Corporation Ltd. t/a KoRa Healthcare, Swords Business Park, Swords, Co. Dublin, Ireland.

Trade Price: £39.50 PIP Code 100 Tablets: 001-3987 EAN Code 5702191001280

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The cover shows a herpes simplex virus
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Inosine Acedoben Dimepranol

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