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Concept paper on the guidance on the non-clinical and clinical development of medicinal products for HIV prevention including oral and topical PrEP

Draft

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Concept paper on the guidance on the non-clinical and clinical development of medicinal products for HIV prevention including oral and topical PrEP

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1. Introduction (background)

Besides the ongoing efforts to develop preventive vaccines, other HIV prevention methods are currently also under development: oral and topical Pre-Exposure Prophylaxis (PrEP) for HIV sexual transmission.

After decades of research in these fields, the *positive* results of two recent studies have called the attention of the scientific community and regulators.

1- tenofovir 1% vaginal gel has been shown to reduce the risk of HIV acquisition by 39% (incidence rate ratio versus placebo = 0.61 (CI: 0.4 to 0.94; p=0.017) in the double blind placebo-controlled **CAPRISA** study performed in 889 women in South Africa.

2- the oral fixed dose combination Truvada (tenofovir and emtricitabine) has been shown to reduce the HIV incidence as compared to placebo by 44% (CI: 15 to 63; p=0.005) in the **iPrEx** study performed in 2499 men who have sex with men (MSM).

These approaches are developed as potential “complementary” tools to the standard prevention that still mainly relies on condom use.

This concept paper addresses the need for a reflection paper on the key aspects to be covered by the non clinical and clinical developments of oral and topical PrEP in view of potential future applications for marketing authorisation, including applications for a scientific opinion under article 58 for countries outside the EU.

Although it is acknowledged that different populations at risk could be targeted by oral and topical (genital and rectal) PrEP in different epidemiological contexts (from low level to generalised HIV epidemics) with varying HIV prevalences, both oral and topical PrEP approaches are being addressed in parallel in this document as they will raise similar issues.

2. Problem statement and discussion on the problem statement

Oral and topical PrEP raise **complex public health issues**, the most important of which are:

- *Condom replacement*:

Condom use is the cornerstone of HIV prevention. When used correctly and consistently, condoms can provide a high protection against the risk of HIV acquisition (*reduction of the risk of HIV heterosexual transmission by 80-90%*). In addition condoms also offer protection against other Sexually Transmitted Infections (STI).

Thus, if condom use is abandoned in favour of less effective pharmacological prevention methods (“condom replacement”), the risk of HIV transmission could increase rather than decrease. This represents a critical concern.

- *Risk compensation*, i.e. increase in risky behaviour by alteration of individuals’ perceptions of their

HIV risk.

- *Viral resistance*: potential negative impact of preventive use of antiretroviral agents on subsequent treatment in seroconverters

- *Tolerance*

- *Adherence*

In view of the challenges involved in the development of oral and topical PrEP, and the putative risks related to public health, **there is a need to predefine what would be regarded as a sufficient benefit for regulatory approval**.

In particular,

-How partial efficacy would be appraised considering the high level of HIV risk reduction with condom, when used correctly and consistently?

- How to best investigate putative effects of the intervention on sexual behaviour, e.g., due to altered risk perception within clinical development, and how to asses “real life” efficacy in the post-marketing phase.

- Given the number of HIV seroconversions observed in clinical trials (38 vs 60 in the CAPRISA study and 36 vs 64 in the iPrEx), difficulties are anticipated in substantiating to what extent wide scale use of the preventive measure could negatively affect the HIV epidemic and treatment.

- The question is raised on what duration of follow up would be required in order to adequately substantiate the long term use of oral and topical PrEP (covering both the coitally dependent (intermittent) and non coitally dependent (daily) approaches).

The **main reasons** prompting the need for elaborating a reflection paper are:

- The number of drugs in the pipeline for PrEP,

- Oral PrEP is currently under evaluation with drugs that are also used for the treatment of HIV infection and positive results are already available as mentioned above. There is a need to clearly establish what would represent an acceptable benefit in view of the theoretical risks that might not be fully covered in the pre-authorisation phase, in order to promote the collection of relevant data from well designed clinical studies and to discourage inappropriate off label use,

- Given the high burden of HIV infection among the female population in some resource-poor settings, there are high expectations on the development of topical PrEP. This could potentially cause difficulties for the conduct of additional placebo-controlled studies once preliminary positive results are obtained with a tested method. There is a need to address effect size issues beyond positivity of results, to clarify for stakeholders in their ongoing and planned development programs in identifying whether their non clinical and clinical development program could satisfy the regulators requirement for a proper benefit/risk assessment.

Particular issues to be covered in the reflection paper would notably include:

1. What would be an adequate non-clinical program to support an authorisation of an oral or topical PrEP?

2. What would be an acceptable efficacy level for oral and topical PrEP, taking into account:

- the efficacy of appropriate condom use, and the risk of PrEP causing a reduction in condom use
- the potential limitations of the non clinical and clinical development to adequately substantiate the risks

The possible input of mathematical modeling will have to be addressed

3. What are the crucial points in the design of pivotal clinical studies?

- *inclusion/exclusion criteria, i.e. definition of the target population (How to define the population at risk for HIV acquisition?– also for later product labelling)*
- *request for stratification, stratification criteria*

- *definition of the primary endpoint*
- *handling of other sexually transmitted infections*
- *data collection on sexual behaviour and use of condoms*
- *data collection on adherence*
- *data collection on resistance*
- *PK/PD correlation,*

5. What criteria should guide the possible extrapolation of clinical data in populations at different risk levels of HIV acquisition (including different regions)?

6. How to derive reassurance through the development program on

- the risk of condom replacement
- the risk compensation
- the risk of resistance
- the risk of long term side effects (including local carcinogenicity for topical PrEP)

7. Post-authorisation studies and Risk Management Programme

8. Specificities in the non clinical and clinical developments of combination approaches

3. Recommendation

The CHMP/IDWP recommends the drafting of a reflection paper on the main issues to be covered within the non clinical and clinical development programmes of oral and topical PrEP.

In order to help the elaboration of this reflection paper an expert meeting will be convened by the EMA, with the involvement of experts in the fields of animal model for HIV transmission, infectious diseases, epidemiology, biostatistics, specialists in at-risk behaviour and with consultations of stakeholders.

4. Proposed timetable

A first draft reflection paper is to be released for consultation not later than 4Q 2011

5. Resource requirements for preparation

Preparation of this reflection paper will involve the IDWP, the anti-viral SAG and members of the EMA ad hog group on HIV prevention strategies.

6. Impact assessment (anticipated)

It is anticipated that this reflection papers will help stakeholders to adapt the development of their drugs to enable adequately substantiating the benefit and risk to ultimately allow a proper benefit/risk assessment by regulators.

7. Interested parties

Interested parties with specific interest in this topic will be consulted during the preparation of this reflection paper, including the European AIDS Clinical Society (EACS), the European AIDS Treatment Group (EATG), National Agencies in limited resource settings, IPM, MDP and WHO.