Levamisole
(Ergamisol®)

Introduction:
Levamisole ((-)-(s)-2,3,5,6-tetrahydro-6-phenylimidazo(2,1-b)thiazole monohydrochloride) is a veterinary drug used to treat parasitic infestation in animals. It is available as a crystalline white powder, and in pastes, gels, tablets, feed premixes and topical and injectable solutions. In Canada, it was marketed by Janssen Pharmaceuticals under the trade name Ergamisol® to treat colon cancer in humans. A few cases of agranulocytosis (blood disorders), a common complication with repeated high doses of levamisole, have been reported in hospitalized patients with a history of cocaine abuse when adulterated with levamisole (CAL).

Licit Uses:
Levamisole is an antihelminthic drug approved for use in veterinary medicine in the United States. Previously, it was used in human medicine as an immunomodulator in rheumatoid arthritis and colorectal cancer therapy. It is no longer available for human use in the United States.

A single dose of 2.5 mg/kg has been recommended for antihelminthic therapy in humans and a dose of 50 mg, three times a day, for three days every other week for colon cancer therapy in levamisole approved countries.

Chemistry:
The chemical structure of levamisole is shown below.

There are two common forms of levamisole, the free base and the hydrochloride salt. The molecular formula of the free base is C_{17}H_{18}N_{3}S having a molecular weight of 204.3. Its melting point is 60-61.5 degrees Celsius (140-143 °F) and is not soluble in water. The hydrochloride salt is soluble in water and melts at 228-230°C (442-446 °F). Other chemical names include (S)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-b]thiazole; and (S)-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole. The Chemical Abstract Service (CAS) number of the free base is 14769-73-4 and the hydrochloride salt is 16595-80-5.

Pharmacology:
Levamisole acts as an antiparasitic, immunomodulator and adjuvant in colorectal cancer. It appears to restore depressed immune function through stimulating antibody formation and enhance T-cell response by stimulating T-cell activation and proliferation. Antiparasitic action appears to be tied to its agonistic activity towards nicotinic receptors in nematode muscles resulting in spastic paralysis. The net effect is a paralyzing of the worm, which is then expelled alive.

Levamisole is rapidly absorbed from the GI tract and extensively metabolized in the liver and excreted mainly by the kidneys (70% over 3 days). Its plasma elimination half-life is 3-4 hours. Due to short elimination half-life, blood levels of levamisole fall more rapidly and go unnoticed in toxicological examination. Data from few clinical studies indicate that the consumption of 50-200 mg/day of levamisole causes agranulocytosis in 0.08 – 5% of the studied population (WHO, FAS 33).

Agranulocytosis is an acute blood condition which leaves patients unable to fight off infections resulting from decreased neutrophil count (neutrophilia). This condition has been reported world-wide in CAL abusers. Higher than recommended doses of levamisole reported to be associated with an increased incidence of autoantibody mediated agranulocytosis. Symptoms of agranulocytosis include sore throat, persistent or recurrent fever, swollen glands and skin infections. Levamisole often interacts with alcohol and warfarin. It discourages alcohol consumption, like disulfiram (antabuse).

Toxicity:
Symptoms of levamisole toxicity mimic organophosphate toxicity (salivation, lacrimation, urination and defecation, hyperesthesia, seizures and irritability). There is no antidote for levamisole toxicity.

Regulatory Guidance:
The World Health Organization reviewed hematological studies in animals and humans and derived acceptable daily intake for levamisole as 0.006 mg/kg body weight. This suggests a person can ingest 0.36 mg of levamisole/day over a lifetime without any appreciable risk.

Illicit Uses:
The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state and local forensic laboratories. The System to Retrieve Information from Drug Evidence (STRIDE) provides information on drug seizures reported to and analyzed by DEA laboratories. Substances identified by federal, state and local forensic laboratories, as containing levamisole, decreased from 2,974 reports in 2011 to 2,067 reports in 2012.

User Population:
Levamisole is mainly encountered in combination with cocaine. Therefore, the levamisole user population includes cocaine abusers.

Control Status:
Levamisole is not scheduled under the Controlled Substances Act (CSA).

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section. Fax 202-353-1263, Phone 202-307-7183, or E-mail ODE@usdoj.gov.