Ergamisol General Information:

An antihelminthic drug that has been tried experimentally in rheumatic disorders where it apparently restores the immune response by increasing macrophage chemotaxis and T-lymphocyte function. Paradoxically, this immune enhancement appears to be beneficial in rheumatoid arthritis where dermatitis, leukopenia, and thrombocytopenia, and nausea and vomiting have been reported as side effects. (From Smith and Reynard, Textbook of Pharmacology, 1991, p435-6)

Action And Clinical Pharmacology: Levamisole is capable of restoring impaired immune responses preferentially of the cell mediated type in compromised hosts. Therapeutic doses of levamisole restore to normal the functions of monocytes (phagocytes) and T lymphocytes but do not directly influence B cells.

Levamisole is rapidly absorbed from the gastrointestinal tract following a single oral ingestion of 150 mg. In patients with neoplastic disease, a mean peak blood level of 0.86 µg/mL is attained within 2 hours of intake.

The half-life of elimination of levamisole alone is between 3 to 4 hours. The metabolites are eliminated more slowly with a terminal half-life of approximately 16 hours. Levamisole is extensively metabolized by the liver in man and excreted mainly by the kidneys (70% over 3 days). Approximately 5% is excreted in the feces. Less than 5% of the unchanged dose is excreted in the urine and less than 0.2% in the feces. In the presence of cirrhosis of the liver the Cax f levamisole is not clearly increased, but the AUC increases 4-fold.

Indications And Clinical Uses: As adjuvant therapy in poor prognosis malignant melanoma following complete surgical excision and exclusion of metastatic disease. In such patients, levamisole has been shown to produce an improvement in relapse-free survival and overall survival when compared to observation alone, particularly in patients aged 55 years or older.

Also indicated as adjuvant therapy, in combination with 5-fluorouracil, in patients with completely resected Dukes' stage C colon cancer. Evidence of metastatic disease must be excluded before initiating therapy. In patients with Dukes' stage C carcinoma of the colon, a regimen of levamisole plus 5-fluorouracil has been shown to produce significant reductions in both cancer recurrence and overall death rate.

Children: Levamisole is recommended for use in high-dose steroid-dependent nephrotic syndrome in children: as adjuvant therapy following relapse on corticosteroids such as prednisone; or as an alternative to the use of an alkylating agent or cyclosporin. In these patients, levamisole has been shown to induce a significant number of complete remissions, reduce the steroid requirements necessary to induce such a remission and decrease the incidence of relapse

of the disease.

Contra-Indications: Known hypersensitivity to the drug or its excipients.
tag_WarningWarnings

Manufacturers' Warnings In Clinical States: Levamisole has been associated with reversible leukopenia and agranulocytosis; therefore, it is essential that appropriate hematological monitoring be done routinely during therapy with levamisole.

Patients should be instructed to report immediately any sudden change in their state of health which may be manifested by influenza-like symptoms (fever, lassitude, sore throat, shivering or sweating) so that appropriate hematological testing can be done.

Leukopenia (total WBC below 3 000/mm is not necessarily a sign of impending agranulocytosis; recovery is possible without withdrawal of the drug. However, with a reduced neutrophil count (less than 20% of the total white blood cell count) levamisole should be discontinued permanently. (Agranulocytosis is attributed to antibody formation and absorption of immune complexes. This process initiates complement activation and cell lysis; levamisole itself does not directly damage granulopoiesis.)

The HLA genotype B27 predisposes to the development of agranulocytosis, particularly in females with concomitant rheumatoid arthritis. The onset is frequently sudden and may be asymptomatic. Following discontinuation of levamisole, neutrophil counts normalize within a week to 10 days. There is no evidence that steroids or WBC transfusions are of significant therapeutic value; prophylaxis of infection during the acute phase of agranulocytosis should be an important consideration.

Precautions: Children (age 1 to 15 years) with Nephrotic Syndrome: It is essential that hematological monitoring be done routinely during therapy with levamisole. In the presence of a reduced neutrophil count (<2 000/mm or in the presence of other evidence of agranulocytosis levamisole should be discontinued permanently.

Drug Interactions: In patients with malignant melanoma and colonic carcinoma the therapeutic effect of levamisole may be antagonized by concomitant administration of corticosteroids.

Additional caution is necessary when levamisole is used in combination with other drugs potentially affecting hemopoiesis.

Because of reports of prolongation of prothrombin time beyond the therapeutic range in patients taking concurrent levamisole and coumarin, it is suggested that the prothrombin time be

monitored carefully, and the dose of coumarin adjusted accordingly, in patients taking both drugs.

Concomitant administration of phenytoin and levamisole plus fluorouracil has led to increased plasma levels of phenytoin. The physician is advised to monitor plasma levels of phenytoin and to decrease the dose if necessary.

Cases of peripheral neuropathy have been reported in patients treated with the 5-fluorouracil-levamisole combination, but a definite causal relationship has not been established. If symptoms and signs suggestive of peripheral neuropathy occur, the risk-benefit ratio of the therapy should be re-evaluated.

Levamisole has been reported to produce Antabuse-like side effects when given concomitantly with alcohol.

Patients with Hepatic Impairment: In patients with cirrhosis of the liver the Cax f levamisole is not clearly increased, but the AUC increases 4-fold. Since the clinical relevance is unclear, it is not known if a dose reduction is indicated. However, patients with cirrhosis of the liver should be closely observed for possible adverse reactions. If such reactions are observed, it may be necessary to reduce the dose of levamisole or discontinue it.

Adverse Reactions: Approximately half of all patients treated with levamisole experience adverse effects of the medication. Due to the intermittent nature of the dosage schedule, drug discontinuation may not be necessary for successful resolution.

The adverse reactions observed when levamisole is used in combination with 5-fluorouracil are consistent with those anticipated if 5-fluorouracil is given alone in a comparable dose and schedule. Cases of peripheral neuropathy have been reported in patients treated with the 5-fluorouracil-levamisole combination, but a causal relationship has not been established.

Mild and asymptomatic abnormalities (e.g., a doubling) in the results of liver-function tests (transaminase, alkaline phosphatase and/or bilirubinemia) have been reported more frequently with the 5-fluorouracil plus levamisole combination, than with levamisole alone, and with untreated controls (11.2% vs 4.0% and 2.8%, respectively). In some instances hepatosteatosis was found. These liver abnormalities were reversible upon discontinuation.

The incidence of adverse reactions for levamisole alone in malignant melanoma patients and for levamisole plus 5-fluorouracil in colonic cancer patients is presented in Table I.

An encephalopathy-like syndrome has been reported. Worldwide postmarketing experience with

the combination therapy of levamisole and fluorouracil has also included several reports of neurological changes associated with demyelination. The onset of symptoms and clinical presentation in these cases are quite varied. Symptoms may include: memory loss, confusion, paresthesia, lethargy, muscle weakness, speech disturbances, coma and seizures. Cerebrospinal fluid examination may show a mild pleiocytosis, and CT and MRI scans often disclose lesions in the white matter suggestive of demyelination. This picture is known in the literature as MILE (multifocal inflammatory leukoencephalopathy). The occurrence of this syndrome necessitates the discontinuation of treatment. As a rule, the condition is at least partially reversible upon discontinuation and treatment with a corticosteroid.

In some patients an increase in serum triglyceride levels, sometimes associated with a cholesterol rise, may occur during levamisole treatment. These increases are reversible after cessation of levamisole therapy. Occasional cases of acute pancreatitis have been reported, not uncommonly in association with hypertriglyceridemia.

Few adverse experiences have been reported with levamisole during the treatment of frequently relapsing steroid-responsive nephrotic syndrome in children. The most common side effects are mild and include: skin rash, vomiting, nausea, transient hematuria and decreased neutrophil levels. However, a few cases of neutropenia (neutrophil count <2 000/mm have also been observed.

In addition, rare cases of fixed drug eruption have also been observed during levamisole therapy.

Symptoms And Treatment Of Overdose: Symptoms: According to animal data, levamisole may have minor anticholinesterase activity, and, on i.v. administration, some positive inotropic and chronotropic cardiac effects. Levamisole exhibits convulsant properties at high doses.

A fatality occurred in a 3-year-old child who ingested 15 mg/kg of levamisole. However, a 7-year-old boy survived a 10 mg/kg overdose, and an 8-year-old girl tolerated a single 1 250 mg dose rather well apart from vomiting. Five adults (ages 13 to 28 years) who took an overdose of 12 to 26 mg/kg survived, but one who ingested 32 mg/kg died.

Adverse experiences reported in acute adult high dose trials (600 mg/day and higher) included: nausea, lethargy, cramps, diarrhea, headache, emesis, dizziness, and confusion.

Treatment: In cases of overdosage, gastric lavage with monitoring of vital signs and general supportive measures are recommended. When symptoms of anticholinesterase activity are present, the use of atropine may be considered.

Dosage And Administration: Malignant Melanoma: Levamisole should be administered at a dose of 2.5 mg/kg given as a single daily dose, preferably at night, on 2 consecutive days every week. Higher doses are not recommended as they are associated with increased toxicity and have not been shown to provide any additional therapeutic benefit.

Dukes' Stage C Carcinoma of the Colon: Levamisole plus 5-fluorouracil should be administered only by or under the supervision of qualified physicians, experienced in cancer chemotherapy, and well versed in the use of potent antimetabolites.

Therapy with levamisole may be initiated as soon after resection as patients are able to tolerate oral medication, but no sooner than 1 week and no later than 5 weeks after surgery.

Levamisole should be administered orally at a dose of 50 mg t.i.d., for 3 consecutive days, every 2 weeks. This therapy should be continued for at least 1 year.

Administration of 5-fluorouracil should be timed to begin concomitantly with the second 3-day course of levamisole. The initial dosage of 5-fluorouracil should be 450 mg/mday, given i.v., for 5 consecutive days.

Four weeks following the initial 5-day course of 5-fluorouracil, patients should begin maintenance therapy on a once weekly basis with an i.v. injection of 5-fluorouracil at a dose of 450 mg/m Treatment should continue for as long as levamisole is administered.

If the patient experiences stomatitis, diarrhea or leukopenia, the weekly 5-fluorouracil administrations should be deferred until these side effects have subsided. If these side effects are moderate to severe in intensity, 5-fluorouracil should be resumed with a 20% reduction in the dose.

Children (age 1 to 15 years) with Frequently Relapsing Steroid-responsive Nephrotic Syndrome: Levamisole should be administered as a single dose of 2.5 mg/kg/day at least twice/week or on alternate days. Hematological monitoring should be done routinely (see Precautions and Warnings).

Availability And Storage: Each white, film-coated biconvex tablet, with L50 inscription on one side and JANSSEN on the other side, contains: levamisole 50 mg as levamisole HCl. Nonmedicinal ingredients: colloidal silicon dioxide, hydrogenated vegetable oil, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, polysorbate and talc. Lactose: 7 mg. Bisulfite-, gluten- and tartrazine-free. Blister packages of 36. Store at 15 to 30°C and protect from moisture and light.