DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Glynn T. Faircloth, Ph.D.
Vice President
PharmaMar, USA, Inc.
320 Putnam Avenue
Cambridge, MA 02139-4616

RE: [ ]Ecteinasicidin-743
MACMIS # 10136

Dear Dr. Faircloth:

This letter notifies PharmaMar, USA, Inc. (PharmaMar) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional materials and activities for Ecteinasicidin-743, an investigational new drug, that are in violation of the Federal Food, Drug, and Cosmetic Act (act) and its implementing regulations. Specifically, PharmaMar distributed a brochure in the commercial exhibit hall at the 37th American Society of Clinical Oncology (ASCO) Annual meeting held in San Francisco, California, May 12-15, 2001, that made conclusions about safety and efficacy for the investigational new drug. Our specific objections follow:

Promotion of an Unapproved New Drug

Sponsors may not represent in a promotional context that an investigational new drug is safe or effective for the uses that are under investigation (see 21 CFR 312.7(a)). Your brochure titled, "The PharmaMar Oncology Pipeline: Meeting Presentations," however, includes many abstracts that present claims and representations concerning the safety or efficacy of Ecteinasicidin-743, an investigational new drug. For example, in the abstract by Demetri et al.[1], you state that the drug achieved objective responses in 6/34 evaluable patients and that progression-free and overall survival rates at 1 year were 18% and 49% for the first-line study. Your conclusion was that "ET-743 yields durable disease control and objective responses in a subset of patients with a variety of STS (soft tissue sarcoma) histologies."

[1] "Ecteinascidin-743 (ET-743) Induces Durable Responses and Promising 1-Year Survival Rates in Soft Tissue Sarcomas (STS): Final Results of Phase 2 and Pharmacokinetic Studies in the USA," George D. Demetri, Judith Manola, Dana-Farber Cancer Institute, Boston, MA. David Harmon, Massachusetts General Hospital, Boston, MA. Robert G. Maki, Memorial Sloan-Kettering Cancer Center, New York, NY. Michael V. Seiden, Jeffrey G. Supko, David P. Ryan, T.A. Puchlaski, Geraldine Goss, Priscilla Sancho, C. Guzman, Jose Jimeno, PharmaMar, S.A., Madrid, Spain. Rocio Garcia-Carbonero.

You further claim in the abstract by Cesne et al.[2] that ET-743 achieved an objective response rate of 11.4% and that its median time to progression of 3 months and the median overall survival of 7 months compare favorably with results obtained with other drugs tested in second-line CT.

Still further, you claim in the abstract by Shtil et al.[3] that ET-743 is "extremely potent (at sub- to low nanomolar concentrations) for a panel of neuroblastoma and rhabdomyosarcoma cell lines in vitro." Thus you conclude that the "diversity of mechanisms involved in cytotoxicity of ET-743 may broaden the therapeutic potential of this compound for childhood solid malignancies."

Requested Action

You should immediately discontinue the use of the above brochure, and any other materials that promote the investigational new drug as safe or effective. You should respond to me regarding this violation by letter no later than July 10, 2001. In your response, you should state how PharmaMar has addressed this violation.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds PharmaMar that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 10136 and IND 50-286.

Sincerely,

(See appended electronic signature page)

Warren F. Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

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[2] "ET-743 is an Active Drug in Adult Soft-tissue Sarcoma (STS): A STBSG-EORTC Phase 2 Trial," Axel Le Cesne, Institut Gustave Roussy, Villejuif, France. Jean-Yves Blay, Centre Leon Berard, Lyon, France. Ian Judson, Royal Marsden Hospital, London, UK. Alan Van Oosterom, U.Z. Gasthuisberg, Leuven, Belgium. Jaap Verweij, A.Z. Rotterdam, Rotterdam, Netherlands. John Radford, Christie Hospital, Manchester, UK. Paul Lorigan, Weston Park Hospital, Sheffield, UK. Sjoerd Rodenhuis, Antoni Van Leeuwenhoekhuis, Amsterdam, Netherlands. Eugenio Donato Di Paola, Martine Van Glabbeke, EORTC, Bruxelles, Belgium. Jose Jimero, PharmaMar, Madrid, Spain. Ole Nielsen, Aarhus Kommunehospital, Aarhus, Denmark.

[3] "Ecteinascidin-743 (ET-743), A Novel Natural Cytotoxic Compound, Is Potent For Human Neuroblastoma and Rhabdomyosarcoma Cell Lines: Multiple Mechanism of Cell Kill" Alexander A. Shtil, E. Anders Holb, Glynn Faircloth, Michael LaQuaglia, Kathleen Scotto, Memorial Sloan-Kettering Cancer Center, New York, NY; PharmaMar USA, Cambridge, MA.

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/s/

Warren Rumble
6/25/01 08:51:58 AM

The PharmaMar Oncology Pipeline: Meeting Presentations

PharmaMar

Unconventional Thinking. Innovative Solutions.

1407

ET-743 IS AN ACTIVE DRUG IN ADULT SOFT-TISSUE SARCOMA (STS): A STBSG-EORTC PHASE II TRIAL

Axel Le Cesne,[1] [1]Institut Gustave Roussy, Villejuif, France. Jean-Yves Blay,[2] [2]Centre Léon Bérard, Lyon, France. Ian Judson,[3] [3]Royal Marsden Hospital, London, UK. Allan Van Oosterom,[4] [4]U.Z. Gasthuisberg, Leuven, Belgium. Jaap Verweij,[5] [5]A.Z. Rotterdam, Rotterdam, Netherlands. John Radford,[6] [6]Christie Hospital, Manchester, UK. Paul Lorigan,[7] [7]Weston Park Hospital, Sheffield, UK. Sjoerd Rodenhuis,[8] [8]Antoni Van Leeuwenhoekhuis, Amsterdam, Netherlands. Eugenio Donato Di Paola[9], Martine Van Glabbeke,[9] [9]EORTC, Bruxelles, Belgium. Jose Jimeno,[10] [10]PharmaMar, Madrid, Spain. Ole Nielsen,[4] [4]Aarhus Kommunehospital, Aarhus, Denmark.

The objectives of this Phase II study were to assess the activity and toxicity of ET-743 (PharmaMar) administered at a dose of 1500 µg/m^2 as 24-hour CI every 3 weeks in patients (pts) with advanced sarcoma. Pts with ET-743 gastrointestinal stromal tumors (GIST) (Group [gp] B) received ET-743 as front-line chemotherapy (CT) while pts with STS received as second/third line CT (gp A and C). Evaluation of response in gp C (started after analysis of gp A pts) was performed with the new system based in RECIST Criteria.

Results: between 5/99 and 11/00, 132 pts have been included (47, 28, and 57 pts in gp A, B, and C respectively). Toxicity (T): there was no alopecia and no severe digestive T. A reversible grade (G) 3-4 transient elevation of transaminases was seen in 40% of pts in gp A. Febrile neutropenia, G 3-4 neutropenia and thrombocytopenia were observed in 14%, 45%, and 27% of pts respectively (gp A). There were 4 toxicity-related deaths in this gp, pts developing a fatal complex multiorgan T after the first 2 cycles (cy). The severe T were highly correlated with an abnormal alkaline phosphatase (ALP) at baseline and a rise of ALP and/or bilirubin (bil) between cy. After protocol amendment (10/99) requiring normal ALP at inclusion and ET-743 dose reduction (1200 µg/m^2) in case of an intercycle rise in bil/ALP, T has been significantly decreased (no toxicity-related deaths). No OR were observed in GIST pts. Among the 47 pts in gp A, 3 did not receive any cy of ET-743. We observed 5 PR, 21 NC (including 2 not confirmed PR and 2 major MR) and 12 PD. The objective response rate in gp A was 11.4% (95% CI: 3.8%-24%). Median time to progression (3 months) and median overall survival (7 months) (gp A) compare favorably with results obtained with other drugs tested in second-line CT. Responses were also observed in gp C and final results will be presented. ET-743 is an active compound in advanced STS. Further studies with a shorter infusion are warranted.

1406

ECTEINASCIDIN-743 (ET-743) INDUCES DURABLE RESPONSES AND PROMISING 1-YEAR SURVIVAL RATES IN SOFT TISSUE SARCOMAS (STS): FINAL RESULTS OF PHASE II AND PHARMACOKINETIC STUDIES IN THE USA

George D. Demetri,[1] Judith Manola,[1] [1]Dana-Farber Cancer Institute, Boston, MA. David Harmon,[2] [2]Massachusetts General Hospital, Boston, MA. Robert G. Maki,[3] [3]Memorial Sloan-Kettering Cancer Center, New York, NY. Michael V. Seiden,[2] Jeffrey G. Supko,[2] David P. Ryan,[2] T. A. Puchlaski,[2] Geraldine Goss,[1] Priscilla Merriam,[1] A. Waxman,[1] S. Slater, Amy Potter,[1] M. T. Quigley,[1] T. Lopez,[3] M. A. Sancho,[4] C. Guzman,[4] Jose Jimeno,[4] [4]PharmaMar, S.A., Madrid, Spain. Rocio Garcia-Carbonero.[1]

ET-743 is a marine-derived tetrahydroisoquinoline alkaloid with cytotoxic activity against a variety of tumors of mesenchymal origin in preclinical and Phase I studies. Based on these data, 2 U.S. multicenter Phase II clinical trials have been conducted to assess the activity of ET-743 in STS patients (pts) with either no prior chemotherapy (CT) or ≤2 prior CT regimens for advanced disease. Thirty-six patients were treated in each trial (total N=72) with ET-743 1500 μg/m^2 given as a 24-h IV infusion every 3 weeks on an outpatient basis. No CSF support was used. Study accrual was completed in August 2000.

Tolerability: Neutropenia and transient transaminitis were the main grade 3-4 toxicities, occurring in 28% and 32% of pts (febrile neutropenia rate <5%). Nausea, vomiting, and fatigue reached grade 2-3 in 17%, 11%, and 32% of the patients. Pharmacokinetic studies were performed during the first cycle of chemotherapy in 44 patients to assess relationships with demographic and pharmacodynamic parameters.

Efficacy: Objective responses were observed in 6/34 evaluable pts in the first-line trial (18% response rate [95%CI, 6%-33%]) and in 3/36 pts in the prior CT trial (9% response rate [95%CI, 2%-23%]). Significant minor responses (25%-45% reduction) also occurred in 5 additional patients. Responses have been noted in leiomyosarcomas, liposarcomas, synovial sarcoma, and other histologies and have been durable up to 14 months with no cumulative toxicity from ongoing treatment. Progression-free and overall survival rates at 1 year were 18% (95%CI, 4%-32%) and 49% (95%CI, 20%-78%) for the first-line study, and 11% (95%CI, -2%-24%) and 55% (95%CI, 35%-75%) for the prior CT study.

Conclusion: ET-743 yields durable disease control and objective responses in a subset of pts with a variety of STS histologies. The pharmacology of ET-743 supports its use as a 3-h IV infusion, and that study is now active in STS. Additionally, a randomized study is planned to assess the survival benefit associated with ET-743 therapy.

4353

ECTEINASCIDIN-743 (ET-743), A NOVEL NATURAL CYTOTOXIC COMPOUND, IS POTENT FOR HUMAN NEUROBLASTOMA AND RHABDOMYOSARCOMA CELL LINES: MULTIPLE MECHANISM OF CELL KILL

Alexander A. Shtil, E. Anders Kolb, Glynn Faircloth, Michael LaQuaglia, Kathleen Scotto, Memorial Sloan Kettering Cancer Center, New York, NY; PharmaMar USA, Cambridge, MA.

The overall event-free survival in children with neuroblastoma and rhabdomyosarcoma remains poor. The rate of relapse of the disease after treatment indicates an incomplete response of tumor cells to the initial therapy. In addition, chemotherapy can induce mechanisms of tumor cell defense, eventually resulting in multifactorial drug resistance. These considerations warrant the search for agents capable of overcoming pleiotropic resistance of solid tumors. Two mechanisms of drug insensitivity, namely, overexpression P-glycoprotein (Pgp) and resistance to retinoids, are widely regarded as major obstacles for treatment of childhood solid malignancies. We show that Ecteinascidin-743 (ET-743), a marine compound currently in phase I-II trials as a novel chemotherapeutic agent, is extremely potent (at sub- to low nanomolar concentrations) for a panel of neuroblastoma and rhabdomyosarcoma cell lines in vitro. Although less potent for cells selected for the multidrug resistance, ET-743 was equally toxic for cells stably infected with Pgp as compared with Pgp-negative cell lines. Furthermore, ET-743 was potent for cells that acquired resistance to several chemotherapeutic drugs in the course of treatment. ET-743 exerted its cytotoxicity in a cell type-specific manner, including mechanisms that execute apoptosis, as well as non-apoptotic pathways. We conclude that diversity of mechanisms involved in cytotoxicity of ET-743 may broaden the therapeutic potential of this compound for childhood solid malignancies.

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