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Committee for Human Medicinal Products (CHMP)

Concept paper on preparation of a guideline on the evaluation of medicinal products indicated for the treatment and prophylaxis of respiratory syncytial virus (RSV) infection

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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 and prophylaxis of respiratory syncytial virus (RSV) infections for which there is no regulatory guidance currently available in the EU.

Respiratory syncytial virus infects all age groups. In healthy adults, adolescents and children from the age of approximately 2 years of age it generally causes mild upper respiratory tract infection (URTI) that does not require hospitalisation or specific treatment. Elderly subjects with or without comorbid conditions such as congestive heart failure, emphysema or asthma appear to be more susceptible.

In infants (especially in the first 6 months of life) and toddlers (< 24 months of age), RSV may cause severe lower respiratory tract infection (LRTI), resulting in bronchiolitis, bronchitis and pneumonia, which often require hospitalisation and which may be life-threatening. The burden of RSV disease in healthy infants and toddlers is large and it is associated with considerable acute and long-term morbidity. Those at the highest risk for severe RSV disease include infants who were born prematurely (≤ 35 weeks gestational age) and those with a wide range of underlying conditions (e.g. bronchopulmonary dysplasia and haemodynamically significant congenital heart disease). In this and other age groups underlying conditions that may predispose to severe RSV disease include neuromuscular diseases, Down's syndrome, cystic fibrosis and immunosuppression.

Currently in the EU there is one product approved for prophylaxis. Palivizumab is a humanised monoclonal antibody directed against RSV indicated for use in specific high-risk groups of children during the RSV season. Inhaled ribavirin is still approved in some EU member states for treatment of RSV bronchiolitis via inhalation but it is hardly used. Currently there are several new antiviral agents in development for treatment of RSV as well as new monoclonal antibodies and vaccines in development for prevention. Some vaccines are directed at specific age and risk groups but others are under development for previously healthy subjects across a wide range of age groups. In addition, some vaccines are under development for use during pregnancy with the aim of preventing severe RSV disease in the first few months of life. 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. There are many issues for clinical trial design and clinical develop programmes that overlap between products intended for prevention and those proposed for treatment. Therefore a single guidance document is proposed to address agents intended for treatment and/or prophylaxis.

2. Problem statement

There is no CHMP guidance available for agents intended to treat or prevent RSV disease. In recent requests for scientific advice on the development of new agents intended for the treatment and/or prophylaxis of RSV several issues have often emerged as being central to development programmes.

There are particular problems associated with the definition of cases of RSV disease suitable for studies of new therapies and cases of RSV disease in studies of new preventive measures. It is clear that there is a need to develop guidance on a range of possible case definitions tailored to the severity of disease proposed to be treated or prevented, including clinical and laboratory confirmation elements. In attempting to assess severity there is a need to avoid criteria that may be influenced more by the healthcare system rather than the presenting clinical syndrome, such as decisions on hospitalisation.

Other issues for preventive therapies include the timing of administration in relation to the RSV season, if the trial is conducted in a region where disease is highly seasonal, and the duration of

follow-up along with the mode of case ascertainment, which may need to encompass a range of healthcare facilities to ensure that cases of all severities are captured.

Specifically for vaccines intended for active immunisation of infants and young children who are expected to be RSV-naïve there is a potential concern for vaccine-associated disease enhancement following on from the past experience with a formalin-inactivated vaccine. Newer vaccines have been developed that are believed to not carry this risk but there is a need to provide guidance on the assessment of risk and the appropriate duration of follow-up.

In treatment studies issues that have arisen include time from diagnosis to initiation of treatment and primary endpoints depending on the age range and disease severity (e.g. ranging from patients managed at home to patients with hypoxaemia needing assisted ventilation). Again, there is a need to try to avoid endpoints that may be influenced by the healthcare system, such as duration of hospitalisation.

Some particular issues have arisen for studies that involve vaccination of pregnant women to prevent RSV disease in their infants, including assessment of the duration of post-natal protection that can be expected and the timing of possible active vaccination of the infant using a different vaccine to that used for the mother.

3. Discussion (on the problem statement)

Several problems arise at an operational level when designing clinical studies intended to support the approval of medicinal products for the prophylaxis or treatment of RSV infection/disease. Due to a resurgence of activity in the development of products intended to treat and/or prevent RSV disease and recognition of recurring issues that have arisen in scientific advice, there is a need to develop CHMP guidance. Due to several overlapping issues, it seems appropriate to develop a single guideline to cover products intended for treatment and prevention.

4. Recommendation

The Infectious Disease Working Party and the Vaccine Working Party recommend drafting a guideline on the evaluation of medicinal products indicated for the treatment and prophylaxis of RSV infection to provide guidance on the overall clinical development programme with a particular focus on the following issues:

- Case definitions based on a combination of clinical and laboratory criteria are needed for treatment or prevention studies. Guidance is needed on definitions, graded by severity, that might be used to determine study eligibility in treatment studies and characterise failures of preventive therapy in prophylaxis studies, including assessment of any amelioration of disease.
- The principles for laboratory data to determine patient eligibility in treatment studies and to confirm the presence of RSV in treatment and prevention studies need to be addressed along with guidance on the extent to which it is expected that the presence of co-infecting pathogens (e.g. human metapneumovirus) should be assessed. Guidance is also needed on the assessment of the effect of treatment or prevention on the duration of viral replication (i.e. it is possible that RSV replication is not prevented but is ameliorated in some subjects).
- In treatment and prevention studies there is a need to address expectations for duration of follow-up depending on where the studies are conducted and the seasonality of RSV disease.

- The design of studies in which pregnant women are vaccinated to prevent RSV disease in their infants needs to be addressed, including issues such as timing of vaccination in relation to delivery and follow-up of infants to assess duration of protection as well as maternal antibody decay and, if appropriate, effects on the infant immune response to subsequent active immunisation.
- In studies of vaccines administered to infants and young children who are likely to be RSV-naïve there is a need to consider the evidence to be collected to assess whether the vaccine could elicit disease enhancement.
- Looking forward, there is a need to consider the most appropriate comparators in treatment and prevention studies. Currently, with the exception of studies that enrol subjects who would routinely receive palivizumab, it should be possible to have control groups that do not receive active treatment or an active preventive measure for RSV. However, in a few years' time that situation may have changed and therefore consideration needs to be given to the impact on study designs.

5. Proposed timetable

Concept Paper to be released for consultation Q4 2016

First draft of the Guideline to be released for consultation by Q3 2017

6. Resource requirements for preparation

The resources needed for this addendum relate to Vaccine Working Party (VWP) and Infectious Disease Working Party (IDWP) members who will develop the draft addendum and proceed to develop a final version after the consultation period. The PDCO will be consulted during the development of the draft and final guidance.

7. Impact assessment (anticipated)

The most important impact is expected to be on:

- The content of CHMP scientific advice.
- The content of paediatric investigational plan of medicinal products intended for the treatment or prophylaxis of RSV

8. Interested parties

Healthcare professionals, pharmaceutical industry, patient organisations, European learned societies involved in RSV research, education and care.

9. References to literature, guidelines, etc.

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