

FINDING OF NO SIGNIFICANT IMPACT

for

IVOME[®] (ivermectin) 0.08%
Oral Solution for Sheep

NADA 131-392

Merck, Sharp and Dohme Research Laboratories
Rahway, NJ

The Center for Veterinary Medicine has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

Merck, Sharp and Dohme Research Laboratories has requested approval of a new animal drug application (NADA 131-392) for the use of IVOME[®] (ivermectin) 0.08% Oral Solution in sheep. The drug is to be administered at a dose of 0.2 mg/kg of body weight for the treatment and control of specified internal parasites. Merck has conducted studies to determine the impact of IVOME[®] Oral Solution on the environment and submitted an environmental assessment dated February 11, 1985 (attached).

The environmental assessment (EA) submitted by Merck is supplemented by a previous environmental document prepared for the use of ivermectin in cattle (NADA 128-409), which is also available for public inspection at the Dockets Management Branch.

Ivermectin is composed of 80% avermectin B_{1a} and 20% avermectin B_{1b}. It is only slightly soluble in water and has a low vapor pressure. It is considered to be bound strongly to soils. In sheep manure, it has an apparent half-life of 1 to 1.5 weeks, although half-lives of up to 52 weeks for steer manure incorporated into soil have been found under various experimental conditions.

The primary mechanism of action of ivermectin is the stimulation of the release of the inhibitory neurotransmitter gamma-aminobutyric acid. Other mechanisms of action have also been reported, such as inhibition of reproduction in the queen fire ant (Solenopsis invicta) or the inhibition of chitin synthesis in brine shrimp.

Ivermectin would primarily be introduced into the environment through manufacturing and through the incorporation of manure from sheep treated with IVOME[®] into agricultural soils. Merck has provided information which indicates that the manufacture of ivermectin will be in compliance with local, State and Federal environmental laws and regulations, and would not be expected to adversely affect the environment. Merck has

estimated that typical soil incorporation rates for manure from treated sheep would result in 0.16 ppb ivermectin. The worst-case incorporation rate was estimated to be 5.1 ppb. The concentration of ivermectin estimated to be in runoff water from typical applications to agricultural fields was estimated to be 0.5 ppt. The worst-case soil concentration was estimated to be 15.3 ppt.

Ivermectin use in the United States would not increase significantly as a result of the approval of the use of IVOMECS® in sheep. Merck has estimated that only 12.4 million sheep are treated with 16.3 million doses of anthelmintic each year. IVOMECS® would be expected to capture a portion of this market. Compared to cattle (111 million cattle; 60 million doses), the use of IVOMECS® in sheep represents a relatively small increase in the overall use of ivermectin.

Ivermectin, in the formulation proposed for this action, could present some hazards from occupational exposures. Data in rodents indicate toxicity could result from dermal exposures of workers and animal handlers to IVOMECS®. For this reason, Merck has incorporated occupational exposure warning statements into the labeling of the product.

Ivermectin has been shown to be extremely toxic to aquatic life, including Daphnia magna (an aquatic invertebrate), Salmo gairdneri (rainbow trout), Lepomis macrochirus (bluegill sunfish), and Artemia salino (brine shrimp). Based on the insecticidal properties of this class of compounds, it is to be expected that ivermectin is extremely toxic to most insects and arthropods, both aquatic and terrestrial. Ivermectin, however, does not appear to bioaccumulate in aquatic organisms. Because of its potential toxicity to aquatic organisms, particularly if spilled accidentally or if spent containers are improperly disposed of, Merck has included a warning to this effect on the product label which includes instructions on the disposal of spent containers and contaminated clean-up materials and soil. Use of ivermectin according to the label is not expected to result in runoff to aquatic environments that will be toxic to invertebrates and fish.

In agricultural fields amended with manure from treated sheep, the expected concentration of ivermectin present should not cause toxicity to plants, microorganisms, or earthworms. Ivermectin residues should degrade at a rate adequate to prevent accumulation of ivermectin from year to year. In fresh manure from treated sheep, larvae of flies and other insects utilizing manure as a breeding medium may be transiently affected.

Therefore, considering the inclusion of occupational and environmental safety instructions on the labeling for IVOMEK® Oral Solution for Sheep, the Center for Veterinary Medicine concludes that the proposed use of the drug will not have a significant impact on the quality of the human environment.

10/21/86
Date

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10-20-86
Date

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Attachment