21 April 2017
EMA/219845/2017

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Synagis

International non-proprietary name: Palivizumab

Procedure no.: EMEA/H/C/000257/P46/049

Marketing authorisation holder (MAH): AbbVie Ltd.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

In January 2017, the MAH submitted the completed post-marketing observational paediatric study P10-410 (PMOS GERM 06-01) entitled "Prospective, non-interventional observation study for the use of palivizumab in high-risk children in Germany" in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has been provided.

The MAH states, that the safety and effectiveness of this study is consistent with the previously established benefit risk profile of Synagis and does not recommend any changes to the SmPC.

Scientific discussion

1.1. Information on the development program

The MAH stated that:

P10-410 (PMOS GERM 06-01) entitled "Prospective, non-interventional observation study for the use of palivizumab in high-risk children in Germany", is a stand-alone study and does not form part of a development programme.

1.2. Information on the pharmaceutical formulation used in the study.

Palivizumab is a humanized monoclonal antibody (IgG1κ) specific for the fusion protein (F-protein) of RSV that has potent neutralizing and fusion-inhibitory activity against a broad range of RSV isolates. Based on clinical studies in preterm infants and children with bronchopulmonary dysplasia the product was licensed in the US in 1998 and in the EU in 1999. Further studies were subsequently conducted in different patient groups. The pharmaceutical formulation used in the study was the lyophilized formulation of palivizumab.

1.3. Clinical aspects

1.3.1. Introduction

Synagis is approved for the prevention of serious lower-respiratory-tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease:

- Children born at 35 weeks of gestation or less and less than six months of age at the onset of the RSV season;
- Children less than two years of age and requiring treatment for bronchopulmonary dysplasia (BPD) within the last six months;
- Children less than two years of age and with haemodynamically significant congenital heart disease (CHD).

1.3.2. Description

Methods

Objective

Post-marketing observational study (PMOS) to describe comprehensive real-world data on the use of palivizumab in high-risk subjects in Germany, to collect data on palivizumab administration, frequency of hospitalisations , drug adherence, and risk factors for RSV disease.

Study design

Observational, non-randomized, longitudinal, single-arm, multi-center, cohort study to assess the safety and effectiveness of palivizumab immunoprophylaxis in children from 2002 – 2016 in preterm infants or infants born with hs-CHD.

Primary care pediatricians from outpatient facilities and neonatologists from inpatient facilities in Germany contributed data to the registry.

The key recorded study variables were: Demographic data, geographic location, risk factors for RSV disease, diagnoses and RSV testing, RSV hospitalization (admission dates, length of stay, ICU admission, supplemental oxygen required, and mechanical ventilation), palivizumab administrations (dates, weight of infant and dose), adverse reactions, and parents' compliance to RSV use.

Inclusion Criteria

The inclusion criteria were as stated in the palivizumab EU Summary of Product Characteristics:

- Subjects born at 35 weeks of gestation or less and less than 6 months of age at the onset of the RSV season.
- Subjects less than 2 years of age and requiring treatment for bronchopulmonary dysplasia (BPD resp. chronic lung disease (CLD)) within the last 6 months.
- Subjects less than 2 years of age and with hemodynamically significant congenital heart disease (hsCHD).

Exclusion Criteria

The exclusion criteria were as stated in the palivizumab EU Summary of Product characteristics:

- Subjects with known hypersensitivity to palivizumab or any component of the formulation, or other humanized monoclonal antibodies.

Characteristics (SmPC): Study population:

A total of 142,723 injections were documented in 29,468 evaluable subjects during the study period, 2002-2016. Results of the study were subdivided into three parts due to procedural changes including changes in the methods of study data reporting:

i) Seasons 2002/03 – 2006/07

i) Seasons 2007/08 and 2008/09,

ii) Seasons 2009/10 – 2015/16.

Statistical Methods:

As this was a descriptive study, summary statistics are provided.

Results

Mean age of subjects upon start of immunoprophylaxis with palivizumab was between 4.3 and 5.9 months; overall 54% of infants were males, 46% female. Median number of palivizumab immunoprophylaxis injections for all study seasons was 5 (range: 1 – 12). The proportion of subjects that received more than 5 palivizumab injections during the corresponding RSV season ranged from 35% to 45%.

Most evaluable subjects were premature (median gestational age, 29-32 weeks). A significant proportion of subjects across the three study periods (19% – 43%) had BPD. Across the three study periods, between 25% and 35% of infants were diagnosed with CHD. A significant proportion of subjects across the three study groups were diagnosed with CLD (19% – 43%).

In 2004 the German regulatory agency added hs-CHD to the list of approved indications for palivizumab. Starting in 2008/09, the investigators could indicate whether hs-CHD was the main reason for prophylaxis; this was documented in 13% – 14.1% of patients.

The average number of RSV-related hospitalizations in infants with CHD diagnosis was 0.8% (n = 26). The RSV-related hospitalization rates over the three study periods were 0.7% – 1.6%. These rates are within the expected margins derived from prospective randomized trials.

Safety results

Overall, 839 adverse events (AEs) were reported. The most frequent serious adverse events (≥ 5% of subjects) were: bronchitis (12%), hospitalization (11%), pneumonia (11%), respiratory syncytial virus bronchiolitis (8%) and pneumonia respiratory syncytial viral infection (5%).

Of note, a hospitalization was by definition considered a serious criterion, and not an event term. Thus, the term "hospitalization" was only coded if no other event term was documented in the reporting form, or if the event was assessed as "non-serious" or as "no case." The majority of AEs were categorized as serious (95.8% of all reported events), which may be due to a potential underreporting of non-serious events.

1.3.3. Discussion on clinical aspects

No new efficacy or safety concerns are identified. The effectiveness and safety observed in this large observational study is in agreement with the registration trials and with other observational studies.

1.4. Rapporteur's overall conclusion and recommendation

The submitted post-marketing paediatric study P10-410 in accordance with article 46 of the Paediatric Regulation, is in agreement with the currently approved SMPC and no further regulatory action is deemed necessary.

☒ Fulfilled:

No regulatory action required.