DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Robert L. Garnick, Ph.D.
Senior Vice President
Regulatory Affairs, Quality & Corporate Compliance
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

RE: NDA 19-676; Nutropin® [somatropin (rDNA origin) for injection]
NDA 20-522; Nutropin AQ® [somatropin (rDNA origin) injection]
NDA 21-075; Nutropin Depot™ [somatropin (rDNA origin) for injectable suspension]
MACMIS ID # 11522

Dear Dr. Garnick:

This letter objects to Genentech, Inc.'s (Genentech) dissemination of promotional panels for Nutropin [somatropin (rDNA origin) for injection], Nutropin AQ [somatropin (rDNA origin) injection], and Nutropin Depot [somatropin (rDNA origin) for injectable suspension] ("Nutropin") that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and applicable implementing regulations. As part of the Division of Drug Marketing, Advertising, and Communications' (DDMAC) routine surveillance, we have reviewed these promotional materials for Nutropin, Nutropin AQ, and Nutropin Depot identified as 7330400 ("2002 Turner's Syndrome Society Meeting Panels"), 7331700 ("Table Top Panels"), and 7339100 ("2002 GRS-GH-IGF Meeting Panel") submitted under cover of Form FDA 2253 on October 25, 2002, and 7331600 ("Adult and Pediatric Representative Table Tops") submitted under cover of Form FDA 2253 on November 27, 2002. The referenced panels prominently display the indications and uses for Nutropin, but fail to provide any risk information. Our specific objection follows:

Indication

Nutropin and Nutropin AQ are approved for the following indications: long-term treatment in pediatric patients with growth failure due to lack of adequate endogenous growth hormone (GH) secretion; treatment of growth failure in pediatric patients associated with chronic renal insufficiency up to the time of renal transplantation; and long-term treatment of short stature in pediatric patients with Turner syndrome.

Nutropin and Nutropin AQ are also approved for the replacement of endogenous GH in adult patients with GH deficiency who meet two criteria:
(1) biochemical diagnosis of adult GH deficiency by means of a subnormal response to a standard growth hormone stimulation test (peak GH≤5 μg/L); and,
(2) adult-onset patients who have adult GH deficiency either alone or with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma or childhood-onset patients who were GH deficient during childhood, confirmed as an adult before replacement therapy with Nutropin is started.

Nutropin Depot is approved for the following indication: the long-term treatment of growth failure in pediatric patients due to a lack of adequate endogenous GH secretion.

Omission of Important Risk Information

Promotional materials are false or misleading if they fail to reveal facts material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. See 21 U.S.C. § 321(n); 21 C.F.R. § 1.21. The promotional panels are misleading because they present the indications and uses for the various formulations for Nutropin but entirely omit important risk information that is critical to the appropriate use of Nutropin. Instead, the reader is advised to actively search out separate sources for the risk information. The reader is given written instructions on the panels to "Discuss with your healthcare provider the risks and benefits associated with growth hormone therapy" or "see a Genentech representative for a copy of the full prescribing information and to see important safety information." These isolated references to seek out risk information do not mitigate the complete omission of risk information in the promotional panels[1]. By failing to include any of the important risk information, Genentech misleadingly suggests that Nutropin, Nutropin AQ, and Nutropin Depot are safer than has been demonstrated by substantial evidence or substantial clinical experience. See 21 C.F.R. § 202.1(e)(6)(i).

Please note, for example, the risk information specified in the approved product labelings (PI's): Nutropin, Nutropin AQ, and Nutropin Depot should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure. GH is contraindicated in these specific patient populations because clinical studies have demonstrated a significant increase in mortality in patients with the above indicated conditions that are treated with Nutropin as compared to placebo. Furthermore, the safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop the above indicated conditions has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illnesses should be carefully assessed in light of the important risks which were not even presented in these promotional materials.

[1] We assume for purposes of this analysis that the risk information at issue is not otherwise provided contiguously.

Additionally, Nutropin, Nutropin AQ, and Nutropin Depot should not be used for growth promotion in pediatric patients with closed epiphyses because the patient would be exposed to the risks associated with Nutropin therapy without any additional benefit with continued treatment.

Similarly, Nutropin, Nutropin AQ, and Nutropin Depot should not be used for patients with active neoplasia because it may exert a detrimental effect to the neoplasia. Therefore, Nutropin therapy should be discontinued if evidence of neoplasia develops.

Patients with diabetes mellitus may require readjustment with their insulin dose when Nutropin therapy is instituted. Because Nutropin may reduce insulin sensitivity, particularly in obese individuals, patients should be observed for evidence of glucose intolerance. Patients with diabetes or glucose intolerance should be monitored closely during Nutropin therapy.

The adverse reactions associated with Nutropin, Nutropin AQ, and Nutropin Depot therapy include leukemia, development of antibodies to the protein, edema, arthralgia, and injection site discomfort.

Requested Action

Genentech should immediately cease dissemination of these violative panels and other promotional materials for Nutropin, Nutropin AQ, and Nutropin Depot that contain the same or similar omissions of risk information. Please submit a written response on or before September 9, 2003, describing Genentech's intent and plans to comply with the above. Your letter should include a list of materials discontinued and the date on which these materials were discontinued. If you have any questions, please direct them to the undersigned by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

Please refer to MACMIS ID # 11522 and the NDA numbers in all future correspondence relating to this matter. DDMAC reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Debi Tran, Pharm.D.
LT, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debi Tran

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Science. Innovation. Service.

Choose Genentech for innovative options in growth hormone therapy.

Nutropin AQ Pen™
for use with
Nutropin AQ Pen™ Cartridge
[somatropin (rDNA origin) injection]

Nutropin AQ®
[somatropin (rDNA origin) injection]

Nutropin DEPOT®
[somatropin (rDNA origin) for injectable suspension]

Nutropin®
[somatropin (rDNA origin) for injection]

Indications and Usage

Nutropin and Nutropin AQ are indicated in pediatric patients for the long-term treatment of 1) growth failure due to a lack of adequate endogenous GH secretion, 2) short stature associated with Turner syndrome, and 3) chronic renal insufficiency up to the time of renal transplantation (therapy should be used in conjunction with optimal management of chronic renal insufficiency).

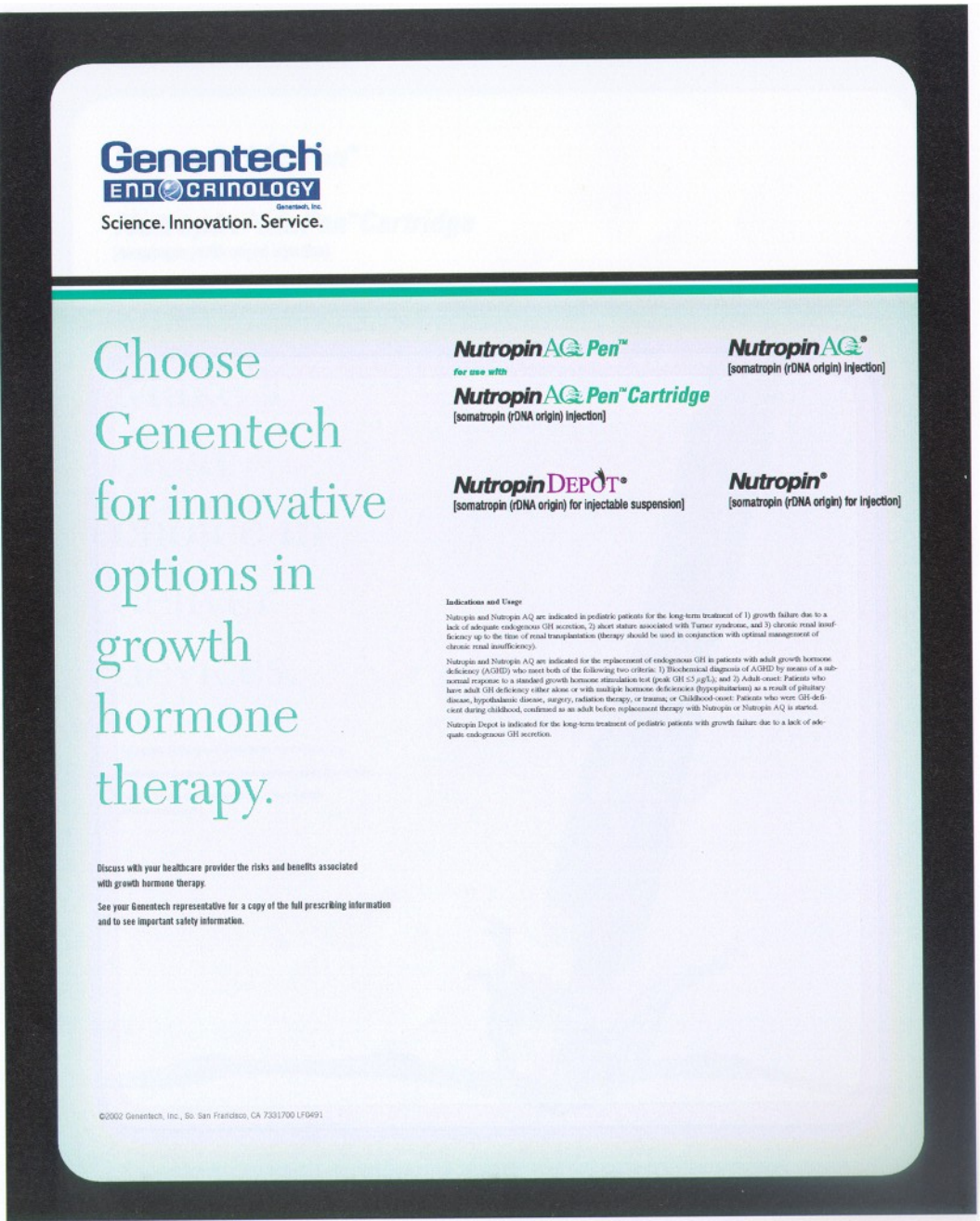
Nutropin and Nutropin AQ are indicated for the replacement of endogenous GH in patients with adult growth hormone deficiency (AGHD) who meet both of the following two criteria: 1) Biochemical diagnosis of AGHD by means of a subnormal response to a standard growth hormone stimulation test (peak GH ≤5 μg/L); and 2) Adult-onset: Patients who have adult GH deficiency either alone or with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or Childhood-onset: Patients who were GH-deficient during childhood, confirmed as an adult before replacement therapy with Nutropin or Nutropin AQ is started.

Nutropin Depot is indicated for the long-term treatment of pediatric patients with growth failure due to a lack of adequate endogenous GH secretion.

Discuss with your healthcare provider the risks and benefits associated with growth hormone therapy.

See a Genentech representative for a copy of the full prescribing information and to see important safety information.

Adult/Pediatric Rep Panels



Nutropin AQ Pen

for use with

Nutropin AQ Pen™ Cartridge

[somatropin (rDNA origin) injection]

Nutropin AQ®

[somatropin (rDNA origin) injection]

Nutropin DEPOT®

[somatropin (rDNA origin) for injectable suspension]

Nutropin®

[somatropin (rDNA origin) for injection]

NCGS NATIONAL COOPERATIVE GROWTH STUDY

SPOC SINGLE POINT OF CONTACT

GrowTrak PLUS For NCGS

ERCC ENDOCRINE REGIONAL CLINICAL COORDINATORS

NCSS NATIONAL COOPERATIVE SOMATROPIN SURVEILLANCE

Genentech Medical Communications

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