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EMA/107944/2017
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/P46/048

## 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 the completed post-marketing paediatric study P10-129, “A One-Year Observational Study of Palivizumab in Infants at Risk for Respiratory Syncytial Virus Infection in Latin America” 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:

**P10-129,** “A One-Year Observational Study of Palivizumab in Infants at Risk for Respiratory Syncytial Virus Infection in Latin America”, 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 children with chronic lung disease the product was licensed in the US in 1998 and in the EU in 1999. Further studies was 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 formulationused in the study was the lyophilized formulation of palivizumab (50 mg and 100 mg).

## *1.3. Clinical aspects*

### 1.3.1. 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).

## Description

## Methods

### *Objective*

To describe patterns of palivizumab usage in high risk-infants in Latin America; to estimate the RSV hospitalization rate during a follow-up period of 1 year after the first dose and to determine the compliance to prescribed usage of palivizumab.

### *Study design*

Non interventional, prospective, and multi-center study conducted in 24 sites across 7 Latin American countries: Argentina, Uruguay, Chile, Mexico, Colombia, Peru, Ecuador.

**Inclusion Criteria**.
Children with a history of bronchopulmonary dysplasia (BPD), infants with a history of prematurity (less than or equal to 35 weeks gestational age), or children with hemodynamically significant congenital heart disease (hsCHD) who received the first dose of palivizumab within 2 weeks prior to the signature of the Informed Consent Form

Written informed consent provided by the child's father, mother or legal Guardian

**Exclusion Criteria**

“Children who did not fulfill the indication for palivizumab per local guidelines.”

### *Study population:*

Four hundred sixty-four (464) subjects were enrolled from February 19, 2011 through September 06, 2012. Six (6) of 464 subjects were excluded due to prior palivizumab administration from prior season, invalid consent, or no follow-up visits were recorded. A total of 458 subjects completed at least one visit. Three hundred and ninety-seven (397) subjects completed 1 year follow-up. Sixty one (61) discontinuations were recorded, most of them corresponding to lost to follow-up (n = 43).

### *Treatments*

### *Outcomes/endpoints:*

Primary endpoint: The proportion of infants among the study population who were hospitalized for LRTI with a positive laboratory diagnostic test for RSV from respiratory secretions or who died due to RSV infection confirmed by autopsy or clinical history and virologic evidence.

Safety: Spontaneously reported non-serious Adverse Events (AEs) and serious AE through the study period.

### *Statistical Methods:*

As this was a descriptive study, summary statistics are provided. The Safety Analysis Set (SAS) included all patients who signed patient authorization form to participate in the study and had any collected data.

## Results

***Recruitment and Baseline data***

Fifty-two percent (52%) of the patients were male and 69% of the patients were Hispanic.
The mean birth weight was 1345 g (SD: 460), and the median gestational age was 31 weeks (range: 23 – 29 weeks). Almost all of the patients in the study were premature (98.2%); 29.2% of patients had BPD, and 10.1% had hsCHD. Prematurity with BPD and/or hsCHD were seen in 33.4%. A total number of 1744 palivizumab doses were administered to 458 subjects. The mean number of doses administered was 3.8 (SD: 1.26) doses per subject. Of the total number of subjects studied, 200 subjects received 5 doses, 66 received 4 doses, 130 received3 doses, 28 received 2 doses and 34 received a single dose.

***Effectiveness results***

Patients received 84% of their expected doses, and 78% (979/1249) of the inter-dose intervals were classified as adherent
A hundred and nineteen (119) hospitalizations were recorded in 90 subjects. Sixty one (61) hospitalizations were reported due to lower respiratory tract infection (LRI) in 52 subjects. Of these, 44 had a single episode during the follow-up year, while 7 children had two and 1 child had 3 admissions. In 12 of 61 LRI hospitalizations, RSV was confirmed as the causative agent. Five (5) of the RSV hospitalizations occurred in 147 subjects enrolled in Colombia where low compliance was reported due to delay inaccess to palivizumab prophylaxis.

***Safety results***

A total of 1165 adverse events were reported. One hundred and thirty-five (135) adverse events reported in 102 subjects (22.3%) were described as serious. Of the serious adverse events reported, the most common event (≥ 5% of patients) was bronchiolitis (n = 28, 6.1%). Ninety-two (92) of the 135 serious adverse events (68.1%) resulted in or prolonged a hospital stay, 29 (21.4%) were classified by the investigator as clinically relevant, and 11 (8.1%) were life-threatening. None of these serious adverse events were related to palivizumab administration as assessed by the investigator. Three deaths (2.2%) were reported during follow-up. The fatal events were cardiopulmonary arrest, sepsis, and hemodynamic failure, respectively, and none of them were considered to be related to prophylaxis with palivizumab or to RSV infection.

## 1.3.2. Discussion on clinical aspects

The submitted “observational” study is poor. It is impossible from these extremely heterogeneous and limited data in different Latin America countries with different access to Synagis to conclude anything meaningful. Many patients were lost to follow up. There was a high rate of missing data. RSV testing was not done systematically.

However, even with these serious limitations, no new efficacy or safety concerns are identified.

## Rapporteur’s overall conclusion and recommendation

The submitted post-marketing paediatric study P10-129 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.

## ☒ Fulfilled:

No regulatory action required.