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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on a guideline on the evaluation of medicinal products indicated for treatment of influenza

Agreed by Infectious Diseases Working Party (IDWP)	December 2016
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Start of public consultation	04 May 2017
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Keywords	***Influenza, antivirals, treatment***

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1. Introduction

This concept paper proposes the development of a guideline on the clinical evaluation of medicinal products indicated for the treatment of influenza for which there is no regulatory guidance currently available within the EU.

2. Problem statement

There are at present two classes of influenza antiviral medicines authorised within the EU: the neuraminidase inhibitors Tamiflu (oseltamivir) and Relenza (zanamivir) and the M2 ion channel inhibitors amantadine and rimantadine (adamantanes). Hitherto no CHMP guidance has been developed on the evaluation of medicinal products indicated for the treatment of influenza. Currently there are several new antiviral agents in development for the treatment of influenza, including directly acting antiviral agents and monoclonal antibodies. In recent requests for CHMP scientific advice on the development of new agents intended for the treatment of influenza several issues have emerged as being central to development programmes. Thus, it has become clear that there is a need to clarify the EU regulatory expectations with regard to the data that should be generated to support the approval of these novel agents.

3. Discussion (on the problem statement)

Approved antivirals have shown to reduce the duration of symptoms in non-severe influenza. No antiviral drug has however shown a definitive clinical benefit in a randomised study in more severe influenza including hospitalized patients. Nevertheless, neuraminidase inhibitors (mainly oseltamivir) have become standard of care for the treatment of this population which has an impact on the study design for new antivirals intended for the treatment of severe influenza: Approved antivirals have shown to reduce the duration of symptoms in non-severe influenza. No antiviral drug has however shown a definitive clinical benefit in a randomised study in more severe influenza including hospitalized patients. Nevertheless, neuraminidase inhibitors (mainly oseltamivir) have become standard of care for the treatment of this population which has an impact on the study design for new antivirals intended for the treatment of severe influenza. Oseltamivir is the stablished standard of care in this population, in accordance with guidance from public health bodies, and the feasibility of randomising patients to placebo treatment without any antiviral agent needs to be considered. Showing superiority over e.g. oseltamivir would convincingly demonstrate efficacy but given the unknown effect of oseltamivir in severe influenza, may be a high hurdle. Because the effect of Oseltamivir over placebo is not well documented, constructing a NI margin that, if met, would establish evidence of efficacy, is problematic at this stage. The CHMP's expectations on the study design need to be clarified.

The patient population having complicated influenza, as defined by for example the World Health Organization (WHO), could be very heterogeneous. In addition to the severity of the disease the range of complications (e.g. secondary bacterial infections) could be very variable. It is in fact possible that a new antiviral agent for the treatment of complicated influenza may show a benefit only in subgroups of this diverse patient population. With regards to trial endpoints, time to alleviation of predefined influenza symptoms has been used as the primary efficacy endpoint in pivotal studies for the treatment of non-severe influenza. In severe influenza there is an ongoing discussion in the scientific community on optimal endpoints. Time to normalisation of vital signs has previously been used in phase 3 studies in this setting, whereas endpoints focusing only on normalisation of respiratory function are under evaluation in several phase 2 studies. An alternative to time-to-alleviation endpoints, which has been proposed, is using an ordinal scale to determine the patient status at a set time post initiation of

therapy. The expectations of the study population and efficacy endpoints particularly in the setting of severe influenza need to be discussed in the guideline.

Other issues that have emerged in recent scientific advice procedures include questions on the most appropriate way to identify the dose regimen for pivotal trials, such as using human challenge studies or studies in uncomplicated influenza rather than a dose-finding study in the target patient population. Furthermore, in case of a monoclonal antibody, some data indicate that antibody-dependent enhancement of influenza infectivity may be possible if the dose is too low.

Extrapolation of efficacy from the adults to the paediatric population which often is possible in many other types of infection may not be appropriate for all age groups. The presence or absence of some degree of natural acquired immunity to the circulating strains and/or the past vaccination history and type of vaccine administered may lead to different magnitudes of treatment effect in children and adults.

In summary, several problems have been identified when designing clinical studies intended to support the approval of medicinal products for the treatment of influenza. Moreover, during the recent years there has been an increase in the number of products under development for the treatment of influenza and recognition of recurring issues that have arisen in scientific advice. Therefore, the development of CHMP guidance seems timely and should include general aspects for therapeutic guidelines (patient selection, assessment of efficacy, design of PK, PD and therapeutic studies, safety aspects and studies in special populations) with a particular focus on the following matters:

- The antiviral data usually expected from non-clinical in vitro and animal model studies to support an application dossier for a new antiviral agent for the treatment of influenza
- Dose selection
- Study design, study population and efficacy endpoints for the treatment of non-severe and severe influenza
- Issues pertaining to paediatric development specifically to clarify the need for controlled efficacy studies and situations (if any) when PK and safety studies could be acceptable to support the indication for treatment of influenza in the paediatric population.

4. Recommendation

The Infectious Diseases Working Party recommends drafting a guideline on the evaluation of medicinal products indicated for treatment of influenza to provide guidance on the clinical development taking into account the issues identified above.

5. Proposed timetable

Proposed date for release of draft guideline Q1 2018.

6. Resource requirements for preparation

The resources needed for this guideline relate to IDWP members who will develop the draft guideline and proceed to develop a final version after the consultation period. It may be considered appropriate at a later stage (e.g. during or immediately following the consultation period) to convene a workshop to facilitate finalisation of the guideline.

7. Impact assessment (anticipated)

The most important impact is expected to be on:

- clinical development programmes to support applications for medicinal products indicated for treatment of influenza,
- the content of CHMP scientific advice.

8. Interested parties

Pharmaceutical industry e.g. European Federation of Pharmaceutical Industries and Associations (EFPIA)

Academic networks and learned societies within the EU

Healthcare professionals

Patient organisations

9. References to literature, guidelines, etc.

1. WHO Guidelines for Pharmacological Management of Pandemic Influenza A (H1N1) 2009 and other Influenza Viruses 2010 (http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf?ua=1)
2. Insight 006 study (https://clinicaltrials.gov/ct2/show/NCT02287467)