Genentech
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080

IMPORTANT DRUG WARNING

Subject: Direct Healthcare Professional Communication on Cases of Necrotizing Fasciitis Reported with Avastin® (bevacizumab)

April 16, 2013

Dear Healthcare Provider,

Genentech, a Member of the Roche Group, would like to inform you of an update to the AVASTIN (bevacizumab) prescribing information to include new safety information regarding necrotizing fasciitis. The updated Avastin Package Insert is enclosed.

Summary

Necrotizing fasciitis, including fatal cases, has been reported in patients receiving Avastin in both clinical trials and in the post-marketing setting.

It is recommended that Avastin be discontinued and appropriate therapy initiated promptly upon diagnosis of necrotizing fasciitis.

Further information on the safety concern

Necrotizing fasciitis is a rare but life-threatening infection of the soft tissue, characterized by rapidly spreading necrosis of superficial fascia and subcutaneous tissue. Immunocompromised patients are at a higher risk of developing necrotizing fasciitis.

The reported cases of necrotizing fasciitis in Roche and Genentech clinical trials and in the global safety database occurred in patients treated in both approved and investigational uses (see enclosed prescribing information for approved indications). Regarding associated medical conditions, the majority of the patients had gastrointestinal perforation, fistula formation or wound healing complications preceding the development of necrotizing fasciitis. Some of these patients died due to complications of necrotizing fasciitis.

Based on these findings, the following information has been added to the WARNINGS and PRECAUTIONS section of the Avastin U. S. Package Insert, under section 5.2, Surgery and Wound Healing Complications:

"Necrotizing fasciitis including fatal cases, has been reported in patients treated with Avastin; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue Avastin therapy in patients who develop necrotizing fasciitis."

This information has also been included in the ADVERSE REACTIONS section of the U. S. Package Insert, under section 6.3, Postmarketing Experience:

"*Infections and Infestations*: Necrotizing fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation"

Please note that this presentation of the risk profile for Avastin is not comprehensive. Please see the accompanying prescribing information for a complete discussion of the risks associated with Avastin, including the Boxed WARNINGS.

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa; for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel; for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy; and in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer.

Please see additional important safety information, including the Boxed WARNINGS for gastrointestinal perforations, surgery and wound healing complications, and hemorrhage at the end of this letter.

Call for reporting

Health care professionals should report any serious adverse events suspected to be associated with the use of AVASTIN to Genentech at 1-888-835-2555. Alternatively, this information may be reported to 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 mailed, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

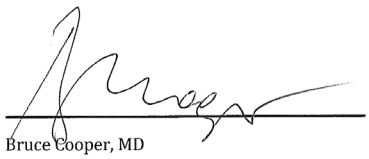
Company contact point

Should you have any questions regarding the use of Avastin, please feel free to contact us at:

Genentech Medical Information/Communications Department at (800) 821-8590

Yours sincerely,

Genentech, a Member of the Roche Group



Bruce Cooper, MD

Senior Vice President, US Medical Affairs

Important Safety Information about Avastin (bevacizumab):

Boxed WARNINGS

- **Gastrointestinal (GI) perforation**
  - — Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls
  - — The incidences of GI perforation ranged from 0.3% to 2.4% across clinical studies
  - — Discontinue Avastin in patients with GI perforation
- **Surgery and wound healing complications**
  - — The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients
  - — Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined
  - — Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound healing complications requiring medical intervention
- **Hemorrhage**
  - — Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%
  - — Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)
  - — Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)

Additional serious adverse events

- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Non-GI fistula formation (≤0.3%)
  - — Arterial thromboembolic events (grade ≥3, 2.6%)
  - — Proteinuria (nephrotic syndrome, <1%)
- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Hypertension (grade 3–4, 5%–18%)
  - — Reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%)
- Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin

Most common adverse events

- Most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were
  - — Epistaxis
  - — Headache
  - — Hypertension
  - — Rhinitis
  - — Proteinuria
  - — Taste alteration
  - — Dry skin
  - — Rectal hemorrhage
  - — Lacrimation disorder
  - — Back pain
  - — Exfoliative dermatitis
- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

Pregnancy warning

- Avastin may impair fertility
- Based on animal data, Avastin may cause fetal harm
- Advise patients of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following the last dose of Avastin
- For nursing mothers, discontinue nursing or Avastin, taking into account the importance of Avastin to the mother

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see full Prescribing Information, including Boxed WARNINGS, for additional important safety information.