ADDENDUM 1 TO
INVESTIGATOR BROCHURE EDITION 5

TRASTUZUMAB EMTANSINE (PRO132365, RO5304020)

SPONSORS: Genentech, Inc.
1 DNA Way
South San Francisco, CA  94080-4990  U.S.A.

F. Hoffmann–La Roche Ltd
Grenzacherstrasse 124
CH-4070 Basel
Switzerland

DATE: June 2011
1. **INTRODUCTION**

This addendum to the Investigator Brochure (IB) for trastuzumab emtansine (formerly trastuzumab-MCC-DM1, also known as T-DM1) provides new guidance to the investigator about the risks of pneumonitis and nodular regenerative hyperplasia which was not available when the original IB Edition 5 was finalized. The Developmental Core Safety Information (DCSI) has been updated to include this new information (see Appendix A). Precautionary information about observed extravasation events is also provided within the Guidance to the Investigator section.

In addition, the description of an adverse event leading to death in Study TDM4374g has been corrected from pneumonitis to the MedDRA preferred term of interstitial lung disease.

2. **CLINICAL SAFETY**

2.1 **DEATHS IN STUDY TDM4374G**

(Corresponds to Section 5.3.1.6.c in Edition 5 of the Investigator Brochure)

As of the data cut-off on 21 June 2010, there has been one patient death within 30 days of the last study treatment. The patient died after experiencing an adverse event of hepatic dysfunction. The patient had preexisting non-alcoholic fatty liver disease as well as multiple other co-morbidities, including renal insufficiency. The patient died as the result of multi-organ failure and had biopsy-confirmed non-alcoholic steatohepatitis. Although the hepatic event was reported to be temporally related to trastuzumab emtansine dosing, confounding medical conditions, including the patient’s declining performance status and exposure to other hepatotoxic drugs trazodone and quetiapine confounds the association with study treatment.

There are two additional deaths that occurred due to AEs that occurred after 30 days after their last trastuzumab emtansine dose. One patient died of interstitial lung disease 37 days from last study drug administration. Another patient died of pneumonia 66 days from last study drug administration. Both deaths were judged by the investigators not to be related to study drug.

3. **GUIDANCE TO THE INVESTIGATOR**

3.1 **IDENTIFIED RISKS**

(Corresponds to Section 6.2 in Edition 5 of the Investigator Brochure)

Thrombocytopenia, elevated liver enzymes, infusion/hypersensitivity reaction, and pneumonitis have been identified as risks with trastuzumab emtansine use.
3.1.1 **PNEUMONITIS**

Severe pulmonary events including interstitial lung disease, dyspnea, pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency, hypoxia, and acute respiratory distress syndrome have been reported with the use of trastuzumab, a component of trastuzumab emtansine. These events may or may not occur as sequelae of infusion reactions and occasionally resulted in fatal outcome. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs may be at greater risk of severe reactions.

Pneumonitis has been rarely reported with trastuzumab emtansine (four cases as of April 2011). Signs, symptoms, and clinical findings include dyspnea, cough, fatigue, and pulmonary infiltrates.

There were no fatalities among the four cases of pneumonitis reported with trastuzumab emtansine; however, in some patients with multiple lung metastases, ventilatory support (mechanical ventilation) was required. Treatment included administration of steroids, oxygen, and study drug discontinuation.

Two cases of interstitial lung disease (ILD) and three cases of acute respiratory distress syndrome (ARDS) have also been reported in trastuzumab emtansine clinical trials to date. However, a causal relationship between these events and trastuzumab emtansine has not been established.

3.2 **POTENTIAL RISKS**

*(Corresponds to Section 6.3 in Edition 5 of the Investigator Brochure)*

3.2.1 **NODULAR REGENERATIVE HYPERPLASIA**

Nodular regenerative hyperplasia has been identified from liver biopsies of two subjects treated with trastuzumab emtansine (as of May 2011). In the first case, a patient who was receiving trastuzumab emtansine plus pertuzumab for 14 months developed abdominal pain and distension with radiologic findings of portal hypertension, including small-volume ascites and esophageal varices. Laboratory data were notable for a progressive increase in serum alkaline phosphatase while serum transaminase and total bilirubin concentrations remained relatively stable. Signs of portal hypertension improved following the discontinuation of study treatment and medical management of the portal hypertension. In the second case, a patient who was receiving single-agent trastuzumab emtansine for 26 months developed progressive disease including brain metastases and developed increased serum transaminases, bilirubin, alkaline phosphatase and ascites following the last dose of trastuzumab emtansine. The patient subsequently died. The cause of death was attributed to liver failure by the investigator. No autopsy was performed. Evaluation of the case suggests the patient died following documented disease progression leading to multi-organ failure.
3.3 WARNINGS AND PRECAUTIONS

(Corresponds to Section 6.4 in Edition 5 of the Investigator Brochure)

3.3.1 Extravasation

Cellulitis or phlebitis was described after paravenous injection of maytansine (weekly i.v. bolus or 24 hour infusions) in a series of 71 patients with leukemia, lymphoma or carcinoma [1]. Cellulitis at the site of extravasation was described in one subject in a series of 29 patients with squamous cell carcinoma of the cervix treated with maytansine every 3 weeks [2].

In trastuzumab emtansine clinical studies one case of extravasation was reported in a 29-year-old subject who developed Grade 2 cellulitis of the right arm due to extravasation of 20-30mL trastuzumab emtansine infusion on study day 113. Treatment included analgesics and antibiotics. The event resolved with no sequelae after approximately 3 weeks. Trastuzumab emtansine treatment was resumed at a later date.

Another case of skin exposure to trastuzumab emtansine occurred in a 39-year-old nurse who experienced accidental exposure to trastuzumab emtansine to the internal part of the auricle of her ear while preparing the drug for a patient. The nurse reported local skin irritation, redness, burning sensation and pain. Treatment consisted of saline solution compresses and hyaluronan cream. The event resolved with no sequelae on the following day.

In trastuzumab emtansine clinical studies, injection site reactions, including reactions secondary to extravasation, have usually been mild and comprised erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently within 24 hours of infusion/extravasation. Rare reports of more severe events such as cellulitis, pain (tenderness and burning sensation), and skin irritation have been received as part of the continuing surveillance of trastuzumab emtansine safety. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. It is advisable to closely monitor the infusion site for possible subcutaneous infiltration during drug administration.

4. REFERENCES


Appendix A

DEVELOPMENTAL CORE SAFETY INFORMATION
VERSION 3, JUNE 2011

<table>
<thead>
<tr>
<th>COMPOUND NO.</th>
<th>RO5304020</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRADENAME®</td>
<td>N/A</td>
</tr>
<tr>
<td>INN</td>
<td>TRASTUZUMAB EMTANSINE</td>
</tr>
</tbody>
</table>

1. CONTRAINDICATIONS

Trastuzumab emtansine (previously known as T-DM1) is contraindicated in patients with known hypersensitivity to any component of the product.

2. WARNINGS AND PRECAUTIONS

There are no warnings yet identified for trastuzumab emtansine.

2.1 PRECAUTIONS

2.1.1 THROMBOCYTOPENIA

Thrombocytopenia is the dose limiting toxicity seen in the phase 1 trials with trastuzumab emtansine. There was no clear association between thrombocytopenia and hemorrhagic events; however, severe Grade 4 thrombocytopenia, some requiring platelet transfusion, associated with trastuzumab emtansine has been uncommonly reported. Monitoring with a complete blood count (CBC) for hematologic toxicity should occur at least every week in the first cycle and in subsequent cycles as described per protocol. Dose reductions for severe thrombocytopenia are described in each individual protocol.

2.1.2 HEPATOTOXICITY

Transient and reversible elevations of liver enzymes (Grade 1-4 transamininitis) have been observed following treatment with trastuzumab emtansine. Although significant hepatotoxicity has rarely been seen in clinical trials with trastuzumab emtansine to date, and when observed, the relationship to trastuzumab emtansine has not been clear, severe liver injury remains an important potential risk. Liver function should be monitored at least weekly for the first 3 cycles, then every cycle thereafter. Dose reductions for severe liver enzyme elevations are described in each individual protocol.
2.1.3 Cardiotoxicity

Treatment with trastuzumab, a component of trastuzumab emtansine, has resulted in subclinical and clinical cardiac failure manifesting as congestive heart failure (CHF), decreased left ventricular ejection fraction (LVEF), and cardiac death. Although significant cardiotoxicity has not been seen in clinical trials with trastuzumab emtansine to date, severe cardiotoxicity remains an important potential risk. Standard cardiac function test (echocardiogram or MUGA) should be assessed at regular intervals in patients receiving trastuzumab emtansine. Specific guidelines regarding dosing if toxicities are observed are provided in the clinical trial protocol.

2.1.4 Pneumonitis

Severe pulmonary events including interstitial lung disease, dyspnea, pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency, hypoxia, and acute respiratory distress syndrome have been reported with the use of trastuzumab, a component of trastuzumab emtansine. These events may or may not occur as sequelae of infusion reactions and occasionally resulted in fatal outcome. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs may be at greater risk of severe reactions.

Pneumonitis has been rarely reported with trastuzumab emtansine (4 cases as of April 2011). Signs, symptoms, and clinical findings include dyspnea, cough, fatigue, and pulmonary infiltrates.

There were no fatalities among the 4 cases of pneumonitis reported with trastuzumab emtansine; however, in some patients with multiple lung metastases, ventilatory support (mechanical ventilation) was required. Treatment included administration of steroids, oxygen, and study drug discontinuation. Two cases of interstitial lung disease (ILD) and 3 cases of acute respiratory distress syndrome (ARDS) have also been reported in trastuzumab emtansine clinical trials to date. However, a causal relationship between these events and trastuzumab emtansine has not been established.

3. Undesirable Effects

This section refers to events considered, after routine/ongoing medical evaluation, to be adverse reactions to the medical product at that stage of development. These events should be considered ‘preliminary Adverse Drug Reactions (ADRs)’ and will be subject to proper adjudication once the development of the compound has been completed.

3.1 Serious Adverse Reactions

- Hepatotoxicity (increase in transaminases)
- Thrombocytopenia
• Infusion related reactions including chills and/or pyrexia
• Hypersensitivity
• Pneumonitis

The list of MedDRA preferred terms associated with these serious ADRs, and hence considered expected for regulatory reporting purposes, is available upon request.

3.2 NON-SERIOUS ADVERSE REACTIONS

• Dry eye
• Lacrimation increased
• Vision blurred
• Visual impairment
• Conjunctivitis
• Peripheral neuropathy
• Anemia
• Neutropenia
• Nausea
• Constipation
• Diarrhea
• Vomiting

4. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal drug–drug interaction studies have been conducted with trastuzumab emtansine. Trastuzumab emtansine is currently being studied in combination taxanes, namely docetaxel and paclitaxel and separately with pertuzumab, a monoclonal antibody that blocks the association of HER2 with other HER family members, including EGFR, HER3, and HER4.

In addition, there is a phase I study combining trastuzumab emtansine with a phosphoinositide 3-kinase (PI3K) inhibitor.
5. USE IN SPECIAL POPULATIONS

5.1 PREGNANCY

Animal reproduction toxicology studies have not been conducted with trastuzumab emtansine. It is not known whether trastuzumab emtansine can cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. However, trastuzumab, a component of trastuzumab emtansine, can cause fetal harm when administered to a pregnant woman; post-marketing case reports indicate that its use during pregnancy increases the risk for oligohydramnios during the second and third trimester. Trastuzumab has also been associated with fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Additionally, the cytotoxic component of trastuzumab emtansine (DM1) targets rapidly dividing cells and is expected to be associated with reproductive and developmental toxicities. Based on these data, trastuzumab emtansine is expected to exhibit an unacceptable developmental and genotoxic profile and the use of trastuzumab emtansine during pregnancy should be contraindicated. Trastuzumab emtansine should not be administered to pregnant women.

5.2 GERIATRIC

The effect of trastuzumab emtansine in the geriatric population has not been specifically evaluated, although advanced age has not been an exclusion criteria in clinical trials.

6. OVERDOSE

There is no information available on the risk or treatment of overdose with trastuzumab emtansine.