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CHMP ASSESSMENT REPORT

FOR

VIRACEPT

International Non-proprietary Name:
NELFINAVIR

Procedure No. EMEA/H/C/164/Z/109

Assessment Report on the lifting of the suspension of the Marketing Authorisation for Viracept as adopted by the CHMP

Glossary of abbreviations used:

ADR	Adverse Drug Reaction
AE	Adverse Event
AS	Active Substance
APR	Antiretroviral Pregnancy Registry
b.i.d.	bis in die, twice a day
CAPA	Corrective and Preventive Action
CD	Core Data Sheet
CH	Switzerland
CHMP	Committee for Medicinal Products for Human Use
CoRapp	Co-Rapporteur
DHPC	Dear Healthcare Professional Communication
EC	European Community, European Commission
ECG	European Crisis Group
EEA	European Economic Area
EMA	European Medicines Agency
EMS	Ethyl Mesylate or Sulfonic acidic ethyl ester or Ethyl Methane Sulfonate
ENU	N-ethyl-N-nitrosourea
ES	Spain
FCT	Film-coated tablet
FDA	Food and Drug Administration (USA)
Health CA	Health Canada
FUM	Follow-up Measures
FP batches	Finished product batches
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HMA	Heads of Medicines Agencies
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
IPC	In-Process Control
LOEL	Lowest Observed Effect Level
LOQ/LOD	Limit of Quantitation/ Limit of Detection
LoQ	List of Questions
MAH	Marketing Authorization Holder
MMS	Methyl Methane Sulfonate
MNU	N-Nitroso-N-Methylurea
MSA	Methane Sulfonic acid
MSC	Methane Sulfonic acid Chloride
NRTIs	Non reverse transcriptase inhibitors
NMT	Not More Than
NOED	No Observed Effect Dose
NOEL	No Observed Effect Level
PhV	Pharmacovigilance
PhVWP	Pharmacovigilance Working Party
PI	Protease inhibitors
PL	Package Leaflet
ppm	parts per million
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PT	Portugal
Q&A	Questions and Answers
QP	Qualified Person
Rapp	Rapporteur
RMP	Risk Management Plan
S&E	Safety & Efficacy
SA	Supervisory Authority
SAEs	Serious Adverse Events
SPC	Summary of Product Characteristics
SWP	Safety Working Party
t.i.d.	ters in die, three times a day
TTC	Threshold of Toxicological Concern
UK	United Kingdom
WHO	World Health Organisation

1 BACKGROUND INFORMATION ON THE PROCEDURE

On the evening of 5 June 2007 the European Medicines Agency (EMA) was made aware by Roche Registration Limited, the Marketing Authorisation Holder (MAH) of the contamination of Viracept (nelfinavir) with a genotoxic substance. As a consequence, Roche recalled the product from the European Union markets with immediate effect. All packs of Viracept available on the market were affected, including packs that patients may have had at home. A Direct Healthcare Professional Communication (DHPC) was released by the MAH on Thursday 7 June 2007 to inform prescribers about the incident and the need to switch patients on Viracept to other alternative antiretroviral therapies. The choice of alternatives was left to the prescriber. The EMA issued a Press Release and Q&A document on the same day.

The MAH had identified the presence of the contaminant ethyl mesilate (also known as methane sulfonic acid ethyl ester or ethylmethane sulfonate, EMS) in some batches of nelfinavir mesilate (the active substance) following patients' complaints about a "strange smell" and one adverse drug report of nausea and vomiting. EMS is known to be genotoxic, carcinogenic and teratogenic in animals. The level of risk to patients resulting from this contamination is currently not known and therefore needs to be further evaluated.

In order to better characterise the toxicological risk associated with EMS, an ad-hoc expert group of toxicologists met at the EMA on Wednesday, 13 June 2007. The group concluded that there were insufficient data to quantify the risk posed by exposure to the levels of EMS present as a contaminant in the affected batches of Viracept. On Monday, 18 June 2007 the EMA convened a Pharmacovigilance expert meeting which discussed the follow-up and monitoring of patients exposed to the contaminant in Viracept and measures to be undertaken by the MAH in order to address the resulting public health concerns.

Swissmedic, in collaboration with the EMA, organised an inspection of the Basel active substance manufacturing site on 11 and 12 June 2007, in order to further investigate the root causes leading to the contamination, other possible GMP failures, and to assess the adequacy of the MAH's CAPA (Corrective and Preventive Action) plan. The results of the inspection were presented to the CHMP on 19 June 2007.

Based on the critical GMP deficiencies found which led to the contamination of the active substance, concerns were raised about the quality of Viracept and its safety under normal conditions of use.

Therefore, the European Commission (EC) initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and referred the matter to the Committee for Medicinal Products for Human Use (CHMP). The EC requested the committee to assess all aspects of quality and safety of the centrally authorised antiretroviral medicinal product containing nelfinavir mesilate (Viracept) from Roche Registration Ltd and to give its opinion under Article 20 of Regulation (EC) No 726/2004, on the measures necessary to ensure the quality and safe use of Viracept and on whether the Marketing Authorisation for this product should be maintained, varied, suspended or withdrawn.

During its plenary session, the CHMP drafted a list of questions which were addressed by the MAH during an oral explanation on Wednesday, 20 June 2007.

During its June plenary session the CHMP reviewed the data submitted by the MAH as well as the recommendations of both the toxicology and pharmacovigilance ad-hoc expert group meetings and the report from the GMP inspection. As a result of these discussions, the CHMP recommended that the Marketing Authorisation for Viracept should be suspended until the MAH could satisfactorily address the deficiencies raised with regards to the manufacturing process of nelfinavir mesilate, which had led to the major quality defect.

Further to the June 2007 CHMP, a meeting was convened at the EMA on 6 July 2007 between the Rapporteur, Co-Rapporteur, representatives of both Swissmedic and WHO, as well as the MAH to

further clarify the conditions to be met in order to convince the CHMP of the satisfactory quality of the product.

Based on the recommendations by the CHMP and the ad-hoc expert group on the non-clinical studies to be undertaken, the MAH submitted 27 June 2007 a study proposal. The CHMP reviewed this proposal and endorsed its comments during the July 2007 CHMP plenary session. The MAH submitted their responses to the comments on 17 August 2007. During the September 2007 CHMP plenary session, the Committee agreed to the proposed study outlines.

During the July sessions of both the CHMP and its Pharmacovigilance Working Party, the draft protocols for the Viracept Registries 1 and 2 were discussed. On 19 July 2007, the CHMP concluded on a List of Outstanding Issues to be addressed by the MAH in writing before the protocols could be found to be acceptable. The MAH submitted their response to the outstanding issues on 3 September 2007. These responses were assessed and discussed during the September 2007 CHMP plenary meeting.

Based on both the conclusion of the June 2007 CHMP and the above July 2007 meeting, the MAH submitted on 16 August 2007 their dossier in response to the quality issues raised by the CHMP and EMEA.

On 7 September 2007, the Rapporteur circulated their assessment report on the MAH's responses to the raised quality, non-clinical and pharmacovigilance issues.

A joint EU-Swissmedic re-inspection was organised at the Basel active substance manufacturing site from 5 to 7 September 2007, in order to assess the adequacy of the MAH's implementation of its CAPA (Corrective and Preventive Action) plan. The results of the inspection were presented to the CHMP on 17 September 2007.

During its September plenary session the CHMP reviewed the MAH's responses and agreed with the Rapporteur's assessment that recommended the lifting of the suspension of the Marketing Authorisation, as the MAH had adequately addressed all conditions as detailed in the June 2007 Opinion.

Both the reasons for the suspension as well as the measures undertaken in response to this major quality defect are addressed in the following scientific discussion, which addresses the concerned quality, non-clinical and pharmacovigilance issues.

2 SCIENTIFIC DISCUSSION

2.1 GMP and Quality aspects

2.1.1 Root cause investigation and corrective/preventive actions

The MAH established that the strange smell came from unexpectedly high residues of the impurity methylsulfonate ethylester or ethyl mesilate (EMS), a known genotoxic compound. Further investigation revealed that there was a GMP failure at the level of the hold tank which is used to store the starting material methanesulfonic acid (MSA). MSA is used in the last step of the synthesis to convert nelfinavir base into nelfinavir mesilate. This hold tank was not included in the cleaning Standard Operating Procedure (SOP) for the equipment used in this last step of the synthesis and had never been cleaned between 2001 and the end of the production campaign as of April 2006. Following non-routine maintenance the hold tank was cleaned according to the SOP procedure (i.e. with ethanol) but, crucially, no drying was performed. The hold tank, therefore, contained residues of ethanol. It was then filled with the starting material methylsulfonic acid (MSA). MSA is routinely tested on receipt from the supplier for its EMS content but not after transfer into the hold tank. The residual ethanol left in the tank reacted with MSA to form high levels of EMS contaminant. The reaction leading to the formation of EMS is an esterification reaction between the ethanol and the MSA and is time dependant, i.e. slow at room temperature. Therefore, the extent to which it is formed is variable depending on the time during which the alcohol and the acid have been in contact.

This contaminated MSA was used for the next October 2006 campaign. Three batches of AS were spray dried and contained increasing amounts of EMS (from <1 ppm to 8 ppm, measured retrospectively). The remaining MSA was stored in the hold tank until the start of the next campaign in January 2007. Due to the long storage time more EMS was formed in the tank, which subsequently contaminated these batches of AS with EMS levels of up to 2300 ppm.

This main root cause for the high level of EMS was quickly identified by the MAH. However, on testing retention samples from previous AS batches manufactured before the October 2006 and Jan/Feb 2007 campaigns, high levels of EMS were observed with contents between 100 and 120 ppm in June 2005 and between 4 and 10 ppm in June 2004.

An inspection of the Basel AS manufacturing site was organised by Swissmedic (competent authority for the site) in close co-operation with the EMEA and the Spanish agency Agemed (competent authority for the Finished Product manufacturing site for the Film-coated tablet presentation that is the most severely affected by this GMP failure with EMS levels above 1000 ppm).

Two other root causes for the unexpectedly high levels were identified by the inspectors:

- due to the design/connections of pipes for ethanol and nitrogen, both used in the final production step, variable quantities of vaporised ethanol may have been transported through the piping to the hold tank containing MSA
- an impurity contained in the MSA named methyl methanesulfonate (MMS) may be slowly transformed into EMS through a transesterification reaction. This reaction can be accelerated by an excess of ethanol (e.g. residues in the AS).

A more general root cause identified by the inspectors was the lack of knowledge and understanding with regard to the manufacturing process; this may be due to the fact that the production process was originally purchased from another company. As the pharmaceutical development was not performed by the MAH, the potential risk for the formation of EMS in the manufacturing and maintenance processes may have been misjudged.

As an outcome of the inspection, the inspectors raised one critical and four major deficiencies and discussed numerous preventative measures to be addressed in the areas of validation of the last step of the process, cleaning procedures and validation, handling of the key starting material MSA, analytical testing and training.

In addition, the MAH noted as a further possibility that MMS is converted to EMS under the conditions of the spray drying of nelfinavir. This inherent risk of alkyl-mesilate formation, in a process

in which low alcohols (ethanol) and MSA are present together, is acknowledged in compendial monographs regarding active substances in mesilate form (e.g. see nelfinavir mesilate monograph in the International Pharmacopoeia) and specific requirements to validate the manufacturing method. The issue of EMS and MMS formation during the manufacture of nelfinavir mesilate had already been considered by the CHMP and addressed by the MAH in Follow-up Measures (FUM 010 and 011 - dated 28 June 2001).

The conclusion of the assessment with regard to FUM 010 and 011 was that they could be considered fulfilled as far as the validation of a suitable assay method, but the CHMP requested that a specification of NMT 3 ppm EMS in MSA should be added to the specification for MSA. The assay of each batch of MSA for EMS content should be continued until an adequate number of batches have been assessed to allow the testing frequency to be reduced to a periodic test.

At that time, based on the batch data provided in FUM 010, it was considered appropriate not to recommend any limits for the MMS and EMS in the active substance because sufficient evidence had been provided that the active substance manufacturing process gave MMS or EMS level below 0.5 ppm in the AS manufactured in the new spray drying facilities. Any excessive increase in the EMS level in the active substance is considered to be a GMP issue.

Arising from the FUMs, a specification limit of 3 ppm for EMS in MSA is currently in place.

As a general principle, the inclusion of relevant limit tests for impurities in reagents prior to use is an accepted way of establishing the purity of the active substance.

The MAH has been instructed not to resume nelfinavir mesilate production until all root causes are identified definitively and with certainty and without prior evaluation and approval of the CAPA plan and without a written authorisation from Swissmedic.

The MAH had also been instructed by Swissmedic and the EMEA not to release any further Viracept finished product batches to their respective markets, i.e. Switzerland and the EU.

The MAH presented an initial CAPA plan on 15 June addressing the observations made during the inspection prior to the issuance of the inspection report. An updated version was presented within the oral explanation to the CHMP on 20 June in the form of a roadmap:

Re-evaluation of salt formation and spray drying process

Preparation of lab study protocol (pH, temp. time): ongoing - 22.06.2007

Lab experiments: 22.06.2007 – 05.07.2007

Quality risk analysis and implementation of CAPA (Corrective Actions & Preventative Actions)

Quality risk analysis: ongoing - 30.06.2007

Implementation of CAPA (e.g. elimination of hold tank): ongoing – 07.07.2007

MMS/EMS testing

Revalidation and implementation of MMS/EMS analytical method: ongoing – 30.06.2007

Process validation

Preparation of process validation protocol: 06.07.2007 – 13.07.2007

- **Need approval for technical lots of spray drying: 16.07.2007**

Production of technical lots: 16.07.2007 – 20.07.2007

Proposal for MMS/EMS specification: 22.07.2007

- **Need approval for validation lots of spray drying: 23.07.2007**

Production of validation lots: 23.07.2007 – 29.07.2007

Extended testing and completion of validation report: 24.07.2007 – 10.08.2007

Submission of data: 14.08.2007

In the meantime, by 30 June the MAH finalised the complete retrospective testing of all AS batches back to 1998 (date of the initial Marketing Authorisation) to establish the complete list of affected batches. Further analytical investigations (i.e. revalidation of the method to ascertain its suitability over the range of the observed EMS contamination values and investigation on the variation of the EMS level during storage and processing) allow a complete and accurate overview of the EMS contamination.

2.1.2 Conclusion of the June 2007 CHMP meeting

Considering the deficiencies identified in the inspection of the Basel (CH) active substance manufacturing site and the inability of the MAH to reassure the CHMP on the quality of the manufacturing and maintenance processes involved in the manufacture of the active substance of Viracept, the CHMP identified a potential risk associated with the safety of Viracept under normal conditions of use. The contamination of the active substance with EMS was considered to be a serious product defect.

During the oral explanation held on 20 June 2007, the MAH proposed a corrective and preventive actions plan as well as plans to conduct non-clinical *in vivo* and *in vitro* studies and to establish a registry to follow-up on all patients exposed to high levels of EMS and vulnerable populations exposed to any level of EMS (i.e. pregnant women, children exposed *in utero* and children up to the age of 18 years). The full realisation of these proposed measures to be undertaken will take some time.

Following the assessment of all available data and having heard oral explanations of the MAH, the CHMP concluded that the quality of Viracept cannot be guaranteed. The identified quality concerns have implications on the safety of Viracept under normal conditions of use. Therefore, the CHMP considered that the benefit risk balance of Viracept is currently negative.

The CHMP considered that there are therapeutic alternatives available, to which patients can be switched.

Therefore, the CHMP recommended the suspension of the Marketing Authorisation of Viracept. Such suspension may be lifted, provided the MAH can reassure the CHMP on the quality of Viracept as indicated below.

The CHMP considered the following requirements must be fulfilled before the suspension of the MA can be lifted:

CAPA

1. The MAH is required to put measures in place to ensure that the GMP deficiencies identified during the inspection on 11 and 12 June 2007 of the active substance manufacturing site F Hoffmann La Roche, Basel (CH) are corrected and prevented from future occurrence. These measures will have to be approved by the inspectors before resumption of nelfinavir mesilate manufacture for commercial production.

Quality

2. A comprehensive process risk analysis should be presented for the synthesis of nelfinavir mesilate and the manufacture of the finished product Viracept tablets, film-coated tablets and oral powder. In particular, appropriate re-validation studies of the last step in the manufacturing process of the active substance should be carried out and the results should be provided.
3. Based on the revised process, a suitable specification limit for EMS and MMS in the active substance should be introduced. This limit should reflect the capability of the process to deliver the lowest achievable level, and in any case should be below the Threshold of Toxicological Concern (TTC), as stated in the Guideline on the Limits of Genotoxic Impurities.
4. The MAH should provide an appropriate and validated analytical method in order to detect and quantify EMS and MMS in the active substance.

In addition, the following follow-up measures should be undertaken by the MAH:

Quality

5. The risk of further formation of EMS or MMS in the active substance during storage as a result of possible interaction with any alcohol residues in the active substance should be considered.
6. Based on the information gathered in this case, the MAH should assess the possibility of formation of MMS and EMS in other medicinal products containing active substances in the form of the mesilate salt, and inform the CHMP on all necessary and appropriate preventive measures to be taken.
7. The MAH should discuss how he will review the quality of his manufacturing and maintenance processes given the recent experience of quality failures for a number of Roche's medicinal products.
8. The MAH should analyse all retention samples of AS.
9. The MAH should establish the stability of EMS in the AS during storage in order to validate the EMS levels found for the re-testing of retention samples.
10. The MAH should develop an analytical method to quantify EMS / MMS in the finished product.

In addition, the MAH was requested to address other CAPA and quality related issues arising from a meeting on 6 July 2007, while emphasis was given to certain points already raised before (e.g. points 11 and 12) This meeting took place at the EMEA and was attended by experts and representatives from all involved competent authorities (EMEA, UK MHRA, Spanish Agemed, Swissmedic, World Health Organisation and European Commission).

11. In the area of Corrective and Preventive Actions, in addition to the inspection deficiencies the MAH is requested to address the issues of the increase of residual EMS during Active Substance storage by reaction of residual MSA with residual ethanol as well as the relevance of this reaction for the dosage forms, and of use of recovered ethanol potentially carrying residual EMS.
12. In the area of Quality / process risk analysis and validation, the MAH is expected to cover as requested both the Active substance process and the Finished product processes (for all forms) to support the assumption that the data from the active substance manufacturing process are reliable for any decision with respect to the Finished products. The storage implications should also be considered.
13. With respect to the quarantined batches to which the MAH referred, the MAH was requested to provide a specific risk assessment on the production and control methods used. Analytical data on the level of EMS and MMS in the active substance batches used should be provided using the 2007 newly validated method.
14. It was acknowledged that it will not be possible for process capability information to be provided immediately, but it would be important to have a commitment that this would be provided at a later stage.

2.1.3 Data submitted on GMP and Quality aspects and assessment

The MAH submitted a full response package on 16th August 2007 addressing each one of the 14 issues as mentioned above. The data provided and discussion follows hereafter.

CAPA

The investigation conducted by the MAH focused basically on identifying all root causes leading to the contamination of the active substance (AS). The root causes related to the elevated EMS levels in the AS and the Corrective and Preventative actions (CAPAs) taken are listed below:

1. Remaining ethanol in MSA hold tank after cleaning.
CAPA: Elimination of MSA hold tank and direct charging from disposable MSA container.
2. Ethanol contamination of the MSA hold tank via exhaust gas and/or vacuum piping.
CAPA: Elimination of MSA hold tank and direct charging from disposable MSA container.

3. MSA containing elevated levels of EMS or methane sulfonic acid chloride (MSC).
CAPA: Specification limit for MSC: max. 0.1ppm (will be implemented prior to the next manufacturing campaign).
In addition: The existing specification limit of 3ppm MMS is reduced to max. 1 ppm MMS/EMS total.

4. Slow formation of EMS during storage of the AS when excess of MSA is present.
CAPA: Restriction of the range of MSA equivalents compared to nelfinavir base from 0.97 – 1.03 to 0.97 to 0.995.
Corresponding restriction of allowed pH range from 3.5 – 1.2 to 3.5 – 3.0 (working range) after salt formation.
Firstly charging of only ca. 90% of the needed MSA and final adjustment of the pH (3.5 – 3.0) by charging the rest of MSA.
Routine testing of the AS for the MSA equivalent.

5. Potentially: Slightly increased formation of EMS during mixing of MSA with the suspension of nelfinavir base in ethanol when suspension exhibits reduced mixing properties.
CAPA: Slower charging of MSA into the suspension of nelfinavir base in ethanol and optimisation of the MSA inlet pipe with regard to improving mixing conditions.

All the CAPAs have been implemented by the time of this assessment and only the following items are still open:

- Review of identification of pipe work: due date: end of 2007
- Review of retest periods: due date: end of 2007

The implementation of the CAPAs is considered sufficient to ensure a robust process, providing nelfinavir mesylate consistently within EMS/MMS specification of max 0.5 ppm MMS/EMS. However, additional QC testing is implemented which includes:

- MMS/EMS in the AS. Maximum 0.5 ppm (Based on TTC and current process capability, to be reviewed by MAH as more data are available.)
- MSA in the AS. 0.97-0.995 mol equivalent compared to nelfinavir
- MMS/EMS in the MSA. Maximum 1 ppm.
- MSC in the MSA: The specification limit of max. 0.1 ppm MSC is not yet reflected in the specification but will be included prior to the next manufacturing campaign.
- MMS/EMS in the ethanol recycled. Maximum 0.01 ppm
- Finally, the trending of the process parameters has been implemented.

2.1.4 Discussion on Quality

The CHMP considered that all CAPAs have been satisfactorily identified and implemented. The MSA tank, the major root cause of the GMP failure and high levels of EMS in the AS, has been eliminated. MSA will be charged via a disposable container, thus eliminating contamination of MSA with ethanol vapour due to exhaust/vacuum piping. Swissmedic has assessed the MAH response to CAPA and closed the 11-12 June inspection with the letter of 9 August 2007; however, a joint EU-Swissmedic follow-up inspection was scheduled on 5-7 Sep 2007 to verify the correct implementation of the corrective measures. The outcome of this inspection is positive.
The MAH is considered to have fulfilled CAPA requirement.

The MAH has provided satisfactory responses and fulfilled the Quality requirements of the CHMP Assessment report dated 28 June 2007 and the additional requirements from the meeting on 6 July 2007, except for some confirmatory issues arising from the response, and the 5-7 September 2007 EU-Swissmedic follow-up inspection of the AS manufacturing site has led to a positive conclusion.

Specifically, the MAH has fulfilled four main requirements set out by the CHMP Assessment Report: namely the implementation of the CAPA measures, the comprehensive process risk analysis including process validation, the introduction of a suitable specification limit for EMS and MMS in the active substance and the provision of an appropriate and validated analytical method in order to detect and

quantify EMS and MMS in the active substance (requirements 1, 2, 3 and 4). The fulfilment of these requirements determines the decision on the lifting of the Suspension of the MA.

In addition, requirements 5, 6, 7, 8, 9 and 12 have also been fulfilled, whereas requirements 10, 11, 13 and 14 have only been partially fulfilled.

The following issues remain to be solved. The MAH committed to address these within an agreed timeframe:

- 1) It should be confirmed that the MAH will develop analytical methods to quantify MMS/EMS in the finished products, with an improved quantitation limit than the 10 ppm in the current method for tablets. (Arising from Q10).
- 2) The MAH should discuss in depth on the hydrolysis products of the EMS especially on the aspects of the chemical pathways of hydrolysis of EMS in contact with water and the potential of these degradation products of hydrolysis to be genotoxic. The MAH is also requested to clarify what these alkylate reactive centres of the tablets/powder matrix are.
- 3) The MAH should confirm that a stability program will be set up addressing the low levels of MMS/EMS in dosage forms as soon as method is available that can detect MMS/EMS down to levels ≤ 0.5 ppm (Arising from Q 11).
- 4) The MAH has provided the general risk assessment of the quarantined batches, but not the specific data related to these batches. This should be provided with a listing of AS batches linked to the quarantined stock, MMS/EMS levels in the AS (determined by the new method HPD99GC1.1), MSA in AS and the corresponding pH value (Arising from Q 13). Any release of these batches will be subject to approval from Supervisory Authorities responsible for the batch release sites.
- 5) The MAH should review the proposed limit of max. 0.5 ppm as soon as sufficient data are available from the revised process and process capability can be assessed. (Arising from Q 14)

CHMP accepted the MAH's proposed specification limit of total 0.5 ppm MMS and EMS in the AS, as well as the proposed specification limits for the MSA in the AS: 0.97-0.995 mol equivalent (compared to nelfinavir), MMS/EMS Maximum 0.01 ppm in the ethanol recycled, MMS/EMS Maximum 1 ppm in MSA and MSC Maximum 0.1 ppm in MSA. In addition the new IPC for pH range (PAR): 2.82-3.50 (working range is pH 3.00 – 3.50) at the last manufacturing step of nelfinavir mesilate (formation of nelfinavir mesylate and spray drying) is also accepted.

2.1.5 Conclusions and Recommendation on GMP and Quality aspects

In conclusion, the CHMP having assessed the totality of the MAH's responses concerning risk analysis, process re-validation, analytical methodology development and validation, revised tighter specification limits for alkyl mesilates, as well as all the measures proposed by the MAH to ensure that the manufacturing processes for the active substance and the finished products are under control, considers that the MAH's proposals are now sufficient to guarantee the satisfactory quality of nelfinavir mesilate active substance and finished products.

Although a number of remaining quality issues have been identified, the CHMP considered that these are minor, and should not preclude the lifting of the Suspension of the Marketing Authorisation, as the MAH has committed to resolve these outstanding issues, within acceptable time frames.

Therefore, and taking into account the positive outcome of the Swissmedic follow-up inspection, the CHMP recommends the lifting of the suspension of the Marketing Authorisation on the basis of the MAH's having resolved the concerns raised that led to the suspension. The CHMP is of the opinion that the MAH has satisfactorily shown that the quality of Viracept can be ensured due to the MAH's CAPA measures.

2.2 Non-clinical issues

2.2.1 Introduction

EMS is known to be a mutagenic carcinogen in animals and has also been shown to be teratogenic in animals. Published data from carcinogenicity studies such as that of Ueo et al., 1979 and Ueo et al., 1981 as well as the review paper on the genetic effects of EMS by Sega, 1984 have established this fact. EMS is characterised as a monofunctional ethylating agent that interacts with DNA. However, unlike other alkylating agents such as methylnitrosourea (N-Nitroso-N-Methylurea, MNU), EMS primarily alkylates N⁷-G and only rarely O⁶-G atoms. This mechanism of action seems to allow for homeostatic maintenance by DNA repair at low EMS doses, as shown by the non-linear dose-response of EMS in micronucleus and gene mutation assays in human lymphoblastoid cells (Doak et al., 2007). Therefore, it may be justified to assume a threshold below which the mutagenic effect of EMS can be effectively counteracted by the human DNA repair system. The same study also showed that for EMS, in this experimental setting, the LOEL is the same for the induction of chromosomal damage and for point mutations. Although these *in vitro* data indicate a non-linear dose-effect-relationship for the genotoxicity of EMS suggesting an exposure level below which there are no effects, there are no available *in vivo* data to support this view.

The available studies with EMS were conducted primarily for academic research purposes and there are no studies that would allow an estimation of a NOEL in animal models, still less a translation into the human situation. This lack of data with regard to EMS exposure and correlation of dose-response makes it impossible to reliably quantify the risk at lower doses/exposures in animals and humans. Therefore, non-clinical studies, designed to allow a correlation of systemic exposure with *in-vivo* mutagenic studies, are necessary in order to allow for the estimation of a threshold dose for EMS below which induction of genotoxic effects might be considered to be highly unlikely. Based on such data, a worst case calculation, together with some general assumptions, might allow for the extrapolation of such a threshold to the human situation.

The CHMP concluded in June 2007 that such studies should be carefully designed, allowing for different scenarios. They should be carefully evaluated prior to initiation. Points to be taken into consideration include selection of appropriate endpoints (gene mutation versus chromosomal damage) and appropriate test models (transgenic gene mutation models versus HPRT model), selection of appropriate dose levels including doses which allow a reliable estimation of the NOED/LOED transition, repeated dose and acute dosing schemes, selection of appropriate target tissues (based on estimated highest exposure, target organs for tumour formation), and integrated TK studies to carefully monitor exposure. In order to prove *in vivo* the non-linear dose-response (= threshold) hypothesis for EMS according to the Doak et al. paper, this study should include one of the compounds showing a linear dose-response (MNU or ENU) as a positive control.

Following these recommendations, the MAH submitted 27 June 2007 a study proposal to address the above. The CHMP reviewed this proposal and concluded on its comments during the July 2007 CHMP plenary session. The MAH submitted his responses to the comments on 17 August 2007. During the September 2007 CHMP plenary, the Committee agreed to the study proposals as outlined below.

2.2.2 Non-clinical activities and studies initiated or planned

- **Comparative *in vivo* MNT (micronuclei) studies with EMS and ENU (Induction of chromosomal damage)**

Aim:

- a) To provide evidence for a sub linear/threshold dose response for EMS in low dose region in contrast to a linear dose response for ENU
- b) To provide further data for dose setting in gene mutation study

Duration / Design:

7 days oral (gavage) treatment. 6 animals per group. EMS: 5 dose levels, ENU 3 dose levels. Endpoint: Micronuclei from bone marrow cells 24h after last dosing. Exposure assessed by formation of haemoglobin adducts. Please note that this study has in agreement with the CHMP commenced.

Status / Timelines:

EMS Study start: 16.07.07
ENU Study start: 23.07.07
Preliminary Data available
Draft Report: Oct. 2007

- **Induction of LacZ gene mutations in the CD2-lac/80/Hazf/BR mouse (MutaMouse study) - Comparative studies with EMS and ENU**

Aim:

To provide evidence for a sub linear/threshold dose response for EMS in low dose region in contrast to a linear dose response for ENU.

Duration / Design:

28 days and acute oral (gavage) treatments. 6 animals per group. EMS: 7 dose levels, ENU 5 dose levels. Endpoint: LacZ mutations in cells from bone marrow, small intestine, and liver. Exposure assessed by formation of haemoglobin adducts.

Status / Timelines:

Study start: as soon as sufficient numbers of transgenic mice available (currently predicted to be December 2007)
Results expected by: ca April 2008

- **General 4-week repeat dose toxicity study with EMS in the rat followed by a 4-week recovery phase**

Aim:

Characterisation of systemic organ toxicity of EMS, identification of potential target organs with assessment of reversibility of effects

Duration / Design:

4 weeks oral (gavage) treatment + 4 weeks recovery. 3 Dose levels, 10 males/10 females per group + 10 satellite animals per group for TK and recovery assessment. Exposure assessed by formation of haemoglobin adducts.

Status / Timelines:

Study start: Oct. 2007
Data availability: Dec. 2007
Draft Report: Feb. 2008

- **Cross-species *in vitro* and *in vivo* evaluation of exposure to EMS and retroactive judgement of exposure to EMS in batches of Viracept containing elevated levels of EMS**

Aim:

To facilitate retroactively exposure judgement in patients having taken elevated levels of EMS via Viracept.

This overall aim will be addressed in the following list of sub-studies:

Study / Activity	Duration / Design	Status / Timelines
Establish relationship between concentration and EMS-haemoglobin adduct formation in mouse blood and kinetics of haemoglobin adducts	Blood <i>in vitro</i> and <i>in vivo</i> (see <i>in vivo</i> genotoxicity studies)	In life part done; sample analysis until mid Oct. 2007
Establish relationship between concentration and EMS-haemoglobin adduct formation in cynomolgus blood and kinetics of haemoglobin adducts	Blood <i>in vitro</i> and <i>in vivo</i>	In life part done; sample analysis until mid Oct. 2007
Establish EMS-haemoglobin adduct formation in cynomolgus blood after administration of Viracept batch contaminated with high EMS	Blood <i>in vitro</i> and <i>in vivo</i>	Oct. – Nov. 2007
<i>In vitro</i> determination of Ki (interaction EMS – Hb) using human erythrocytes incubated with EMS	Blood <i>in vitro</i>	Oct. – Nov. 2007
<i>In vitro</i> stability of EMS to check feasibility of analysis of unchanged EMS	<i>In vitro</i>	Oct. – Nov. 2007
Pharmacokinetics of EMS in mice and if feasible monkey (provided analysis of unchanged EMS feasible)	<i>In vivo</i> mouse and monkey (under consideration)	Nov. – Dec. 2007

2.2.4 Discussion

In the absence of both NOEL and LOEL values, calculations which define the risk for patients as low cannot be accepted. The CHMP therefore concluded that further studies are urgently needed in order to allow a more informed risk assessment. The suggestion of a threshold for the mutagenic risk of EMS is supported by the available *in vitro* data and may enable the establishment of a daily exposure with negligible risk. This could have the potential to re-assure patients having been exposed to contaminated batches of Viracept and refine the patient population requiring follow-up.

In this respect, the MAH's study proposals are considered to be appropriate, given the commitment to discuss the need for either longer or further studies to fully elucidate the quantitative risk associated with the EMS exposure in patients having taken those batches of Viracept with high EMS levels.

However, given the current lack of available data, any quantitative risk assessment remains speculative. Therefore, the limit of EMS should be specified to be in line with the Threshold of Toxicological Concern (TTC), as stated in the Guideline on the Limits of Genotoxic Impurities.

The TTC (Threshold of Toxicological Concern) is defined in the CHMP Guideline on the Limits of Genotoxic Impurities as a limit of 1.5 µg maximum daily dose of a potentially genotoxic substance. Based on this recommendation, it could be considered as acceptable for establishing a specification of the sum of MMS and EMS in the active substance. Taking the Maximum Daily Dose in an approved Viracept regimen into account, this translates to a maximum of not more than 0.6 ppm for the sum of MMS and EMS in the active substance nelfinavir mesilate.

2.2.5 Conclusion

Taking into account the data presented above, the CHMP concluded the following:

- Patients exposed to EMS during the 3-month period in 2007 of possible contamination of above 1000 ppm should be monitored for adverse effects.
- Pregnant women and children, including those exposed *in utero*, who have taken Viracept at any given time, should be monitored as well. In the case of pregnant women, the purpose is to follow-up the outcome of the pregnancy.
- The TTC (Threshold of Toxicological Concern) limit of 1.5 µg maximum daily dose of a potentially genotoxic substance as defined in the CHMP Guideline on the Limits of Genotoxic Impurities could be considered as acceptable for establishing a specification of the sum of MMS and EMS in the active substance. This translates into a maximum of 0.6 ppm.
- The MAH has agreed to undertake both the studies as outlined above, to discuss the study protocol for the one month repeat dose study to establish dose-effect for mutation induction by EMS over a wide range of doses in transgenic mice prior to its initiation with the toxicology experts of the CHMP and to discuss the need for further studies in the light of the results obtained with the above outlined studies.

2.3 Pharmacovigilance

2.3.1 EU Risk Management Plan

The MAH's initial draft RMP was considered by the CHMP at its June and July meetings and the CHMP advised that the draft RMP needed to contain more detail on the MAH's proposals and timelines for submission of study protocols. The key concerns of the CHMP in relation to the three main sections of the RMP were as follows:

Safety Specification

The MAH's draft version lacked details on safety profile of EMS and needed to be amended to:

- fully reflect all data on EMS, referenced as appropriate;
- reflect the conclusions of the expert group meeting on toxicological risk.

The tabular summary on identified and potential risks required considerable amendment – it was considered to down play the seriousness of risk, implied low frequency and the section on preventability focused on recall and communication but did not consider any corrective measures to address the identified issues surrounding the manufacturing processes or the need for long term monitoring of exposed patients.

Pharmacovigilance Plan

This section needed to be amended to include:

- full detail of MAH's proposals for further studies, including proposals for long term follow-up and monitoring, via a registry, of the following patient groups;
- all patients exposed to the batches with high level EMS (i.e. above 1000 ppm);
- all pregnant women exposed during therapy (in order to follow pregnancy outcome);
- all children exposed during therapy;
- all children exposed *in utero* (including those born HIV negative).

The MAH was also requested to consider how existing cohorts such as EUROSIDA, CHIC, DAD, MITOC and COHERE could be used to assess the risk associated with the exposure of patients to the high EMS levels in the affected Viracept batches.

In addition, the MAH needed to consider establishing an expert panel to evaluate the results of the non-clinical studies as they emerged. The findings of these studies would then be used as a basis to devise a plan for specific screening for patients exposed to EMS levels with an insufficient safety margin. The MAH was asked to submit to the CHMP an action plan on how to implement such a screening program.

Risk Minimisation Plan

This section of the RMP required amendment to provide full details of the corrective action plan to address the identified issues surrounding the manufacturing processes. The MAH was also asked to consider the need for targeted follow up of spontaneous reports, in particular to gain full information on patients' past medical history. The MAH was also asked to consider the possibility of publishing the final agreed Risk Management Plan.

Final Revision 1 of Risk Management Plan

The MAH submitted its revised draft Risk Management Plan on 9 August 2007, which seeks to address the CHMP concerns detailed above. The efforts of the MAH in improving the quality of this Risk Management Plan are acknowledge. A detailed assessment of this revised Risk Management Plan is attached in attachment 2, however, outlined below are the key outstanding points that need to be addressed by the MAH:

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks		
Exposure to EMS (EMS impurity)	Analysis of reports and frequency of reports in 6 monthly cycles on the WHO database and on Roche internal database in order to detect changes of frequency or changes of terms of reported drug reactions.	Elimination of further exposure to all affected drug via a patient level recall of all possible affected drug. A detailed CAPA plan to prevent further impurities.
Important potential risks		
Exposure of pregnant women (EMS impurity)	Close observation through Antiretroviral pregnancy registry for HAART. Roche will use the Registry to collect information and the outcome of pregnancies of all patients exposed to nelfinavir (with and without exposure to affected batches).	DHCP letter was sent to inform providers and patients.
Genotoxicity (EMS impurity)	Gain more information on possible genotoxicity by animal studies. Close observation of reported events in the Antiretroviral pregnancy registry for HAART. Conduct of <i>in vivo</i> repeat dose mutation induction study in transgenic mice to establish information on whether mutations as induced by EMS have non-linear dose-response characteristics and whether the exposure to EMS via Viracept was reliably below a level for mutation induction. Further, cross-species evaluation of protein alkylation by EMS will form a basis of comparison of exposure required to induce mutations versus likely exposure as given by EMS in humans via Viracept.	

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Carcinogenicity (EMS impurity)	<p>Gain more information on possible genotoxicity by animal studies.</p> <p>Close observation of reported events in the Registries.</p> <p>Conduct of <i>in vivo</i> repeat dose mutation induction study in rodents. Genotoxicity is likely the major underlying cause for the carcinogenicity of EMS. This will drive the risk assessment for the exposure scenarios that occurred with EMS as an impurity in Viracept.</p> <p>Roche will use Registries to collect follow up information on patients exposed to the affected batches. In addition, patient populations most at risk will be followed up if they have taken Viracept at any given time.</p>	
Teratogenicity (EMS impurity)	<p>Gain more information on possible genotoxicity by animal studies.</p> <p>Close observation of reported events in the Antiretroviral pregnancy registry for HAART.</p> <p>Conduct <i>in vivo</i> repeat dose mutation induction study in rodents as genotoxicity is the basis for teratogenicity. The study shall provide data for a better quantitative risk assessment, which is currently based on linear incidence calculation from animal teratogenicity data.</p>	
Exposure of infants through lactation (EMS impurity)	Close observation of reported events in the Antiretroviral pregnancy registry for HAART.	The SPC contains a corresponding warning not to use Viracept during lactation.
Direct toxicity of EMS after ingestion (EMS impurity)	Analysis of reports and frequency of reports in 6 monthly cycles on the WHO database and on Roche internal database in order to detect changes of frequency or changes of terms of reported drug reaction.	

Outstanding issues – Risk Management Plan

General points

- The MAH should provide detailed information on the actions that need to be completed before the RMP can be approved along with firm timelines for completion of each of these actions.
- It should be made clear throughout the RMP what the MAH consider to be high and low doses of EMS and short and long-term exposure. The MAH should state where appropriate whether single dose or multi dose data from EMS animal studies are used and what NOELs and LOEL concentrations are or if they have not yet been determined, and reflect more accurately the uncertainties regarding EMS toxicity.

- The section on exposure figures from the table shows that the UK received 1958 packs of Viracept film coated tablets containing 200-999ppm EMS, however this is not reflected in the corresponding pie chart.
- The analysis of spontaneous reports will need to be repeated since there is often a long delay before national authorities submit reports to the WHO database and since many exposed pregnancies may not yet be delivered. It would be helpful for repeat analyses if the MAH obtain the earliest and latest report dates for each group.
- The MAH has provided an analysis on production of secondary cancers by alkylating agents. This should be related more closely to the implications for EMS exposure.
- The MAH should discuss how they will measure the success of the product recall.
- The MAH should provide a response to previous recommendation to publish this RMP.
- The Pharmacovigilance Plan and Risk Minimisation Plan should be updated as follows:
 - section 2.2 - summary of safety concerns - there should be reference to specific studies/registries, protocol numbers.
 - section 2.4- Study protocols are missing in this chapter, MAH should refer to specific studies using their unique identifiers
 - section 3.1 - All safety concerns (identified and potential risks and missing info) should be included here for assessment of a need for risk minimisation
- A summary table of the Risk Management Plan is missing and needs to be included.
- The MAH should ensure that RMP version control is employed.
- The MAH is currently in discussion with the French competent authority about the possibility of conducting epidemiologic studies within the existing French cohorts of HIV patients. Once agreed these studies should be included in this Risk Management Plan.

Pregnant and Lactating Mothers

- The MAH has highlighted a publication which showed that tamoxifen had a modulating effect on EMS toxicity. The MAH should indicate whether the effects of oestrogen on EMS toxicity will be investigated in the pre-clinical studies. The MAH should also consider if this information could be of relevance to pregnant women or breastfeeding mothers.
- The MAH need to clarify whether breastfeeding mothers or their children will be captured in these registries.
- It was noted in the 12th PSUR that Pfizer is conducting a study of nelfinavir in pregnancy, but this is not mentioned here; this study should be discussed in the RMP.

Children

- The MAH has stated that a linear incidence extrapolation from animal lowest observed effect data to the potential body burden of EMS in pregnant women for the occurrence of effects on the developing embryo shows that the calculated risk is at least two orders of magnitude below the spontaneous malformation incidence in the human population. The MAH should clarify what is meant by this statement and its relevance to detecting adverse effects in exposed populations.
- The MAH has confirmed that Viracept powder was not contaminated with EMS, however it is not clear if it has been contaminated in the past and doesn't obviate the need to include children in registries since some may have been taking tablets.

Post-Exposure Prophylaxis

- Nelfinavir has been a standard component of Post-Exposure Prophylaxis (PEP) treatment since 2004 until the beginning of 2007 in some member states. The MAH should discuss the effects of nelfinavir contamination on this group and detail how they will ensure that those exposed through post-exposure prophylaxis to the highest levels of EMS contamination will be included in the registry.

2.3.2 Registry proposals

The MAH submitted draft protocol synopses for registries for patients exposed to Viracept containing EMS at high levels (>1,000 ppm) and pregnant women and children. At the request of the CHMP these were discussed at the July meeting of the Pharmacovigilance Working Party (PhVWP).

The CHMP and its PhVWP considered that greater detail was required in relation to the MAH's registry protocols and it was recommended that the MAH should provide updated registry proposals taking into account the relevant comments (including those relating to duration of follow-up, identification of patients, data capture and analysis), or provide reasonable justification why outstanding issues have not been addressed.

The MAH was requested to update the registry proposals to take on board these recommendations and submit by 31 August 2007 full detailed protocols for consideration by the CHMP at its September meeting.

The MAH's response and revised registry proposals were submitted on 3 September 2007.

Overview of revised registry proposals

Registry 1 A Safety Registry of Patients with Potential Exposure to Viracept containing >1,000 ppm EMS

Objectives

Primary Objectives

- ◆ To detect new onset neoplasms in patients with potential exposure to EMS in Viracept produced from active substance containing EMS at levels > 1,000 ppm in the 01/03/07 to 30/06/07 time period.
- ◆ To estimate the incidence of specific new onset neoplasms in patients with potential exposure to Viracept produced from active substance containing > 1,000 ppm EMS.
- ◆ To compare incidence of specific new onset neoplasm in patients with potential exposure to EMS in Viracept produced from active substance containing > 1,000 ppm EMS to comparison groups with no such exposure.

Secondary Objectives

- ◆ To explore possible exposure response relationship of level and duration of exposure to EMS and new onset neoplasm.

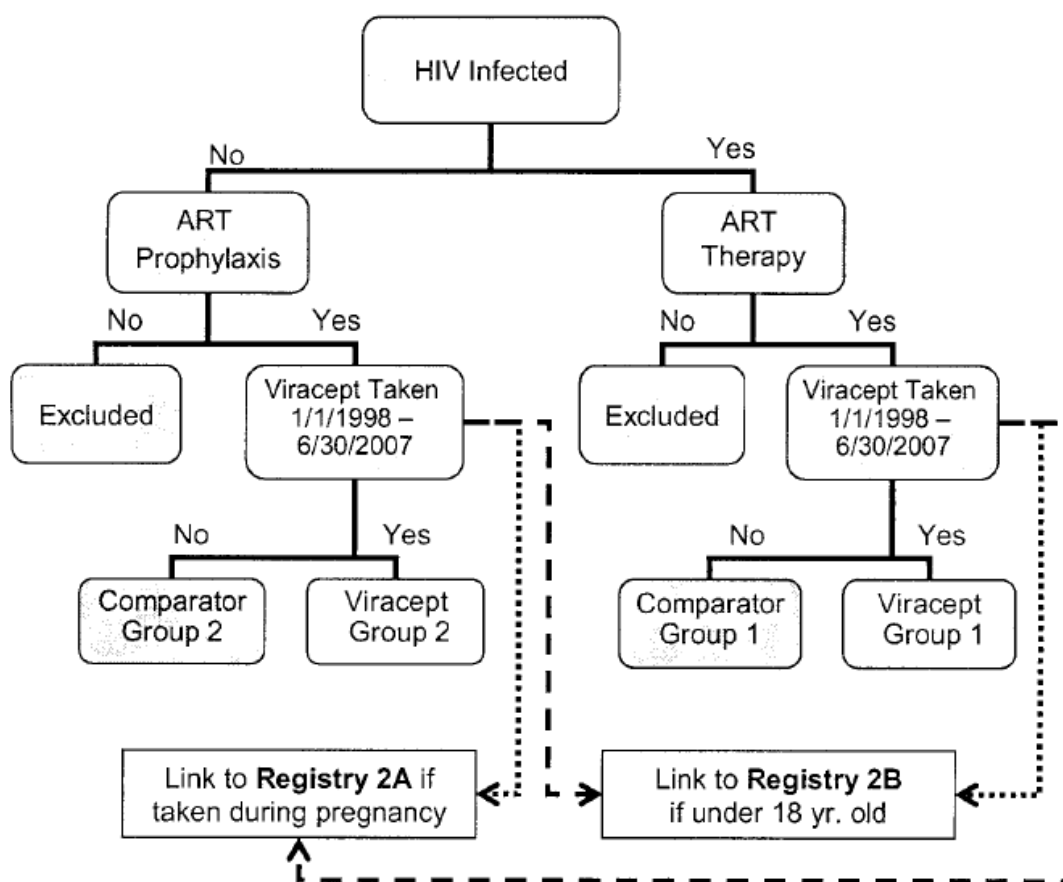
Study Design

The Registry will consist of a Registry of Existing HIV/AIDS Registries in affected countries and where no registries are available a Patient Log of non-registered exposed patients. The Registry will conduct baseline and follow-up assessments, on a 6-month basis, on new onset neoplasms among Viracept-exposed and comparison groups.

The Registry of existing registries will be a non-interventional, long-term, observational registry of existing HIV registries in all affected countries, composed of:

- a) Patients who were potentially exposed to EMS in Viracept produced from active substance containing > 1,000ppm EMS, and
- b) Comparator patients not exposed to Viracept during the period 01/03/07 to 30/06/07.

Figure 1. Subject Selection for Vira-EMS Registry 1



For each country, an estimate of the number of patients believed to be exposed to Viracept will be developed from distribution information. This estimate will then be compared with the number of identified patients known to be exposed to Viracept in the time period of interest based upon the data in existing registries. If the latter number is <85% of the estimated number of patients in a particular country or region, one or both of the following strategies might be implemented:

- The existing HIV registries will be encouraged to reach out for further recruitment of all or a portion of the remaining potentially exposed individuals.
- For those who are not covered by any existing HIV/AIDS registries, a Patient Log of the remaining potentially exposed individuals will be established.

Exposed patients will be assessed on a 6-monthly basis and the duration of the observation period will be 10 years after the registry enrolment.

It is proposed that there will be one Coordinating Organisation charged with organising the Registry of registries as well as the patient log, segmented by country.

Study Population

The primary target population is made up of individuals who took Viracept produced from active substance containing EMS at levels >1,000 ppm at any time between 01/03/2007 and 30/06/2007.

The suitable comparator patients are those individuals who are matched to Viracept subject by age, gender, HIV status and treatment, and documented not to have been exposed to Viracept produced from active substance containing >1,000 ppm EMS.

Exclusion criteria

- ◆ Individuals exposed to Viracept exclusively in the US, Canada or Japan.
- ◆ Cancer history prior to first Viracept exposure during period 01/03/2007 to 30/06/2007.
- ◆ Patients receiving Viracept where it can be documented that no lots received by patient contained Viracept produced from active substance containing >1,000 ppm EMS.
- ◆ Patients receiving Viracept where it can be documented that there was no distribution of any lots with Viracept produced from active substance containing >1,000 ppm EMS.

Data Collection

This Registry will collect data on patients who potentially or ideally were documented to have taken Viracept any time during the period 01/03/2007 to 30/06/2007 in countries where Viracept containing EMS impurity at levels >1,000ppm were distributed. Data collection may be partially or wholly web-based with appropriate security and confidentiality safeguards.

The Registry will work with existing HIV registries/observational cohorts in order to provide data both retrospectively and prospectively to meet the study objectives. Where subjects may also be eligible for Registries 2A or 2B, efforts will be made to identify and flag up any duplication in order to avoid double counting across the registries.

For the Patient Log, where possible, basic background history, HIV status and treatment will be recorded along with relevant contact information for follow-up. The MAH considers that in order to maximise participation in such Patient Logs the procedures and data collection must be kept as simple as possible and afford patient confidentiality. Efforts will be made to identify any duplication of patients in the log and the registries.

Assessments

At baseline information will be collected on start and end dates of Viracept exposure (if possible with lot numbers and dates dispensed), medical history (including cancer history), HIV status, CD4 and Viral Load data, and major HIV-related co-morbidities and therapy.

For the registry, follow up visits will collect health status, particularly whether the patients has experienced any new onset neoplasms since last visit, HIV status, CD4 and Viral Load data, and most recent treatment regimens.

For the Patient Log, follow up information will be collected on any new onset neoplasms.

Data Analysis

Primary Analysis

Rates of new onset neoplasms will be compared between the Viracept group and comparator group. The specific analysis plan will be developed in conjunction with representatives of the existing HIV registries/observational cohorts, as well as the Viracept Registry Scientific Advisory Committee.

Additional Analyses

Where possible, patients will be stratified as per potential exposure to EMS based on i) documented lot number distributed to or received from patients, and b) lot numbers known to have been available for distribution at the site or pharmacy from which the patient received Viracept:

- ◆ Patients who took Viracept during the period 01/03/2007 to 30/06/2007 with potential exposure to EMS at unknown level of exposure.
- ◆ Patients with definite maximum exposure to Viracept produced from active substance containing >1,000ppm EMS based on lot numbers dispensed to/ returned from patients or based on lot numbers available for distribution at site or pharmacy.
- ◆ Patients with potential maximum exposure to EMS >1,000 ppm based on lot numbers available for distribution at site or pharmacy.

Registry 2A A Safety Registry of Pregnant Women with Potential Exposure to EMS in Viracept

Objectives

Primary Objectives

- ◆ To assess pregnancy outcomes in women potentially exposed to EMS impurity in Viracept during pregnancy at any time between 01/01/1998 to 30/06/07.
- ◆ To measure the rate of birth defects in children potentially exposed *in utero* to EMS contained in Viracept.
- ◆ To compare the incidence of birth outcomes and defects in children potentially exposed *in utero* to EMS contained in Viracept in comparison with groups with no such exposure.

Secondary Objectives

- ◆ To explore possible exposure response relationship of level and duration of exposure to EMS with rates of birth defects.

Study Design

The Registry will consist of a Registry of Existing HIV/AIDS Pregnancy Registries in affected countries and where no registries are available a Patient Log of non-registered exposed patients. The Registry will conduct baseline and follow-up assessments of birth outcomes at birth and 6 months post-birth, among Viracept-exposed and comparator women.

The Registry of existing registries will be a non-interventional, long-term, observational registry of existing HIV registries in all affected countries, composed of:

- a) Women who took Viracept during pregnancy and were potentially exposed to EMS in Viracept at any time between 01/01/1998 to 30/06/2007.
- b) Comparator women on ART who were not exposed to Viracept during pregnancy.

For each country, an estimate of the number of pregnant women believed to be exposed to Viracept will be provided. This estimate will then be compared with the number of identified women known to be exposed to Viracept in the time period of interest based upon the data in existing registries. If the latter number is <85% of the estimated number of patients in a particular country or region, one or both of the following strategies might then be implemented:

- a) The existing HIV registries will be encouraged to reach out for further recruitment of all or a portion of the remaining potentially exposed individuals.
- b) For those who are not covered by any existing HIV/AIDS pregnancy registries, a Patient Log of the remaining potentially exposed pregnant women will be established.

The observation of birth outcomes will occur immediately after birth and at 6 months post birth.

As for Registry 1, it is proposed that there will be one Coordinating Organisation charged with organising the Registry of registries as well as the patient log, segmented by country.

Study Population

The primary target population is made up of pregnant women who took Viracept during pregnancy at any time between 01/01/1998 and 30/06/2007.

The suitable comparator patients are those pregnant women documented not to have been exposed to Viracept during pregnancy in a comparative time period.

Exclusion criteria

- ◆ Pregnant women exposed to Viracept exclusively in the US, Canada or Japan.
- ◆ Known foetal abnormality prior to first Viracept exposure.

Data Collection

This Registry will collect data both retrospectively and prospectively to capture all women potentially exposed to Viracept through to the time of withdrawal plus 3 months (30/09/2007). Data collection may be partially or wholly web-based with appropriate security and confidentiality safeguards.

The Registry will work with existing HIV pregnancy registries/observational cohorts in order to provide data both retrospectively and prospectively to meet the study objectives. Where subjects or their offspring may also be eligible for Registries 1 or 2B, efforts will be made to identify and flag up any duplication in order to avoid double counting across the registries.

For the Patient Log, where possible, basic background history, pregnancy status, HIV status and treatment will be recorded along with relevant contact information for follow-up. As with Registry 1, the MAH considers that in order to maximise participation in such a Patient Log the procedures and data collection must be kept as simple as possible and afford patient confidentiality. Efforts will be made to identify and flag up any duplication of patients in the log and the registries.

Assessments

At baseline information will be collected on demographics of pregnant women, start and end dates of Viracept exposure (if possible with lot numbers and dates dispensed), obstetric/gynaecological history, pregnancy status, history of foetal abnormality, HIV status, CD4 and Viral Load data, and major HIV-related co-morbidities and therapy.

For the registry, follow up visits will collect pregnancy outcomes, breast feeding, neonate birth weight, birth defects, vital status of neonates, HIV status, CD4 and Viral Load data, and most recent treatment regimens.

Data Analysis

Primary Analysis

Birth outcomes and rates of birth defects will be compared between the Viracept group and comparator group. The specific analysis plan will be developed in conjunction with representatives of the existing HIV pregnancy registries/observational cohorts, as well as the Viracept Registry Scientific Advisory Committee.

Additional Analyses

Where possible, pregnant women will be stratified as per potential exposure to EMS based on i) documented lot number distributed to or received from patients, and b) lot numbers known to have been available for distribution at the site or pharmacy from which the patient received Viracept:

- ◆ Women who took Viracept during pregnancy with potential exposure to EMS at unknown level of exposure.
- ◆ Women with definite maximum exposure to Viracept based on lot numbers dispensed to/ returned from patients or based on lot numbers available for distribution at site or pharmacy.
- ◆ Women with potential maximum exposure to Viracept based on lot numbers available for distribution at site or pharmacy.

Registry 2B A Safety Registry of Children with Potential Exposure to EMS in Viracept

Objectives

Primary Objectives

- ◆ To detect new onset neoplasms in children under 18 years old with potential exposure to EMS in Viracept during the 01/01/1998 to 30/06/07 time period.
- ◆ To estimate the incidence of specific new onset neoplasms in these potentially EMS exposed children.
- ◆ To compare incidence of specific new onset neoplasm in children potentially exposed to EMS in Viracept in comparison to groups with no such exposure.

Secondary Objectives

- ◆ To explore possible exposure response relationship of level and duration of exposure to EMS and new onset neoplasm.

Study Design

The Registry will consist of a Registry of Existing HIV/AIDS Paediatric Registries in affected countries and where no registries are available a Patient Log of non-registered exposed children. The Registry will conduct baseline and follow-up assessments, on a 6-month basis, on new onset neoplasms among Viracept-exposed and comparison groups.

The Registry of existing registries will be a non-interventional, long-term, observational registry of existing HIV paediatric registries in all affected countries, composed of:

- a) Children who took Viracept and/or were potentially exposed to Viracept *in utero* at any time between 01/01/1998 to 30/06/2007. The registry will enrol both HIV- infected and uninfected children who took ART for treatment or prophylaxis, and
- b) Comparator children not exposed to Viracept.

For each country, an estimate of the number of children believed to be exposed to Viracept will be provided. This estimate will then be compared with the number of identified children in existing HIV registries known to be exposed to Viracept in the time period of interest based upon the data. If the latter number is <85% of the estimated number of patients in a particular country or region, one or both of the following strategies might then be implemented:

- a) The existing HIV paediatric registries will be encouraged to reach out for further recruitment of all or a portion of the remaining potentially exposed individuals.
- b) For those who are not covered by any existing HIV/AIDS registries, a Patient Log of the remaining potentially exposed individuals will be established.

The paediatric patients will be followed up to reaching age 18 for the long-term assessment of risk of cancer.

It is proposed that there will be one Coordinating Organisation charged with organising the Registry of registries as well as the patient log, segmented by country.

Study Population

The primary target population is made up of children who took Viracept or were exposed to the drug *in utero* at any time between 01/01/1998 and 30/06/2007.

The suitable comparator children are those children documented not to have been exposed to Viracept in a comparative period of time. Comparators will be matched to Viracept exposed children by age, gender, HIV status and treatment.

Exclusion criteria

- ◆ Children exposed to Viracept exclusively in the US, Canada or Japan.
- ◆ Cancer history prior to first Viracept exposure.

Data Collection

This Registry will collect data both retrospectively and prospectively on children who were potentially exposed to Viracept. Data collection may be partially or wholly web-based with appropriate security and confidentiality safeguards.

The Registry will work with existing HIV registries/observational cohorts in order to provide data both retrospectively and prospectively to meet the study objectives. Where subjects may also be eligible for Registries 1 and 2A, efforts will be made to identify and flag up any duplication in order to avoid double counting across the registries.

For the Patient Log, where possible, basic background history, HIV status and treatment will be recorded along with relevant contact information for follow-up. The MAH considers that in order to maximise participation in the Patient Logs the procedures and data collection must be kept as simple as possible and afford patient confidentiality. Efforts will be made to identify and flag up any duplication of patients in the log and the registries.

Assessments

At baseline information will be collected on the demographics of the exposed children and/or mothers, the start and end dates of Viracept exposure (if possible with lot numbers and dates dispensed), medical history (including cancer history), HIV status, CD4 and Viral Load data, and major HIV-related co-morbidities and therapy.

For the registry, follow up visits will collect health status, particularly whether the patients has experienced any new onset neoplasms since last visit, HIV status, CD4 and Viral Load data, and most recent treatment regimens.

For the Patient Log, follow up information will be collected on any new onset neoplasms.

Data Analysis

Primary Analysis

Rates of new onset neoplasms will be compared between the Viracept group and comparator group. The specific analysis plan will be developed in conjunction with representatives of the existing HIV paediatric registries/observational cohorts, as well as the Viracept Registry Scientific Advisory Committee.

Additional Analyses

Where possible, patients will be stratified as per potential exposure to EMS based on i) documented lot number distributed to or received from patients, and b) lot numbers known to have been available for distribution at the site or pharmacy from which the patient received Viracept:

- ◆ Children who took Viracept with potential exposure to EMS at unknown level of exposure (unable to map lot numbers to patient or to site or pharmacy).
- ◆ Patients with definite maximum exposure to Viracept produced from active substance containing >1,000ppm EMS based on lot numbers dispensed to/ returned from patients or based on lot numbers available for distribution at site or pharmacy.
- ◆ Children potentially exposed *in utero*.

Outstanding issues – Registry proposals

The MAH's proposal to establish a Registry of registries is considered acceptable; however, there are a number of outstanding points that need to be addressed by the MAH and these are listed below:

General points

- The MAH should provide detailed information on the actions that need to be completed before the registries can be initiated along with firm timelines for completion of each of these actions.
- The MAH should also provide regular reports on these Registries. Once the Final registry protocols have been agreed and whilst the registries are in the initial stages of being established the MAH should provide progress reports on a quarterly basis. Once the registries are established these reports should be submitted annually.

Specific points

- Figure 1 from Registry 1 will need to be amended to more accurately represent the patients selected for this study. In particular to clarify that only patients potentially exposed to Viracept containing EMS >1,000 ppm during the period 01/03/2007 to 30/06/2007 will be included in this registry.
- The MAH will have to discuss, whether the cut-off date of 30/06/2007 is appropriate. This discussion will be based on the documented success of the recall. The need to add a larger safety margin to the proposed cut-off date will have to be addressed in this respect. The CHMP recommends to prolong this date by 3 months in order to capture any patients which were potentially exposed to Viracept batches containing >1,000 ppm EMS beyond the proposed cut-off date.
- The exclusion criteria for registries 1 and 2B are not acceptable. The exclusion of patients with a cancer history will reduce the power to detect any possible signal of acceleration of tumour growth. Matching on, adjusting for or stratifying by cancer history is considered to be a more advisable way forward.

- The MAH should also use the information obtained from the pre-clinical studies to determine whether there are any specific cancers which should be particularly closely monitored.
- The duration of follow-up proposed by the MAH for registry 2B is not acceptable as it could mean that children/adolescents exposed will get very little follow-up. It is recommended that children should be followed up for at least 10 years or until they reach 18 years of age, whichever is longest time period. The period of follow-up may need to be extended beyond 10 years depending on the findings from pre-clinical studies or preliminary findings from the registry analyses.
- The MAH should provide information on how many of the Viracept exposed patients are likely to be included in the MAH's proposed Registry of registries.
- With regard to the identification of duplicates, the MAH should provide information on how they will deal with patients who could potentially be in more than one registry at the same time (i.e. adolescent who becomes pregnant).
- The MAH has provided information on the list of registries for inclusion and this list contains some surveillance surveys- the MAH should provide clarification that these will be able to obtain the correct data and are not simply AIDS prevalence/incidence surveys.
- In the supplementary information provided by the MAH the rates quoted for cancers (after table 3) have no denominator.
- In the supplementary information the MAH has also provided Power calculations. It is considered that as we are dealing with rare outcomes standard power calculations are not helpful, a signal may be detected but there may be insufficient power to demonstrate statistical significance according to clinical trial standards for efficacy. In relation to the power calculations, the MAH is requested to provide the denominator for the rate.
- With regard to Registry 2A, the MAH should clarify that the 6 month follow-up after birth applies to the infant and the child will then go into registry 2b. The MAH should also clarify whether the mother will go into registry 1 if they were exposed to high dose EMS. Also it is assumed that the exclusion criteria relating to foetal abnormality prior to first Viracept exposure apply to the current pregnancy.
- For Registry 2A the MAH should also use this to examine the rate of early abortion in pregnant women exposed to Viracept from March 2007.
- The MAH should also provide clarification on whether adolescents exposed to Viracept (initiating in registry 2b) will enter registry 1 on turning 18 if they have been exposed to high dose EMS. Any adolescents initiating Viracept will otherwise only be followed for a short time and the MAH should ensure that these patients will continue to be included in the Registry.
- The MAH should provide updates on the progress made with respect to the capture of information on the patients' past and current medical and treatment history as the data collection gets under way. This information should be included in the regular reports that are required to be submitted.
- Once the main registry protocols have been agreed by the CHMP the MAH should also submit draft CRFs for agreement by the CHMP.
- The MAH should re-evaluate whether the collection of blood samples for examination of possible biomarkers would be valuable in light of the findings from the the pre-clinical studies.
- With regard to the mechanisms to ensure that all neoplasms will be captured, the MAH should provide an update regarding this issue following the discussions with experts in Cancer registries.
- The MAH should explore further and discuss with relevant experts whether a pooled analysis across the separate registries will provide greater power to examine the overall incidence of cancers.

2.3.3 Discussion

While in the updated protocols for the Viracept Registries, the MAH has taken many comments into account and made some adequate progress, questions remain. With the proposal of the MAH to use a “Registry of Registries” the issues with regards to feasibility and statistical power have been addressed. Generally, this proposal is acceptable. However, there remain a series of both general and specific issues that need to be addressed by the MAH. It is expected that the revised protocols, which should be submitted by the end of November 2007 will take all of the above raised points into account. Mainly, the adequacy of the time of follow-up, the exclusion criteria and the degree to which Viracept exposed patients will be excluded in the Registries are in need of further clarification.

2.3.4 Conclusion on Pharmacovigilance

The outline of the Registries could be satisfactory, provided that the MAH takes the above comments into account and submits updated protocols by the end of November 2007. The MAH will have to take further comments by the CHMP into consideration when developing the final protocols.

3 OVERALL DISCUSSION AND RECOMMENDATION

The CHMP, having reviewed the data submitted by the Marketing Authorisation Holder in the context of the suspension and having re-assessed the benefit/risk profile of the medicinal product, on 20 September 2007, recommended the following:

3.1 Quality

The CHMP, having assessed the totality of the MAH’s responses concerning risk analysis, process re-validation, analytical methodology development and validation, revised tighter specification limits for alkyl mesitates, as well as all the measures proposed by the MAH to ensure that the manufacturing processes for the active substance and the finished products are under control, considers that the MAH’s proposals are now sufficient to ensure the satisfactory quality of nelfinavir mesilate active substance and finished products.

Although a number of remaining quality issues have been identified, the CHMP considered that these are minor, and should not preclude the lifting of the Suspension of the Marketing Authorisation, as the MAH has committed to resolve these outstanding issues, within acceptable time frames.

Therefore, and taking into account the positive outcome of the Swissmedic follow-up inspection, the CHMP recommends the lifting of the suspension of the Marketing Authorisation on the basis of the MAH having resolved the concerns raised that had led to the suspension. The CHMP is of the opinion that the MAH has satisfactorily shown that the quality of Viracept can be ensured due to the MAH’s CAPA measures.

However, as follow-up commitments the MAH should address the following remaining issues arising from their quality response.

- It should be confirmed that the MAH will develop analytical methods to quantify MMS/EMS in the finished products, with an improved quantitation limit than the 10 ppm in the current method for tablets.
- The MAH should discuss in depth on the hydrolysis products of the EMS especially on the aspects of the chemical pathways of hydrolysis of EMS in contact with water and the potential of these degradation products of hydrolysis to be genotoxic. The MAH is also requested to clarify what these alkylate reactive centres of the tablets/powder matrix are.

- The MAH should confirm that a stability program will be set up addressing the low levels of MMS/EMS in dosage forms as soon as method is available that can detect MMS/EMS down to levels ≤ 0.5 ppm.
- The MAH has provided the general risk assessment of the quarantined batches, but not the specific data related to these batches. This should be provided with a listing of AS batches linked to the quarantined stock, MMS/EMS levels in the AS (determined by the new method HPD99GC1.1), MSA in AS and the corresponding pH value. Any release of these batches will be subject to approval from Supervisory Authorities responsible for the batch release sites.
- The MAH should review the proposed limit of max. 0.5 ppm as soon as sufficient data are available from the revised process and process capability can be assessed.

3.2 Non-Clinical

Based on the assessment of the non-clinical data available so far, the CHMP concluded the following:

- Patients exposed to EMS during the 3-month period in 2007 of possible contamination of above 1000 ppm should be monitored for adverse effects.
- Pregnant women and children, including those exposed *in utero*, who have taken Viracept at any given time, should be monitored as well. In the case of pregnant women, the purpose is to follow-up the outcome of the pregnancy.
- The TTC (Threshold of Toxicological Concern) limit of 1.5 μg maximum daily dose of a potentially genotoxic substance as defined in the CHMP Guideline on the Limits of Genotoxic Impurities could be considered as acceptable for establishing a specification of the sum of MMS and EMS in the active substance. This translates into a maximum of 0.6 ppm.

The MAH has addressed the comments made by the CHMP during its June 2007 meeting on the assessment of the genotoxicity of EMS. The MAH has highlighted the fact that they consider all their proposals as forming the basis for further discussion with the CHMP, rather than being the MAH's final decisions. In general, the CHMP endorsed the MAH's proposals, seeking from the MAH one specific commitment. The commitment is that the MAH agree to conduct a MutaMouse study of longer duration than 28 days if the results of that study are considered to be insufficiently informative and/or raise further findings requiring clarification on the relationship between treatment duration and mutation formation.

3.3 Pharmacovigilance

In relation to the Pharmacovigilance issues, a revised Risk Management Plan has been submitted by the MAH. This is a significant improvement on the previous version, however, there remain a number of issues which still need to be addressed and these are detailed in section 2.3.1 above.

The revised registry proposals have been submitted and are considered to be acceptable, pragmatic and make good use of the available information. The revised approach will ensure that appropriate comparator data are available and it is hoped will maximise healthcare professional involvement. There are, however, a number of outstanding issues that need to be addressed by the MAH (see assessment as given in section 2.3.2 of this assessment report).

The outline of the Registries could be satisfactory, provided that the MAH takes the above comments into account and submits updated protocols at the end of November 2007. The MAH will have to take further comments by the CHMP into consideration when developing the final protocols.

3.4 Overall Recommendation

Having reviewed all available data on quality, non-clinical issues and Pharmacovigilance, the CHMP considered during its September 2007 plenary meeting that the MAH has satisfactorily addressed the concerns raised during the June 2007 meeting.

The MAH has reassured the CHMP on the quality of Viracept he intends to release on the market. The corrective and preventive actions undertaken, as well as the validation of the modified manufacturing process have convinced the CHMP that the MAH is in a position to produce nelfinavir consistently with a satisfactory quality. As discussed in the quality section of this assessment report, the MAH has shown that the manufacturing process allows reducing the limit of the sum of EMS and MMS below the TTC limit of 0.6 ppm to 0.5ppm. The CHMP agreed to this new specification of NMT 0.5 ppm for the sum of EMS and MMS in the active substance.

The non-clinical study plans have been endorsed and will help to further characterise and quantify the risk associated with the EMS exposure of affected patients. The results of these studies will be assessed and considered in the future follow-up of patients having been exposed to EMS in Viracept.

The protocols for the requested registries have been endorsed and will be further refined. Thereby, the MAH will follow-up any patients more vulnerable to the exposure of a genotoxic substance as well as all patients having been exposed to the high levels of EMS in the batches marketed between March and June 2007.

4 CONCLUSION

The CHMP consequently, on 20 September 2007 recommended the lifting of the suspension of the Community Marketing Authorisation for the medicinal product Viracept, subject to the additional commitments undertaken (see below).

The MAH quality response and the acceptability of the proposed limit of 0.5 ppm MMS/EMS in the active substance are considered sufficient to lift the suspension of the marketing authorisation.

Relevant changes to the Annex II are indicated in attachment 3 and reflect the conditions of the Marketing Authorisation:

4.1 Conditions of the Marketing Authorisation

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management Systems for medicinal products for human use.

4.2 Follow-up measures following the lifting of the suspension of the Marketing Authorisation

There are a number of outstanding quality, non-clinical and pharmacovigilance issues, which the MAH should address as follow-up commitments.

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below:

Area	Description	Due date
Quality	The MAH commits to develop an analytical method to quantify MMS/EMS in the finished product, with a limit of quantitation less than 10 ppm.	Currently Ongoing Status Report by 31.12.2007
Quality	Upon the availability of a method to detect MMS/EMS down to levels of <u><0.5 ppm</u> a stability program for the film-coated tablet formulation will be set up addressing these low levels.	As soon as required test method is available

Quality	The MAH will discuss in depth the hydrolysis products of the EMS, especially the aspects of the chemical pathways of hydrolysis of EMS in contact with water and the potential of these degradation products of hydrolysis to be genotoxic. The MAH is also requested to clarify what these alkylate reactive centres of the tablets/powder matrix are.	31.10.2007
Quality	A list with specific data of MMS/EMS levels of the API batches linked to the quarantined batches will be provided (determined by the new method HPDF99GC1.1), together with the levels of residual MSA in API and the corresponding pH value.	28.09.2007
Quality	The MAH will review the proposed limit of max. 0.5 ppm as soon as sufficient data are available from the revised process and process capability can be assessed. The number of available batches will depend on the market demand.	Annual update First: 31.3.2008
Non-clinical	<u>Comparative <i>in vivo</i> MNT studies with EMS and ENU (7 day daily treatment by oral gavage)</u> To confirm the threshold dose-response curve for EMS in contrast to ENU under repeat dose conditions. Preliminary results unexpectedly showed no effects for EMS up to the highest dose of 80 mg/kg EMS but the expected linear dose response curve for ENU.	In-life phase completed, evaluation ongoing, Draft reports expected mid of October 2007
Non-clinical	<u>A one month repeat dose study to establish dose-effect for mutation induction by EMS over a wide range of doses in transgenic mice</u> To provide evidence for a sublinear/threshold dose response for genotoxic effects of the direct alkylating agent EMS into the low dose region as delineated from the Viracept impurity case Duration of treatment: extension to 3 months is not currently foreseen but may be considered dependent on the outcome of ongoing studies; this will be further discussed with the CHMP upon availability of the first results and in line with the assessment on the toxicological responses as submitted by the MAH on 16 August 2007.	Start expected in December 2007
Non-clinical	<u>General 4-week toxicity study in the rat with EMS (new proposal).</u> To provide data on EMS organ toxicity and clinical chemistry/haematology assessments in conjunction with exposure data.	Start October 2007
Non-clinical	<u>Cross-species <i>in vitro</i> and <i>in vivo</i> evaluation of exposure to EMS</u> To retroactively facilitate exposure judgement in patients having been exposed to elevated levels of EMS via Viracept Full details on the modelling approach to estimate the exposure in patients to be provided.	Activities ongoing
Non-clinical	Furthermore the MAH commits to discuss the implications of the results derived from the above outlined non-clinical studies (a risk assessment symposium involving all parties is planned). In case further studies are found necessary and appropriate in order to further substantiate the quantitative risk assessment for the levels of EMS found in Viracept and the duration/characteristics of exposure of patients the MAH will be ready to undertake this.	Pending data availability of studies mentioned under 1-4
Non-clinical	The MAH expresses their intention to publish the results of the non-clinical investigations on EMS and ENU and the outcome of the planned risk assessment symposium in a suitable peer reviewed journal	Intended for 2 nd -3 rd Q 2008

PhV	<u>Risk Management Plan</u> The Risk Management Plan (from Version 1) will be updated in line with the recommendations in both the Rapporteur's updated assessment report on the RMP dated 19 September 2007 and the CHMP Assessment Report dated 20 September 2007.	Revised RMP submitted by 30. November 2007
PhV	<u>Registries:</u> The Registries protocols will be updated in line with the recommendations in the CHMP Assessment Report dated 20 September 2007. Reports will be submitted on a quarterly basis until the Registries are established and on an annual basis thereafter.	Revised Registry protocols submitted by 30 November 2007

4.3 Changes to the terms of the Marketing Authorisation

The lifting of the Marketing Authorisation suspension requires amendments to the terms of the Community Marketing Authorisation. The following annex has been amended: Annex II.

5 REFERENCES

CHMP Guideline on the Limits of Genotoxic Impurities (CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006); <http://www.emea.europa.eu/pdfs/human/swp/519902en.pdf>

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