FILE COPY

Review of a Request for Orphan Drug Designation

Date of submission: May 21, 1998
Received by reviewer: May 22, 1998
Review initiated: July 20, 1998
Review completed: July 30, 1998

Designation

Drug Name:
code name:
generic name: octreotide acetate depot injection
trade name: Sandostatin LAR[R] Injection

Sponsor's Name:
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 0793-1080

Contact Person:
Eileen A. Ryan, Associate Director, Regulatory Affairs
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 0793-1080
Tel: (973) 781-7661
FAX: (973) 781-6325

Drug Manufacturer:

Proposed Designation:
For the treatment of acromegaly.

Regulatory Status:
Sandostatin LAR[R] is currently under investigation in the United States for use in:

Reducing Growth Hormone and IGF-1 in acromegaly

Inhibiting the severe diarrhea and flushing associated with carcinoid tumors

Inhibiting the profuse, watery diarrhea associated with VIPoma

Disease/Condition Background Information:
Acromegaly is usually caused by a growth hormone (GH) secreting anterior pituitary tumor. Rarely, it may be due to pituitary hyperplasia with GH hypersecretion. The External manifestations, appear slowly over a decade or more and consist of soft tissue swelling and hypertrophy of the face and extremities. The skin of the face becomes thickened and leathery, and there is coarsening of the features. The fingers become spatulate in nature and the volume of the hands and feet increases. Bony changes include cortical thickening and osteophyte proliferation in the phalanges and facial bones. Hypertrophic arthropathy results in severe arthritis. Hypertrophy of the vocal cords causes deepening of the voice and hypertrophy of the nasopharynx leads to sleep apnea. Peripheral neuropathy, particularly carpal tunnel syndrome, is common because of nerve entrapment by tissue overgrowth. Paresthesias and peripheral muscle weakness and fatigue are also common. Generalized visceromegaly, including cardiomegaly, is present and cardiomyopathy may occur. Carbohydrate intolerance and diabetes are noted in 25% of patients. Headache and visual abnormalities may occur due to pituitary tumor expansion.

The mortality rate in acromegalics is about 2.5 times that of the general population, with death due most commonly to cardiac disease or malignancy. Overall survival is reduced by about 10 years. Effective treatment has been shown to decrease the mortality rate to a level that is not significantly different from that of the general population.

Population Estimate:
The National Organization for Rare Disorders (NORD) data base estimates that the prevalence for acromegaly is 18,800.

Rationale for Use:
Octreotide is a synthetic octapeptide analogue of the inhibitory hormone somatostatin with pharmacological properties similar to that of somatostatin. It suppresses luteinizing hormone (LH) response to gonadotropin releasing hormone (GnRH), decreases splanchnic blood flow, inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide, and is an inhibitor of growth hormone, glucagon, and insulin.

The mechanism of action of somatostatin is not well understood. Somatostatin inhibits adenylate cyclase formation and enhances phosphodiesterase activity, both of which actions would impair cyclic AMP mediated hormone release. Somatostatin also inhibits transmembrane calcium transport and may have other effects on exocytosis.

Because of these pharmacologic properties, octreotide is highly useful in the treatment of acromegaly, metastatic carcinoid tumors, and vasoactive intestinal peptide secreting adenomas. The currently marketed formulation of octreotide requires two to four subcutaneous injections per day to control signs and symptoms of the indicated disorders. The new formulation

Sandostatin LAR[R] Depot Injection provides a long-acting release formulation that mimics continuous subcutaneous infusion and, after steady state is reached, maintains constant plasma levels of octreotide over a 4 week period.

Evaluation and Recommendation:
While the Office of Orphan Product Development has always designated the active ingredient in a product and not the formulation, the regulations allow for a reformulated product to be considered a different product if it is more efficacious, safer, or if it makes a major contribution to patient care. This product would represent a significant improvement in patient care if the sponsor's claim that patients can be managed with one injection per month instead of sixty to ninety injections is supported in clinical trials. In addition the agency has considered liposomal preparations as different drugs for a number of years and while the sponsor does not call this a liposomal preparation, both the pharmacokinetic properties and the method of preparation of the microsphers resemble a liposome. For the above reasons, it seems reasonable to consider octreotide acetate depot injection a different product than octreotide acetate.

Since octreotide acetate has been approved for the treatment of acromegaly for several years and there is preliminary human evidence that octreotide acetate depot injection can achieve therapeutic levels the sponsor has provided adequate rationale to justify designation. The prevalence (18,000) is less than a tenth of statutory limit and clearly qualifies; therefore, it is recommended that octreotide acetate depot injection be designated.

John J McCormick, M.D.
Medical Reviewer, Office of
Orphan Products Development
(HF-35)

Concur: Marlene E Haffner Date: 8/5/98

Marlene E. Haffner, M.D., M.P.H.
RADM USPHS
Director, Office of Orphan Products Development

cc: