SYNAGIS 50 mg, powder and solvent for solution for injection
Pack of 1 (CIP: 352 314-1)

SYNAGIS 100 mg, powder and solvent for solution for injection
Pack of 1 (CIP: 352 155-0)

Applicant: ABBOTT France

calivizumab

ATC code: J06BB16

List I

Date of first MA: 13/08/1999
Date of last clinical variation of MA: 25/07/2006

Inclusion on the list of medicines approved for use by hospitals and various public services

Reason for request: Examination of the pediatric cohort study of children treated by Synagis (study requested by the Transparency Committee in its opinion of 13 October 2004 and 8 November 2006).
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Palivizumab

1.2. Indications
Synagis is indicated for the prevention of serious lower respiratory tract infections caused by respiratory syncytial virus (RSV), requiring hospitalisation in children at high risk for RSV disease:
- Children born at 35 weeks of gestation or less and aged less than 6 months at the start of the seasonal RSV epidemic.
- 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 with haemodynamically significant congenital heart disease.

1.3. Dosage
The recommended dose of palivizumab is 15 mg/kg, given once a month during periods of RSV risk in the community. Where possible, the first dose should be administered prior to commencement of the RSV season. Subsequent doses should be administered monthly throughout the season.
The majority of experience including the pivotal phase III clinical trials with palivizumab has been gained with 5 injections during one season. Greater than 5 doses available data being limited, the benefit in terms of protection beyond 5 doses has not been established.
To reduce risk of rehospitalisation, it is recommended that hospitalised children with RSV receiving palivizumab continue to receive monthly doses of palivizumab for all the duration of the RSV season.
For children undergoing cardiac bypass, it is recommended that a 15 mg/kg of body weight injection of palivizumab be administered as soon as child is stable after surgery to ensure adequate palivizumab serum levels. Subsequent doses should be administered monthly through the remainder of the RSV season to children that continue to be at high risk of RSV infection.

2. REMINDER OF THE COMMITTEE’S OPINION AND LISTING CONDITIONS

Committee Opinion of 19 January 2000
The actual benefit is moderate
The improvement in actual benefit is slight (level III) in terms of efficacy.

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus in children at high risk of hospitalisation:
- Children aged less than 6 months at the start of the epidemic, born at 35 weeks of gestation or before, with a history of bronchopulmonary dysplasia
- Children aged less than 2 years, born at 35 weeks of gestation or before, with bronchopulmonary dysplasia and receiving long-term treatment at the start of the epidemic season.
Bronchopulmonary dysplasia is defined in a preterm infant by oxygen dependence at twenty-eight days after birth.

Committee Opinion of 13 October 2004

Synagis provides a level III improvement in actual benefit in children aged under two years affected by haemodynamically significant congenital heart disease as defined by the Paediatric Cardiology section of the French Cardiology Society.

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the population of children aged under two years affected by haemodynamically significant congenital heart disease as defined by the Paediatric Cardiology section of the French Cardiology Society.

3. SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2006)
J : General anti-infective for systemic use
J06 : Immune sera and immunoglobulins
J06B : Immunoglobulins
J06BB : Specific immunoglobulins
J06BB16 : palivizumab

3.2. Medicines with a similar therapeutic aim
There is no alternative medication.

4. UPDATING WITH DATA OBTAINED SINCE PREVIOUS OPINION (8 November 2006)

Background

In its opinion of 13/10/2004, the Committee requested the conduct of “A follow-up study of children treated by Synagis to investigate the patterns of use of Synagis, its safety and the risk of hospital admission for RSV infection”.

The company set up a longitudinal study in December 2005, with a one-year follow-up of a cohort of children treated by Synagis during the 2005-2006 epidemic season in hospital neonatology units. The applicant submitted the final report of this study on 26 July 2007.
Post-listing study (Cf. appendixes)

The protocol planned to include between 3,500 and 4,000 children (out of a total of 5,000 Synagis-treated children), recruited in 135 neonatology units and followed-up for one year after institution of Synagis treatment. In fine, 1,420 children were included by 64 centres (1,394 in neonatology units and 26 in paediatric cardiology-pneumology departments).

The mean age of children at the first injection of Synagis was 5 months (95 CI = [4.8; 5.3]). The children included in the study were more often boys (54.2%). The children had a mean birth weight of 1,428 grams (95 CI = [1,388; 1,468]), mean gestational age of 30.2 weeks (95 CI = [30; 30.4]) and were born of multiple births in 30.1% of cases. Finally, 39.2% of the children received oxygen beyond day 28.

Synagis was administered at a mean dose of 15 mg/kg and the mean number of injections was 4.5 (median 5) per child.

Information about the reasons and criteria for prescribing Synagis used to study the adequacy to the MA indications and the reimbursable indications was available for 1,378 children (97% of included children):
- 1,162 (84.3%) of the children received Synagis within the scope of the MA indications
- 589 (42.7%) of the children received Synagis within the scope of the reimbursed indications.

The mean duration of the study follow up was 10.9 months.
1,215 (87%) of the 1,394 children recruited in neonatology units were followed up for a full year (whatever their compliance with MA and/or reimbursable indications).
367 (30.2%) of these children had at least one non-elective hospital admission. This hospitalisation was due to:
- A non-RSV lower respiratory tract infection (LRTI) in 125 children (10.3% of children followed up)
- A RSV LRTI in 38 children (3.1%)
- A LRTI of non-investigated or unknown origin in 58 children (4.8%)
- An unknown reason or a reason other than a LRTI in 146 children (12%).

For the 26 children recruited in paediatric cardiology-pneumology departments, 25 were followed up for a full year and 14 were admitted non-electively to hospital at least once. This hospitalisation was due to:
- A non-RSV lower respiratory tract infection in 1 child
- A RSV lower respiratory tract infection (LRTI) in 5 children
- A LRTI of non-investigated cause in 2 children
- An unknown reason or a reason other than LRTI in 6 children.

Six deaths occurred during the follow-up period. According to the investigators, none of these deaths was related to Synagis.
In addition, 30 serious adverse events were reported by 4 investigator centres during the follow-up period like that were “probably” related to Synagis. One of these centres reported 24. These events were mainly adverse respiratory or ENT effects. The outcome of all these events was positive with improvement or recovery.
Conclusion:
The representativity of the centres and children included in the observational study was not guaranteed.
The following remarks may be made about the presented results:
- The MA indications were generally respected (84.3%)
- On the contrary, only 42.7% of children received Synagis within the scope of its reimbursed indications.
- The patterns of use of Synagis (dose, number of injections, timeframe between two injections) complied with the SPC.
- The child hospitalisation rate of 3.1% for a LRTI with a documented positive RSV test was probably underestimated in neonatology units (for 4.8% of children, the cause of the LRTI was not investigated or was unknown and could therefore have been due to RSV).
- Six deaths occurred during the one-year follow-up period, (unrelated to the product according to investigators) and 30 serious adverse events were reported by 4 investigator centres.

Accordingly, the conduct and data of this study are not sufficient to conclude about the risk of hospitalisation for RSV infection and the tolerance of Synagis in routine practice but provide descriptive data about its use.

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit
Lower respiratory tract infection due to respiratory syncytial virus (RSV) is not usually a serious condition when it is treated in the normal manner with respiratory physiotherapy in particular. However, in a high risk population, this infection may cause respiratory distress requiring hospitalisation, oxygen therapy and mechanical ventilation in the most severe forms with a risk of sequelae and death.

This proprietary product is intended for preventive treatment. The efficacy of Synagis was demonstrated versus placebo on the hospitalisation rate (one study in the preterm infant and one study in children with congenital heart disease). It was not found to reduce complications (except on the intensive care admission rate and number of days with oxygen therapy) and mortality due to RSV-related lower respiratory tract infection.
The efficacy/safety ratio is low in children born at 32 weeks of gestation or less and at high risk because of respiratory sequelae and in children aged under two years with haemodynamically significant congenital heart disease.
There is no alternative medication to this product.

The observational study provided descriptive data on hospitalisation rates observed during one RSV epidemic season. The results showed that Synagis is widely used outside recommended treatment conditions.
It did not confirm the reduction in hospitalisation rate with a sufficient level of evidence.
Overall it seems not possible to quantify the effect of this medicinal product on clinical criteria studied long after its marketing.

The actual benefit of this proprietary medicine must therefore be considered to be low.
5.2. Improvement in actual benefit
Taking into account the choice of primary efficacy endpoint for the clinical studies and after reviewing the descriptive data of the observational study, the Transparency Committee considers that SYNAGIS only provides a minor improvement in the actual benefit (level IV) of treatment strategy of:
- infants under 6 months of age at the start of the epidemic season, born at 32 weeks of gestation or before and at high risk because of respiratory sequelae for whom severity is shown by an oxygen requirement > 28 days after birth;
- children aged under 2 years at the start of the epidemic season, born at 32 weeks of gestation or before, at high risk because of respiratory sequelae for whom severity is shown by an oxygen requirement > 28 days after birth and requiring treatment for bronchopulmonary dysplasia within the last 6 months;
- children aged under two years with haemodynamically significant congenital heart disease as defined by the Paediatric Cardiology section of the French Cardiology Society.

5.3. Therapeutic use
The Transparency Committee considers that Synagis should not be prescribed systematically but only after a clinical analysis of each individual case. It recommends to take the decision to prescribe this product after discussion with neonatologists or specialists following up the child.

A - Children without heart disease
In 2007, the French Society of Neonatology recommended the use of Synagis in the following cases:
1. Children aged less than 2 years at the start of the epidemic with bronchopulmonary dysplasia treated within 6 months before the start of the epidemic of RSV infection, by mechanical ventilation and/or prolonged oxygen therapy and/or continuous pharmacotherapy (corticosteroids; bronchodilators; diuretics).
2. Preterm infants of gestational age < 32 weeks of amenorrhoea:
   a. gestational age < 28 weeks and 6 days of amenorrhoea, and aged less than one year at the start of the RSV epidemic.
   b. gestational age between 29 weeks and 31 weeks and 6 days of amenorrhoea and aged less than 6 months at the start of the RSV epidemic.

In the absence of specific clinical data in these populations, the Transparency Committee again distinguishes the two following situations for the use of Synagis:
- infants aged under 6 months at the start of the epidemic season, born at 32 weeks of gestation or before and at high risk because of severe respiratory sequelae shown by an oxygen requirement for more than 28 days after birth,
- children aged under 2 years at the start of the epidemic season, born preterm at 32 weeks of gestation or before and at high risk because of severe respiratory sequelae shown by an oxygen requirement for more than 28 days after birth and requiring treatment for bronchopulmonary dysplasia within the last 6 months;
Factors related to the social and family environment (siblings at school or child care centre, parents who are heavy smokers, home in an urban environment or in the North of France) are not in themselves indications, but are factors to be taken into consideration during the case-by-case analysis.

Concerning the measures for preventing this disorder and its spread, it is recommended not to place children under six months of age in institutional care. The importance of passive smoking cessation, washing hands and sanitising infected surfaces and objects1 should be underlined.

1 Consensus Conference - Management of bronchiolitis in infancy, 21 September 2002
B - Children with heart disease

The Paediatric Cardiology section of the French Cardiology Society considers that the decision to institute palivizumab prophylaxis for RSV infections in children with congenital heart disease must be made in collaboration with the paediatric cardiologist managing the child after an objective evaluation of the haemodynamic and respiratory repercussions of the heart disease. This treatment should be restricted to children at high risk of respiratory complications in the case of RSV infection and two situations may be distinguished:

**Children in whom the expected benefit of palivizumab prophylaxis is highest**

Children aged under one year with haemodynamically significant congenital heart disease who have not received surgical treatment, who are receiving palliative treatment or after partial repair.

- Heart disease causing only left-to-right shunting with high pulmonary flow leading to heart failure and/or pulmonary arterial hypertension: large ventricular septal defect, complete form of atrioventricular canal defect, single ventricle, other complex congenital heart diseases.
- Congenital heart diseases causing right-to-left shunting with reduced pulmonary flow and leading to overt cyanosis (resting transcutaneous oxygen saturation below 80%): Fallot's tetralogy, pulmonary atresia with ventricular septum defect, pulmonary atresia with intact ventricular septum, Ebstein abnormality, single ventricle and other related heart diseases.
- Heart diseases with mixed shunts leading to cyanosis, heart failure and pulmonary hypertension: complex transpositions of the large vessels, common arterial trunk, single ventricle and other non-repairable congenital heart diseases.
- Valvular heart disease: tight pulmonary artery or aortic stenosis with ventricular dysfunction, valve regurgitation with ventricular dilatation and heart failure.
- Prophylaxis is particularly recommended in children at high respiratory risk in the case of RSV infection: poorly tolerated heart disease in infants aged under 6 months at the start of the epidemic season, persistent heart failure despite medical treatment, respiratory discomfort, hypotrophy, severe pulmonary arterial hypertension and dilatation, overt resting hypoxemia (transcutaneous saturation < 80%).

Children aged under one year with myocardiopathy resulting in heart failure of whatever type: dilated or hypertrophic heart failure, and whatever cause: ischemic, metabolic, mechanical, genetic or infectious origin.

Children aged under one year with major pulmonary arterial hypertension of whatever cause: primary or secondary.

Children aged under one year with a risk of hospitalisation during the epidemic season for a surgical procedure or for cardiac catheterisation.

Certain children aged over one year with poorly tolerated complex heart disease, including those already treated during the previous season.

**Children not requiring palivizumab prophylaxis**

Children with minor or well-tolerated congenital heart disease not requiring medical or surgical treatment during the first two years: atrial septal defect, persistence of ductus arteriosus, ventricular septal defect with low-to-moderate shunt, minor or moderate valve abnormality, uncomplicated aortic coarctation, etc.

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Children with a cardiac malformation satisfactorily treated by surgery or interventional catheterisation.

Palivizumab must not be systematically prescribed in all children with “haemodynamically significant” congenital heart disease. This definition in fact covers situations of very variable seriousness. It is important to reserve this treatment for patients at high respiratory risk in the case of infection with RSV, as defined above. The paediatric cardiologist must specify this risk through objective clinical and paraclinical parameters evaluating the hemodynamic and respiratory repercussions of the congenital heart disease. Associated abnormalities and social, familial and cultural environment factors must also be taken into account.

5.4. Transparency Committee Recommendations
The Transparency Committee recommends maintaining SYNAGIS on the list of medicines approved for use by hospitals and various public services in the following populations:

- Children aged under 6 months at the start of the epidemic season, born preterm at 32 weeks of gestation or before and at high risk because of respiratory sequelae for whom severity is shown by an oxygen requirement for more than 28 days after birth;
- Children aged under 2 years at the start of the epidemic season, born preterm at 32 weeks of gestation or before, at high risk because of respiratory sequelae for whom severity is shown by an oxygen requirement for more than 28 days after birth and requiring treatment for bronchopulmonary dysplasia within the last 6 months;
- Children aged under two years affected by haemodynamically significant congenital heart disease as defined by the Paediatric Cardiology section of the French Cardiology Society.

The Committee requests that SYNAGIS is only prescribed at hospital by the paediatrician following up the child (Cf. Art. 128 of the law of 9 August 2004).
OPINION OF THE PUBLIC HEALTH IMPACT GROUP
ON THE FINAL RESULTS (July 2007) OF THE SYNAGIS® STUDY AFTER INCLUSION ON
THE REIMBURSEMENT LIST

PROTOCOL: Observational study of the use of SYNAGIS (2005-2006 Season)
VERSION: Final report of July 2007
PRODUCT: Synagis®
COMPANY: Abbott France
DATE OF OPINION: 04/09/2007

I. GENERAL DATA

Synagis (palivizumab) is a monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) requiring hospitalisation in children at high risk of RSV infection:
- Children born at 35 weeks of gestation or less and aged under 6 months at the start of the RSV season (MA of 13 August 1999).
- Children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months (MA of 13 August 1999).
- Children less than 2 years of age and with haemodynamically significant congenital heart disease (MA of 20 October 2003).

This indication is reimbursed by National Health Insurance only in the indications specified hereafter:
- Infants aged under 6 months at the start of the epidemic period, born preterm at 32 weeks of gestation or before and at high risk because of respiratory sequelae for whom severity is shown by an oxygen requirement for more than 28 days after birth;
- Children aged under 2 years at the start of the epidemic period, born preterm at 32 weeks of gestation or before, at high risk because of respiratory sequelae for whom severity is shown by an oxygen requirement for more than 28 days after birth and requiring treatment for bronchopulmonary dysplasia within the last 6 months;
- Children aged under two years affected by haemodynamically significant congenital heart disease as defined by the Paediatric Cardiology section of the French Cardiology Society.

Synagis may only be prescribed by hospital paediatricians following up the children concerned.

II. SUMMARY OF REQUEST

The study request was issued by the DGS and reproduced in the Economic Committee for Health Products agreement of 21/03/2003 and then in Transparency Committee opinions. The final wording about the study (October 2004) was as follows: “The Committee requested the conduct of a follow-up study of children treated by Synagis to investigate the patterns of use of Synagis, its safety and the risk of hospital admission for RSV infection”.

The study protocol was validated on 17/05/2005 by the ISP group. The study began on December 2005. It was a longitudinal study with one-year follow-up of a cohort of children treated by Synagis during the 2005-2006 epidemic season, in hospital neonatology units or cardiology or paediatric pneumology departments. The protocol planned to include between 3,500 to 4,000 children (out of a total of 5,000 Synagis-treated children), recruited in 135 neonatology units and followed-up one year after institution of Synagis treatment.

III. REMARKS ON THE STUDY DESIGN

Recruitment of centres
Eight-one (60%) of the 135 centres contacted agreed to take part and 64 centres were finally active (included patients).
The reason for the non-participation of 15 centres for “administrative” reasons is rather vague and could have been better explained. The representativity of the centres at national level is not entirely guaranteed. In particular the type of centre differed between those taking part and those not taking part in the study. In fact, 57.8% of the centres taking part were level 3 neonatology units whereas this proportion was only 39.4% for those not taking part. Conversely, the proportion of level 2 centres was 35.9% of participating centres versus 52.1% of non-participating centres.

Recruitment of children
Children starting a treatment were identified from the dispensing hospital pharmacy registries. The list was sent to the local coordinating physician who included the children.

It was not very easy to understand from which dispensing date a child was potentially eligible. It was reported that the drug was dispensed to a total of 2156 children, but there is no information about treatment start or end dates.
The study was proposed to only 1555 parents of children and the other 601 children were considered to be non-eligible “because of a delay in the study start date to December 2005 and the start of the epidemic season”. This non-inclusion may have created a selection bias due to the enrollment of children treated in the middle of the epidemic season.

In addition, the representativity of included children was not fully guaranteed: According to the registry database of children who received Synagis, 8.8% of these children were managed by paediatric cardiology and pneumology departments, 22.4% by level 2 neonatology units and 68.8% by level 3 neonatology units. These proportions were 0.7%, 26.1% and 73.2% respectively for the included children (p<0.001). The distribution of included children compared to those of the registry also differed according to region: the Ile de France region (19.1% versus 26.5% for the registry children) was underrepresented while the north-west, south-west and south-east regions were overrepresented (p<0.001).

After contacting the parents, 1367 children were included. Another 53 children followed up by the centres but for whom the drug was dispensed by another pharmacy were also included, giving a total of 1420 children (1394 in neonatology units and 26 in paediatric cardiology and pneumology departments).
IV. REMARKS ON THE RESULTS PRESENTED IN RESPONSE TO THE STUDY REQUEST

Characteristics of included children and prescription patterns
The study report did not systematically present the characteristics of the treated children according to reimbursement criteria. The average age of the children at the time of the first injection of Synagis was 5 months in neonatology and 8.6 months in cardiology-pneumology. The children included in the study were generally boys (54.2%). Children had a mean birth weight of 1,428 grams, a mean gestational age of 30.2 weeks and were born of multiple births in 30.1% of cases. Finally, 39.2% of the children received oxygen after day 28.

Information about the reasons and criteria for prescribing Synagis used to study the compliance with MA indications and reimbursable indications was available for 1,378 children (97% of included children):
- 1162 (84.3%) of the children received Synagis within the scope of the MA indications.
- 589 (42.7%) of the children received Synagis within the scope of the reimbursed indications.

Synagis was administered at a mean dose of 15 mg/kg and the mean number of injections was 4.5 (median 5) per child. However, 15% of the children in neonatology and 12% in cardiology-pneumology had more than 5 injections.

Tolerance
Six deaths occurred during the follow-up period. According to the investigators, none of these deaths was related to Synagis.
In addition, 30 serious adverse events were reported by 4 investigator centres during the follow-up period that were “probably” related to Synagis. One of these centres reported 24. These events were mainly respiratory or ENT disorders. The outcome of all these events was positive with improvement or recovery.
These results should be compared with the pharmacovigilance data.

Risk of hospitalisation due to RSV infection
The mean duration of follow-up in the study was 10.9 months.
1,215 (87%) of the 1,394 children recruited in a neonatology unit were followed up for a full year (whatever the respect of MA and/or reimbursable indications).
367 (30.2%) of these children were admitted non-electively to hospital at least once.
This hospitalisation was due to:
- A non-RSV lower respiratory tract infection (LRTI) in 125 children (10.3%)
- A RSV LRTI in 38 children (3.1%)
- A LRTI of non-investigated or unknown origin in 58 children (4.8%)
- An unknown reason or a reason other than LRTI in 146 children (12%)

There were too few results for children seen in paediatric cardiology-pneumology for interpretation.
For the 26 children recruited in paediatric cardiology-pneumology departments, 25 were followed up for a full year and 14 had at least one non-elective hospital admission.
This hospitalisation was due to:
- A non-RSV lower respiratory tract infection in 1 child
- An RSV LRTI in 5 children
- A LRTI of non-investigated cause in 2 children
- An unknown reason or a reason other than LRTI in 6 children
It was planned to present the incidences of hospitalisation as incidence density rates. Only the proportions are presented in this report. The descriptive analysis could have used Kaplan-Meier survival curves to better show the outcome of hospitalisations according to the start of treatments.

The comparability of the results of this observational study and clinical trials, is an interesting part of the analysis. Its results should nevertheless be considered with caution: they are aggregated data as it was impossible to take the differences between groups into account.

V. DETAILED REPORT

Overall, 1,420 children were included by 64 active centres.

**Baseline characteristics**

Characteristics of centres

64 of the 135 centres to which the study was proposed were active. These were divided into 37 level 3 centres (participation rate: 57%), 23 level 2 centres (participation rate: 38%) and 4 paediatric cardiology-pneumology centres (participation rate: 40%). There was no statistically significant difference according to region for those centres participating and those not participating in the study.

Baseline characteristics of children

The registry of all children treated by Synagis was available in 59 of the 64 active centres. The study was proposed by the local coordinating physician to the parents of 1,555 (72.1%) of the 2,156 children for whom Synagis was dispensed by the hospital pharmacy and consent for participation was obtained for 1,367 children (63.4%). 601 children (27.9%) were not invited to take part in the study as the study start date was delayed (December 2005) relative to the commencement of the epidemic season (October 2005).

Most of the children were included by level 2 and 3 neonatology units (1,394) whereas only 26 children were included by paediatric cardiology or pneumology departments.

The mean age of children at the time of the first injection of Synagis was 5 months. The children included in the study were more often boys (54.2%) with a mean birth weight of 1428 grams, a mean gestational age of 30.2 weeks and were born of multiple births in 30.1% of cases.

There were statistically significant differences between the characteristics of children from neonatology units and those from paediatric cardiology or pneumology departments:

- The mean age of children at the time of the first injection of Synagis was 5 months in neonatology compared with 8.6 months in paediatric cardiology or pneumology departments;
- 30.6% of children were born of multiple pregnancies in neonatology versus 4% in paediatric cardiology or pneumology;
- Children included in neonatology centres had a lower gestational age than the other children included in paediatric departments (30.1 weeks versus 37 weeks) and their mean birth weight was 1,406 g versus 2,672 g in paediatrics;
- Finally, 41.5% of the children in neonatology units versus 24% of those in paediatric departments received oxygen after day 28.

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3 Maternity Clinic Level : The perinatal care decree of 9 October 1998 set out a framework for organising healthcare in networks in order to ensure that the level of care provided by a maternity clinic was appropriate for the risk level of mother and child. Three maternity clinic levels were defined: a clinic is considered to be “level 3” if it has an obstetrics department, a neonatal critical care department and a neonatology unit on the same site; it is considered to be “level 2” if it has a neonatology unit on the same site as the obstetrics department and “level III ” if it has an obstetrics department.
On the contrary, there was no statistically significant difference between children born in centres with a low recruitment (less than 10 children) and the other centres.

**Synagis treatment patterns**

Synagis was administered at a mean dose of 15 mg/kg and the mean number of injections was 4.5 (median 5) per child. Information on the mode of administration was available for 1,383 children (99.2%) from neonatology units. Most (44.9%) received 5 injections, 13.2% 6 injections and 1.7% 7 injections (the other children received from 1 to 4 injections). The mean interval between two injections was 1 month.

For paediatric centres, 14 children out of 25 (56%) received 5 injections, 2 children received 6 injections and 1 child received 7 injections.

**Analysis of compliance of Synagis prescriptions with the MA indications or reimbursable indications**

Information was available for 1,378 children (97% of included children).

84.3% (n=1162) of these latter children received Synagis within the scope of the MA indications:

- 895 children born at 35 weeks of gestation or less and aged less than 6 months at the start of the RSV season.
- 104 children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months (MA of 13 August 1999).
- 163 children less than 2 years of age with haemodynamically significant congenital heart disease (MA of 20 October 2003).

For the other 216 children (15.5% of cases), Synagis was administered off-label. The reason for prescription was then given for only 73 children (34.3% of cases) and was most often bronchopulmonary dysplasia for 19 of the 174 children over 6 months (10.9%) or diaphragmatic hernia for 8 of the 39 children under 6 months (20.5%).

589 of the 1,378 children (42.7%) received Synagis within the scope of the reimbursable indications.

- 331 children were aged less than 6 months with a gestational age of 32 weeks or less and had bronchopulmonary dysplasia defined by an oxygen requirement at 28 days;
- 95 children were aged under 2 years with a gestational age of 32 weeks or less and were at high risk because of respiratory sequelae for whom severity is shown by an oxygen requirement for more than 28 days after birth and had required treatment for bronchopulmonary dysplasia within the last 6 months;
- 163 children were aged under two years and presented congenital heart disease (specified in the JO + haemodynamically significant as defined by the Paediatric Cardiology section of the French Cardiology Society).

For the other 789 children (57.3% of cases), Synagis was administered out the scope of reimbursable indications.

642 children were aged less than 6 months:

- 529 children had a age gestational age of less than 32 weeks but did not present bronchopulmonary dysplasia
- 32 children had a gestational age of more than 32 weeks and did not present bronchopulmonary dysplasia
- 3 children had bronchopulmonary dysplasia with an oxygen requirement for more than 28 days, but their gestational age was greater than 32 weeks (and lower than 35 weeks)
- Another diagnosis was made for 39 children and when this was noted, it was usually diaphragmatic hernia.
- 183 children were aged from 6 months to 2 years and had neither cardiopathy, nor bronchopulmonary dysplasia requiring oxygen therapy for more than 28 days.
- finally, 3 children were aged over 2 years.

**Follow-up data**

*General data*

The mean duration of follow-up in the study was 10.9 months. There were no telephone follow-up data for 96 (6.8%) of the 1,420 included children but medical questionnaires were available for 94 of these children. Telephone follow-up was incomplete for 84 other children (6 children died and 78 children moved during the study).

Overall no medical questionnaire or telephone interview of the parents was available for only 2 children (i.e. 0.1% of included children).

1,215 (87%) of the 1,394 children recruited in a neonatology unit were followed up for a full year. These included 658 (54.2%) who saw their primary care doctor for a respiratory problem. The average number of visits over the period was 2.6. 191 (30%) of these children had more than two episodes of bronchitis or bronchiolitis during the follow-up period.

Twenty-five of the 26 children recruited in paediatric cardio-pneumology units had a complete follow-up and 9 (36%) consulted their primary care doctor for a respiratory problem; the average number of visits over the period was 1.9.

**Number of hospitalised children**

- **Children hospitalised over the one year follow-up period after the first injection of Synagis**

For the 1,215 children recruited in neonatology units with a full follow up, 367 (30.2%) were admitted non-electively to hospital at least once.

- 38 (3.1%) were admitted to hospital for a LRTI with a documented positive RSV test;
- 125 children (10.3%) were hospitalised for a non-RSV LRTI;
- 58 children (4.8%) for LRTI of non-investigated or unknown cause;
- 146 children (12%) for an unknown reason or a reason other than a LRTI.

For the 25 children recruited in paediatric cardiology-pneumology departments, 14 (56%) were admitted non-electively to hospital at least once.

- 5 children were admitted to hospital for a LRTI with a documented positive RSV test;
- 1 child was hospitalised for a non-RSV LRTI;
- 2 children for a LRTI of non-investigated or unknown cause;
- 6 children for an unknown cause or a reason other than a LRTI.

In addition, 4 of the 43 children admitted to hospital (whatever the type of centre) for LRTI with a documented positive RSV test had to be transferred to paediatric intensive care with ventilation. They had received 1 (n=3) or 2 (n=1) injections of Synagis before this hospitalisation.

- **Children hospitalised over the period from day 7 after the first injection to day 30 after the last injection of Synagis**

For the 1,215 children from neonatology units followed up over a period corresponding to the protection period conferred by Synagis, 235 (19.3%) were hospitalised non-electively at least once during this period, including 29 (2.4%) for a LRTI with a documented positive RSV test.

**Children admitted to hospital with respect to Synagis prescription patterns**

- **Hospitalised children aged under 2 years who received Synagis within the scope of its reimbursable indications (GA<=32 WA with bronchopulmonary dysplasia)**

In this population, 373 children out of 426 (87.6%) were followed up for one year. 33% of children born between 28 and 32 weeks of amenorrhoea and 36.5% of children born at less than 28 WA were admitted non-electively to hospital at least once.
For 5.7% of children born between 28 and 32 WA and 3.6% of the children born before 28 WA, this was for LRTI with a documented positive test for RSV.

- **Hospitalised children aged under 6 months with gestational age <=32 WA but without bronchopulmonary dysplasia (outside reimbursable indications)**

In this population, 458 children out of 529 (86.6%) were followed up for one year. 25.4% of children born between 28 and 32 weeks of amenorrhoea and 21.2% of the children born before 28 WA were admitted non-electively to hospital at least once. For 2.5% of children born between 28 and 32 WA this was for a LRTI with a documented positive test for RSV. No LRTI with a documented positive RSV test was reported in the children born before 28 WA.

- **Hospitalised children aged under 2 years who received Synagis off-label**

In this population, 191 children out of 213 (89.7%) were followed up for one year. 24.1% of these children were admitted non-electively to hospital at least once. For 2.6% of children, this was for a LRTI with a documented positive test for RSV.

**Total number of hospital admissions**

The total number of hospital admissions registered for the 1,394 children from neonatology units during the one-year follow-up period after the first injection of Synagis was 902, i.e. 0.65 hospitalisations per child. Forty-seven (5.2%) of these hospital admissions were due to a LRTI with a positive test for RSV.

For the 26 children in paediatric departments there were 59 hospital admissions (rate of 2.7). Five (8.4%) of these hospital admissions were due to a LRTI with a positive test for RSV.

**Death and serious adverse events**

Six deaths occurred during the one year follow-up period because of underlying heart disease (2 cases), pulmonary agenesis (1 case), necrotising enterocolitis (1 case). In 1 case, the physician was unable to determine the exact cause of death which was noted as unrelated. The last case could not be documented as the investigator withdrew from the study. According to the investigators, none of these deaths was related to Synagis.

Thirty serious adverse events were reported by 4 investigator centres during the follow-up period as “probably” related to Synagis. One of these centres reported 24. Most diagnoses comprised respiratory or ENT disorders: asthma, bronchiolitis, rhinitis, pneumonitis, RSV infection with respiratory distress.

The outcome of all these events was positive with improvement or recovery.

These events were reviewed by an “independent clinical events committee” which concluded that they were not related to Synagis.

**Comparison of the results of the observational study and the results of the clinical trials**

The Impact-RSV pivot study was summarised in the opinion of 19 January 2000. A child hospitalisation rate for LRTI of 4.8% was reported in the Synagis-treated group (n=1002), versus 10.6% in the placebo group (n=500).

During the current observational study a similar sub-group of 919 children (same inclusion criteria, exclusion of children with congenital heart disease, children for whom a follow-up visit 1 month after the last injection of Synagis is available), were selected. The child hospitalisation rate for LRTI was 3.2% (n=29) in this sub-group.
VI. CONCLUSION

This report partly answers the questions raised by the health authorities about prescription patterns and safety. There may have been some selection bias because of the moderate participation of centres and the delay in starting the study 2 months after the commencement of the epidemic season.

These results only apply only to children treated in neonatology units. The sample size of children treated in cardiology-pneumology departments was too low for valid interpretation.

They show that children were treated outside reimbursable indications in 57.3% of cases (including 15.7% in off-label indications). Approximately 15% of the children received more than 5 injections, and it would have been useful to give the reasons for stopping injections in other children who received less than 5 injections. Cross-comparison of the criteria to be respected would have made it easier to interpret these deviations.

No unexpected effect was detected during the safety study. However the size of the cohort was too small to detect all adverse reactions. Additional pharmacovigilance data may be presented.

With regard to the risk of hospitalisation for RSV infection, the rate presented was the same as that found during trials. However, a certain number of children were not tested for RSV. The proportion of hospitalisations may also have been biased by treating children with a lower risk of RSV infection and therefore, a fortiori, with a lower risk of hospitalisation for RSV. Risk analysis may have provided more useful information if Kaplan-Meier survival analysis was performed.