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[redacted]

Withdrawal of the clinical Type II variation for a new indication (NSCLC) for Erbitux®
(MA numbers EU/1/04/281/003 and 005)
EMA variation number: EMEA/H/C/558/II/0043

Dear Dr. Salmonson

We would like to inform you that, at this point in time, Merck KGaA (the MAH) has taken the decision to withdraw the application for a new indication for Erbitux® (5 mg/mL) for the treatment of NSCLC.

This withdrawal is based on the following reasons:

On March 2011 the MAH submitted a clinical Type II variation concerning an extension of indication in non small cell lung cancer (NSCLC) based on biomarker data for Erbitux.

The submission was based on the pivotal Phase III study, EMR 62202-046 (FLEX) with an overall survival benefit for Erbitux treatment seen in the patient population with high EGFR expression in the tumor (defined as EGFR histo score ≥ 200 (assessed by immunohistochemistry) and supported by additional preclinical and clinical data.

EMR 62202-046 has met its primary objective to show superior overall survival (OS) in the ITT population with a median OS time difference for cetuximab + chemotherapy vs chemotherapy of 1.2 months (11.3 vs 10.1 months) with a HR of 0.87 (95% CI 0.762, 0.996; p = 0.044). The MAH performed further analyses and identified high EGFR expression in the tumor as a potential predictive biomarker in NSCLC. In the high EGFR expression group the median OS benefit was doubled with 2.4 months (12.0 vs 9.6 months) for cetuximab + chemotherapy vs chemotherapy with a HR of 0.73 (95% CI 0.58, 0.93; p = 0.011). The safety profile in the high EGFR expression group was consistent with the overall safety population.

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In the assessment report the CHMP acknowledged the biological and scientific rationale related to EGFR expression and Erbitux efficacy but raised concerns regarding the uncertainties on the magnitude of the effect since the data were mainly derived from only one phase III study. Based on this, the CHMP requested further data on the potential utility of Erbitux for the treatment of patients with NSCLC with high EGFR expression.

The current available data package suggests that further data will be required to overcome the uncertainties raised by CHMP and therefore the MAH decided to withdraw the application within the EU.

There are no consequences on the use of Erbitux in its approved indications as the benefit-risk ratio remains positive in these indications (CRC and SCCHN).

The MAH reserves the right to make further submissions at a future date in this or other therapeutic indication(s).

The MAH agrees for this letter to be published on the EMA website.

Yours sincerely,

Merck KGaA

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