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Committee for Medicinal Products for Human Use (CHMP)

Synagis

(Palivizumab)

Procedure No. EMEA/H/C/000257/A45/030

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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Rapporteur

Assessment Report
Paediatric data

Synagis
(palivizumab)

Marketing Autorisation Holder:

Abbott Laboratories Ltd.

Rapporteur:	Steffen Thirstrup (DK)
Paediatric assessment Procedure start date:	19th October 2008
Deadline for Rapporteur's report:	25th November 2008
Deadline for members states comments:	4th February 2009
Date of this report:	2nd February 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Synagis
INN (or common name) of the active substance(s):	Palivizumab
Applicant:	Abbott Laboratories Ltd.
Indication(s)	Synagis is indicated for the prevention of serious lower respiratory tract disease requiring hospitalization caused by respiratory syncytial virus (RSV) in children at 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 that 2 years of age and with haemodynamically significant congenital heart disease.
Pharmaco-therapeutic group (ATC Code):	J 06 BB 16
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for injection, 50 mg and 100 mg

I. SCIENTIFIC DISCUSSION

I.1 Clinical aspects

The MAH has according to article 45 in the Paediatric Regulation 1901/2006 submitted 2 studies: Study BELG-99-011 and Study FRAN-05-003.

Clinical efficacy and safety

Study BELG-99-011:
A poster entitled "Results of an Expanded Access Program with Synagis during the Winter Seasons 1998/1999, 1999/2000 and 2000/2001 in Belgium and Luxembourg." is the only available information on this study:

The study design was a Phase III / IV, multi-center, single-arm, open-label program to collect additional (to the IMpact-RSV Study) efficacy and safety data of palivizumab in Belgium and Luxemburg (where palivizumab at that time was not readily available) for children with a history of prematurity with or without BPD: Children <35 weeks gestational age or less at birth AND <6 months of age at time of enrolment OR children with BPD who are <24 months of age at enrollment (age is based on actual age, not corrected age) AND requiring medical intervention/management (i.e., oxygen, steroids, diuretics, bronchodilators) within the previous six months.

Informed consent was obtained from the child's parent or legal guardian.

Participants received up to 5 monthly injections of 15 mg/kg palivizumab.

For patients hospitalized for respiratory illness, source documentation was followed up to assess pathogen identification.

The children were followed for Adverse Events for a maximum of 150 days (concluding 30 days after the last injection). Serious Adverse Events (SAE's) were reported to the Abbott International Pharmacovigilance Department.

Data presented in the poster were analyzed from this safety database.

A total of 166 children were enrolled at 11 centers in Belgium and Luxemburg.

The total number of serious adverse events reported was 39. Three adverse events were considered to be medically important. One of these was a dermographism suspected to be possibly related to palivizumab therapy. One death, due to underlying BPD with superinfection (Streptococcus and H. influenzae) and thus not related to palivizumab therapy, was reported. Six SAE's were reported being hospitalizations for surgery not related to palivizumab therapy. Furthermore 28 patients (16.8%) were hospitalized (30 hospitalizations) during the three seasons. None were considered related to palivizumab. 27 were hospitalizations associated with respiratory illness. Of the 27 patients hospitalized for respiratory illness, 4 (2.4% of the treated population) were RSV positive but they didn't spend any time in intensive care or didn't require mechanical ventilation. Of the 27 respiratory hospitalizations, 18 hospitalizations were RSV negative, 4 were diagnosed for other pathogens or pathology, and there was no need for RSV testing, and one was not tested for RSV or was not diagnosed for other pathogens. Eight patients (4.8%) were diagnosed with RSV but did not require hospitalization.

Assessor's comments:
The MAH has not provided any information regarding presentation of this poster: Has the poster been presented? Was it presented at a peer reviewed conference/meeting? When was it presented? Has the study been published?
A protocol for the study and/or a more detailed study report should be available?
The observation that four or 2.4% of the treated population were hospitalized and RSV positive is comparable to the results of the IMpact study in which 4.8% of 1002 palivizumab treated high-risk children were hospitalized due to RSV. Also the safety profiles of palivizumab were comparable between the IMpact study and this expanded access program. However, the population size was small.

Main study

FRAN-05-003: An observational cohort study of children treated by Synagis in France (season 2005-2006)

Objectives:
The objectives of the study, which was requested by the French Health Authorities, were to describe

- The current use of Synagis by French paediatricians and the profiles of children benefiting from the prophylaxis;
- The safety of the drug;
- The morbidity and mortality observed over a one-year follow-up period starting after the first injection in children treated by Synagis

Methods
A partly prospective and partly retrospective cohort was set up for the season 2005-2006 with a one-year follow-up starting at the first injection of Synagis on a national representative sample of children.

The current utilisation of Synagis was described by the following items:

- The profiles of the children treated with Synagis (medical history, clinical profile, sociodemographic characteristics of children and family);
- The characteristics of the injections of Synagis (number, dates and doses);
- The status of the centres where the prophylaxis was prescribed;
- The utilisation of medical services: general or hospital based practitioners, oxygen treatment, respiratory physiotherapy;
- The side effects having occurred during the follow-up period;

The evaluation of morbidity and mortality was based on an analysis of all relevant clinical events, attributable or not to the RSV infection, during the one-year follow-up period:

- Death;
- Hospitalization;
- Other use of medical services;
- Causes and circumstances of those events.

Study population
The following centres were eligible to participate in the study:

- the whole set of the French tertiary level care centres which are highly specialized paediatric hospital centre" (so-called "level 3");
- all secondary level care centres, which are specialized paediatric hospital centres" (so-called "level 2" in France) having prescribed Synagis to at least 15 children during the preceding season (2003-2004);
- all cardio and pneumo-pediatry hospital centres.

The participation in the study was proposed to all eligible centres through mail and telephone contacts. If they agreed to participate, a physician was designated in each centre to play the role of Local Coordinator (LC) for the study during the whole period of the data collection.

Inclusion criteria
All children for whom Synagis had been initiated during the season 2005-2006 in the participating centres were eligible to participate.

Exclusion criteria
The study was proposed to the parents after the first Synagis injection.

A written agreement signed by at least one legal representative of the child was requested by the French regulatory system to participate in the study. Children whose parents refused to sign this document for any reasons were then excluded.

Results & Discussion

The study was proposed to 135 centres; 64 (47.4%) participated. The participation rates were higher among highly specialized neonatalogy centres (level 3) (37/65=56.9 %) compared to specialized neonatalogy centres (level 2) (23/60=38.3%) and to cardio/pneumo-pediatry centres (4/10=40%).

This reflects the prescription situation in France where Synagis is mainly initiated in highly specialized neonatalogy centres. Differences in levels of participation between regions and between the various types of centres are moderate which reflects the representation of the participating centres across the country. The regions with a high birth rate are also those with a high level of participation.

According to the type of study, the parents refusal rate of participation seems relatively moderate and thus data was collected on an important proportion in which Synagis was delivered in France during the 2005-2006 season: 1614 children in the 64 centres were eligible for the study, 1420 (88%) were included.

In this observational study 1,420 children were included, which represents 22% of the estimated number of children who received Synagis in France during the season 2005-2006 (around 6,500 according to sales estimation). The majority of the children were included in neonatology centres (1394) and 26 children came from centres of cardio or pneumo-paediatrics.

The average duration of follow-up of the children in the study was of 10.9 months and only 2 children were lost to follow-up.

Unsurprisingly the baseline characteristics of the children from neonatology centres are statistically different from those of cardio or pneumo-paediatrics centres: Premature babies who represent the majority (only 134 children had a GA > 37weeks) of the cohort came mainly from neonatology centres.

- The mean age of the children at the time of their first injection was 5 months in neonatology and 8.6 months in cardio or pneumo-paediatrics.
- The mean gestational age was of 30.1 weeks in neonatology and of 37 weeks in cardio or pneumo-paediatrics.

These results reflect the differences in the 2 populations in which Synagis is approved: premature babies on one hand, children with hemodynamically significant congenital heart disease on the other hand.

Synagis was generally administered throughout the whole RSV season in the cohort population: Among the 1394 children from neonatology centres for whom the information was available a mean of 4.4 injections per child was performed. 621 (44.9%) of 1383 children from neonatalogy centres received 5 injections of Synagis, 183 (13.2%) received 6 injections and 24 children (1.7%) received 7.

Among the 1,341 children from neonatology centres for whom the information was available, 895 (66.7%) met the criteria that all intervals between Synagis injections were in the range 23-37 days. The remaining 446 children had at least one interval between 2 injections that was below 23 days or above 37 days.

Among the 26 children from cardio/pneumo-pediatry centres, a mean of 4.6 injections per child was administered. 14 (56%) of 25 children from cardio/pneumo-pediatry centres received 5 injections of Synagis, 2 (8%) received 6, and 1 child received 7. Twelve (48%) met the criteria that all intervals between Synagis® injections were in the range 23-37 days. The remaining 13 children had at least one interval between 2 injections that was below 23 days or above 37 days.

Children hospitalized over the period of follow-up of one year after the first injection of Synagis:

Among children from neonatology centres (n=1215):

- 367 (30.2%) were hospitalized at least once for an unplanned hospitalization,
- 221 (18.2%) were hospitalized for a LRTI,
- 38 (3.1%) were hospitalized for a RSV-LRTI

Considering the children from neonatology hospitalized over a period from the 7th day after the first injection to 30 days after the last injection which corresponds to the protection period of Synagis, only 29 children (2.4 %), were hospitalized for a RSV-LRTI.

Among children from cardio/pneumo-paediatric centres (n=25):

- 14 (56%) were hospitalized at least once for an unplanned hospitalization,
- 8 (32%) were hospitalized for a LRTI,
- 5 of the 25 children from cardio/pneumo-paediatric centres (20%) were hospitalized for a RSV-LRTI

Among the 25 children from cardio/pneumo-pediatry centres for whom a one-year follow-up was available, 20% (5) children were hospitalized for a RSV-LRTI infection that occurred between 7 days after the 1st injection until 30 days after the date of last injection.

The analysis of use of Synagis showed that it was used according to its approved indications in 84.3% (1,162) of the 1,378 children for whom the information was available:

● 426 (30.9%) of the children who received Synagis were less than 2 years of age with a GA <32 weeks **and** BDP. In this population, the number of children hospitalized with positive RSV during the one-year follow-up was 7 (3.6%) in those with less than 28 weeks of GA and 10 (5.7%) in the group of 28-32 GA.

This study demonstrated that children who received Synagis prophylaxis had rates of RSV hospitalization similar to the rates observed in children who receive Synagis in previous observational studies in France and in other countries:

- 3.9 % in the study IRIS *(Pedraz C et al. Paediatr Infect Dis J 2003;22:823-7)*
- In the study of the Perinatal Network of Burgundy the hospitalization rates were 11.8 % for the season 2000-2001 (first season of Synagis use in France) then 3.8 % for the season 2001-2002. *(Grimaldi et al. Paediatr Infect Dis J 2004;23:1081-5)*

Furthermore, in the present observational study, the hospitalization rates were lower than those observed in the untreated children groups from previous observational studies: 13.25 % in the IRIS study and 46.2 % in the Burgundy study.

● Of the children who received Synagis, 529 (38.4%) were young children (0 to 6 months) with a GA <32 weeks **without** BDP. In this population, the number of children hospitalized with positive RSV during the one-year follow-up was 10 (2.5%) in the group of 28-32 GA. No children with a GA < 28 weeks were hospitalized.
These results are in line with those of a sub-group (n=506) of children < 35 weeks of GA without DBP from IMpact clinical study *(Pediatrics 1998;102:531-7),* in which 9 children (1.8%) were hospitalized.

In the present observational study, children with severe malformations and various pulmonary diseases (detailed information provided in an appendix) represent 15.5% (n=213) of the cohort. In this population, 2.6% or 5 children were hospitalized for RSV-LRTI during the one-year follow-up.

The analysis of the predictive factors associated with a high risk of hospitalization for RSV infection in a cohort of children having received Synagis could help to identify those who, in addition to Synagis, must be followed and watched over very closely.

During the one year follow-up no new safety signal was observed. The number of deaths (6) reported during the one-year period of follow-up after the first injection of Synagis was low.

Assessor's comments:
Agree with the MAH concluding, that this observational study conducted in a large French cohort confirmed in real conditions that children receiving Synagis had a low RSV-LRTI hospitalization rate. The tolerance of Synagis was good during the follow-up period of one year after the last injection. These results confirmed those already seen in previous pivotal and observational studies.

II. OVERALL CONCLUSION

The MAH has according to article 45 in the Paediatric Regulation 1901/2006 submitted 2 studies: Study BELG-99-011 and Study FRAN-05-003.

Regarding Study BELG-99-011 the MAH has only submitted a poster – more detailed information may be available.

Regarding Study FRAN-05-003 the MAH has submitted a comprehensive Clinical Report. The study is observational which tantamount to no controls. However, the observations in the study are in agreement with the results shown in clinical studies with Synagis, especially the IMpact study, which was the pivotal study in the MAA.

The MAH has not, as suggested in the "Best Practice Guide Article 45 – Paediatric Regulation", submitted a short critical expert overview clarifying the context of the data.

Nor has the MAH submitted a SPC/PL proposal or justification that changes are not necessary. However; the observations done in the two submitted studies support the indication as stated in the approved SPC, they do not add anything new and since it cannot be ruled out that the results of the FRAN-05-003 Study is influenced by less than half of the centres proposed for the study participated, there is no need for a revision of the SPC.

III. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RAPPORTEUR

Other concerns

Clinical efficacy

Q 1. Regarding Study BELG-99-011 the MAH has only submitted a poster – more detailed information may be available and should be submitted.

Q 2. The MAH has not, as suggested in the "Best Practice Guide Article 45 – Paediatric Regulation", submitted a short critical expert overview clarifying the context of the data, the MAH should explain.

Q 3. According to "Best Practice Guide Article 45 – Paediatric Regulation", the MAH is expected to submitt a SPC/PL proposal or justification that changes are not necessary. The MAH should comment.

IV. ASSESSMENT OF MAH RESPONSES

The MAH has now submitted also to the Rapporteurs and CHMP members the above requested information including a short critical expert Overview on Clinical Efficacy and Safety and justification that changes to the SPC are not necessary. These data were previously only submitted to EMEA.

Conclusion:
All issues are now resolved.