

14 July 2008

Direct Healthcare Professional Communication on Important Safety Information regarding the unapproved combined use of Avastin[®] ▼ (bevacizumab) and sunitinib malate.

Dear Healthcare Provider:

Summary

- Roche would like to inform you of important new safety information, concerning the combined use of AVASTIN[®] (bevacizumab) and sunitinib malate. Please note that Avastin is not approved for use in combination with sunitinib malate for any indication. To date, there are insufficient clinical data available to draw any firm conclusions regarding the safety of combining Avastin with sunitinib malate.
- This information concerns adverse events that occurred in an investigator-sponsored Phase I dose-escalation study combining Avastin and escalating doses of sunitinib malate in patients with metastatic renal cell carcinoma (mRCC). Five of 12 patients at the highest sunitinib malate dose level (50 mg once daily) exhibited laboratory findings consistent with microangiopathic haemolytic anaemia (MAHA).
- The communication of this information to Avastin prescribers, Heads of Oncology Departments and oncology pharmacists, has been agreed by the CHMP and Medicines and Healthcare products Regulatory Agency.

Extended information on the safety finding

The safety and maximum tolerated dose (MTD) of sunitinib malate in combination with bevacizumab was assessed in patients with mRCC in a phase I study, exploring 3 cohorts using a fixed dose of Avastin at 10 mg/kg/IV every 2 wks and escalating doses of sunitinib that included 25 mg, 37.5 mg, and 50 mg orally daily given in a 4 wk on / 2 wk off schedule.

To date, a total of 25 patients have been treated in this study with 12 assigned to the highest sunitinib dose level. Five out of the 12 patients in this cohort exhibited laboratory findings consistent with microangiopathic hemolytic anemia (MAHA). No patient assigned to the lower sunitinib dose cohorts was diagnosed with MAHA. MAHA is a subgroup of hemolytic anemia caused by thrombotic lesions in the microvessels and other mechanical causes, and is associated with thrombocytopenia and red blood cell fragmentation. This is diagnosed by schistocytes on microscopy of the blood film, together with other laboratory abnormalities such as LDH increase and reductions in serum haptoglobin.

Two of the 5 cases were considered severe with presence of additional adverse events such as thrombocytopenia, anaemia, reticulocytosis, reductions in serum haptoglobin, modest increases in serum creatinine levels, and severe hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), and proteinuria. The findings in these two cases were reversible within three weeks upon discontinuation of both drugs without additional intervention.

PRESCRIBING INFORMATION

Refer to Avastin Summary of Product Characteristics (SPC) for full prescribing information

AVASTIN® ▼ (bevacizumab) 25mg/ml concentrate for solution for infusion

Indications: In combination with fluoropyrimidine-based chemotherapy for treatment of metastatic carcinoma of the colon or rectum. In combination with paclitaxel for first-line treatment of metastatic breast cancer. In addition to platinum-based chemotherapy for first-line treatment of unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology. In combination with interferon alfa-2a for first-line treatment of advanced and/or metastatic renal cell cancer.

Dosage and Administration: Single use vials (25mg/ml bevacizumab) as 100mg/4ml or 400mg/16ml. Physicians experienced in antineoplastic medicines should supervise Avastin administration. *Recommended dose:* Continue until progression of underlying disease. *Colorectal cancer:* either 5 mg/kg or 10 mg/kg every 2 weeks or 7.5 mg/kg or 15 mg/kg every 3 weeks; *Breast cancer:* 10mg/kg every 2 weeks or 15mg/kg every 3 weeks. *Lung cancer:* 7.5mg/kg or 15mg/kg every 3 weeks in addition to platinum-based chemotherapy for up to 6 cycles, then as monotherapy. *Renal cell cancer:* 10mg/kg every 2 weeks. Administration times; *initial dose:* 90 minute IV infusion; *second dose:* 60 minute IV infusion if initial dose well tolerated; *subsequent doses:* 30 minute IV infusion if second dose well tolerated. Do not administer as IV push or bolus or mix with glucose. Dose reduction for adverse events not recommended. If indicated, discontinue or temporarily suspend therapy. Not recommended in children or adolescents. No dose adjustment in the elderly.

Contraindications: Hypersensitivity to bevacizumab, Chinese hamster ovary cell products, recombinant human or humanised antibodies or any excipients. Pregnancy. Lactation. Untreated CNS metastases.

Precautions: *Gastrointestinal (GI) perforation;* intra-abdominal inflammatory process may cause increased risk in metastatic colorectal cancer patients; permanently discontinue in patients developing GI perforation. *Fistulae;* permanently discontinue in tracheo-oesophageal or any Grade 4 fistula, consider discontinuation in non-GI fistula. *Wound healing;* do not initiate for at least 28 days following major surgery or until surgical wound has healed; withhold for elective surgery. *Hypertension;* control pre-existing hypertension prior to initiation. Diuretics not recommended for hypertension control with cisplatin. Monitor blood pressure during therapy and treat as per SPC. Permanently discontinue if medically significant hypertension remains uncontrolled or for hypertensive crisis/encephalopathy. *Reversible Posterior Leukoencephalopathy Syndrome (RPLS);* should RPLS develop, confirm by imaging, treat symptoms and discontinue Avastin. RPLS signs include: seizures, headache, altered mental status, visual disturbance or cortical blindness with/without associated hypertension. *Proteinuria;* test prior to and monitor during treatment. Permanently discontinue if Grade 4 proteinuria (nephrotic syndrome) develops. *Arterial thromboembolism* including cerebrovascular accidents, transient ischaemic attacks and myocardial infarctions, especially if prior history or elderly. Permanently discontinue if arterial thromboembolic events develop. *Venous thromboembolism* including pulmonary embolism; discontinue in Grade 4 pulmonary embolism and monitor where ≤Grade 3. *Haemorrhage, especially tumour-associated haemorrhage;* discontinue permanently if Grade 3/4. Caution in patients with congenital bleeding diathesis, acquired coagulopathy or during anticoagulant therapy. *Serious/fatal pulmonary haemorrhage/haemoptysis in non-small cell lung cancer;* do not use where recent significant pulmonary haemorrhage/haemoptysis (>2.5 ml of red blood). *Congestive Heart Failure (CHF);* caution in patients with clinically significant cardiovascular disease or pre-existing CHF. *Neutropenia. Fatal infection with severe neutropenia in combination with myelotoxic chemotherapy.*

Drug Interactions: Safety and efficacy with concomitant radiotherapy not established.

Pregnancy and Lactation: Contraindicated. No data on use in pregnancy; may inhibit foetal angiogenesis. Women of childbearing potential must use effective contraception during treatment and for 6 months after last dose. Discontinue breast-feeding during treatment and for 6 months after last dose.

Side-effects and Adverse Reactions: For full listings please refer to the Avastin SPC. *Serious reactions, very common:* Leucopenia, thrombocytopenia and neutropenia. Peripheral sensory neuropathy. Diarrhoea, nausea, vomiting. Venous thromboembolic events. Fatigue. *Serious reactions, common:* Febrile neutropenia, anaemia. Sepsis, abscess, infection. Dehydration. Cerebrovascular accident, syncope, somnolence, headache. Supraventricular tachycardia, CHF. Arterial thromboembolism, deep vein thrombosis, haemorrhage, including pulmonary haemorrhage. Pulmonary embolism, dyspnoea, hypoxia. Ileus, intestinal perforation and obstruction, abdominal pain, GI disorder. Palmar-plantar erythrodysesthesia syndrome. Muscular weakness. Proteinuria, urinary tract infection. Lethargy. *Serious reactions, uncommon/rare:* Fistulae. Hypertensive encephalopathy. RPLS (with or without associated hypertension), pulmonary hypertension, nasal septum perforation. *Other, very common:* Wound healing delay. Anorexia. Dysgeusia. Eye disorder. Hypertension. Epistaxis. Rectal haemorrhage. Dyspnoea, rhinitis. Constipation, stomatitis. Exfoliative dermatitis, dry skin, skin discolouration. Pyrexia, Asthenia. Pain. Any of the above may become serious. Elderly; increased risk of severe leucopenia and thrombocytopenia; neutropenia, nausea, headache, diarrhoea, fatigue, or arterial thromboembolic events. Laboratory abnormalities – refer to SPC.

Legal Category: POM

Presentation and Basic NHS Cost: Pack of one 100mg vial: £242.66. Pack of one 400mg vial: £924.40. Excluding VAT

Marketing Authorisation Numbers: 100mg/4ml: EU/1/04/300/001; 400mg/16ml: EU/1/04/300/002

Marketing Authorisation Holder: Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom. Registered in England No. 3028626

Avastin is a registered trade mark

Date of Preparation: February 2008

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Roche Products Limited. Please contact UK Drug Safety Centre on: 01707 367554



Roche Products Limited

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Oncology Business Unit

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The information above led to the closure of a Genentech-sponsored Phase II trial of sunitinib at 50 mg with or without Avastin, with a similar dosing schedule in first line mRCC. In this study a preliminary review identified two additional cases of MAHA similar to those described above.

Another dose-escalation Phase I, NCI-sponsored study of sunitinib in combination with Avastin in multiple tumor types has not reported evidence of MAHA to date.

Similarly, to date, no events of MAHA have been reported in two other Genentech-sponsored studies of this combination added to chemotherapy in NSCLC and breast cancer. However, these two Genentech studies, which had different dosing regimes from those of the studies discussed above (full dose Avastin and escalating doses of sunitinib up to 37.5mg) were also closed due to poor tolerability, primarily due to myelosuppression, fatigue and gastrointestinal complications (e.g, diarrhea, anorexia, dehydration, stomatitis).

Avastin is not approved for use in combination with sunitinib malate for any disease state.

AVASTIN is approved in combination with:

- *fluoropyrimidine-based chemotherapy for treatment of patients with metastatic carcinoma of the colon or rectum,*
- *paclitaxel for first-line treatment of patients with metastatic breast cancer,*
- *platinum-based chemotherapy for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology*
- *interferon alfa-2a for first line treatment of patients with advanced and/or metastatic renal cell cancer.*

The current AVASTIN prescribing information can be found at <http://www.medicines.org.uk>.

Call for reporting

Healthcare professionals should report any adverse event suspected to be associated with the use of AVASTIN to the Medicines and Healthcare products Regulatory Agency (MHRA) using a Yellow Card available directly from the MHRA, CHM Freepost, London SW8 5BR or electronically via the MHRA website at <http://www.yellowcard.gov.uk>. Adverse events should also be reported to Roche by phone on 01707 367554, by fax on 01707 367582 or e-mail at welwyn.uk_dsc@roche.com.

For further information or any questions on MAHA associated with the use of Avastin, please contact Roche Medical Information on 0800 3281629 or 01707 361 010.

Yours sincerely,



Dr Michelle Rashford

Medical Director

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