29 April 2010

Association of bevacizumab, Avastin® with Hypersensitivity and Infusion reactions

Dear Healthcare Professional

Summary

Roche Products (Ireland) Limited would like to inform you of an important update to the safety information regarding the use of AVASTIN (bevacizumab).

A risk of Avastin-treated patients experiencing Hypersensitivity reactions/Infusion reactions has been identified in up to 5 % of patients.

A systematic premedication is not warranted.

The majority of reactions are mild to moderate. More severe reactions were noted in 0.2 % of patients.

Patients should be closely monitored during and after Avastin infusion.

If a reaction occurs, the infusion should be stopped and appropriate therapies administered.

The decision to re-challenge patients should be based upon individual goals of therapy and accurate assessment of the severity of the hypersensitivity/infusion reaction.

The communication of this information has been agreed by the European Medicines Agency (EMA) and the Irish Medicines Board (IMB).

Further information on the safety concern

To date, Avastin has been administered to more than 500,000 cancer patients.

273 case reports were retrieved from the company safety database, ADVENT, which includes data from clinical trials as well as spontaneously submitted adverse drug reaction reports. The majority of cases were confounded by concomitant chemotherapy. However seven cases of positive rechallenge and two cases with a positive cutaneous test were identified.

In clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Avastin in combination with chemotherapy than with chemotherapy alone. The

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incidence of these reactions in clinical trials of Avastin is common (up to 5% in bevacizumab treated patients). No fatal cases with a clear causal association to bevacizumab treatment have been reported so far from clinical trials. In addition, postmarketing reports have been received which included immune system disorders like hypersensitivity and infusion reactions (frequency not known).

Similar anaphylactic, anaphylactoid-type and infusion reactions have been reported with many intravenously administered monoclonal antibodies, although at different frequencies, with the following possible co-manifestations: dyspnoea / difficulty breathing, flushing / redness / rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea / vomiting[1].

Although no data are available specifically on Avastin, in general, patients experiencing mild to moderate hypersensitivity/infusion reactions (grade 1 or 2 of the National Cancer Institute Common Toxicity Criteria for Adverse Events v 3.0 for Hypersensitivity and Acute Infusion Reactions[2]) in particular after the first exposure may tolerate readministration of the agent at reduced infusion rates and with treatment using antihistamines and corticosteroids after complete resolution of symptoms. Re-challenge is generally discouraged in patients who experienced a severe initial reaction (grade 3 or 4).

In light of this information, Roche considers there is sufficient evidence to confirm the causal role of bevacizumab in the occurrence of hypersensitivity reactions and infusion reactions.

The Summary of Product Characteristics for Avastin has been updated to include new safety information on hypersensitivity reactions and infusion reactions, as follows

4.4 Special warnings and precautions for use

Patients may be at risk of developing infusion / hypersensitivity reaction. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

4.8 Undesirable Effects

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Avastin in combination with chemotherapy than with chemotherapy alone. The

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[1] Kang PS, Saif MW. Infusion-related and Hypersensitivity Reactions of Monoclonal Antibodies Used to Treat Colorectal Cancer – Identification, Prevention and Management.

[2] Lenz HJ. Management and Preparedness for Infusion and Hypersensitivity Reactions. The Oncologist 2007;12:601-609. www.theoncologist.com

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incidence of these reactions in some clinical trials of Avastin is common (up to 5% in bevacizumab treated patients).

Postmarketing

Immune system disorders: Hypersensitivity, infusion reactions (frequency not known); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting.

Call for reporting

Healthcare professionals are reminded to continue to report serious adverse events suspected to be associated with the use of Avastin to the Drug Surveillance Centre at Roche (either by mail, telephone [01 4690700], fax [01 4690793] or e-mail [Ireland.drug_surveillance_centre@roche.com]). Alternatively, adverse events may be reported to the pharmacovigilance section of the IMB in the usual manner.

Communication information

Should you have any questions or require additional information regarding Hypersensitivity reactions and Infusion reactions associated with the use of Avastin, please contact Medical Information at Roche (either by mail, telephone [01 4690700], fax [01 4690791] or e-mail [Ireland.druginfo@roche.com]).

Yours sincerely,

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