SUMMARY

nirsevimab

BEYFORTUS 50 and 100 mg

solution for injection in pre-filled syringe

Indication extension and reassessment at the request of the TC

Adopted by the Transparency Committee on 23 October 2024

Summary of opinion

Favourable opinion for reimbursement in the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in:

- **Neonates and infants during their first RSV season;**
- **Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.**

BEYFORTUS should be used in accordance with official recommendations.

Transparency Committee's conclusions

Clinical Benefit

Population ineligible for SYNAGIS (palivizumab)

- In usual care conditions, RSV lower respiratory tract infection is not usually serious. In at-risk populations, these infections can cause respiratory distress, which may require hospitalisation, oxygen therapy and mechanical ventilation in the most severe forms, with a risk of sequelae and mortality.
- The proprietary medicinal product BEYFORTUS (nirsevimab) is a preventive treatment.
- The efficacy/adverse effects ratio is moderate. In fact, the efficacy of nirsevimab was demonstrated versus placebo on the reduction of RSV lower respiratory tract disease (D5290C00003, MELODY and HARMONIE studies) in neonates and infants at low risk of severe RSV disease (absence of comorbidities such as immune deficiencies and ineligibility for palivizumab, exclusion criteria in the clinical trials). In these low-risk populations, the reduction in hospitalisations endpoint was marked by contradictory results. Nonetheless, although limited in terms of their methodological robustness (case-control studies), data from French observational studies suggest a relative reduction in the risk of hospitalisations and intensive care unit admissions due to RSV-associated bronchiolitis.

- There is a therapeutic alternative: ABRYSVO (Respiratory Syncytial Virus (RSV) vaccine (bivalent, recombinant)) in all infants, with or without risk factors.
- This is a first-line treatment in view of the therapies available.

Public health benefit

Considering:

- the seriousness, contagiousness and impact on the organisation of care, particularly in neonates and infants with risk factors (consultations, emergency department visits, hospitalisations and critical or intensive care unit admissions);
- the inadequately met medical need in the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season;
- the fact that BEYFORTUS (nirsevimab) provides a partial response to the identified medical need, particularly in neonates and infants born with or without risk factors and ineligible for palivizumab, during their first RSV season, due to:
  - evidence of an additional impact on morbidity (reduction in the incidence of RT-PCR-confirmed MA RSV LRTI within 150 days following administration),
  - an expected additional impact on severity criteria (reduction in RSV LRTI hospitalisations within 150 days following administration) but not demonstrated on mortality,
  - an expected additional impact on the care and life pathway of treated subjects (pharmacokinetic property enabling a single intramuscular injection providing protection for a period of 5 months),
  - the lack of evidence of an additional impact on the organisation of care (reduction in intensive care unit admissions and reduction in the requirement for supplemental oxygen),

BEYFORTUS (nirsevimab) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BEYFORTUS (nirsevimab) is moderate in the prevention of RSV lower respiratory tract disease in neonates and infants with or without risk factors, as defined by the national recommendations, and ineligible for palivizumab, during their first RSV season.

The Committee issues a favourable opinion for inclusion of BEYFORTUS (nirsevimab) in both the list of covered drugs for outpatients and the list of covered drugs for inpatients approved for use at the MA dosages and in the prevention of RSV lower respiratory tract disease in neonates and infants with or without risk factors, as defined by the national recommendations, and ineligible for palivizumab, during their first RSV season.

Population eligible for SYNAGIS (palivizumab) in accordance with the MA

- In usual care conditions, RSV lower respiratory tract infection is not usually serious. In at-risk populations, these infections can cause respiratory distress, which may require hospitalisation, oxygen therapy and mechanical ventilation in the most severe forms, with a risk of sequelae and mortality.
- The proprietary medicinal product BEYFORTUS (nirsevimab) is a preventive treatment.
- The efficacy/adverse effects ratio is moderate.

➔ Therapeutic alternatives are available: SYNAGIS (palivizumab) in infants with risk factors and ABRYSVO (Respiratory Syncytial Virus (RSV) vaccine (bivalent, recombinant)) in all infants, with or without risk factors.

➔ This is a first-line treatment in view of the therapies available.

➔ Public health benefit

Considering:

- the seriousness, contagiousness and impact on the organisation of care, particularly in neonates and infants with risk factors (consultations, emergency department visits, hospitalisations and critical or intensive care unit admissions);
- the inadequately met medical need in the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season;
- the fact that BEYFORTUS (nirsevimab) provides a partial response to the identified medical need, particularly in neonates and infants at high risk of RSV infection and eligible for palivizumab, during their first and second RSV season, due to:
  - an expected additional impact on the care and life pathway of treated subjects (pharmacokinetic property enabling a single intramuscular injection providing protection for a period of 5 months),
  - the lack of evidence of an additional impact on morbidity and mortality (reduction in the incidence of RT-PCR-confirmed medically attended lower respiratory tract infection (MA RSV LRTI) and RSV LRTI hospitalisations within 150 days following administration, as well as reduction in mortality) and on the organisation of care (reduction in intensive care unit admissions and reduction in the requirement for supplemental oxygen);

BEYFORTUS (nirsevimab) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BEYFORTUS (nirsevimab) is moderate in the MA indication in the prevention of severe RSV lower respiratory tract disease requiring hospitalisation in neonates and infants at high risk of RSV infection and eligible for palivizumab, during their first and second RSV season:

- **Infants born at a gestational age of 35 weeks or under and under 6 months of age entering their first RSV season;**
- **Infants under 2 years of age having required treatment for bronchopulmonary dysplasia in the past 6 months;**
- **Infants under 2 years of age with congenital heart disease with a haemodynamic impact.**

The Committee issues a favourable opinion for maintenance of inclusion of BEYFORTUS (nirsevimab) in both the list of covered drugs for outpatients and the list of covered drugs for inpatients approved for use in the MA indication and at the MA dosages in the prevention of severe RSV lower respiratory tract disease requiring hospitalisation in neonates and infants at high risk of RSV infection and eligible for palivizumab, during their first and second RSV season:

- **Infants born at a gestational age of 35 weeks or under and under 6 months of age entering their first RSV season;**
- **Infants under 2 years of age having required treatment for bronchopulmonary dysplasia in the past 6 months;**

- **Infants under 2 years of age with congenital heart disease with a haemodynamic impact.**

Clinical Added Value

Population ineligible for SYNAGIS (palivizumab)

Considering:

- the inadequately met medical need in the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season;
- the effect size of BEYFORTUS (nirsevimab) in terms of reduction in the incidence of MA RSV LRTI within 150 days following administration in neonates and infants at low risk of severe RSV disease (absence of comorbidities such as immune deficiencies and ineligibility for palivizumab, exclusion criteria in the clinical trials), which was statistically significant in:
  - the phase IIb trial (D5290C00003): 2.6% (25/969) versus placebo 9.5% (46/484), i.e. an RRR = 70.1% [52.3; 81.2], p < 0.0001,
  - the phase III trial (MELODY): 1.2% (12/994) versus placebo 5.0% (25/496), i.e. an RRR = 74.5 [49.6; 87.1], p < 0.001;
- an expected impact on the relative reduction of the risk of hospitalisations related to RSV LRTI, but for which the heterogeneous results (significant or otherwise) reflect uncertainties for this endpoint of major clinical interest, with, for:
  - the phase IIb trial (D5290C00003): 0.8% (8/969) versus placebo 4.1% (20/484), i.e. an RRR = 78.4% [51.9; 90.3], p = 0.0002,
  - the phase III trial (MELODY): 0.6% (6/994) versus placebo 1.6% (8/496); i.e. an RRR = 62.1% [-8.6; 86.8], NS;
- the results of the phase IIIb, pragmatic, open-label trial (HARMONIE) relative to the incidence of RSV LRTI hospitalisations: 0.3% (11/4,038) versus no intervention 1.6% (64/4,019), i.e. an RRR = 84.0% [69.5; 92.4], p < 0.0001;
- the absence of data supporting a potential impact of BEYFORTUS (nirsevimab) in terms of reducing hospital stay duration or the rate of transfer to critical or intensive care units and mortality;
- an acceptable safety profile of nirsevimab (BEYFORTUS) marked by predominantly grade 1 (mild) or 2 (moderate) adverse events (AEs), such as upper respiratory tract infections, rhinopharyngitis, pyrexia or gastroenteritis, and adverse events of particular interest, such as the skin rashes reported in the clinical studies and in line with the information indicated in the SmPC, as well as the absence of any important identified or potential risks in the context of its European RMP;
- French observational data that are reassuring, despite being limited in terms of their methodological robustness (case-control studies), suggesting a relative reduction in the risk of hospitalisations due to RSV-associated bronchiolitis of between 73% [61; 84] and 83.0% [7.4; 89.2] in favour of nirsevimab (Institut Pasteur study and ENVIE) and a relative reduction in the risk of cases of RSV-associated bronchiolitis admitted to an intensive care unit of 75.9% [48.5; 88.7] (Santé Publique France study);
- the ease of use of the medicinal product due to its intramuscular administration as a single dose (long half-life of nirsevimab);
- the use as monotherapy and long half-life of nirsevimab potentially leading to a risk of selection of resistant variants (see section 5.1 Pharmacological properties in the SmPC);

the Committee deems that BEYFORTUS (nirsevimab) provides a minor clinical added value (CAV IV) in the prevention of RSV lower respiratory tract disease in neonates and infants with or without risk factors and ineligible for palivizumab, during their first RSV season.

Population eligible for SYNAGIS (palivizumab) in accordance with the MA

Considering:

- the inadequately met medical need in the prevention of RSV lower respiratory tract disease in neonates and infants during their first and second RSV season;
- the lack of evidence of a superiority or non-inferiority of nirsevimab compared to palivizumab (clinically relevant comparator in infants at high risk of severe forms) in terms of clinical efficacy, despite this comparison being possible;
- limited clinical data in patients eligible for palivizumab based on the MEDLEY study, which aimed to determine the safety profile and pharmacokinetics of nirsevimab compared to palivizumab in high-risk infants (preterm infants or with chronic lung disease or a haemodynamically significant congenital heart disease);
- the fact that the efficacy of nirsevimab in infants at higher risk of severe RSV infection is extrapolated from the efficacy of nirsevimab in the D5290C00003 and MELODY studies (primary cohort) based on pharmacokinetic exposure;
- the safety profile of nirsevimab used during a first and/or second RSV exposure season, which is acceptable and appears to be comparable to that of palivizumab. The adverse events were predominantly grade 1 (mild) or 2 (moderate), such as upper respiratory tract infections, rhinopharyngitis, pyrexia or gastroenteritis, and adverse events of particular interest, such as the skin rashes reported in the clinical studies and in line with the information indicated in the SmPC. However, in the MEDLEY study, serious AEs were reported more frequently in the NIRS/NIRS and PALI/NIRS groups than in the PALI/PALI group, respectively: 12.8% (23/180) versus 10.0% (4/40) versus 4.8% (2/ 42);
- the absence of data supporting a potential impact of BEYFORTUS (nirsevimab) in terms of reducing hospital stay duration or the rate of transfer to critical or intensive care units and mortality;
- the ease of use of the medicinal product due to its intramuscular administration as a single dose (long half-life of nirsevimab);
- the use as monotherapy and the long half-life of nirsevimab potentially leading to a risk of selection of resistant variants;

the Committee deems that BEYFORTUS (nirsevimab) provides a minor clinical added value (CAV IV) in the prevention of severe RSV lower respiratory tract disease requiring hospitalisation in neonates and infants at high risk of RSV infection and eligible for palivizumab, during their first and second RSV season.