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EMA/107943/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Synagis

palivizumab

Procedure no: EMEA/H/C/000257/P46/047

Note

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

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1. Introduction

On 17 November 2016, the MAH submitted a final study report for the post-marketing observational paediatric studies P10-128 and P11-060, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. These two Polish studies were similar, but conducted during 2008-2009 and 2010, respectively.

A short critical expert overview has also been provided.

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

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted:

Studies P10-128 and P11-060, both entittled**:** "Multicentre, Retrospective, Non-interventional Study to Evaluate the Incidence of Respiratory Infections in Children with BPD Receiving Prophylaxis with Synagis.

The MAH confirms that these studies are stand-alone and does not form part of a development programme.

2.2. 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 premature infants and children with chronic lung disease 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 currently approved indications are:

SYNAGIS is indicated 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 6 months of age at the onset of the RSV season.
• Children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months.
• Children less than 2 years of age and with haemodynamically significant congenital heart disease."

The pharmaceutical formulations used in these studies were:

In the EU palivizumab in a lyophilized formulation of and a liquid solution for injection are approved in the EU. Lyophilized palivizumab (maximum of 5 doses) was administered as recommended by the manufacturer and product label with an interval of 30 days between subsequent doses.

2.3. Clinical aspects

2.3.1. Introduction

Synagis (Pavalizumab) received marketing authorization through the centralised procedure in 1999. Synagis was 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).

The MAH submitted a final report for:

Studies P11-060 and P10-128: Multicentre, Retrospective, Non-interventional Study to Evaluate the Incidence of Respiratory Infections in Children with BPD Receiving Prophylaxis with Synagis.

Description

Methods

Study P11-060: In Poland, a program for the prophylaxis of RSV disease in prematurely born infants diagnosed with bronchopulmonary dysplasia by was conducted from December 2008 to April 2009.The study was supervised by the Neonatology Country Consultant in 25 medical centers selected by District Consultants.

Study P10-128: A similar subsequent program of RSV prophylaxis with palivizumab in preterm infants with BPD) was initiated in Poland from January 2010 to April 2010.

Evaluation of the prophylaxis program was conducted as an open label, retrospective, non-interventional study by AbbVie.

Objective

The objectives of studies P11-060 and P10-128 were to evaluate the
- Patient characteristics and palivizumab administration in the prophylaxis program
- Number of respiratory tract infections
- Number of hospitalizations caused by respiratory infections
- Tolerability/safety of palivizumab and the number of deaths caused by respiratory infections

Inclusion Criteria

Study P11-060
Children with bronchopulmonary dysplasia (BPD)
- Born in 2008 at no more than 30 weeks post-conception
- Born in 2007 at no more than 26 weeks post-conception
- Infants with severe course of BPD requiring ongoing administration of Bronchodilators

Study P10-128
Children with BPD defined as the need for oxygen supplementation (with oxygen concentration exceeding 21 percent) at 28 days of life meeting one of the following criteria:
- Children at gestational age of < 30 weeks, who were younger than 3 months of age at the beginning of RSV infection season (children born after 08 January 2009)

● Children at gestational age of < 28 weeks, who were younger than 6 months of age at the beginning of RSV infection season (children born after 05 January 2009).

Exclusion Criteria
Children with hypersensitivity to the active substance (palivizumab) or any of the excipients of the preparation. Contraindication for passive immunization

Outcomes / endpoints:

-demographic data

-palivizumab doses and dates of administration

-all episodes of infections and hospitalizations (no later than 35 days following last palivizumab administration)

-incidence and type of adverse reactions occurring within 48 hours of palivizumab administration

-number of deaths and identified causes

Statistical Methods:

The usual descriptive statistics.

Results

Recruitment / Number analysed

Study P11-060

In total, over 2001 palivizumab doses were administered. Children were given from 1 to 5 palivizumab doses (mean 3.6 ± 1). Mean interval between subsequent palivizumab doses ranged from 29 to 32 days.

Study P10-128

In total, 1240 palivizumab doses were administered. Children received from 1 to 5 palivizumab doses. Mean interval between subsequent palivizumab doses ranged from 30 to 38 days.

Baseline data

Study P11-060
Palivizumab was administered to 557 children [female: 302 (54%), male: 255 (46%)]. The number of enrolled patients in specific centers ranged from 3 to 68 (mean: 22 ± 17). The age range of enrolled children was 4 weeks to 2 years, with mean age of 39 ± 21 weeks. Mean age of infants receiving prophylaxis varied for specific centers.
Patient gestational age ranged from 22 to 34 weeks (median 26), and birth weight from 450 to 2730 grams (median 900).

Study P10-128
Palivizumab was administered to 464 children [female: 214 (46%), male: 250 (54%)]. The number of enrolled pediatric patients in specific centers ranged from 2 to 44 (mean ± SD 17.8 ± 12.6). Distribution of patient sex remained relatively uniform throughout all centers. The age range of enrolled children was 3 to 45 weeks, with a mean age of 23 ± 10 weeks. Mean age of infants receiving prophylaxis varied for specific centers. Patient gestational age ranged from 22 to 29 weeks (median 27), and birth weight from 400 to 1880 grams (median 900).

Effectiveness results

Study P11-060

Four hundred thirty-six (436) episodes of respiratory infection were reported. The proportion of patients experiencing at least one episode of respiratory tract infection decreased from 23% after dose 1 to 7.5% following the fifth dose of palivizumab (Fisher's exact test: $p = 0.001$). There was a statistically significant decrease in the mean number of respiratory infection episodes per infant decreasing from 0.24 ± 0.46 after the first dose to 0.08 ± 0.27 after dose 5 (Kruskal-Wallis analysis, $p < 0.001$).

Decrease in the percentage of patients experiencing at least one episode of respiratory infection was mainly due to systematic, statistically significant decrease in the number of infection episodes affecting the lower airways (a total of lower respiratory tract infections and mixed infections). After the first dose of palivizumab, episodes of lower airway infection were 46% of all infections; after dose 5 no episodes were reported (Fisher's exact test, $p < 0.001$).

A total of 183 hospitalization episodes were reported, including 91 (49.7%) caused by respiratory diseases. The percentage of all hospitalized patients decreased from 10.2% from dose 1 to 2.2% after the fifth dose (Fisher's exact test, $p < 0.01$).

Mean number of respiratory-related hospitalizations per infant decreased from 0.05 ± 0.23 after the first dose to 0 following the fifth dose of palivizumab (Kruskal-Wallis analysis, $p < 0.01$). Additionally, there was a statistically significant decrease in the duration of hospitalization episodes from 15 ± 12 days after dose 1 to 6 ± 2 days after dose 4 (Kruskal-Wallis analysis, $p = 0.01$).

Study P10-128

Two hundred and two (202) episodes of respiratory infection were reported.

The proportion of patients experiencing at least one episode of respiratory tract infection was approximately the same between doses 1 and 4. No episodes were reported after 5 doses from 6 patients. Mean number of respiratory infection episodes per child following immunoprophylaxis doses remained stable. Mean number of lower respiratory infections significantly decreased from 0.07 ± 0.25 after dose 1 to 0.03 ± 0.16 after dose 3 and 0.02 ± 0.13 after dose 4.

A total of 124 hospitalization episodes in 114 patients (25%, 114/464) were reported. Mean number of all hospitalizations in the period of 35 days postdose decreased from 0.12 ± 0.1 after dose 1 to 0.05 ± 0.05 after dose 4, but the difference was not statistically significant. Causes were not specified for 5 hospitalizations. Of the remaining 119 hospitalizations, 53 (44%, 53/119) were due to respiratory disease.

Change in the duration of respiration-related hospitalization was not statistically significant.

For respiratory-related hospitalizations, there was no reported change in the incidence of corticosteroid use, bronchodilator administration or assisted respiration following palivizumab doses 1 – 4.

Safety results

Study P11-060

Incidence of adverse reactions following palivizumab administration ranged from 1.2 to 4.8%. Adverse reactions were first reported following the administration of 72 (3.6%) out of the total 2001 doses given. Five children participating in the program died (male-3, female-2). They were of 25 – 30 weeks gestational age, and birth weight of 700 – 1140 g. The children received from 2 to 5 doses of palivizumab. Deaths occurred at the age of 4 – 11 months and during the period from 17 to 52 days after palivizumab administration, and none of the deaths were related to palivizumab. No cases of RSV infection were identified as the cause of death.

Study P10-128

Incidence of adverse reactions following the administration of a palivizumab dose ranged from 0 to 5.2% (incidence per dose number, 1st through 5th). In total, 36 adverse reactions (2.9%, 36/1240 total number of doses) were reported in 31 children after administration of 32 palivizumab doses (2.6%, 32/1240). Nervousness was the most frequently reported reaction (1.1%, 14/1240) followed by fever (6.5%, 8/1240). There was no report of injection site reaction.
Two children participating in the program died (male 1, female 1). Both were infants born at 24 weeks of gestational age, with birth weight of 600 – 700 g. The children received from 1 to 2 palivizumab doses. Deaths occurred at the age of 6 – 8 months, on the 6th and 11th day after palivizumab, respectively. No cases of RSV infection were identified as the cause of death.

2.3.2. Discussion on clinical aspects

In these post-marketing observational studies no new safety or efficacy concerns were identified

3. Rapporteur's overall conclusion and recommendation

The findings from the submitted Polish observational studies seems overall consistent with the established efficacy and safety of palivizumab.

The results submitted in accordance with article 46 of the Pediatric Regulation are in agreement with the currently approved SMPC and no further regulatory action is deemed necessary.

4.

☒ **Fulfilled:**

No regulatory action required.