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GUIDELINE ON CARCINOGENICITY EVALUATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF HIV INFECTION

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE ON CARCINOGENICITY EVALUATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF HIV INFECTION

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1 EXECUTIVE SUMMARY

Different classes of medicinal products for the treatment of the Human Immunodeficiency Virus (HIV-1) infection have been and are being developed. Some classes have shown equivocal genotoxic properties while others have shown to be clearly genotoxic, and nearly all agents were found to induce tumours in rodents. The benefit of treatment of HIV-infected patients has thus far outweighed the risk of carcinogenicity in humans because of the short life expectancy of HIV-infected patients. However the life expectancy of HIV-infected patients has increased significantly since these medicinal products were first introduced to the market. Therefore, the weight of the carcinogenic risk posed by the available agents may need to be reconsidered. It is in principle expected that carcinogenicity studies are submitted before granting the marketing authorisation. However, for medicinal products intended for the treatment of patients with limited treatment options or a clearly demonstrable added value, the submission of the results of the carcinogenicity studies as a post-approval commitment may be accepted. The need for carcinogenicity testing should be addressed prior to long term exposure in paediatric clinical trials considering the length of treatment or cause for concern.

2 INTRODUCTION

Different classes of medicinal products for the treatment of the Human Immunodeficiency Virus (HIV-1) infection, with different modes of action and toxic profiles have been and are being developed. Current options for anti-retroviral therapy (ART) for the treatment of HIV-1 infection consist of four classes of compounds: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs), protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and fusion inhibitors (FIs). Due to the inherent high mutation rate in HIV, the combined use of at least three active medicinal products, so called Highly Active Anti-retroviral Therapy (HAART), is currently considered essential in the standard of care of HIV-1 infected patients. The choice of the combination regimens depends on the status of the patient, particularly in terms of plasma viral load (HIV RNA), CD4 cell counts, previous treatment(s), prior relapse and intolerance to treatment.

NRTIs have shown genotoxic properties and nearly all agents have exhibited positive findings in the available two-year rodent carcinogenicity studies. The benefit of treatment of HIV-infected patients has thus far outweighed the risk of carcinogenicity in humans because of the short life expectancy of HIV-infected patients. However life expectancy of HIV-infected patients has increased significantly since these medicinal products were first introduced to the market. Available clinical data provide evidence that the development of HAART has reduced the incidence of the majority of HIV-associated tumours and has generally improved their responsiveness to therapy (Mayor et al.2005, Yarchoan et al.2005). Nevertheless, the weight of the carcinogenic risk posed by the available agents may need to be reconsidered. In case of biotechnology-derived pharmaceuticals developed for the treatment of HIV, genotoxicity and carcinogenicity testing may not be applicable according to preclinical safety evaluation of biotechnology-derived pharmaceuticals guideline (CPMP/ICH/ 302/95).

The development of this Guideline is a consequence of recent scientific knowledge in this field and the need for a “state-of-the-art” update. It is intended to make the assessments of applications for Marketing Authorisation of anti-HIV medicinal products by regulators more consistent, set clear standards and expectations for industry, and thereby helping to harmonise regulatory policy.

3 SCOPE

The present Guideline applies to the development of new medicinal products for the treatment of HIV infection.

The main objective of this guideline is to define the timing of and conditions under which carcinogenicity studies should be conducted during development and before marketing authorisation for any new anti-HIV Medicinal Product, if applicable.

In addition, it will provide recommendations for describing this non-clinical information in the SPC (section 5.3 Preclinical safety data).

4 LEGAL BASIS

This document should be read in conjunction with Directive 2001/83/EC (as amended) and all relevant CHMP and ICH Guidelines.

This document is meant as guidance only. Deviations from this guidance should be justified and, seeking European regulatory Scientific Advice is recommended, especially when compounds belonging to new classes of ART are under development.

Guidance documents that are especially important are listed under the References (Section 8).

5 GENERAL CONSIDERATIONS

Some classes of these anti-retroviral agents have shown equivocal genotoxic properties while others have shown to be clearly genotoxic. Nearly all agents have exhibited positive findings in the available two-year rodent carcinogenicity studies. Also, there is evidence that additive or synergistic mutagenic effects correlate with additive or synergistic antiviral effects of these drug combinations (Meng et al. 2000. Therefore, the weight of the carcinogenic risk posed by the available agents may need to be reconsidered.

The ICH Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals defines the circumstances when carcinogenicity studies are required (CPMP/ICH/140/95). This Guideline establishes that carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months. In general, when carcinogenicity studies are required, they usually need to be completed pre-authorisation except for pharmaceuticals developed to treat certain serious diseases, as is the case of Acquired Immune-deficiency Syndrome (AIDS). This is to speed up the availability of pharmaceuticals for life-threatening or severely debilitating diseases especially, where no satisfactory alternative therapy exists.

When these anti-HIV medicinal products were first introduced on to the market during the last decades, the life-expectancy of HIV patients was limited and the potential hazard of a carcinogenic effect was considered to be of relatively low relevance. Today, life expectancy of HIV-infected patients has increased significantly and thus HIV infection is to a certain extent considered as a chronic condition. Therefore, the need and timing of carcinogenicity studies in the development of anti-HIV medicinal products need to be reconsidered as well as their weight in the overall benefit/risk evaluation of these products, as compounds with less risk might be available.

6 NEED AND TIMING FOR CARCINOGENICITY EVALUATION

6.1 Carcinogenicity studies

Considering on the one hand the chronic course of the HIV infection among treated patients and their life expectancy, and on the other hand that nearly all antiretroviral agents have exhibited positive findings in the available two-year rodent carcinogenicity studies (but not all are relevant to humans), it is in principle expected that, as for any pharmaceutical for which the intended clinical use is longer than 6 months, carcinogenicity studies are submitted before granting the marketing authorisation. However, according to the NfG on *The need for Carcinogenicity Studies of Pharmaceuticals* (CPMP/ICH/140/95), for medicinal products intended for the treatment of patients with limited treatment options or a clearly demonstrable added value, the submission of the results of the carcinogenicity studies as a post-approval commitment may be accepted. European regulatory Scientific Advice is recommended, especially when compounds belonging to new classes of ART are under development.

In case of positive findings in carcinogenicity studies, sponsors should clarify the human relevance of the findings with supportive data to explain the tumour findings.

6.2 Combination of anti-HIV Products

Carcinogenicity studies of HIV drug combinations are usually not needed if the individual components have been adequately tested. In case of positive findings with the individual compounds, additive effects when tested in combination can be expected and should provide the basis for hazard evaluation without further testing. Deviations from this approach might be needed if knowledge of possible interactions is available, suggesting a potential to synergistically enhance adverse effects, not detectable from the data profile of the individual compounds.

6.3 Paediatric use

The standard battery of genotoxicity tests should be available if applicable, prior to the initiation of clinical trials in paediatric populations with new anti-HIV agents. The need for carcinogenicity testing should be addressed prior to long term exposure in paediatric clinical trials considering the length of treatment (or cause for concern) (CPMP/ICH/286/95).

6.4 Use in pregnant women

The need to further optimise anti-retroviral therapy in pregnant women is fully recognised, balancing the risk of sub-optimal therapy, viral resistance and vertical viral transmission against foetal toxicity and long-term consequences for the child. Currently, HAART combinations are highly effective in preventing HIV-1 vertical transmission. However, some of the anti-HIV agents are strong transplacental carcinogens in animal species. Also, transplacental genotoxicity enhancement has been reported for combined antiretroviral nucleoside analogue therapy in animal species (Olivero OA et al., 2002), and the potential long-term consequences of foetal exposure to most HAART combinations remain unknown.

Carcinogenicity studies should be provided before marketing authorisation submission if it is possible that the new agent may be used in pregnant women. For medicinal products intended for the treatment of pregnant women with limited treatment options or clearly demonstrable added value, the submission of the results of the carcinogenicity studies as a post-approval commitment may be accepted.

It should be considered that as the use of new compounds during pregnancy is partly inevitable, applicants for Marketing Authorisations should commit to provide reliable follow-up data of children exposed *in-utero* to anti-retroviral compounds, at least until a reasonably founded benefit-risk assessment is achievable. This should include long-term follow-up as far as possible as regards potential carcinogenic effects (CPMP/EWP/633/02).

The standard battery of genotoxicity tests should be conducted if applicable prior to the inclusion of pregnant women in clinical trials with new anti-HIV agents.

7 NON-CLINICAL DATA IN THE SPC

In the Summary of Products Characteristics (SPC), section 5.3 (Preclinical safety data), adequate information should be given on any findings in the genotoxicity and carcinogenicity studies which could be of relevance for the prescriber in recognising the genotoxic and carcinogenic potential of anti-HIV medicinal products.

Any genotoxic and carcinogenic positive finding should be indicated in relation to the maximal expected human exposure at the recommended therapeutic doses.

In case of tumour findings in the carcinogenicity studies, the mechanism of tumour formation and the potential relevance for humans should be stated.

Statement examples and recommendations given in the Guideline on Summary of Products Characteristics (CHMP/64302/2005) should be followed. Too much detail in relation to the specific aspects of the studies conducted is not recommended; it should be described in brief and qualitative statements as outlined in the following example statements (this is not an exhaustive list of possibilities):

Genotoxicity:

- [Active substance] was not mutagenic or clastogenic in conventional genotoxicity assays.
- [Active substance] was or was not genotoxic *in vivo* at doses that gave plasma concentrations e.g. around. 20-fold (in round figures) the anticipated clinical plasma levels.
- [Active substance] was genotoxic in *in vitro* tests.

Carcinogenicity:

- Carcinogenicity studies of [Active substance] in mice and rats did not show any carcinogenic potential.
- Carcinogenicity studies of [Active Substance] in mice and rats revealed tumourigenic potential specific for these species, but are regarded as of no relevance for humans.
- Carcinogenicity studies of [Active Substance] in mice and rats revealed tumourigenic potential specific for these species, but their clinical significance is unknown.
- [Active substance] was carcinogenic in animal species (organ tumours) at high exposure levels. No carcinogenicity was noted at doses corresponding to exposures (rough estimate) times the expected human exposure, respectively, suggesting an insignificant carcinogenic potential of [Active Substance] in clinical therapy.
- Carcinogenicity studies showed an increased incidence in (organ tumour) in (animal species). The mechanism of tumour formation and the potential relevance for humans is not known. Carcinogenicity studies in (animal species) were negative. While the carcinogenic potential is unknown, these data suggest that the clinical benefit of [Active substance] outweighs the potential carcinogenic risk to humans.

8. REFERENCES

- Note for Guidance on Carcinogenic Potential (CPMP/SWP/2877/00)
- Note for Guidance on the Need For Carcinogenicity Studies of Pharmaceuticals (CPMP/ICH/140/95)
- Note for Guidance on Carcinogenicity Testing for Carcinogenicity of Pharmaceuticals (CPMP/ICH/299/95)
- Note for Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals (CPMP/ICH/383/95)
- Note for Guidance on Addition of a Limited Dose and Related Notes (CPMP/ICH/366/96)
- Conclusions and Recommendations of Use of Genetically modified animal models for carcinogenicity assessment (CPMP/SWP/2592/02).
- Note for Guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95)
- Guidance on specific aspects of regulatory genotoxicity test (CPMP/ICH/141/95)
- Note for Guidance on Genotoxicity: a Standard Battery for genotoxicity testing of pharmaceuticals ((CPMP/ICH/174/95)
- Guideline on Clinical Evaluation of Medicinal Products for the treatment of HIV infection.(CPMP/EWP/633/02).
- Guideline on Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6-CPMP/ICH/302/95)
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