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Direct Healthcare Professional Communication on Important Safety Information regarding the unapproved combined use of Avastin® 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 has been agreed by the Irish Medicines Board and the EMEA's Committee for Medicinal Products for Human Use (CHMP).

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.

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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 1st 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 than 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.*

Please find enclosed the current Avastin prescribing information for your information.

Call for reporting
Healthcare professionals should report any serious adverse events suspected to be associated with the use of AVASTIN to the Drug Surveillance Desk at Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24, Tel: 01-4690700; Fax: 01-4690793; E-mail: Ireland.drug_surveillance_centre@roche.com or to the pharmacovigilance section of the Irish Medicines Board in the usual manner.

For further information or any questions on MAHA associated with the use of Avastin, please contact medical information at Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24, Tel: 01-4690700; Fax: 01-4690791; Email: Ireland.druginfo@roche.com.

Yours sincerely,

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Director of Medical Affairs

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