SUMMARY

nirsevimab

BEYFORTUS 50 and 100 mg,

solution for injection in pre-filled syringe

Initial inclusion

Original French opinion adopted by the Transparency Committee on 19 July 2023

The legally binding text is the original French opinion version

Transparency Committee's conclusions

Clinical Benefit

Population eligible 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 of BEYFORTUS (nirsevimab) has not currently been adequately established. In fact, the efficacy data (MEDLEY study) extrapolated on the basis of pharmacokinetic exposure do not enable the clinical benefit of nirsevimab to be assessed in comparison with palivizumab. These very limited data suggest a clinical benefit 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 RSV season.
- There is a therapeutic alternative: the proprietary medicinal product SYNAGIS (palivizumab).
- This product is a first-line treatment.

- **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 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),
  - but in the absence 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 low, in the same way as SYNAGIS (palivizumab), 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 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 inclusion of BEYFORTUS (nirsevimab) in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use at the MA dosages and 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 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.**

➔ **Recommended reimbursement rate for inclusion in the retail list of reimbursed proprietary medicinal products approved for use: 15%**

Population ineligible for SYNAGIS (palivizumab)

- In usual care conditions, respiratory syncytial virus (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. These limited data suggest a clinical benefit 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.
- There are no therapeutic alternatives.
- This product is a first-line treatment.

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),
  - but in the absence 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 hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products 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.

➔ **Recommended reimbursement rate for inclusion in the retail list of reimbursed proprietary medicinal products approved for use: 30%**

Clinical Added Value

Population eligible 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 absence of demonstration 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 haemo-dynamically significant congenital heart disease):
- 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 appears to be comparable to that of palivizumab, despite a higher incidence in the nirsevimab group (n = 614) than in the palivizumab group (n = 304) in terms of serious adverse events (bronchiolitis [11 cases versus 4 cases], bronchitis [5 cases versus 2 cases], pneumonia [5 cases versus 1 case], RSV bronchiolitis [4 cases versus 2 cases], upper respiratory tract viral infections [3 cases versus 1 case]), death (5 deaths versus 1 death), adverse events of particular interest reported only in the nirsevimab group (1 case of heparin-induced thrombocytopenia, 1 case of thrombocytopenia and 1 case of maculopapular rash), as well as hypersensitivity-type adverse events, including anaphylaxis (18.1% [111/614] versus 15.1% [46/304]);
- 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 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 no clinical added value (CAV V) compared to SYNAGIS (palivizumab) 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 RSV season.

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 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 phase IIIb, pragmatic, open-label trial (HARMONIE): 0.3% (11/4,037) versus no intervention 1.5% (60/4,021), i.e. an RRR = 83.2% [67.8; 92.0], 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 effects, 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;
- 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.