Genentech
IN BUSINESS FOR LIFE

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August 28, 2006

Dear Healthcare Provider:

As the manufacturer of AVASTIN® (bevacizumab) and LUCENTIS™ (ranibizumab), Genentech, Inc., would like to inform you of a potential safety risk regarding the unapproved intravitreal use of humanized anti-vascular endothelial growth factor-A (VEGF) antibodies for the treatment of retinopathy of prematurity (ROP). Neither product is indicated for ROP nor have they been studied in premature neonates. We do not recommend use of AVASTIN or LUCENTIS in this condition outside the setting of a well-controlled and monitored clinical study.

The intravitreal use of VEGF inhibitory agents has not been studied in premature neonates; however, systemic exposure following intravitreal administration of VEGF inhibitors may be significant in this population. Partial inhibition of VEGF in a newborn animal model has been shown to cause potentially fatal serious developmental adverse effects, including severe growth retardation and impaired growth of vital organs such as kidneys, lungs, and liver (Gerber HP, Development, 126: 1 149-59, 1999).

AVASTIN is approved in combination with intravenous 5-fluorouracil-based chemotherapy for the first- or second-line treatment of patients with metastatic colorectal cancer; it is not formulated for intravitreal injection. In clinical trials, the most serious adverse events associated with Avastin were: GI perforation, wound healing complications, hemorrhage, arterial thromboembolic events, hypertensive crises, nephrotic syndrome, and congestive heart failure. The most common adverse events in patients receiving AVASTIN were asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria. The safety and effectiveness of AVASTIN in pediatric patients has not been established.

LUCENTIS is approved for the intravitreal treatment of (wet) age-related macular degeneration. LUCENTIS is contraindicated in patients with ocular or periocular infections. Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachment. Increases in intraocular pressure have been noted within 60 minutes of intravitreal injection. Serious adverse events included endophthalmitis and rarely events related to the injection procedure such as rhegmatogenous retinal detachment, and iatrogenic traumatic cataract. Although there was a low rate (<4%) of arterial thromboembolic events (ATEs) observed in LUCENTIS clinical trials, there is a theoretical risk of ATEs following intravitreal use of inhibitors of

VEGF. The safety and effectiveness of LUCENTIS in pediatric patients has not been established.

Accompanying this letter are the package inserts for AVASTIN and LUCENTIS. Should you have any questions regarding the use of the above products, please call our Medical Information/Communications Department at 1-800-821-8590.

Healthcare professionals should report any serious adverse events suspected to be associated with the use of AVASTIN and LUCENTIS to Genentech at 1-888-835-2555. Alternatively, this information may also be reported to the FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/), or by mail, using MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Sincerely,

Hal Barron, M.D.
Senior Vice President, Development
Chief Medical Officer
Genentech, Inc.