Gensia files NDA for GenESA for cardiac testing

FT. COLLINS, Colo.—The Food and Drug Administration (FDA, Bethesda, MD) recently handed Gensia (San Diego, CA) a setback when it refused to consider the company's new drug application (NDA) for its heart-surgery drug, Protara, formerly called Arasine, until Gensia completed a supplemental phase III trial in the U.S. and Canada. Undaunted, Gensia responded by filing an NDA for a second drug, its coronary-artery-disease diagnostic system, GenESA. If approved, GenESA will provide cardiologists with a pharmacological stress test to augment the traditional exercise stress test now used with electrocardiography (ECG), echocardiography, and radionuclide imaging to diagnose silent-coronary-artery disease. Gensia has also applied for marketing approval for GenESA in Europe and will file for such approval later this month in Canada.

Currently, some 14 million exercise stress tests, used in conjunction with one of the three diagnostic modalities, are performed each year in the U.S. to detect patients who are at risk for heart attacks. However, up to 3 million U.S. candidates for such tests are unable to exercise adequately because of physical limitations, such as peripheral vascular disease or arthritis. In addition, of the nearly 7 million annual exercise stress tests performed with ECGs, 15 percent are inconclusive, because the patients are unable to increase their heart rates sufficiently during exercise.

The two-component GenESA system is designed to replace exercise as a means of raising heart rate by providing computer-controlled, intravenous administration of arbutamine, a novel, pharmacologic stress agent. The delivery device—designed for Gensia by Protocol Systems (San Diego, CA)—uses a closed-loop sensor that continuously adjusts the amount of arbutamine delivered to maintain a constant, elevated heart rate, as determined by a diagnostic technician. Arbutamine, developed at Gensia, is a synthetic catecholamine that acts at the alpha-adrenergic receptor in heart muscle to increase heart rate. Dobutamine—a synthetic catecholamine that treats congestive heart failure and that is made by Gensia and other manufacturers—has found some use as a pharmacologic stress agent, but dobutamine acts at the related beta$_1$-adrenergic receptor, increasing heart-muscle contractility more than heart rate.

Gensia scientists will present the results of GenESA's phase III trials later this month in Atlanta at the meeting of the American College of Cardiology, so company officials are reluctant to provide details of the trials, although they did say that approximately 700 patients were enrolled at 63 centers in the U.S., Canada, and Europe. According to R. Brandon Fradd, a biotech analyst at Montgomery Securities (San Francisco, CA), "the results for GenESA were identical to those seen with exercise stress tests." He expects rapid FDA approval and anticipates that GenESA will be on the market no later than the first quarter of 1995. Fradd is projecting GenESA revenues of $100 million in the U.S. in 1995 and $230 million in 1997. European revenues should add an additional $33 million in 1995 and $76 million in 1997.

Gensia plans to market GenESA, as well as its other products, through its own sales force, a step that often holds pitfalls for small drug companies. But industry analysts believe that Gensia's 1991 purchase of the generic-drug manufacturer, Kendall McGaw Pharmaceuticals, now known as Gensia Laboratories, makes this the right move. "Gensia Laboratories' line of generic injectables provides a powerful marketing entree for GenESA into the acute-care-hospital market," says Gregory Brown, a biotech analyst at Vector Securities International (Deerfield, IL). In addition, Gensia Laboratories came with a turnkey manufacturing facility and a long list of products—35 and counting—that should begin generating positive revenues this year.

In the meantime, Gensia's Protara—after earning mixed results in earlier phase III trials in the U.S., Canada, and Europe—is seeking, through its supplementary phase III trials, an initial indication of preventing heart attacks during coronary-artery-bypass grafting (CABG). Protara is designed to protect the heart from myocardial infarctions around the time of surgery by boosting the levels of endogenous adenosine in tissue where blood flow is too low. Such increased adenosine levels increase blood flow to the ischemic tissue, reduce platelet aggregation, and inactivate free radicals and other oxidants released by damaged tissue.

In Protara's earlier phase III trials in Europe, the compound did not show a statistically significant benefit. Yet the problem was with the execution of the European study, not with Protara itself, say Gensia officials. And biotech analysts agree. "In the European studies, blood samples taken to assess levels of the heart-muscle enzyme, creatine kinase, had to be mailed to a central site in London, which meant that, in many instances, the samples were at room temperature for several days, and it's likely that they deteriorated," says one biotech analyst. Adds Montgomery Securities' Fradd, "The ECG data showed a clear difference between treated high-risk patients and controls in the European study, and I fully expect the supplementary-trial data to satisfy the FDA." The new trial has already enrolled 1,000 CABG patients, with a goal of 1,500 patients, and Gensia expects to have the additional data compiled and analyzed by the middle of this year.

Gensia has also begun phase III trials of Protara in noncardiac-surgery patients who may be at risk of heart attacks while undergoing major surgeries, such as hip replacements. The trials will enroll between 3,000 and 4,000 patients at 75 centers in the U.S., Canada, and Europe. The incidence of heart attacks during general surgery in patients known to have heart disease is about 4.5 percent, the same as in such patients undergoing CABG. While the number of U.S. patients undergoing CABG is approximately 350,000 a year, the number of high-risk patients having noncardiac surgery annually exceeds 5 million. Biotech analysts project that worldwide revenues for Protara could reach $100 million in 1995 and could top $700 million in 1999. **—Joseph Alper**

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