Coversheet on evidence assessment by ATAGI using the GRADE framework for nirsevimab (Beyfortus) (Sanofi) RSV monoclonal antibody in infants aged <8 months born during or entering their first RSV season

A summary of key methods and decisions on evidence assessment using the GRADE framework for developing ATAGI recommendations on the use of nirsevimab (Beyfortus) in infants <8 months of age born during or entering their first RSV season for the Australian Immunisation Handbook

Background

- Nirsevimab (Beyfortus) was approved by the Therapeutic Goods Association (TGA) in November 2023 for neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe respiratory syncytial virus (RSV) disease through their second RSV season.
- ATAGI undertook assessment using the GRADE framework in 2024/25 to make relevant recommendations on the use of nirsevimab, which became available in several states and territories in early 2024.
- In July 2024, the PBAC did not recommend the listing of nirsevimab on the National Immunisation Program (NIP), citing an underestimated and highly uncertain incremental cost-effectiveness ratio.
- At the time this GRADE assessment was undertaken in 2024/25 ATAGI recommended nirsevimab for infants who were born:
  - to women who did not receive RSV vaccine during pregnancy
  - within 2 weeks after the mother received RSV vaccine during pregnancy.
- Nirsevimab is also recommended for the following infants after assessment by their treating doctor to confirm potential clinical benefit:
  - infants with risk conditions for severe RSV disease, regardless of maternal vaccination (see List. Conditions associated with increased risk of severe RSV disease in infants and young children)
  - infants born to mothers with severe immunosuppression, where the immune response to maternally administered RSV vaccine was impaired (see People who are severely compromised)
  - infants whose mothers have lost effective passive immunisation:
    - those whose mothers have received RSV vaccine in pregnancy but who have subsequently undergone a treatment after birth, such as exchange transfusion, cardiopulmonary bypass or extracorporeal membrane oxygenation, that may lead to loss of maternal antibodies OR
    - those who have already received nirsevimab but have subsequently undergone one of the procedures above (noting this would be a repeat dose of nirsevimab).

Research questions

1. Should one dose of nirsevimab (Beyfortus) (Sanofi) be recommended for all infants <8 months of age born during or entering their first RSV season to prevent RSV disease?

Table 1: Population, Intervention, Comparator, Outcomes (PICO) 1: nirsevimab vs placebo

Population	All infants aged <8 months born during or entering their first RSV season
Intervention	Nirsevimab (Beyfortus) (50 mg if weight <5kg or 100 mg if weight ≥5kg)
Comparator	Placebo/no nirsevimab
Outcomes	*Efficacy* • RSV (laboratory confirmed) medically attended lower respiratory tract illness/disease LRTI/LRTD – Critical • Hospitalisation for RSV-associated LRTI/LRTD – Critical • Death due to RSV respiratory illness – Critical • Duration of protection - Important *Effectiveness* • Hospitalisation for RSV-associated LRTI/LRTD – Critical • Intensive Care Unit (ICU) admissions for RSV-associated LRTI/LRTD – Critical • Death due to RSV respiratory illness – Critical *Safety* • Serious adverse events (SAEs) – Critical • Adverse events of special interest (AESI) – Critical

Literature search

The literature search was undertaken on 11 October 2023 using Medline, Embase and Cochrane CENTRAL databases to identify studies assessing efficacy, effectiveness, and/or safety outcomes of nirsevimab in infants born during or entering their first RSV season. Details of the search methods are presented in Appendix A. The citations were selected for review if they met the following criteria:

- *Study type:* Randomised controlled trial (RCT) Phase 2 or 3, observational study
- *Population:* Infants born during or entering their first RSV season
- *Intervention:* Nirsevimab
- *Comparator:* Placebo or no nirsevimab
- *Outcomes:* Effectiveness, efficacy, safety

Citations were excluded if they were non-English papers. A total of 14 citations met the above pre-defined inclusion criteria. Of these, 4 were clinical trials and 10 were observational studies. The included studies are summarised in Appendix B.

Inclusion criteria and rationale

Table 2: Rationale for PICO and inclusion criteria

Inclusion criteria	Rationale
Study type: RCT, observational study, effectiveness studies	Vaccine efficacy, effectiveness, and safety studies are available for the PICO question. The search criteria allow for future capture of relevant effectiveness and observational studies. Excludes phase I studies.
Population	Population of interest for this vaccine. All infants aged <8 months born during or entering their first RSV season.
Intervention: Nirsevimab (Beyfortus) (Sanofi) long-acting monoclonal antibody	Current formulation in terms of manufacturing and dosage. For infants born during of entering their first RSV season the recommended dose for nirsevimab is 50mg in 0.5mL if weight is <5kg, or 100 mg in 1mL if weight is ≥5kg.
Comparator	For the purposes of this GRADE assessment, placebo is the preferred comparator.
Outcomes	Included outcomes as stated above in Table 1. Included iteratively according to outcomes found in the studies
	Ranking of importance discussed in many iterations with portfolio leads and ATAGI full panel.
	General framework (depending on outcomes measured in studies available): *Critical* • RSV (laboratory-confirmed) medically attended LRTI/LRTD • Hospitalisation for RSV-associated LRTI/LRTD • SAEs • AESI *Important* • Duration of protection Note: some outcomes may be missing in GRADE projects due to no data from available studies. Extra outcomes added due to relevance.

Abbreviations: AESI=adverse events of special interest; LRTD=lower respiratory tract disease; LRTI=lower respiratory tract infection; RCT=randomised controlled trial; RSV=respiratory syncytial virus; SAE=serious adverse events

Risk of bias assessment

Risk of bias (RoB) was assessed for all selected studies using the standard GRADE criteria. Two assessors independently undertook this using the ROB 2.0 tool for randomised controlled trials (Appendix B) and The Risk of Bias in Non-randomised Studies – Of Interventions (ROBINS-I) assessment tool (Appendix C).

Appendix A: Literature Search Strategy

Cochrane Library Central Register of Controlled Trials (CENTRAL), Issue 9 of 12, September 2024: RSV - use of Nirsevimab (as at 11.10.24)

ID Search Hits
#1 MeSH descriptor: [Respiratory Syncytial Virus, Human] explode all trees 158
#2 MeSH descriptor: [Respiratory Syncytial Virus Infections] explode all trees 550
#3 (respiratory NEAR/1 syncytial):ti,ab,kw 1365
#4 rsv:ti,ab,kw 1243
#5 #1 OR #2 OR #3 OR #4 1638
#6 nirsevimab*:ti,ab,kw 30
#7 beyfortus*:ti,ab,kw 1
#8 ("MED 18897" OR "MED-18897" OR MED18897):ti,ab,kw 0
#9 #6 OR #7 OR #8 30
#10#5 AND #9 29

EMBASE: RSV - use of Nirsevimab (as at 11.10.24)

Database: Embase <1974 to 2024 October 09>
Search Strategy:
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1 exp Human respiratory syncytial virus/ (10803)
2 exp respiratory syncytial virus infection/ (9470)
3 (respiratory adj syncytial).tw. (22363)
4 rsv.tw. (22153)
5 1 or 2 or 3 or 4 (35259)
6 exp nirsevimab/ (382)
7 nirsevimab$.tw. (244)
8 beyfortus$.tw. (35)
9 ("MED 18897" or MED-18897 or MED18897).tw. (0)
10 6 or 7 or 8 or 9 (401)
11 5 and 10 (375)

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MEDLINE: RSV - use of Nirsevimab (as at 11.10.24)

Database: Ovid MEDLINE® All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current>
Search Strategy:
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1 exp Respiratory Syncytial Virus, Human/ (4596)
2 exp Respiratory Syncytial Virus Infections/ (9595)
3 (respiratory adj syncytial).tw. (18103)
4 rsv.tw. (16465)
5 1 or 2 or 3 or 4 (24383)
6 nirsevimab$.tw. (177)
7beyfortus$.tw. (12)
8 ("MED 18897" or MED-18897 or MED18897).tw. (0)
9 6 or 7 or 8 (178)
10 5 and 9 (169)

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Appendix B: Risk of Bias: ROB 2.0

Study	Outcome	Randomisation process	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Griffin et al (2020)[1]	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Muller et al (2023)[2]	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Drysdale et al (2023)[3]	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low

Appendix C: Risk of Bias: The Risk of Bias in Non-randomised Studies – Of Interventions (ROBINS-I) assessment tool

Study	Design	Confounding	Selection	Intervention classification	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
López-Lacort (2024)[4]	Case-control (test negative)	Serious	Moderate	Low	Low	Low	Low	Low	**Moderate**
Ezpeleta (2024)[5]	Cohort	Moderate	Low	Low	Low	Low	Low	Low	**Low**
Coma (2024)[6]	Cohort	Moderate	Low	Low	Low	Low	Low	Low	**Low**
Agüera (2024)[7]	Case-control (test negative)	Serious	Moderate	Moderate	Low	Low	Low	Low	**Moderate**
Ares-Gomez (2024)[8]	Cohort	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**
Moline (2024)[9]	Case-control (test negative)	Moderate	Moderate	Low	Low	Low	Low	Low	**Serious**
Paireau (2024)[10]	Case-control (test negative)	Low	Moderate	Low	Low	Low	Low	Low	**Moderate**
Assad (2024)[11]	Matched case-control	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**
Carbajal (2024)[12]	Case-control	Moderate	Moderate	Low	Low	Moderate	Low	Low	**Moderate**
Del Buey (2024)[13]	Cohort	Low	Moderate	Low	Low	Low	Low	Low	**Low**

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