CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-271

ENVIRONMENTAL ASSESSMENT and/or FONSI

This section (EA/FONSI) is not applicable. Exemption from conducting an EA covered by Dr. Kowblansky's 1st cycle review dated April 11, 2001.

/S/ 3-14-03

Alice Kacuba

Environmental Assessment

Approval is being requested to market a new biological drug product for the prevention of [redacted] This product, desirudin vials for injection (lyophilized recombinant Hirudin), is intended to be marketed along with the solution for reconstitution, mannitol 15mg/0.5 ml (3 %) solvent, for parenteral use in ampoules. The [redacted] product is packaged in [redacted] to USP., with stoppers made from [redacted], on the product side. The stoppers are held in place by a one-piece aluminum flip-off seal. Mannitol solvent for reconstitution is packaged in [redacted] according to USP. The product is manufactured at [redacted] The facility has been approved for the production of biologicals by the European authorities.

A fifth year market projection, for the United States, for desirudin, and all expected approved applications, gives a total of [redacted] of drug substance. From this quantity the Expected Introduction Concentration (EIC) value is calculated to be [redacted] Thus the effect of this product on entry into the environment does not significantly affect the quality of the human environment. As this value represents a level far below 1 ppb for the EIC, the categorical exclusion is requested.

[redacted] states that the action requested, i.e., for naturally occuring substances which do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment, is for a Categorical Exclusion from the environmental assessment requirements under 21 CFR Part 25.31(c).

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4.0.3. Environmental Assessment

The potential environmental effects of CGP 39393 have been appraised from the particular aspects of its clinical use, storage and disposal. Within the bounds of the current proposals for its use and storage it is considered that no environmental risk is present.

CGP 39393 has a high water solubility and is susceptible to enzymatic degradation. After disposal it will most likely be confined to the aquatic compartment and dispersion in soil and air is a negligible factor.

The peptide structure of CGP 39393 also points towards a negligible level of risk even if the parent compound or its degradation products were released into the aquatic compartment of the environment. Three factors strongly support this viewpoint. Firstly, the active substance is not mutagenic. Secondly, the active substance will undergo rapid enzymatic proteolysis by micro-organisms which are residents in wastewater systems resulting in a mixture of unmodified natural amino acids which are then dispersed with equal rapidity. Finally, the massive dilutions involved would only allow very low aqueous concentrations in any event.

The other components of the clinical formulations such as mannitol, magnesium and sodium chloride are in common and constant use as excipients in many medicinal drugs and have been so for many years. They are also highly soluble and will be rapidly diluted and dispersed in the aquatic compartment so that they, in turn, present no environmental risk.

[redacted]

[redacted]

$$EIC = 1.72 \times 10^{-4} \text{ ppb or } 1.72 \times 10^{-1} \text{ ppt}$$

On the basis of the argument presented above and since the EIC is less than one part per billion (assuming), Tier 0 criteria (from the 1995 FDA EA Guidance) are met. Therefore, no environmental assessment section is included in this application.

APPEARS THIS WAY
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