



August 2<sup>nd</sup>, 2007

Corinne Taeron  
94-102 rue de Buzenval  
75020 Paris

Dear Miss Taeron,

Thank you for your letter of July 10 bringing your concerns on the recall of Viracept to our attention.

Roche is absolutely committed to open dialogue with patient groups, non-government organization treatment providers and all humanitarian organizations.

We hope that our willingness to meet with you, and other patient groups, at the IAS Congress in Sydney, demonstrates our transparency and general concern for patient welfare.

What follows is our response to the specific questions you raised in the appendix of your letter.

With kindest regards,

A handwritten signature in black ink, appearing to read "J. Edge-Dallas".

Jennifer Edge-Dallas  
Global Leader of Roche HIV Franchise

cc: Dr. F. B. Humer  
S. Komowski-Bonnet

List of questions from the Appendix to your letter

**1. Regarding the contamination and quality controls:**

**What are the usual quality control procedures for production in your laboratories?**

Roche adheres to the strictest standards of quality production, and manufactures all our medicines according to Good Manufacturing Practices.

**Is the detection of organoleptic defects such as smell, looks and colours not scheduled prior to batch release?**

Appearance of the tablets is part of the specification for release testing. However, organoleptic tests such as smell are not part of the release specifications and are not routinely tested.

**Have you drawn up a list of contaminated batches? What are their shipping dates and their code numbers? What proportion do they represent out of all the batches produced?**

We have established the list of Viracept finished product batches with elevated levels of EMS. Since this information has just been determined we are not yet in a position to give you the proportion of batches that contained elevated levels of EMS. Once this has been calculated we will share the information with patient groups and NGOs.

**What are the quantities of EMS found by monitoring the various incriminated batches (maximum quantity per tablet/average quantity per tablet from the same monthly treatment bottle)?**

- Maximum impurity in Viracept finished product tablets: 920 parts per million (ppm) of EMS
- Maximum duration of use of these batches with elevated levels of impurity: 3 months
- Maximum calculated daily dose of EMS: 2.8 mg or 0.06 mg/kg  
(based on daily dose 2.92g of nefinavir base for a patient weighing 50 kg)

This daily exposure is considerably below the dose levels which induce genotoxic effects in single dose animal studies.

**Are you able to track the contaminated lots?**

We have just completed the analysis of the finished lots of Viracept to determine the level of EMS, and we know which countries were shipped batches of Viracept tablets with elevated levels of EMS. However, once a medication is distributed within a country and then dispensed, it is not possible to determine which patient received which batch.

**What about Invirase? Does the manufacturing process also contain alkyl mesylates? If so, what controls did you do? Is there a risk of the contamination recurring?**

Invirase is indeed a mesylate but is manufactured on a separate line and has a different manufacturing process. We have analysed Invirase and have not found elevated levels of EMS.

**The presence of EMS is tolerated at under 1 ppm in your manufacturing process. Did you specify the presence and the quantity when the pre-market approval and NDA requests were made? How old is the latest definition of presence and quantity, done during routine quality tests prior to releasing Viracept batches? How many contamination-research-per-sub-standard doses of EMS were planned by your fabrication standards and at what intervals? How many of them were carried out? Were they just paper checks or were batch analyses done? At what intervals? And dates?**

At the time of receiving the marketing authorization (in 1998) the manufacturing process was considered safe and robust and the analysis of EMS levels was not included in the quality specifications. Nevertheless, in 2001, upon request from the authorities who were scrutinizing mesylate salts, Roche performed several tests which revealed the presence of only extremely low levels of EMS (< 0.5 ppm). As a consequence, no analysis of EMS level was included in the quality specifications of Viracept. Obviously, this will now be included as part of our process improvements.



## 2. Regarding EMS

**Certain press releases have mentioned carcinogenic, mutagenic and teratogenic effects. Where do we stand?**

The International Agency on Cancer (IARC) categorizes EMS as Group 2B carcinogen (possibly carcinogenic to humans but with no human data; sufficient evidence in animals). EMS reacts directly with proteins and DNA, and causes an alkylation reaction.

There appears to be a threshold effect for EMS, which is different from other alkylating agents, where low exposures to EMS do not result in DNA damage or mutations. This data originates from animal and laboratory studies. Roche is in the process of conducting additional animal studies in order to confirm this information.

**Tests have been conducted in rats. Can you indicate the precise types of tests done (absorbed dose, how administered, the number of animals involved etc)? What were the exact effects observed? With what frequencies? Were the effects noted only EMS-related or in synergy with other molecules? After how many administrations did they appear? Were these effects dose dependent?**

A bibliography of EMS literature is provided in the appendix to this letter. In addition, we provide the Expert Toxicology statement which provides an overview of the EMS literature. In summary:

- Formal carcinogenicity risk assessment is difficult
  - Limited high quality carcinogenicity studies available
  - No specific tumor or organ preference known
- Most animal studies investigate EMS administered by intraperitoneal (i.p.) injection (Bishop et al 1980; Anderson et al 1981; Generoso W et al 1980; Platzek T et al 1995)
  - Doses between 33 and 372 mg/kg i.p. (single dose and up to three doses with weekly intervals) induced tumours in various organs (lung, kidney, brain)
  - These doses are much higher than the maximum dose we calculate is possible from exposure to EMS
- Two studies of short term exposure via drinking water have been performed (Ueo et al 1979, Ueo et al 1980)

- Mammary tumours seen in mice exposed to EMS for 3 months exposure via drinking water (estimated daily dose of 40 mg/kg)
- Non-linear kinetics indicates that there may be a threshold level under which effective cellular repair mechanisms repair EMS-induced damage (Doak et al, 2007; Jansen et al 2005)
  - This threshold level is thought to be greater than the maximum possible human exposure to EMS. However, Roche will be conducting additional animal studies to further investigate this effect
- We have not found any literature referring to synergy of EMS

**How many test and on what kinds of animals – including gestating females, newborn and young animals – are you going to do, and when do you intend to make the results available?**

We will be conducting two additional animal studies to better understand the threshold level of EMS. These studies will be conducted in healthy mice. These studies are starting in August and results are expected at the end of the year.

From the literature, we know that the 'no-effect' dose for structural malformation in rodents is approx. 100 mg/kg i.p. (Platzek et al 1995). This 'no-effect' dose is 1,500 fold higher than the maximum daily EMS level that a patients could have been exposed to. We are therefore not planning to conduct additional studies in pregnant animals, new born animals or young animals.

**What do you know about the stability of EMS? Do the detected quantities in later analyses correspond to the quantities absorbed by patients?**

There is no reason to believe that EMS decreases during normal storage. At the moment we have to assume, that detected EMS quantities correspond to quantities absorbed by patients. Stability tests of tablet batches with elevated EMS levels have been initiated.



### 3. Regarding your commitment to patients

**A statement made last June 22<sup>nd</sup> by Mr William Burns mentioned the follow-up of patients who have taken this treatment. Can you specify the way in which you register these people as well as the kind of the follow-up they received? What commitments have you made to them?**

Roche is currently working with the health authorities and independent experts to establish two Viracept patient registries. We have submitted the planned protocols to the health authorities and have conducted the first of several advisory boards to gain insight into the best way to set up these registries. Detailed information on the registries will be communicated once they have been finalized with the health authorities. The registries will include:

- Women who took the medicine during pregnancy and children who have taken Viracept at any time or were exposed to it in utero.  
This registry will be established in countries where Roche has supplied Viracept.
- Patients who may have been exposed to elevated levels of EMS (Viracept batches manufactured from API containing >1000 ppm of EMS)

Additionally, in France, Afssaps has appealed to all hospital and office based practitioners to identify all persons treated with Viracept, since the date of commercialization of the product in France. They have also requested doctors to identify patients treated with Viracept following HIV exposure accidents, as well as all children exposed *in utero* (infected or not by HIV).

**Concerning patients not able, for whatever reason, to use other protease inhibitors than nefinavir, do you plan to supply this Pfizer- or Cipla-made treatment free of charge?**

As you know, the nature of HIV means that treatments need to be tailored for the individual patient. With complex and complicated treatment regimes, even in resource limited settings, it is not ethically or medically possible for Roche to provide just one option for patients to switch too. Prior treatments, virological factors, CD4 count, prior medication and polypharmacy make it essential that Viracept patients seek advice and consultation with their treatment specialists in order to switch.

Roche is in discussions with Pfizer in order to enable supply of Pfizer-produced Viracept in Roche territories. Since the Pfizer manufacturing process is not registered within the Roche territories, there are a number of issues that need to be addressed before this can occur. Once we are in a position to re-supply Viracept, the medication will be provided according to our established pricing policy.

**What do you intend to do about the possible resumption of the production of Viracept in your laboratories?**

Roche intends to manufacture Viracept again, and to get this medicine to patients as quickly as possible. We are in discussions with the health authorities to lift the marketing authorisation suspension and are working together to re-engineer the manufacturing lines, and to validate the process to make Viracept. We have had several meetings with the EMEA about the marketing authorisation, and are working to provide details of the re-validation process at the September, 2007 EMEA meeting.

**In the Southern countries, especially in Africa, what are you planning to do for people to be correctly informed and able to benefit free of charge from a real adapted change of medication as fast as possible?**

We realise the challenges of HIV management in Africa. While we don't have offices in all countries in Africa, we have established a Roche taskforce of people to work on the Viracept recall. Roche is actively working with the NGO treatment providers who have purchased Viracept stock from Roche to supply to African countries. These NGOs have been informed about the recall, about the need to switch patients to alternative treatments and about the planned patient registries. We are convening an NGO advisory board meeting in order to discuss the patient registries particularly in these resource limited countries. In addition, these NGOs have also been informed that Roche will reimburse all reasonable costs and expenses related to the recall and incurred by patients, such as additional doctor visits and costs linked to the registration into the patient registry.

**What compensation measures are you planning for the victims?**

Roche will reimburse all reasonable costs and expenses related to the recall, such as additional doctor visits and costs linked to the registration into the patient registry.



## Additional questions/comments from the letter

### **Speed of reaction by Roche**

During the entire recall process, Roche has acted in the interest of patient welfare. Within 24 hours of the determination of EMS impurity within some Viracept formulations, we informed the health authorities and initiated an international recall of all medication. Within 48 hours, we had written to doctors, pharmacists, wholesalers and the NGO treatment providers. Within this timeframe, we also contacted many HIV community groups. Additional information has been shared with the health authorities, doctors, healthcare providers, NGOs and patient groups as soon as it has become available.

It's important to recognise that a number of investigations were started at the beginning of the recall that have provided additional understanding to the situation. For example, our scientists needed time to analyse all API batches (active pharmaceutical ingredient batches) in order to determine which countries were supplied with batches of Viracept containing elevated levels of EMS. Obviously, this analysis needed to be completed accurately and with extreme care.

### **Manufacturing at Roche**

Roche takes this breach in the manufacturing of one of our medicines extremely seriously. We adhere to the very highest standards of quality control within our manufacturing sites and therefore implemented a company wide review of our manufacturing procedures in order to ensure that no other medicine is at risk of elevated levels of EMS. We have determined that no other medicine is at risk of elevated levels of EMS.

In consultation with the health authorities, we are re-validating the manufacturing process for Viracept in order to have the marketing authorisation re-instated.

### **Risk following potential exposure to EMS**

Roche is committed to the welfare of the patients who have taken our medications. Based on the available data on EMS, Roche assesses the risk to patients who took the contaminated Viracept to be low. This is based on the knowledge that the maximum possible exposure is well below the levels of EMS that have been shown to cause



cancer in animal studies. However, Roche is undertaking additional animal studies to further understand the dose effect of EMS.

#### **How Roche is addressing the recall within Africa**

We understand the difficulties of health management in African countries. While we don't have offices in all countries in Africa, we have established a Roche taskforce of people to work on the Viracept recall. These are people who understand the needs of health care providers, patients and governments in these countries. It's also important to reassure you that we informed NGO treatment providers and the national health authorities in Africa of the Viracept recall within the same time frame of informing authorities in Europe and other regions.

Within the African region, supply of the medication is usually through NGO treatment providers and third party distribution channels, and we have been working extensively with these groups on the recall. For example; within 48 hours of starting the recall, we informed all third party distributors to whom we sell Viracept in order to stop supply and get the returned product back to Basel. We are also working within French speaking and English speaking African countries to set up registries that will gather the same information as we are gathering in Europe and Rest of the World. NGO treatment providers and the third party distributors will be reimbursed for all reasonable costs associated with the recall. These include costs of collecting returned Viracept, additional physician visits, and costs for destroying returned stock.

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