

**7.03 NIRSEVIMAB,****Solution for injection 50 mg in 0.5 mL pre-filled syringe****Solution for injection 100 mg in 1 mL pre-filled syringe****Beyfortus<sup>®</sup>,****SANOFI-AVENTIS AUSTRALIA PTY LTD.****1 Purpose of submission**

- 1.1 The Standard Re-entry resubmission requested inclusion of nirsevimab on the National Immunisation Program (NIP) for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease (LRTD) in: (i) neonates and infants born during or entering their first RSV season; and (ii) children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Throughout these minutes, the word infant refers to an individual under 1 year of age. These populations were unchanged from those previously considered by the PBAC when PBS listing of nirsevimab was requested in July 2024.
- 1.2 Inclusion of nirsevimab on the NIP was requested on the basis of (i) a cost-effectiveness analysis versus placebo (no immunisation) for infants born during or entering their first RSV season; and (ii) a cost-effectiveness analysis versus placebo (no immunisation) for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.
- 1.3 The key components of the clinical issue addressed by the submission are presented in Table 1. The only difference compared to the first submission was that the resubmission nominated no immunisation as the comparator for the population of children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, consistent with previous PBAC advice (paragraph 7.11, nirsevimab July 2024 Public Summary Document (PSD)).

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Table 1: Key components of the clinical issue addressed by the submission (as stated in the resubmission)

Component	Description
Population	(i) Neonates and infants born during or entering their first RSV season (ii) Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season
Intervention	Nirsevimab 50 mg/0.5 mL and 100 mg/mL solution for injection in prefilled syringes <ul style="list-style-type: none"> <li>The recommended dose of nirsevimab for infants weighing &lt; 5 kg born during or entering their first RSV season is 50 mg (0.5 mL), administered by intramuscular injection.</li> <li>The dose of nirsevimab for infants weighing ≥ 5 kg born during or entering their first RSV season is 100 mg (1 mL), administered by intramuscular injection.</li> <li>The recommended dose of nirsevimab for older children entering their second RSV season is 200 mg, administered as two intramuscular injections (2 x 1 mL of the 100 mg/mL formulation) at two different sites (preferably separate limbs, or else separated by 2.5 cm) during the same visit.</li> </ul>
Comparator	<u>Population (i) Neonates and infants born during or entering their first RSV season:</u> <ul style="list-style-type: none"> <li>Main comparator – no immunisation</li> <li>Near market comparator – recombinant RSV prefusion F protein maternal vaccine (Abrysvo®, RSVpreF)</li> </ul> <u>Population (ii) Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season:</u> <ul style="list-style-type: none"> <li>Main comparator – no immunisation</li> </ul>
Outcomes	Efficacy: Incidence of MA RSV LRTI, incidence of MA RSV LRTI resulting in hospitalisation Safety: TEAEs/TESAEs, AESIs, NOCD
Clinical claim	<u>Population (i) Neonates and infants born during or entering their first RSV season:</u> Nirsevimab vs no immunisation <ul style="list-style-type: none"> <li>Superior in terms of comparative clinical effectiveness</li> <li>Non-inferior in terms of comparative safety</li> </ul> Nirsevimab vs RSVpreF (near market comparator) <ul style="list-style-type: none"> <li>Superior in terms of clinical effectiveness</li> <li>Non-inferior in terms of safety</li> </ul> <u>Population (ii) Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season:</u> Nirsevimab vs no immunisation <ul style="list-style-type: none"> <li>Superior in terms of clinical effectiveness</li> <li>Non-inferior in terms of safety</li> </ul>

Source: Table 1.1.1 on p3 of the resubmission

Blue shading is indicative of information previously considered by the PBAC

AESIs = adverse events of special interest; MA RSV LRTI = medically attended RSV-associated lower respiratory tract infection; NOCD = new onset chronic disease; PI = product information; RSV = respiratory syncytial virus; TEAEs = treatment-emergent adverse events; TESAEs = treatment-emergent serious adverse events

## 2 Background

### Registration status

2.1 Nirsevimab (Beyfortus®) was registered by the TGA on 24 November 2023 for the prevention of RSV LRTD in:

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

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- 2.2 The TGA-approved indication also states that nirsevimab should be used in accordance with official recommendations.

***National Immunisation Program***

- 2.3 The resubmission stated that the NIP is the most appropriate framework for funding a whole of population immunisation program for protection against RSV, to ensure optimal uptake and coverage. The resubmission acknowledged that the current legislative framework underpinning the NIP may not support the inclusion of passive immunisation strategies like nirsevimab.
- 2.4 The ESC noted that a pathway for listing of passive immunisation strategies on the NIP would need to be established before the PBAC could recommend listing of nirsevimab on the NIP.
- 2.5 The ESC considered that the proposed NIP listing which would provide funding under a national program, would be preferable to different funding arrangements across the states and territories.

***RSV Mother & Infant Protection Program (RSV-MIPP)***

- 2.6 The National RSV Mother and Infant Protection Program (RSV-MIPP) commenced on 3 February 2025. The RSV chapter in the AIH was updated to reflect the RSV-MIPP on 17 January 2025, including recommendations for the use of RSVpreF and nirsevimab.<sup>1</sup>
- 2.7 The RSV-MIPP provides free access to maternal RSVpreF vaccine under the NIP. States and territories also offer nirsevimab free of charge to eligible infants as part of the program. Infants recommended to receive nirsevimab include babies born to mothers who did not receive RSV vaccine and infants at risk of severe disease from RSV infection, although precise eligibility criteria vary by jurisdiction<sup>2</sup>.
- 2.8 The ESC noted Australian Technical Advisory Group on Immunisation (ATAGI)'s advice that uptake of nirsevimab in states that have implemented programs has been high, although estimates have not yet been published. The ATAGI advice stated that the goal will be to encourage strong RSVpreF vaccine uptake, and to offer nirsevimab to infants whose mothers do not receive the vaccine (or who meet other eligibility criteria). It is currently unclear whether a pattern of provider or parental choice will emerge, and the relative uptake of nirsevimab vs maternal RSVpreF is currently unknown, noting that for the majority of infants only one approach will be used.

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<sup>1</sup> <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/respiratory-syncytial-virus-rsv>

<sup>2</sup> <https://ncirs.org.au/ncirs-releases-suite-new-and-updated-rsv-resources-infant-protection-programs-launched-across>

*Public Summary Document - May 2025 PBAC Meeting***ATAGI advice**

- 2.9 The ATAGI provided pre-submission advice for the PBAC to consider for this resubmission, dated 26 March 2025. The ATAGI also provided post-submission advice, dated 26 March 2025.

**Previous relevant PBAC considerations****Recombinant RSV prefusion F protein maternal vaccine (Abrysvo<sup>®</sup>, RSVpreF)**

- 2.10 Submissions seeking inclusion of the RSVpreF maternal vaccine (referred to as RSVpreF hereafter) on the NIP for the prevention of LRTD caused by RSV in infants from birth through to 6 months of age by active immunisation of pregnant individuals were considered by the PBAC at its meetings in March and May 2024. The PBAC did not recommend RSVpreF in March 2024. Inclusion of RSVpreF on the NIP was recommended in May 2024.
- 2.11 On 19 January 2025 (after the resubmission was lodged), it was announced that RSVpreF would be included on the NIP from 3 February 2025<sup>3</sup>.
- 2.12 The AIH recommends a single dose of RSVpreF for use in pregnant women. Administration is recommended at 28–36 weeks gestation, but may be given beyond 36 weeks gestation. Infants are not adequately protected unless they are born at least 2 weeks after their mother received the vaccine. The AIH states that advice on revaccination in subsequent pregnancies will be provided when data are available<sup>4</sup>.

**Nirsevimab**

- 2.13 A submission requesting General Schedule PBS listing of nirsevimab for the prevention of RSV LRTD in (i) neonates and infants born during or entering their first RSV season; and (ii) children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season was considered by the PBAC at its meeting in July 2024, and not recommended.
- 2.14 Table 2 summarises the key matters of concern from the previous PBAC consideration and how the resubmission addressed those concerns.

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<sup>3</sup> <https://www.health.gov.au/ministers/the-hon-mark-butler-mp/media/protection-against-rsv-for-mums-and-bubs-with-free-vaccine-available-from-3-february-0> [Last accessed: 20 Jan 2025]

<sup>4</sup> <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/respiratory-syncytial-virus-rsv>

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**Table 2: Summary of key matters of concern from the PBAC’s consideration of the first submission in July 2024 and how the resubmission addressed the issues**

Matter of concern	How the resubmission addresses the issues
<b>Appropriate funding mechanism</b>	
<p>The ESC advised that inclusion on the NIP would likely increase uptake of nirsevimab and optimise use, in comparison with the proposed PBS listing, as it would reduce prescription and co-payment barriers. The ESC considered that a coordinated population-based program under the NIP would be preferred for nirsevimab, rather than PBS listing (Para 3.4, July 2024 PSD).</p>	<p>Addressed</p> <p>The resubmission proposed inclusion of nirsevimab on the NIP rather than the PBS.</p>
<b>Comparator</b>	
<p>Palivizumab was not accepted as the main comparator for nirsevimab in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season; no immunisation was considered the appropriate main comparator for Season 2 (Para 7.1, 7.11, 7.15 &amp; 7.23, July 2024 PSD).</p>	<p>Addressed</p> <p>The resubmission nominated no immunisation as the appropriate comparator for nirsevimab when used in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. However, the evidence presented has limitations.</p>
<p>Clinical comparison of nirsevimab versus RSVpreF would remain relevant in a resubmission (Para 7.23, July 2024 PSD).</p>	<p>Addressed</p> <p>The resubmission provided a clinical comparison of nirsevimab versus RSVpreF. However, the evidence presented has limitations.</p>
<b>Eligibility criteria</b>	
<p>The PBAC advised that recommendations in the RSV chapter of the Australian Immunisation Handbook (AIH) for use of vaccines and monoclonal antibodies for prophylaxis of RSV disease should be taken into account in proposing restrictions, especially in relation to instances where it may be appropriate to administer nirsevimab to an infant after maternal vaccination has occurred, and additional considerations in regard to eligibility for nirsevimab in high-risk infants (Para 3.9 – 3.10, 7.9 – 7.10, July 2024 PSD).</p> <p>Regarding the restriction relating to children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, the definition of the high-risk group needed refinement to ensure that current ATAGI advice is incorporated (Para 7.10, July 2024 PSD).</p>	<p>Partially addressed</p> <p>The proposed NIP listing for nirsevimab in the resubmission are stated to be based on the consideration that RSVpreF and nirsevimab would be two alternative forms of immunisation against RSV infection. The proposed listing excludes infants born to mothers who had received RSVpreF more than 2 weeks before delivery from receiving nirsevimab unless the infant has a risk condition. The clinical trials for nirsevimab excluded infants where the mother had received RSVpreF. However, the proposed listing does permit the use of both products in the following populations: (i) those in whom the immune response to RSVpreF may be impaired due to it being administered within 2 weeks of the infant’s birth; and (ii) for infants with risk conditions born during or entering their first RSV season. As discussed in paragraphs 3.1 to 3.5 below, the AIH also suggests that nirsevimab use is appropriate if the mother received RSVpreF at a time of severe immunosuppression or the infant had a treatment associated with loss of maternally derived antibodies (such as cardiopulmonary bypass or extracorporeal membrane oxygenation). This population was not included in the proposed listing in the resubmission.</p>

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Matter of concern	How the resubmission addresses the issues
<b>Clinical evidence</b>	
<p>Data for the overall infant population and for the high-risk subgroup should be presented separately (Para 7.23, July 2024 PSD).</p>	<p>Partially addressed</p> <p>The resubmission presented some information for infants with risk conditions; however, the presentation of evidence was limited. Furthermore, the resubmission did not recognise that the proposed listing of nirsevimab for infants with risk conditions would permit the use of both RSVpreF and nirsevimab in some infants and no evidence demonstrating additional benefit with nirsevimab + RSVpreF versus RSVpreF alone was presented.</p>
<p>Clinical evidence to support the proposed listing of nirsevimab in the second season was limited (Para 7.1, July 2024 PSD).</p> <p>In relation to listing of nirsevimab in the second season (where no immunisation should be the main comparator), the resubmission would need to present corresponding clinical evidence to support this proposed listing (Para 7.23, July 2024 PSD).</p>	<p>Partially addressed</p> <p>The resubmission noted that there is limited clinical evidence for this population. It presented observational data from the WA nirsevimab program. The resubmission requested the PBAC take a “pragmatic” approach to its consideration of this population.</p>
<p>Clinical evidence does not support a conclusion of superiority between nirsevimab and the near-market comparator RSVpreF in Season 1 due to substantial transitivity issues between the nirsevimab trials and the RSVpreF MATISSE trial (Para 7.16 &amp; 7.23, July 2024 PSD).</p> <p>The effectiveness of nirsevimab presented in the submission was estimated from a pooled analysis of the MELODY study and the Phase 2b study (Simões 2023). The PBAC considered that the result from the MELODY trial (74.5%) should be used, as this was sourced from a randomised trial undertaken in the target population, rather than a post hoc analysis (Para 7.51, July 2024 PSD).</p>	<p>Not adequately addressed</p> <p>The resubmission maintained that, although the modality and target population for nirsevimab and RSVpreF are different, the objective of both interventions is the same, and as such the most relevant approach to assess the comparative efficacy and safety of the alternate immunisation strategies is to compare the outcomes of the two immunisation programs. The transitivity issues were acknowledged by the resubmission. The resubmission maintained that nirsevimab is superior to RSVpreF based on a qualitative comparison of evidence for nirsevimab from the meta-analysis of the MELODY and Phase 2b trials (as reported by Simões 2023) and evidence for RSVpreF from the MATISSE trial. The comparison presented was not consistent with the previous PBAC advice regarding only including the results from the MELODY trial in an ITC.</p>
<b>Economic evaluation (cost-effectiveness)</b>	
<p>The ICER for nirsevimab for the first RSV season was substantially underestimated and also highly uncertain given the results were highly sensitive to small variations in several inputs (Para 7.1 &amp; 7.17, July 2024 PSD).</p>	<p>Not adequately addressed</p> <p>The ICER generated by the revised economic analysis did not incorporate several of the modifications that had been advised by the PBAC; and the ICER remained underestimated, uncertain and highly sensitive to key variables.</p>
<p>Economic evaluation and financial estimates should be provided separately for the overall infant population and for the high risk subgroup (Para 7.21 and 7.23, July 2024 PSD).</p> <p>In relation to listing of nirsevimab in the second season (where no immunisation should be the main comparator), the resubmission would need to present corresponding economic evidence to support this proposed listing (Para 7.23, July 2024 PSD).</p>	<p>Partially addressed</p> <p>Although an economic analysis estimating an overall ICER for children with risk conditions was presented, the structure of the model did not permit separate estimation of ICERs in Season 1 and Season 2 in children with risk conditions.</p>

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<b>Matter of concern</b>	<b>How the resubmission addresses the issues</b>
<p>The PBAC noted that the timing of RSV outbreaks varies with the climate across different regions of Australia and that the timing of administration of nirsevimab, in relation to the RSV season, was a key driver of the economic model. (Para 7.13, July PSD)</p> <p>The PBAC considered that the optimal administration assumed by the model did not reflect the likely use of nirsevimab in clinical practice, and noted 'the sensitivity analysis which showed that delaying the administration by one month in the model... resulted in an increase in the ICER of █████%.' (Para 6.81, July 2024 PSD)</p> <p>The PBAC noted that the ICERs for the tropical and temperate populations differed considerably (\$█████<sup>1</sup>/QALY and \$█████<sup>2</sup>/QALY, respectively) in the submission base case (Para 7.17, July PSD)</p>	<p>Not adequately addressed</p> <p>The resubmission model did not address the issue of inappropriately assuming optimal timing of administration of nirsevimab, noting that the MELODY trial inclusion criteria specified recruitment of "Infants who were entering their first RSV season at the time of screening." Thus, the trial population were optimally dosed with respect to timing, but optimal use of nirsevimab may not occur in clinical practice.</p>
<p>The PBAC agreed with the amendments to the economic model proposed by the ESC as a minimum set of changes to be considered (i.e., removal of mechanical ventilation costs; application of updated disutilities; removal of asthma and recurrent wheezing; and adjustment of the case fatality rate to 0.002). Further, the PBAC agreed with the ESC's advice that additional amendments should be considered to address other issues (application of MELODY results rather than the meta-analysis of MELODY and the Phase 2 trial; reduction in rate of hospitalisation from 4.2% to 2.33%, reducing costs associated with hospitalisation so that they would not capture admissions unrelated to RSV) (Para 7.18, July 2024 PSD)</p>	<p>Partially addressed</p> <p>Although the resubmission claimed that the base case economic evaluation was revised to include the minimum set of changes, it continued to assume benefits due to reduced incidence of wheezing and asthma.</p> <p>Furthermore, the base case economic model inappropriately:</p> <ul style="list-style-type: none"> <li>• continued to be informed by estimates of effectiveness from the meta-analysis of MELODY and the Phase 2b trials (rather than the MELODY trial alone);</li> <li>• assumed an overall 4.2% hospitalisation rate in infants without risk conditions (where a 2.33% rate was considered appropriate);</li> <li>• continued to apply costs for hospitalisation over 6 months to each instance of hospitalisation in the model (whereas the ESC previously advised reducing the costs of subsequent hospitalisations).</li> </ul> <p>The resubmission model also only partially addressed the inputs for hospitalisation of the high risk population.</p> <p>Other limitations of the model structure were noted by the PBAC in July 2024 and remain unaddressed by the resubmission (see paragraph 6.64).</p> <p>A more detailed review of the PBAC's July 2024 concerns regarding the economic evaluation and changes made in the resubmission is provided in Table 25.</p>

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Matter of concern	How the resubmission addresses the issues
<p><b>Financial implications</b></p> <p>The PBAC considered that the uptake rates remained uncertain but that high uptake in the first year of life should be the goal for the proposed listing, in order to maximise clinical benefits for infants (Para 7.12, July 2024 PSD).</p> <p>The PBAC considered that the assumed uptake rates in Season 1 required further consideration and justification (Para 7.22, July 2024 PSD).</p> <p>The PBAC considered that a number of updates should be considered in a resubmission in relation to the financial estimates, including updates to the proposed eligible population considering ATAGI recommendations (Para 7.22, July 2024 PSD)</p>	<p>Not adequately addressed</p> <p>The resubmission noted that the high uptake rates proposed in the first submission were considered reasonable by DUSC. Uptake rates in the resubmission for infants in their first RSV season were increased to 80% for a NIP listing (reduced to 70% in PSCR). This was stated to be based on feedback from DUSC, the 2024 Australian state based programs and RWE from other countries. The uptake rate for infants entering their second RSV season remained 90%.</p> <p>The uptake rates applied in the resubmission did not incorporate the availability of RSVpreF on the NIP.</p> <p>The resubmission's estimates also do not consider the potential financial implications of use of both nirsevimab and RSVpreF in some populations (e.g., some infants with risk conditions born during or entering their first RSV season).</p>

Source: Adapted from Section 7 of the public summary document (PSD) detailing the PBAC's consideration of the nirsevimab submission in July 2024 and from Table 1.1.9 on pp20-23 of the resubmission.

BPD = bronchopulmonary dysplasia; DUSC = Drug Utilisation Sub-Committee; ICER = incremental cost-effectiveness ratio; MBS = MedPSD = public summary document; RSV = respiratory syncytial virus.

The redacted values correspond to the following ranges:

<sup>1</sup> \$35,000 to < \$45,000

<sup>2</sup> \$5,000 to < \$15,000

*For more detail on PBAC's view, see section 7 PBAC outcome.*

### 3 Requested listing

- 3.1 The resubmission requested inclusion of nirsevimab in the NIP as shown in Table 3. The resubmission stated that the proposed listing was aligned with the AIH, however, the resubmission did not adequately consider the possible scenarios in which nirsevimab may be used, particularly in relation to situations in which the AIH supports use of nirsevimab in an infant after the mother received RSVpreF (see paragraph 3.5).
- 3.2 As with the first submission, the resubmission requested listing for nirsevimab in either 50 mg/0.5 mL or 100 mg/1 mL of solution for use in neonates and infants younger than 12 months of age. Infants weighing <5 kg would receive 50 mg and infants weighing ≥5 kg would receive 100 mg. Additionally, for children requiring nirsevimab in their second year, a 200 mg dose was requested. This would require administration of two 100 mg/1 mL injections given in one sitting.

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**Table 3: Listing of nirsevimab on the NIP for prevention of RSV infection in infants and children as proposed in the resubmission**

Respiratory syncytial virus (RSV) vaccination schedule for prevention of lower respiratory tract infection		
Age(s) of administration(s) other restrictions or details:		
Disease	Recommended Dosage	Comments
Neonates and infants born during or entering their first RSV season	For infants weighing < 5 kg: a single intramuscular injection of nirsevimab 50 mg (0.5 mL) For infants weighing ≥5kg: a single intramuscular injection of nirsevimab 100 mg (1 mL)	<ul style="list-style-type: none"> <li>• Patient's mother was not vaccinated at least 2 weeks before delivery,</li> </ul> OR <ul style="list-style-type: none"> <li>• Who are at increased risk of severe disease</li> <li>• Special circumstances for infants in their first season can receive two doses<sup>a,b</sup></li> </ul>
Children 12 to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season	Nirsevimab 200 mg administered as two intramuscular injections (2 x 100 mg [1 mL]) during the same visit	Conditions associated with increased risk of severe RSV disease in infants and young children: <ul style="list-style-type: none"> <li>• Preterm birth &lt; 32 weeks gestational age</li> <li>• Haemodynamically significant congenital heart disease</li> <li>• Significant immunosuppression, such as from solid organ transplant, haematopoietic stem cell transplant, or primary immune deficiencies such as severe combined immunodeficiency (SCID)</li> <li>• Chronic lung disease requiring ongoing oxygen or respiratory support</li> <li>• Neurological conditions that impair respiratory function</li> <li>• Cystic fibrosis with severe lung disease or weight for length &lt; 10<sup>th</sup> percentile</li> <li>• Trisomy 21 or another genetic condition that increases the risk of severe RSV disease</li> </ul> Special circumstances for additional dose in second season <sup>a,c</sup>

<sup>a</sup> For children undergoing cardiac surgery with cardiopulmonary bypass, an additional dose of nirsevimab is recommended as soon as the child is stable after surgery to ensure adequate nirsevimab serum levels. The recommended dosage of nirsevimab is administered as an IM injection

<sup>b</sup> First RSV season:

- If surgery is within 90 days after receiving nirsevimab, the additional dose should be based on body weight at the time of the additional dose
- If more than 90 days have elapsed since receiving nirsevimab, the additional dose should be 50 mg regardless of body weight

<sup>c</sup> Second RSV season:

- If surgery is within 90 days after receiving nirsevimab, the additional dose should be 200 mg, regardless of body weight.
- If more than 90 days have elapsed since receiving nirsevimab, the additional dose should be 100 mg, regardless of body weight

Source: Table 1.4.2 on p35 of the resubmission

3.3 Table 4 shows further details for NIP listing of nirsevimab that would be consistent with the recommendations detailed in the RSV chapter of the Australian Immunisation Handbook (AIH). Notably, the AIH endorses the use of nirsevimab in high-risk infants entering their first RSV season regardless of maternal vaccination with RSVpreF (see Table 4).

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**Table 4: Listing of nirsevimab on the NIP for prevention of RSV infection in infants and children that would be in accordance with the Australian Immunisation Handbook (last updated 17 January 2025)**

Age	Dose	Notes
Birth to < 8 months	<p>For infants weighing &lt; 5 kg: a single intramuscular injection of nirsevimab 50 mg (0.5 mL)</p> <p>For infants weighing ≥ 5 kg: a single intramuscular injection of nirsevimab 100 mg (1 mL)</p>	<p>Administer to infants where the mother did not receive RSVpreF (Abrysvo®) during pregnancy (Population A in Figure 1).</p> <p>OR</p> <p>Administer to infants, regardless of maternal vaccination, if the infant has one of the following risk conditions (Population C in Figure 1):</p> <ul style="list-style-type: none"> <li>▶ preterm birth (&lt; 32 weeks gestational age)</li> <li>▶ haemodynamically significant congenital heart disease</li> <li>▶ significant immunosuppression (such as solid organ transplant, haematopoietic stem cell transplant, or primary immune deficiency such as severe combined immunodeficiency)</li> <li>▶ chronic lung disease that requires ongoing oxygen or respiratory support</li> <li>▶ neurological conditions that impair regulatory function</li> <li>▶ cystic fibrosis with severe lung disease or weight for length &lt; 10<sup>th</sup> percentile</li> <li>▶ trisomy 21 or another genetic condition that increases the risk of RSV</li> </ul> <p>OR</p> <p>if the infant has suboptimal RSV antibodies despite the mother having received the RSVpreF vaccine (Population B in Figure 1) because</p> <ul style="list-style-type: none"> <li>▶ the mother received RSV vaccine in pregnancy at a time of severe immunosuppression</li> <li>▶ the infant subsequently underwent a treatment that likely led to loss of maternal antibodies (such as cardiopulmonary bypass or extracorporeal membrane oxygenation)</li> <li>▶ The mother was vaccinated within 2 weeks of the infant's delivery</li> </ul>
≥ 8 months to < 24 months	<p>For older children entering their second RSV season: 200 mg, given as 2 intramuscular injections (2 × 1 mL of the 100 mg/mL formulation) at 2 different sites (preferably separate limbs, or else separated by 2.5 cm) during the same visit</p>	<p>Administer to infants and young children if at risk of severe RSV infection due to one of the following risk conditions (Population D in Figure 1):</p> <ul style="list-style-type: none"> <li>▶ preterm birth (&lt; 32 weeks gestational age)</li> <li>▶ haemodynamically significant congenital heart disease</li> <li>▶ significant immunosuppression (such as solid organ transplant, haematopoietic stem cell transplant, or primary immune deficiency such as severe combined immunodeficiency)</li> <li>▶ chronic lung disease that requires ongoing oxygen or respiratory support</li> <li>▶ neurological conditions that impair regulatory function</li> <li>▶ cystic fibrosis with severe lung disease or weight for length &lt; 10<sup>th</sup> percentile</li> <li>▶ trisomy 21 or another genetic condition that increases the risk of RSV</li> </ul>

Source: Adapted from the AIH at: <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/respiratory-syncytial-virus-rsv> [Last accessed: 17 Jan 2025].

3.4 A diagrammatic representation of the scenarios covered by the AIH recommendations for use of nirsevimab applying at the time of the evaluation is presented in Figure 1. These scenarios for use of nirsevimab are described as Populations A, B, C and D, noting that Population C is comprised of two parts, which are labelled C(a) and C(b).

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Figure 1: Scenarios considered in the AIH recommendations (prepared during the evaluation)

Current scenario – only RSVpreF available on NIP				
Mother vaccinated with RSVpreF with subpopulations as follows:			Mother NOT vaccinated with subpopulations as follows	
Vaccine effectiveness not impaired & infant does not have a risk condition	Immune response to the maternal RSVpreF vaccine effectiveness may be impaired <sup>1</sup>	Infant has a risk condition <sup>2</sup>	Mother not immunised; infant has a risk condition <sup>2</sup>	Mother not immunised; infant does not have a risk condition
			Infants with a risk condition <sup>2</sup> - Season 2	
			Not immunised	
AIH scenario – both RSVpreF and nirsevimab available on NIP				
Population: Infants susceptible to RSV in Season 1 where mother was vaccinated with RSVpreF AND			Population: Infants susceptible to RSV in Season 1 where mother was NOT vaccinated with RSVpreF with subpopulations as follows	
Vaccine effectiveness not impaired & infant does not have a risk condition	Immune response to the maternal RSVpreF vaccine effectiveness may be impaired <sup>1</sup>	Infant has a risk condition <sup>2</sup>	Mother not immunised; infant has a risk condition <sup>2</sup>	Mother not immunised; infant does not have a risk condition
Not eligible for nirsevimab	Population B Eligible for a first dose of nirsevimab (used as add-on to immunisation with RSVpreF)	Population C(b) Eligible for a first dose of nirsevimab (used as add-on to immunisation with RSVpreF)	Population C(a) Eligible for a first dose of nirsevimab (used alone)	Population A Eligible for a first dose of nirsevimab (used alone)
			Infants with a risk condition <sup>2</sup> - Season 2	
			Population D Eligible for a second dose of nirsevimab (used alone)	

AIH = Australian Immunisation Handbook; RSV = respiratory syncytial virus

<sup>1</sup> Immune response to RSVpreF may be impaired if: (i) RSVpreF was administered within 2 weeks of the infant’s birth; (ii) the mother received the RSVpreF vaccine at a time of severe immunosuppression; or (iii) the infant had a treatment associated with loss of maternally derived antibodies (such as cardiopulmonary bypass or extracorporeal membrane oxygenation).

<sup>2</sup> Risk conditions = preterm birth (< 32 weeks gestational age); haemodynamically significant congenital heart disease; significant immunosuppression (such as solid organ transplant, haematopoietic stem cell transplant, or primary immune deficiency such as severe combined immunodeficiency); chronic lung disease that requires ongoing oxygen or respiratory support; neurological conditions that impair regulatory function; cystic fibrosis with severe lung disease or weight for length < 10th percentile; trisomy 21 or another genetic condition that increases the risk of RSV.

3.5 As can be seen when comparing Table 3 with Table 4, the listing requested is not entirely consistent with the recommendations in the AIH. Key points include:

- Both the resubmission’s proposed listing and the AIH recommendations primarily position RSVpreF maternal vaccination and nirsevimab as alternatives, with no preference expressed between the two alternatives.
- Both the resubmission’s proposed listing and the AIH recommendations indicate that nirsevimab should be used in addition to RSVpreF maternal vaccination in circumstances where either: the mother was immunised < 2 weeks prior to the infant’s birth; or where the infant has a risk condition.

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- Both the resubmission's proposed listing and the AIH recommendations recommend use of nirsevimab in children aged <24 months with risk conditions who are entering their second RSV season.
- The resubmission appropriately noted that infants born to mothers whose ethnicity was recorded as Aboriginal and Torres Strait Islander have been reported to be at increased risk of hospitalisation due to RSV infection and it includes Aboriginal and Torres Strait Islander infants with its estimates of children with risk conditions entering a second RSV season. However, neither the resubmission's proposed listing nor the AIH recommendations for nirsevimab included Aboriginal and Torres Strait Islander children as a vulnerable group for access to nirsevimab. The ESC noted the ATAGI's advice that it was appropriate for eligibility for nirsevimab to be based on medical risk factors as set out in the AIH, and it did not support additional criteria specifically for Aboriginal and Torres Strait Islander infants and children based on current evidence.
- There are three differences between the listing proposed in the resubmission and the recommendations in the AIH:
  - The AIH recommends use of nirsevimab (after administration of the RSVpreF maternal vaccine) in infants that may have suboptimal levels of RSV antibodies because they were born to a mother who had received RSVpreF but: (i) the mother received the RSVpreF vaccine in pregnancy at a time of severe immunosuppression; and/or (ii) the infant had a treatment associated with loss of maternally derived antibodies (such as cardiopulmonary bypass or extracorporeal membrane oxygenation). The resubmission's proposed listing does not include these infants.
  - The availability of nirsevimab for infants being exposed to their first season of RSV is not limited by the infant's age in the proposed listing. This is consistent with the approved PI for nirsevimab, which states: "For neonates and infants born during or entering the RSV season, administer BEYFORTUS starting from birth. For infants born outside the RSV season, administer BEYFORTUS once prior to the start of the RSV season considering duration of protection provided by BEYFORTUS." In contrast, the AIH recommends use through to a maximum of 8 months of age (unless the infant has a risk condition). The ESC noted ATAGI's advice that the recommendation for the use of nirsevimab in infants <8 months of age is consistent with recommendations from international bodies such as the US Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP). The ESC considered that it would be appropriate to add the 8-month age limit to the proposed NIP listing for infants born during or entering their first RSV season, consistent with the AIH.
  - As can be seen from the footnotes to Table 3, the listing proposed in the resubmission recommends an additional dose ("replacement dose") of

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nirsevimab in children undergoing cardiac surgery with cardiopulmonary bypass as soon as the child is stable after surgery to ensure adequate nirsevimab serum levels, with dosing based on whether the child is entering their first or second season of potential exposure to RSV, and based on time since the previous dose of nirsevimab ( $\leq 90$  days vs  $> 90$  days). This recommendation is consistent with the approved PI for nirsevimab but is not included in the AIH. The ESC noted ATAGI’s advice which indicated that a new point will be added to the AIH, corresponding to this situation for “Infants who have undergone a procedure, such as cardiopulmonary bypass or extracorporeal membrane oxygenation, that has led to loss of anti-RSV antibodies.”

- 3.6 The Pre-Sub-Committee Response (PSCR) acknowledged that “Cost effectiveness may be compromised in scenarios where infants receive both therapies” and proposed that “nirsevimab should be given preferentially”. The PSCR also proposed that any “reduction in overall cost effectiveness caused by a failed RSVpreF vaccination followed by immunisation with nirsevimab should not be borne by nirsevimab”. The PSCR considered that “An infant in this scenario is identical to an unvaccinated infant and, therefore, should be considered within that cost effectiveness framework.” The ESC did not agree with the PSCR that all infants receiving nirsevimab in Season 1 should be considered a single population.
- 3.7 The prices proposed for nirsevimab are summarised in Table 5. The prices were identical to the ex-manufacturer prices requested in the July 2024 submission. The resubmission stated that \$ [REDACTED] is the nationally negotiated price for state programs.

**Table 5: Proposed pricing of nirsevimab on the NIP**

Name, form	Maximum quantity (units)	Price	Proprietary name and Sponsor
Nirsevimab, 50 mg/0.5 mL, pre-filled syringe Season 1 < 5 kg	1	\$ [REDACTED]	BEYFORTUS Sanofi-Aventis Pty Ltd
Nirsevimab, 100 mg/1 mL, pre-filled syringe Season 1 $\geq 5$ kg	1	\$ [REDACTED]	BEYFORTUS Sanofi-Aventis Pty Ltd
Nirsevimab, 100 mg/1 mL, pre-filled syringe Season 2	2	\$ [REDACTED]	BEYFORTUS Sanofi-Aventis Pty Ltd

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 RSV is the most common viral cause of bronchiolitis and pneumonia in children under five (50% to 80% of cases), posing a significant risk to infants in their first six months of life. It has been estimated that hospitalisation rates range from 2.2 to 4.9 per 1,000

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- among children under five years old and between 8.7 and 17.4 per 1,000 among children under one year old<sup>5</sup>.
- 4.2 Symptoms typically include a low-grade fever, cough, and respiratory distress, potentially escalating to severe conditions requiring hospital care<sup>6</sup>. Risk factors for severe RSV and RSV-associated hospitalisation include very young age, particularly less than three months old, preterm birth, certain congenital heart conditions, chronic lung diseases, and environmental factors like exposure to tobacco smoke<sup>7</sup>. High-risk infants often experience longer hospital stays and may require intensive care.
- 4.3 RSV is spread in respiratory secretions by contact with infected surfaces, and then transferred into the eyes or respiratory tract or by inhaling virus particles via aerosols. Viral shedding typically occurs for 7–10 days but can continue for up to 30 days.<sup>8</sup> In familial settings, infants often contract RSV from older siblings or parents. Research in Australia has shown that infants less than a year old with one, two, or  $\geq 3$  older siblings face a significantly increased risk of RSV infection compared to those infants without siblings.<sup>9</sup>
- 4.4 The COVID-19 pandemic notably disrupted the typical patterns of RSV transmission. Measures taken to curb the spread of COVID-19, such as social distancing and mask-wearing, also impacted the transmission of RSV, leading to changes in the usual seasonal patterns of the virus. For instance, Australia saw a significant decline in RSV cases in 2020 due to COVID-19 related restrictions, followed by a surge in cases the following year.<sup>10</sup>
- 4.5 The resubmission noted that, although most RSV cases in Australia occur in temperate climatic regions of Australia, nationwide RSV control would require specific

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<sup>5</sup> Ranmuthugala G., Brown L., Lidbury B.A. Respiratory syncytial virus – the unrecognised cause of health and economic burden among young children in Australia. *Communicable Diseases Intelligence*. 2011;35(2):177-84. Available at: <https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3502h.htm> [Last accessed: 28 Nov 2024]

<sup>6</sup> Smith D.K., Seales S., Budzik C. Respiratory Syncytial Virus Bronchiolitis in Children. *Am Fam Physician*. 95(2):pp94-9 <https://www.aafp.org/pubs/afp/issues/2017/0115/p94.pdf> [Last accessed: 28 Nov 2024]

<sup>7</sup> Havalda L.B., Bøås H., et al. Risk factors associated with severe disease in respiratory syncytial virus infected children under 5 years of age. *Frontiers in Pediatrics*. 2022;10:1004739 <https://doi.org/10.3389/fped.2022.1004739> [Last accessed: 28 Nov 2024]

<sup>8</sup> Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health and Aged Care, Canberra, 2024. Chapter: Respiratory syncytial virus (RSV) <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/respiratory-syncytial-virus-rsv#nature-of-the-disease> [Last updated: 9 October 2024]

<sup>9</sup> Jacoby P., Glass K., Moore H.C. Characterizing the risk of respiratory syncytial virus in infants with older siblings: a population-based birth cohort study. *Epidemiol Infect*. 2017;145(2):266-71 <https://doi.org/10.1017/s0950268816002545> [Last accessed: 28 Nov 2024]

<sup>10</sup> Chuang Y.C., Lin K.P., et al. The Impact of the COVID-19 Pandemic on Respiratory Syncytial Virus Infection: A Narrative Review. *Infect Drug Resist*. 2023;16:661-75 <https://doi.org/10.2147/idr.s396434> [Last accessed: 28 Nov 2024]

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programmatic measures to address the pattern of RSV circulation seen in northern tropical and sub-tropical climatic regions of Australia.

- 4.6 Nirsevimab is a recombinant neutralising human IgG1 $\kappa$  long-acting monoclonal antibody to the prefusion conformation of the RSV F protein. Nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion. The duration of protection offered by a single dose of nirsevimab is at least 5 months based on clinical and pharmacokinetic data (TGA approved PI).
- 4.7 The first submission stated that potential emergence of variants of RSV that may theoretically impact the efficacy of nirsevimab is being monitored with surveillance virology and clinical virology analysis programs, to genotypically track the prevalence and emergence of F protein sequence variations among RSV isolates, and to phenotypically evaluate the impact of these amino acid substitutions on the efficacy of nirsevimab using an in vitro neutralisation susceptibility assay. The ESC previously considered that the potential for resistance to nirsevimab, and the possibility that variants with reduced susceptibility to nirsevimab will emerge and become prevalent in the future, are both areas of uncertainty.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 Table 6 summarises the comparators, including those nominated by the resubmission, and evaluation comments. The resubmission did not adequately consider the possible scenarios in which nirsevimab may be used.
- 5.2 The ESC agreed with the evaluation that two comparators are relevant for the populations in which the infant's mother did not receive RSVpreF, no immunisation and RSVpreF. RSVpreF maternal vaccine, was included on the NIP from 3 February 2025 (see paragraph 2.11). The PSCR stated that parents will ultimately be given a choice between infant immunisation and maternal vaccination, and reiterated that nirsevimab would be the immunisation option utilised in the majority of cases in clinical practice when both options are available on the NIP (80% uptake estimated in resubmission, reduced to 70% in the PSCR and maintained in pre-PBAC response).
- 5.3 The PBAC agreed with ESC and the evaluation, that for populations in which the infant's mother received RSVpreF, the appropriate comparison would be nirsevimab + RSVpreF versus RSVpreF alone.

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Table 6: Comparators for each AIH population including those nominated by the resubmission

Population	Nominated comparator	Comment
<b>Infants entering their first RSV season (birth to &lt;8 months)</b>		
<b>Population A:</b> infants where the mother did not receive RSVpreF and where the infant does not have a risk condition	No immunisation & RSVpreF maternal vaccination	The nominated comparators are appropriate and are consistent with PBAC's determinations in July 2024
<b>Population B:</b> infants where the mother received the RSVpreF vaccine but where the immune response to the vaccine (in terms of prevention of RSV disease in the infant) may be impaired	Not specified in the resubmission	ESC agreed with the evaluation that the appropriate comparison in this population would be nirsevimab + RSVpreF (with potentially impaired efficacy) versus RSVpreF alone (with potentially impaired efficacy).
<b>Population C(a):</b> infants with risk conditions where the mother did not receive RSVpreF	This population is not explicitly specified in the resubmission but the comparator is implied to be no immunisation & RSVpreF	Presentations of comparisons of nirsevimab to no immunisation and to RSVpreF would be appropriate for this population.  The PSCR proposed that assessment of this group was not required (included in Population A).
<b>Population C(b):</b> infants with risk conditions where the mother did receive RSVpreF	This population is not explicitly specified in the resubmission but the comparator is implied to be no immunisation & RSVpreF	ESC agreed with the evaluation that the appropriate comparison to present for this population would be nirsevimab + RSVpreF versus RSVpreF alone.
<b>Infants entering their second RSV season (≥8 months to &lt;24 months)</b>		
<b>Population D:</b> infants with risk conditions (regardless of whether the mother did or did not receive RSVpreF), and regardless of whether the child received nirsevimab previously in their first RSV season	No immunisation is recognised by the resubmission to be a viable comparator for this population and states that it takes a pragmatic approach using this comparator	No immunisation is the appropriate comparator and its nomination as the main comparator is consistent with the PBAC's determinations in July 2024.

For more detail on PBAC's view, see section 7 PBAC outcome.

## 6 Consideration of the evidence

### Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the use of nirsevimab in Western Australia following its introduction via state funding arrangements, with a focus on research published by Wadia et al. (2025)<sup>11</sup>, and to be published by Bloomfield et al. (2025)<sup>12</sup>. The PBAC considered that the hearing was

<sup>11</sup> Wadia U, Moore HC, Richmond PC, Levy A, Bell L, Pienaar C, Harvey J, Finucane C, van der Helder E, Bloomfield L, Cheng A, Effler P, Blyth CC. Effectiveness of nirsevimab in preventing RSV-hospitalisation among young children in Western Australia 2024. *J Infect.* 2025 Apr;90(4):106466. doi: 10.1016/j.jinf.2025.106466. Epub 2025 Mar 10. PMID: 40074179.

<sup>12</sup> Bloomfield LE, Pingault NV, Foong RE, French S, Morgan JA, Wadia U, Moore HC, Blyth CC, Richmond PC, Armstrong PK, Effler PV. Nirsevimab immunisation of infants and respiratory syncytial virus (RSV)-associated hospitalisations, Western Australia, 2024: a population-based analysis. *Med J Aust.* 2025 Apr 28. doi: 10.5694/mja2.52655. Epub ahead of print. PMID: 40293046.

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informative as it provided an Australian perspective on the value of nirsevimab in clinical practice.

**Consumer comments**

- 6.2 The PBAC noted and welcomed the input from 6 organisations via the Consumer Comments facility on the PBS website in relation to the resubmission. The PBAC recalled that it had previously received consumer input when it considered nirsevimab in July 2024, including individuals (15), health care professionals (2) and organisations (8). Consumer comments from the July 2024 meeting are summarised in the previous PSD (paragraphs 6.2 to 6.6, July 2024 PSD). The PBAC noted that consumer input consistently supported national access to nirsevimab to protect infants and young children from the potentially serious impacts of RSV.
- 6.3 The organisations that provided comments in relation to the resubmission are listed below, with key input summarised.
- Asthma Australia – RSV infections in infants have been associated with childhood allergic asthma;
  - Immunisation Foundation of Australia – babies with severe RSV may require hospitalisation and in some cases intensive care and intubation, which impacts on breastfeeding and physical/mental health of all involved;
  - Lung Foundation Australia – nirsevimab will reduce the risk of disease, disability and death associated with RSV, funding through the NIP will provide a more standardised approach to eligibility criteria for nirsevimab, in comparison with state and territory funding arrangements;
  - National Aboriginal Community Controlled Health Organisation (NACCHO) – Aboriginal and Torres Strait Islander infants experience a high burden of disease due to RSV, access to treatment is harder for those in rural and remote locations and jurisdictional programs may create inequalities of eligibility and access. NACCHO also noted that the seasonality of the RSV season differs in tropical areas compared with temperate areas this needs to be accounted for in the restrictions, in particular the use of nirsevimab should not be limited to a specific season. For example, NACCHO noted that hospitalisations may be higher in the first four months of the year in the Northern Territory, rather than traditional “winter peak” months;
  - National Paediatric Medicines Forum – Expanding access to nirsevimab will improve uptake particularly for rural and remote areas that may not be part of a hospital local area network, a national listing would also address equity concerns surrounding current variation in jurisdictional access restrictions;
  - RSV and Other Respiratory Illnesses Community Reference Group – discussed the impacts of RSV on children and their carers, not only in terms of the disease itself but also affecting the access of children suffering chronic conditions to undergo

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scheduled hospital-based procedures on the planned dates, even during RSV season. The group suggested access to nirsevimab will reduce the incidence of infection and severe complications and will reduce the financial impacts on parents in terms of medical expenses and loss of earnings from caring for sick children.

**Clinical evidence**

- 6.4 The trials and studies presented in the resubmission are detailed in Table 7. Descriptions detailing the populations, interventions, comparators and outcomes assessed in each of the studies are provided in Table 8. Trials and studies presented in the first submission are shown with blue shading. Several observational studies were provided with the resubmission with the objective of demonstrating that results observed in a real world setting are consistent with those observed in the MELODY trial. Information from nirsevimab programs introduced in some states of Australia was also provided by the sponsor.
- 6.5 During the evaluation of the resubmission, an independent search of the literature located two published reports with updated results from the MELODY trial (Muller 2023, Dagan 2024). An updated clinical study report for the MELODY trial was requested from the sponsor during the evaluation and was provided.

**Table 7: Trials and studies presented in the submission**

Trial ID	Report / Publication title	Publication citation
<b>Nirsevimab vs. placebo (for no immunisation)</b>		
MELODY	A Phase III Randomised, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Nirsevimab (MEDI8897), a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants (MELODY)	Interim Clinical Study Report – Primary Analysis 27 September 2021
		Interim Clinical Study Report – Primary Analysis and Safety Analysis 31 August 2022
		Final Clinical Study Report – Primary Analysis, Safety Analysis, and Final Analysis 20 June 2023
	Hammitt, L.L., Dagan, R., et al (MELODY Study Group). Nirsevimab for prevention of RSV in healthy late-preterm and term infants	New England Journal of Medicine 2022;386(9):837-846 <a href="https://doi.org/10.1056/nejmoa2110275">https://doi.org/10.1056/nejmoa2110275</a>
	Muller W.J., Madhi S.A., et al (MELODY Study Group). Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants.	New England Journal of Medicine 2023;388(16):1533-1534. <a href="https://doi.org/10.1056/NEJMc2214773">https://doi.org/10.1056/NEJMc2214773</a>
Dagan R., Hammitt, L.L., et al (MELODY Study Group) Infants Receiving a Single Dose of Nirsevimab to Prevent RSV Do Not Have Evidence of Enhanced Disease in Their Second RSV Season.	Journal of the Pediatric Infectious Diseases Society. 2024;13(2):144-147 <a href="https://doi.org/10.1093/jpids/piad113">https://doi.org/10.1093/jpids/piad113</a>	
Phase 2b	Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants	Clinical Study Report Version 1.0, 20 May 2019
	Griffin, M.P., Yuan, Y., et al (Nirsevimab Study Group). Single-dose nirsevimab for prevention of RSV in preterm infants	New England Journal of Medicine 2020;383(5):415-425 <a href="https://doi.org/10.1056/nejmoa1913556">https://doi.org/10.1056/nejmoa1913556</a>

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Trial ID	Report / Publication title	Publication citation
Simões 2023	Simões, E.A., Madhi, S.A., et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials.	The Lancet Child & Adolescent Health, 2023;7(3):180-189 <a href="https://doi.org/10.1016/s2352-4642(22)00321-2">https://doi.org/10.1016/s2352-4642(22)00321-2</a>
Turalde-Mapili 2023	Turalde Mapili, M.W.R., Mapili, J.A.L., et al. The efficacy and safety of nirsevimab for the prevention of RSV infection among infants: A systematic review and meta analysis.	Frontiers in Pediatrics 2023;11:1132740 <a href="https://doi.org/10.3389/fped.2023.1132740">https://doi.org/10.3389/fped.2023.1132740</a>
HARMONIE	A Phase IIIb randomized open-label study of nirsevimab (versus no intervention) in preventing hospitalizations due to respiratory syncytial virus in infants (HARMONIE)	Primary Clinical Study Report Version 1.0 26 June 2023
	Drysdale, S.B., Cathie, K., et al. Nirsevimab for prevention of hospitalizations due to RSV in infants.	New England Journal of Medicine 2023;389(26):2425-2435 <a href="https://doi.org/10.1056/nejmoa2309189">https://doi.org/10.1056/nejmoa2309189</a>
<b>RSVpreF vaccine vs. placebo</b>		
MATISSE	Kampmann, B., Madhi, S.A., et al (MATISSE Study Group). Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants.	New England Journal of Medicine 2023;388(16):1451-1464. <a href="https://doi.org/10.1056/nejmoa2216480">https://doi.org/10.1056/nejmoa2216480</a>
<b>Nirsevimab vs. palivizumab</b>		
MEDLEY	A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (MEDLEY)	Clinical Study Report – Final Analysis 22 June 2023
	Domachowske, J., Madhi, S.A., et al (MEDLEY Study Group). Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity	New England Journal of Medicine 2022;386(9):892-894. <a href="https://doi.org/10.1056/nejmc2112186">https://doi.org/10.1056/nejmc2112186</a>
	Domachowske, J.B., Chang, Y., et al (MEDLEY Study Group). Safety of re-dosing nirsevimab prior to RSV season 2 in children with heart or lung disease.	Journal of the Pediatric Infectious Diseases Society 2023;12(8):477-480 <a href="https://doi.org/10.1093/jpids/piad052">https://doi.org/10.1093/jpids/piad052</a>
<b>Observational studies</b>		
Riccò 2024	Riccò, M., Cascio A., et al. Impact of Nirsevimab Immunization on Pediatric Hospitalization rates: A Systematic Review and Meta Analysis	Vaccines 2024;12(6):640 <a href="https://doi.org/10.3390/vaccines12060640">https://doi.org/10.3390/vaccines12060640</a>
Barbas Del Buey 2024	Barbas Del Buey, J.F., Íñigo Martínez J, et al. The effectiveness of nirsevimab in reducing the burden of disease due to respiratory syncytial virus (RSV) infection over time in the Madrid region (Spain): a prospective population based cohort study.	Frontiers in Public Health 2024;12:1441786 <a href="https://doi.org/10.3389/fpubh.2024.1441786">https://doi.org/10.3389/fpubh.2024.1441786</a>
Assad 2024	Assad, Z., Romain A. et al. Nirsevimab and hospitalization for RSV bronchiolitis.	New England Journal of Medicine 2024;391(2):144-154 <a href="https://doi.org/10.1056/nejmoa2314885">https://doi.org/10.1056/nejmoa2314885</a>
Carbajal 2024	Carbajal, R., Boelle P., et al. Real world effectiveness of nirsevimab immunisation against bronchiolitis in infants: a case-control study in Paris, France.	The Lancet Child & Adolescent Health 2024;8(10):730-739 <a href="https://doi.org/10.1016/s2352-4642(24)00171-8">https://doi.org/10.1016/s2352-4642(24)00171-8</a>
Agüera 2024	Agüera, M., Soler-Garcia A., et al. Nirsevimab immunization's real-world effectiveness in preventing severe bronchiolitis: A test-negative case-control study.	Pediatric Allergy and Immunology 2024;35(6):e14175 <a href="https://doi.org/10.1111/pai.14175">https://doi.org/10.1111/pai.14175</a>
Lassoued 2024	Lassoued, Y., Levy C., et al. Effectiveness of nirsevimab against RSV bronchiolitis in paediatric ambulatory care: a test negative case-control study.	The Lancet Regional Health–Europe 2024;44:101007 <a href="https://doi.org/10.1016/j.lanpe.2024.101007">https://doi.org/10.1016/j.lanpe.2024.101007</a>

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Trial ID	Report / Publication title	Publication citation
Ares Gómez 2024	Ares Gómez, S, Mallah N., et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population based longitudinal study.	The Lancet Infectious Diseases 2024;24(8):817-828 <a href="https://doi.org/10.1016/s1473-3099(24)00215-9">https://doi.org/10.1016/s1473-3099(24)00215-9</a>
<b>Unpublished observational studies from state-implemented nirsevimab immunisation programs in Australia</b>		
REVIVE (Western Australia)	Blyth C.C., Wadia U., et al. Evaluating the Nirsevimab RSV prevention program in Western Australia -early insights into program impact.	Presentation to the 2024 Options XII for the control of Influenza Conference, Brisbane. October 2024
Queensland paediatric RSV prevention program	Shrestha A., Rajmohan, M., et al. Letter. Impact of 2024 Respiratory Syncytial Virus Immunisation Program in Queensland, Australia	Letter submitted to New England Journal of Medicine on 18 Aug 2024 (Manuscript ID: 24-10507)
New South Wales RSV vulnerable babies' program	Data extraction (12 Sep 2024) from New South Wales RSV vulnerable babies' program	Unpublished report

Source: Table 2.2.1, Table 2.2.2 and Table 2.2.3 on pp45-47 of the resubmission and additional reports identified during the evaluation  
Blue shading is indicative of information previously considered by the PBAC.

Table 8: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Nirsevimab vs placebo RCTs</b>						
MELODY	1,490	R, DB, MC 510 days	low	Healthy infants in their first year of life and born $\geq$ 35 weeks 0 days GA and entering their first RSV season	<ul style="list-style-type: none"> <li>MA RSV LRTI</li> <li>RSV LRTI-hospitalisations</li> <li>Safety and tolerability</li> <li>PK</li> <li>ADA</li> </ul>	Used
Phase 2b D5290C00003	1,453	R, DB, MC 1 year	low	Healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA.	<ul style="list-style-type: none"> <li>MA RSV LRTI</li> <li>RSV LRTI-hospitalisations</li> <li>Safety and tolerability</li> <li>PK</li> <li>ADA</li> </ul>	Used
HARMONIE	8,058	Pragmatic, R, OL, MC 1 year	low	Healthy infants, first season of RSV	<ul style="list-style-type: none"> <li>RSV LRTI-hospitalisation</li> </ul>	Not used
<b>Nirsevimab vs palivizumab RCTs</b>						
MEDLEY	925	R, DB, MC 2 years	low	Preterm infants in their first year of life and born $\leq$ 35 weeks 0 days gestational age without CHD or CLD entering their first RSV season (preterm cohort) and children with CLD and/or CHD entering their first RSV season	<ul style="list-style-type: none"> <li>MA RSV LRTI</li> <li>Safety and tolerability</li> <li>PK</li> <li>ADA</li> </ul>	Not used

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Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
				(CLD/CHD cohort) eligible to receive palivizumab and infants in their first year of life		
<b>RSVpreF vaccine vs placebo RCTs</b>						
MATISSE	7,392	R, DB, MC 2 years	low	Pregnant women between 24 – 36 weeks GA.	<ul style="list-style-type: none"> <li>MA-LRTI</li> <li>Severe MA-LRTI</li> </ul>	Used
<b>Meta-analyses of nirsevimab vs placebo</b>						
Simões 2023	2,350	Meta-analysis of MELODY & Phase 2b <sup>a</sup>	low	Infants from the phase 2b <sup>a</sup> and MELODY trials	<ul style="list-style-type: none"> <li>MA RSV LRTI</li> </ul>	Used
Turalde-Mapili 2023	2,943	Meta-analysis of MELODY & Phase 2b <sup>b</sup>	low	Infants from the MELODY and Phase 2b <sup>b</sup> trials.	<ul style="list-style-type: none"> <li>MA RSV LRTI</li> <li>RSV LRTI- hospitalisations</li> <li>Safety</li> </ul>	Not used
Riccò 2024	43,294	Meta-analysis of 19 studies (RCTs and observational studies)	high	Children <2 entering their first RSV season	<ul style="list-style-type: none"> <li>Hospitalisation due to RSV</li> </ul>	Not used
<b>Observational studies involving nirsevimab (presented as supportive evidence)</b>						
Barbas Del Buey 2024	37,067	Prospective, cohort study	High	Infants born between 1 April and 31 December 2023 who resided in the Madrid region of Spain during the follow- up period (1 October 2023 to 29 February 2024)	<ul style="list-style-type: none"> <li>Primary care episodes</li> <li>Hospital ED presentations</li> <li>Hospital admissions</li> <li>Hospital admissions requiring intensive care</li> </ul>	Not used
Assad 2024	1,035	Prospective, MC, matched case control study	High	Infants < 12 months of age hospitalised in France between 15 October and 10 December 2023	<ul style="list-style-type: none"> <li>RSV-associated bronchiolitis hospitalisation</li> </ul>	Not used
Carbajal 2024	2,786	Test-negative case-control study	High	Infants < 12 months of age, presenting to a paediatric ED and tested for RSV in Paris, France between 14 October 2023 and 29 February 2024	<ul style="list-style-type: none"> <li>ED visits for all- cause bronchiolitis</li> </ul>	Not used
Agüera 2024	234	Test-negative case-control study	High	Infants < 12 months of age hospitalised and tested for RSV across three hospitals in Spain	<ul style="list-style-type: none"> <li>RSV-associated bronchiolitis hospitalisation</li> <li>Severe RSV disease</li> </ul>	Not used
Lassoued 2024	833	Test-negative case-control study	High	Infants < 12 months of age with bronchiolitis attending a network of 107 ambulatory	<ul style="list-style-type: none"> <li>RSV-associated bronchiolitis hospitalisation</li> </ul>	Not used

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Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
				paediatricians and tested for RSV in France between 15 September 2023 and 1 February 2024	<ul style="list-style-type: none"> <li>Severe RSV disease</li> </ul>	
<b>Observational studies investigating association between RSV and short- to mid-term morbidity</b>						
Ares Gómez 2024	6,626	Matched case-control	High	Infants hospitalised for RSV	<ul style="list-style-type: none"> <li>Primary Health Care and emergency services visits for RSV</li> <li>Prescriptions for respiratory airway obstructive disease</li> <li>Antibacterial prescriptions</li> </ul>	Used
<b>Observational studies of nirsevimab effectiveness based on Australian State Nirsevimab Programs</b>						
REVIVE	840	Test-negative case-control study	High	Infants and children hospitalised in a paediatric unit and tested for RSV in Western Australia over 24 weeks	<ul style="list-style-type: none"> <li>Hospitalisation with RSV positive acute respiratory infection</li> </ul>	Used
Queensland paediatric RSV prevention program 2024	Sample size not reported	Observational before-and-after study	High	Infants < 12 months of age	<ul style="list-style-type: none"> <li>Hospitalisation for RSV in 2023 vs. 2024 (before &amp; after the introduction of the Queensland paediatric RSV prevention program that provides RSV prophylaxis with nirsevimab to infants at high risk of severe RSV)</li> </ul>	Not used
New South Wales RSV Vulnerable Babies Program 2024	141,958 in 2023 and 146,017 in 2024	Observational before-and-after study	High	Infants < 12 months of age	<ul style="list-style-type: none"> <li>Total RSV notifications between 1 March and 1 August 2024 (after the introduction of the Vulnerable Babies Program which provided nirsevimab) to infants with risk conditions</li> </ul>	Not used

Sources: Table 2.2.3, p47, Table 2.3.1, pp48-49, Table 2.3.2, p50, Table 2.4.1, p51, and Table 2.4.2., pp52-55, Table 2.5.10, pp86-87, text on pp83, 89-92 of the resubmission, Ricco 2024

Blue shading is indicative of information previously considered by the PBAC.

ADA = anti-drug antibodies; CHD = congenital heart disease; CLD = chronic lung disease; DB = double blind; ED = emergency departments; GA = gestational age; IM = intramuscular; MA RSV LRTI = medically attended respiratory syncytial virus lower respiratory tract infection; MC = multicentre; N = number of participants; OL = open-label; PK = pharmacokinetics; R = randomised; RSV = respiratory syncytial virus

<sup>a</sup> excluding infants from the Phase 2b trial who weighed ≥ 5 kg and received a 50 mg dose

<sup>b</sup> including the full intention-to-treat populations

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6.6 Table 9 classifies the studies detailed in Table 8 according to the populations and relevant comparisons, as detailed in Table 6, they could inform. The highest available level of evidence is presented such that if, for example, directly relevant RCTs are available then supportive observational studies are not listed in the table.

**Table 9: Classification of the evidence by the comparisons required to inform PBAC decision-making**

Population	Studies that could inform the relevant comparison
<p><b>Population A:</b> infants aged &lt; 8 months being exposed to their first RSV where the mother did not receive RSVpreF and where the infant does not have a risk condition</p>	<p><u>Comparison of nirsevimab vs no immunisation:</u>                      MELODY, Phase 2b &amp; HARMONIE RCTs (including a meta-analysis of outcomes from these trials). HARMONIE was proposed as supportive evidence in the first submission on the grounds that it was an open-label trial and thus potentially subject to bias. The resubmission, reasonably, excluded the HARMONIE trial from consideration in the resubmission.</p> <p>Infants born with a gestational age <math>\leq 32</math> weeks are considered to have a risk condition according to the AIH. Pooling of results from the MELODY trial (which recruited only infants with a gestational age <math>\geq 35</math> weeks) with results from the Phase 2b trial (which recruited infants born with gestational age between <math>\geq 29</math> weeks and <math>&lt; 35</math> weeks) inappropriately assumes that, in practice, the proportion of infants born with gestational age between <math>\geq 29</math> weeks and <math>&lt; 35</math> weeks is approximately equal to the proportion of infants born with gestational age <math>\geq 35</math> weeks. According to the AIHW Australia's mothers and babies report<sup>13</sup>, most babies (91%) born in Australia were born at term (37-41 weeks) in 2022. Pooling of the outcomes will inappropriately give an undue greater weight to outcomes from the Phase 2b trial. Approximately 35% of infants in the Phase 2b trial would be considered to have a risk condition due to being born with a gestational age <math>\leq 32</math> weeks.</p> <p>The PBAC previously considered that "a claim of superior comparative effectiveness was reasonable for the main comparison between nirsevimab and no immunisation in Season 1, as supported by the relative risk reduction in MA RSV LRTI for nirsevimab patients compared with placebo in the MELODY and Phase 2b studies. The PBAC was also satisfied that the claim of non-inferior safety was reasonable based on the similar rates of AEs observed in the nirsevimab and placebo arms of both studies" (paragraph 7.14, nirsevimab July 2024 PSD).</p> <p><u>Comparison of nirsevimab vs RSVpreF:</u>                      An indirect comparison of nirsevimab and RSVpreF was previously considered by the PBAC. The PBAC considered that "the clinical evidence did not support a conclusion of superiority between nirsevimab and the near-market comparator RSVpreF in Season 1, due to substantial transitivity issues between the nirsevimab trials and the RSVpreF MATISSE trial." (paragraph 7.15, nirsevimab July 2024 PSD).</p> <p>A qualitative ITC of nirsevimab and RSVpreF was provided by the resubmission. The comparison provided results from the meta-analysis of nirsevimab versus placebo trials reported by Simões 2023 and from the MATISSE RSVpreF versus placebo trial but a formal ITC was not presented in the resubmission on the grounds that the PBAC considered the ITC presented in the first submission to be unreliable and subject to substantial transitivity issues.</p>

<sup>13</sup> <https://www.aihw.gov.au/reports/mothers-babies/australias-mothers-babies/contents/baby-outcomes/gestational-age> [Last accessed: 17 Dec 2024]

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Population	Studies that could inform the relevant comparison
	<p>An ITC comparing nirsevimab and RSVpreF, using placebo (as a proxy for no immunisation) as the common reference, informed by the final results from the MELODY nirsevimab vs placebo trial and by the MATISSE RSVpreF vs placebo trial was presented in the resubmission and additional analyses were conducted during the evaluation, noting that transitivity issues continue to apply.</p>
<p><b>Population B:</b> infants where the mother received the RSVpreF vaccine but where the immune response to the vaccine (in terms of prevention of RSV disease in the infant) may be impaired</p>	<p>No data are presented in the resubmission to inform a comparison of nirsevimab + RSVpreF maternal vaccination (with potentially impaired efficacy) versus RSVpreF maternal vaccination alone (with potentially impaired efficacy).</p> <p>The PBAC previously considered that “additional benefits of maternal vaccination plus nirsevimab would be difficult to assess due to limited data; however, it considered that there may be a small number of instances where it may be clinically appropriate for an infant to receive nirsevimab after the mother had been vaccinated”. The PBAC further considered that “if clinically justified, these infants should not be precluded from accessing nirsevimab, as outlined in the ATAGI’s advice to the PBAC” (paragraph 7.10, nirsevimab July 2024 PSD).</p>
<p><b>Population C(a):</b> infants with risk conditions entering their first season of possible exposure to RSV where the mother did not receive RSVpreF</p>	<p><u>Comparison of nirsevimab vs no immunisation:</u>  Evidence for this comparison was not provided by the first submission. The PBAC stated that “data for the overall infant population and for the high-risk subgroup should be presented separately” in a resubmission (paragraph 7.23, July 2024 PSD). Such data would permit the PBAC to assess whether risk conditions were a prognostic variable or a modifier of the effectiveness of nirsevimab.</p> <p>No trials of nirsevimab versus placebo (for no vaccination) in infants with risk conditions have been performed. However, the MEDLEY trial of nirsevimab vs palivizumab included infants with risk conditions (preterm birth, CLD or CHD) entering their first RSV season and children with CLD or CHD in the Season 2 phase of the trial. In the absence of head-to-head evidence comparing nirsevimab and no immunisation, an ITC using palivizumab as the common reference based on the MEDLEY trial (comparing nirsevimab and palivizumab) and trials comparing palivizumab to placebo (for no immunisation) in infants with risk conditions could be informative. A pragmatic (not systematic) search of the literature conducted during the evaluation identified the following trials comparing palivizumab and placebo (for no immunisation) in infants with risk conditions:</p> <ul style="list-style-type: none"> <li>• Feltes T.F., Cabalka A.K., et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. <i>J Pediatr</i> 2003;143(4):532-540  <a href="https://doi.org/10.1067/s0022-3476(03)00454-2">https://doi.org/10.1067/s0022-3476(03)00454-2</a></li> <li>• IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. <i>Pediatrics</i> 1998;102(3 Pt 1):531-537  <a href="https://publications.aap.org/pediatrics/article-pdf/887238/531.pdf">https://publications.aap.org/pediatrics/article-pdf/887238/531.pdf</a></li> <li>• Tavsu I., GURSOY T., et al. Palivizumab prophylaxis: does it have any influence on the growth and development of the infants? <i>Am J Perinatol.</i> 2014;31(8):667-672  <a href="https://doi.org/10.1055/s-0033-1356485">https://doi.org/10.1055/s-0033-1356485</a></li> </ul> <p>The resubmission did not present such an indirect comparison rather relied on observational data to support its claim that nirsevimab is superior to no immunisation in protecting infants with risk conditions from RSV-related illness.</p> <p>None of the observational studies were specifically designed to investigate the efficacy of nirsevimab in infants with risk factors, although some of the studies did include some infants with risk factors. The NSW RSV prevention program appears to be limited to infants and children with risk conditions. Thus, analyses of data from that program could potentially be informative. However, the analyses of data presented are</p>

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Population	Studies that could inform the relevant comparison
	<p>limited to comparisons of rates of RSV disease in 2023 (before the introduction of the programs) with those in 2024 after the introduction of the programs. The potential for confounded results (e.g., due to greater or lesser circulating levels of RSV in the community) is high.</p> <p><u>Comparison of nirsevimab vs RSVpreF:</u> Although infants with risk conditions were included in the MATISSE trial, results for this subgroup of patients were not reported separately in the published report of the trial (Kampmann 2023). Comparison of nirsevimab and RSVpreF maternal vaccination in infants with risk conditions was thus hampered and it was therefore not possible to determine whether one approach (nirsevimab or RSVpreF) is superior to the other.</p>
<p><b>Population C(b):</b> infants with risk conditions entering their first season of possible exposure to RSV where the mother did receive RSVpreF</p>	<p>No data were presented in the resubmission to inform a comparison of nirsevimab + RSVpreF maternal vaccination versus RSVpreF maternal vaccination alone in infants with risk conditions. A pragmatic (not systematic) search of the literature conducted during the evaluation did not identify any relevant studies examining the use of nirsevimab following RSVpreF that would inform such a comparison. There is thus no evidence indicating that nirsevimab + RSVpreF maternal vaccination confers greater protection against RSV-related illness compared to either maternal RSVpreF vaccination or nirsevimab alone for infants with risk conditions.</p>
<p><b>Population D:</b> infants with risk conditions entering their second season of possible exposure to RSV (regardless of whether the mother did or did not receive RSVpreF)</p>	<p>Given that palivizumab is not funded under any federal program (e.g., NIP or PBS), no immunisation is the appropriate comparator and the nomination of no immunisation as the main comparator is consistent with the PBAC's determinations in July 2024.</p> <p>The only trial evidence available for nirsevimab for children with risk conditions entering their second RSV season is for children with CLD/CHD in the MEDLEY trial versus palivizumab. The potential for conducting an ITC to placebo (as a proxy for no immunisation), using palivizumab as the common reference, was not investigated in the resubmission. However, a pragmatic search of the literature during the evaluation did not identify any trials comparing palivizumab and placebo (for no immunisation) in children with risk conditions entering their second RSV season.</p> <p>The primary source of evidence presented in the resubmission to support use of nirsevimab in children with risk conditions experiencing their second season of RSV was preliminary data from state programs in Western Australia and NSW. However, as noted for Population C(a), the analyses of data from NSW are limited to a comparison of rates of RSV disease in 2023 (before the introduction of the programs) with those in 2024 after the introduction of the programs. The potential for confounded results (e.g., due to greater or lesser circulating levels of RSV in the community) is high.</p>

AIHW = Australian Institute of Health and Welfare; CLD = chronic lung disease; CHD = congenital heart disease; ITC = indirect treatment comparison; NIP = National Immunisation Program; RSV = respiratory syncytial virus.

**Comparative effectiveness**

**Evidence for nirsevimab versus no immunisation in Population A - infants born during or entering their first RSV season where the mother did not receive RSVpreF and where the infant does not have a risk condition**

Phase 2b trial - nirsevimab vs placebo in infants with gestational age between 29 and 35 weeks

6.7 The Phase 2b trial (reported by Griffin 2020) limited recruitment to preterm infants born with gestational age between 29 weeks and < 35 weeks. Approximately 35% of infants recruited to this trial were born with a gestational age ≤ 32 weeks and would be classified as infants with a risk condition according to the AIH.

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- 6.8 As detailed in Table 10, 25/969 (2.6%) infants in the nirsevimab group and 40/484 (9.5%) infants in the placebo group of the Phase 2b trial required medical attendance for RSV LRTI. Efficacy of nirsevimab in preventing MA RSV LRTI was thus estimated at 70.1% (95% CI: 52.3% - 81.2%).
- 6.9 As detailed in Table 10, 8/969 (0.8%) infants in the nirsevimab group and 20/484 (4.1%) infants in the placebo group required hospitalisation for RSV-associated LRTI. Efficacy of nirsevimab in preventing RSV-associated hospitalisations was estimated at 78.4% (95% CI: 51.9% - 90.3%).

**Table 10: Outcomes from the Phase 2b trial through to 150 days post-dose**

End Point and Analysis	Nirsevimab n/N (%)	Placebo n/N (%)	Efficacy RRR (95% CI) <sup>a</sup>	P Value
<b>MA RSV LRTI</b>				
Observed events	25/969 (2.6%)	46/484 (9.5%)	<b>70.1%</b> <b>(52.3%, 81.2%)</b>	<b>&lt;0.0001</b>
<b>Hospitalisation for RSV LRTI</b>				
Observed events	8/969 (0.8%)	20/484 (4.1%)	<b>78.4%</b> <b>(51.9%, 90.3%)</b>	<b>0.0002</b>

Source: Table 2.5.4, p105 of the submission.

Blue shading is indicative of information previously considered by the PBAC.

CI = confidence interval; MA RSV LRTI = medically attended RSV associated lower respiratory tract infection; N = number of participants; RRR = relative risk reduction; RSV = respiratory syncytial virus.

<sup>a</sup> Efficacy defined as the relative risk reduction (calculated as 1 minus the RR, where the RR was estimated with the use of a Poisson regression model with robust variance) in the nirsevimab group compared with the placebo group (observed data) and is expressed as a percentage.

Note: **Bold text** indicates a statistical difference between arms.

MELODY – nirsevimab vs placebo in healthy infants

- 6.10 The MELODY trial (reported by Hammitt 2022) recruited healthy infants born with gestational age ≥ 35 weeks who were entering their first RSV season.
- 6.11 As detailed in Table 11, 12/994 (1.2%) infants in the nirsevimab group and 25/496 (5.0%) infants in the placebo group of the MELODY trial required medical attendance for RSV LRTI. Efficacy of nirsevimab in preventing MA RSV LRTI was thus estimated at 74.5% (95% CI: 49.6% - 87.1%).
- 6.12 As detailed in Table 11, 6/994 (0.6%) infants in the nirsevimab group and 8/496 (1.6%) infants in the placebo group required hospitalisation for RSV-associated LRTI. Efficacy of nirsevimab in preventing RSV-associated hospitalisations was thus not significant and estimated at 62.1% (95% CI: -8.6% - 86.8%).
- 6.13 Updated results, as reported by Muller 2023 but not included in the resubmission have also been provided in Table 11. The PBAC has not previously considered these results.

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Table 11: Outcomes from the MELODY trial through to 150 days post-dose

End Point and Analysis	Nirsevimab n/N (%)	Placebo n/N (%)	Efficacy RRR (95% CI) <sup>a</sup>	P-value
<b>MA RSV LRTI</b>				
Observed events (interim analysis)	12/994 (1.2%)	25/496 (5.0%)	<b>74.5%</b> <b>(49.6%, 87.1%)</b>	<b>&lt;0.001</b>
Observed events (final analysis)	24/2009 (1.2%)	54/1003 (5.4%)	<b>76.4%</b> <b>(62.3%, 85.2%)</b>	NR
<b>Hospitalisation for RSV LRTI</b>				
Observed events (interim analysis)	6/994 (0.6%)	8/496 (1.6%)	62.1% (-8.6%, 86.8%)	0.07
Observed events (final analysis)	9/2009 (0.4%)	20/1003 (2.0%)	<b>76.8%</b> <b>(49.4%, 89.4%)</b>	NR
<b>Very severe medically attended RSV LRTI<sup>b</sup></b>				
Observed events (interim analysis)	5/994 (0.5%)	7/496 (1.4%)	64.3% (-12.0%, 88.6%)	0.07
Observed events (final analysis)	7/2009 (0.3%)	17/1003 (1.7%)	<b>75.6%</b> <b>(48.8%, 91.0%)</b>	NR

Source: Table 2.5.1, p78 of the resubmission and Table 37 of the MELODY CSR, Table 26, Table 30, Table 37 and Table 55 of the final clinical study report for MELODY

Blue shading is indicative of information previously considered by the PBAC.

CI = confidence interval; MA RSV LRTI = medically attended RSV-associated lower respiratory tract infection; RRR = relative risk reduction; RSV = respiratory syncytial virus.

<sup>a</sup> Efficacy was defined as the relative risk reduction (calculated as 1 minus the relative risk, where the relative risk was estimated with the use of a Poisson regression model with robust variance) in the nirsevimab group as compared with the placebo group and is expressed as a percentage.

<sup>b</sup> Very severe medically attended RSV-associated LRTI was defined as infection for which hospitalisation and supplemental oxygen or intravenous fluids were warranted. Results for this exploratory endpoint were not reported in the clinical study report reporting outcomes of the interim analysis. The results of the analyses for the cohort included in the interim MELODY, however, have been reported in Table 55 of the final clinical study report.

Note: **Bold text** indicates a statistical difference between arms.

6.14 In addition to updated outcomes through to Day 150, outcomes in the periods from 152-361 days post-dose and outcomes in the second year following dosing were also available in the public domain (published by Dagan 2024) but were not presented in the resubmission. The key results, summarised in Table 12, indicate that the difference in the effectiveness of nirsevimab versus placebo beyond 150 days is no longer significant. The resubmission, appropriately, made no claim of effectiveness of nirsevimab beyond 150 days. The results reported by Dagan 2024 indicate no antibody-dependent enhancement of infection during the second year after nirsevimab administration. The evaluation considered that the potential for limited duration of protection from MA RSV LRTI with nirsevimab could be an important consideration in determining the most appropriate overall RSV immunisation strategy and for advising on the timing of administration, as the risk of RSV can persist year-round in the tropical and subtropical regions of Australia.

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**Table 12: Incidence of RSV-associated respiratory disease 152–361 days post-dose in the MELODY trial**

Event	Nirsevimab arm n/N (%)	Placebo arm n/N (%)	Unadjusted RRR <sup>a</sup> (95% CI)
Medically attended RSV LRTI (per-protocol definition)	16/1977 (0.8%)	13/985 (1.3%)	39% (-27%, 70%)
Medically attended RSV LRTI (per-protocol definition) with hospitalisation	2/1977 (0.1%)	2/985 (0.2%)	50% (-253%, 93%)
Medically attended RSV-associated LRTI (in investigator's judgement) on any test result (central reference test for the trial or a local test performed in the context of clinical care)	25/1977 (0.8%)	19/985 (1.3%)	34% (-18%, 64%)
Hospitalisation for any respiratory illness (including upper respiratory tract infection) due to RSV on any test result	3/1977 (0.2%)	2/985 (0.2%)	25% (-347%, 87%)

Source: Supplementary Table 2, Dagan 2024

<sup>a</sup> Estimated during the evaluation

RSV = respiratory syncytial virus; RSV LRTI = RSV-associated lower respiratory tract infection.

6.15 The outcomes from the observational studies listed in Table 8 were consistent with the evidence from the MELODY trial.

#### Meta-analyses of Phase 2b and MELODY trials

6.16 Table 13 presents the results of the meta-analysis of the Phase 2b and MELODY trials, as reported by Simões 2023.

6.17 Figure 2 presents the results of the meta-analysis of the Phase 2b and MELODY trials, as reported by Turalde-Mapili 2023.

6.18 The difference in results reported by the two published meta-analyses is because the meta-analysis reported by Turalde-Mapili 2023 included the ITT population from the Phase 2b trial whereas the meta-analysis reported by Simões 2023 excluded the subpopulation of infants from the Phase 2b trial who weighed  $\geq 5$  kg and received a 50 mg dose. Following the Phase 2b trial, drug exposure-response analyses determined that a 50 mg dose was suboptimal in infants weighing  $\geq 5$  kg and this subsequently led to the use of the 100 mg dose of nirsevimab in infants weighing  $\geq 5$  kg in the MELODY trial. The exclusion of subjects who weighed  $\geq 5$  kg and received a (suboptimal) 50 mg dose from the meta-analysis reported by Simões 2023 thus resulted in improved estimates of the efficacy of nirsevimab compared to those reported by Turalde-Mapili 2023.

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Table 13: Outcomes from the Simões 2023 meta-analysis of the MELODY and Phase 2b trials through to 150 days post-dose

End Point and Analysis	Nirsevimab n/N (%)	Placebo n (%)	Efficacy RRR (95% CI) <sup>a</sup>	P Value
<b>MA RSV LRTI</b>				
Observed events	19/1564 (1%)	51/786 (6%)	<b>79.5%</b> <b>(65.9%, 87.7%)</b>	<b>&lt;0.0001</b>
<b>Hospitalisation for RSV LRTI</b>				
Observed events	9/1564 (1%)	21/786 (3%)	<b>77.3%</b> <b>(50.3%, 89.7%)</b>	<b>0.0002</b>

Source: Table 2.5.4, p105 of the submission.

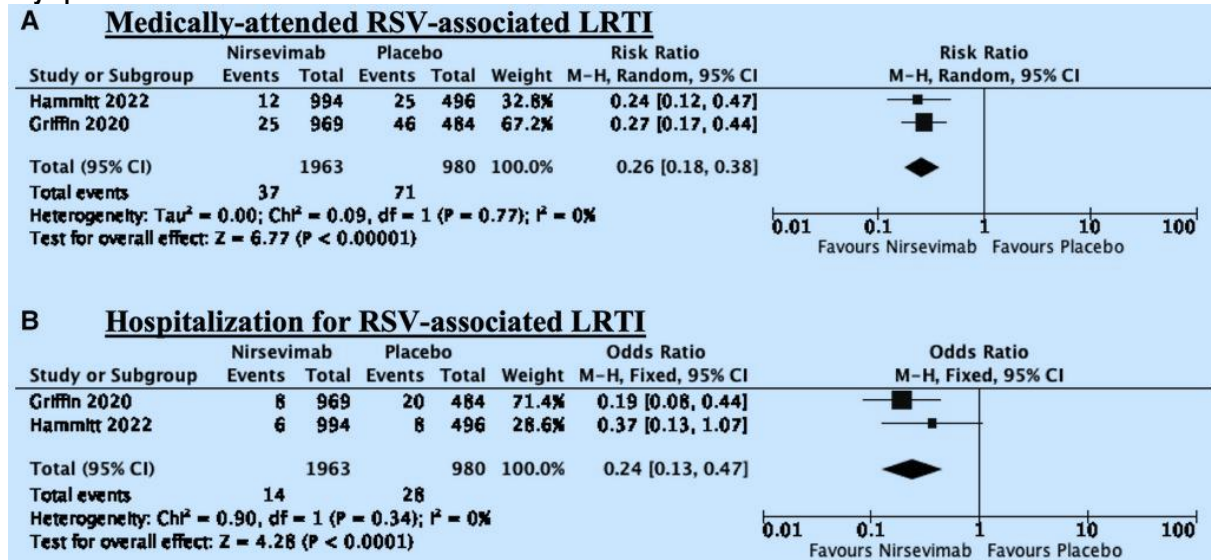
Blue shading is indicative of information previously considered by the PBAC.

CI = confidence interval; MA RSV LRTI = medically attended RSV associated lower respiratory tract infection; N = number of participants; RSV = respiratory syncytial virus.

<sup>a</sup> Efficacy defined as the relative risk reduction (calculated as 1 minus the RR, where the RR was estimated with the use of a Poisson regression model with robust variance) in the nirsevimab group compared with the placebo group (observed data) and is expressed as a percentage.

Note: **Bold text** indicates a statistical difference between arms.

Figure 2: Outcomes from the Turalde-Mapili 2023 meta-analysis of the MELODY and Phase 2b trials through to 150 days post-dose



Source: Table 2.5.4, p105 of the submission.

Blue shading is indicative of information previously considered by the PBAC.

**Evidence for the comparator, RSVpreF versus no immunisation (Population A) - infants experiencing their first RSV season**

MATISSE - maternal RSVpreF vs placebo trial

- 6.19 The MATISSE trial was conducted in women with uncomplicated singleton pregnancies at 24 through 36 weeks' gestation. Women with high-risk pregnancies were excluded from the trial.
- 6.20 As detailed in Table 14, 47/3495 (1.3%) infants in RSVpreF group and 99/3480 (2.8%) infants in the placebo group of the MATISSE trial required medical attendance for RSV LRTI. Efficacy of RSVpreF in preventing MA RSV LRTI in infants was thus estimated at 52.5% (97.58% CI: 28.7% - 68.9%).

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- 6.21 As detailed in Table 14, 17/3495 (0.5%) infants in RSVpreF group and 39/3480 (1.1%) infants in the placebo group of the MATISSE trial required hospitalisation for RSV-associated LRTI. Efficacy of RSVpreF in preventing RSV-associated hospitalisations in infants was estimated at 56.4% (99.17% CI: 5.2% - 81.5%).
- 6.22 The endpoint assessed in the MATISSE trial is from birth whereas the endpoint assessed in the nirsevimab trials is from administration of nirsevimab. A lower incidence of MA RSV LRTI and hospitalisations for RSV LRTI was observed in the placebo arm of the MATISSE trial compared to the nirsevimab trials. This will, at least partially, be because it is not possible to time the birth of an infant relative to the start of the RSV season. For example, infants born at the end of an RSV season in a temperate region will be less likely to become infected with RSV in the five months after their birth.

Table 14: Outcomes from the MATISSE trial

End Point and Analysis	RSVpreF vaccine n/N (%)	Placebo n/N (%)	Efficacy RRR (CI) <sup>a</sup>	P Value
<b>MA RSV LRTI</b>				
Observed events 150 days after birth	47/3495 (1.3%)	99/3480 (2.8%)	<b>52.5%</b> <b>(97.58% CI: 28.7%, 68.9%)</b>	NR
Observed events 180 days after birth	57/3495 (1.6%)	117/3480 (3.4%)	<b>51.3%</b> <b>(97.58% CI: 29.4%, 66.8%)</b>	NR
<b>Hospitalisation for RSV LRTI</b>				
Observed events 150 days after birth	17/3495 (0.5%)	39/3480 (1.1%)	<b>56.4%</b> <b>(99.17% CI: 5.2%, 81.5%)</b>	NR
Observed events 180 days after birth	19/3495 (0.5%)	44/3480 (1.3%)	<b>56.8%</b> <b>(99.17% CI: 10.1%, 80.7%)</b>	NR

Source: Table 2.5.5, p82 of the resubmission and Figure 2 & Table S7, Kampmann 2023 (p20 of the supplement)

Blue shading is indicative of information previously considered by the PBAC.

CI = confidence interval; MA RSV LRTI = medically attended RSV associated lower respiratory tract infection; N = number of participants; RSV = respiratory syncytial virus.

<sup>a</sup> Vaccine efficacy was calculated as  $1 - (P/[1 - P])$ , where P is the number of cases of illness in the RSVpreF group divided by the total number of cases of illness. At intervals beyond 90 days, 97.58% confidence intervals (CIs) were based on a two-sided alpha level of 0.0483 adjusted with the use of the Bonferroni procedure.

Note: **Bold text** indicates a statistical difference between arms.

### Indirect treatment comparison in Population A of nirsevimab versus RSVpreF using placebo as the common reference, based on evidence from MELODY (nirsevimab vs placebo) and MATISSE (RSVpreF vs placebo) - infants experiencing their first RSV season

- 6.23 The resubmission provided a qualitative comparison of outcomes from the meta-analysis of the MELODY and Phase 2b trials (nirsevimab vs placebo) as reported by Simões 2023, and the outcomes from the MATISSE trial (RSVpreF vs placebo), as summarised in Table 15. A formal ITC of nirsevimab and RSVpreF was not presented in the resubmission on the grounds that the PBAC considered the ITC presented in the first submission to be unreliable and subject to substantial transitivity issues. Both the interim and final results from the MELODY trial have been added to the table given that the meta-analyses have an over-representation of pre-term infants that can be considered to have a risk condition (Table 15).

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Table 15: Qualitative comparison outcomes from the meta-analysis reported by MATISSE trial through to 150 days after birth

End Point and Analysis	Intervention n/N (%)	Placebo n/N (%)	Efficacy RRR (Confidence Interval)
<b>MA RSV LRTI in the MELODY trial</b>			
	<b>Nirsevimab</b>	<b>Placebo</b>	
Observed events (interim analysis)	12/994 (1.2%)	25/496 (5.0%)	<b>74.5% (95% CI: 49.6%, 87.1%)</b>
Observed events (final analysis)	24/2009 (1.2%)	54/1003 (5.4%)	<b>76.4% (95% CI: 62.3%, 85.2%)</b>
<b>MA RSV LRTI, as reported by Simões 2023</b>			
	<b>Nirsevimab</b>	<b>Placebo</b>	
Observed events	19/1564 (1%)	51/786 (6%)	<b>79.5% (95% CI: 65.9%, 87.7%)</b>
<b>MA RSV LRTI in the MATISSE trial</b>			
	<b>RSVpreF</b>	<b>Placebo</b>	
Observed events	47/3495 (1.3%)	99/3480 (2.8%)	<b>52.5% (97.58% CI: 28.7%, 68.9%)</b>

Source: Table 2.6.4, p101 of the resubmission (with 95% confidence limits reported by Simões 2023).

Blue shading is indicative of information previously considered by the PBAC.

Note: **Bold text** indicates a statistical difference between arms.

- 6.24 An issue that arises with the comparison of nirsevimab and RSVpreF is the timepoint at which the comparison is provided. The MATISSE trial reported a time-to-event analysis for the MA RSV LRTI endpoint that permits a comparison of outcomes over a long time horizon, whereas results are not presented in this way for the MELODY trial which hampers any comparison beyond 150 days. This is a particularly relevant consideration when determining appropriate RSV immunisation strategies in regions that have extended RSV seasons. Other issues that arise with the comparison of nirsevimab and RSVpreF are discussed below.
- 6.25 The first submission (July 2024) presented ITCs of nirsevimab and RSVpreF using placebo as the common reference based on the results of meta-analyses of the MELODY and Phase 2b trials (nirsevimab vs placebo) and the MATISSE trial (RSVpreF vs placebo), as summarised in Table 16. The PBAC considered that the evidence did not support a conclusion of superiority for nirsevimab over RSVpreF in Season 1 due to substantial transitivity issues between the nirsevimab trials and the RSVpreF MATISSE trial (paragraph 7.16, July 2024 PSD). Differences were noted in the proportion of premature infants, timing of administration (with nirsevimab targeting the RSV season) and the timing of the end point assessment (the nirsevimab trials reported MA RSV LRTI from the time of dosing while MATISSE reported from the time of birth), and different event rates in the placebo arms (paragraph 6.44, July 2024 PSD).

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**Table 16: Results of the indirect comparison (Bucher method) of nirsevimab and RSVpreF using placebo as common reference based on the outcome of MA RSV LRTI at 150 days after administration (nirsevimab) or after birth (RSVpreF)**

Results	RRR (95% CI)
ITC based on Simões 2023 (meta-analysis of trials of nirsevimab vs placebo) and MATISSE (RSVpreF maternal vs placebo); Endpoint: MA RSV LRTI at 150 days after administration of nirsevimab in nirsevimab trials and 150 days after infant birth in MATISSE	<b>56.8%</b> <b>(16.7%, 77.6%)</b>
Turalde-Mapili 2023 (meta-analysis of trials of nirsevimab vs placebo) and MATISSE (RSVpreF maternal vs placebo); Endpoint: MA RSV LRTI at 150 days after administration of nirsevimab in nirsevimab trials and 150 days after infant birth in MATISSE	<b>45.3%</b> <b>(4.30%, 68.7%)</b>
ITC based on interim results from MELODY and MATISSE; Endpoint: MA RSV LRTI at 150 days after administration of nirsevimab in nirsevimab trials and 150 days after infant birth in MATISSE	46.3% (95% CI: -16.2%, 75.2%)
ITC based on final results from MELODY and MATISSE; Endpoint: MA RSV LRTI at 150 days after administration of nirsevimab in nirsevimab trials and 150 days after infant birth in MATISSE	<b>50.3%</b> <b>(10.2%, 72.5%)</b>
ITC based on final results from MELODY and MATISSE; Endpoint: MA RSV LRTI at 150 days after administration of nirsevimab in nirsevimab trials and 180 days after infant birth in MATISSE	<b>51.5%</b> <b>(95% CI: 14.1%, 72.7%)</b>

Source: Table 12, paragraph 6.31, nirsevimab July 2024 PSD and additional rows added during evaluation.

Blue shading is indicative of information previously considered by the PBAC.

RRR = relative risk reduction; RSVpreF = respiratory syncytial virus prefusion F vaccine.

6.26 Notwithstanding issues relating to transitivity of the populations of infants included in the nirsevimab and RSVpreF trials, and some differences in the criteria for establishing an infant had an RSV LRTI between the trials as acknowledged in the resubmission, sensitivity analyses around the ITC were conducted during the evaluation to assess the impact of removing the Phase 2b trial in pre-term infants from the ITC (i.e., including only the results of the MELODY and MATISSE trials). The approach taken to the conduct of the sensitivity analyses aligned with the Bucher method<sup>14</sup>, noting that a 97.58% confidence interval was reported for the estimates of vaccine efficacy in the MATISSE trial and this was appropriately considered. Results of the sensitivity analyses have been added to Table 16. When the results of the Phase 2b trial are excluded from the ITC and only the interim results from MELODY as reported in Table 11 (and Table 15) are applied, the difference in efficacy of nirsevimab vs RSVpreF maternal vaccination is no longer statistically significant. However, when the final results from MELODY as reported in Table 11 (and Table 15) are applied, the difference is statistically significant (RRR for nirsevimab vs RSVpreF is 50.3% [95% CI: 10.2%, 72.5%]). When the outcomes at 180 days (rather than 150 days) after birth from the MATISSE trial are used in the indirect comparison along with the updated results at 150 days after dosing of nirsevimab from MELODY, the RRR for nirsevimab compared with maternal RSVpreF is 51.5% (95% CI: 14.1%, 72.7%).

<sup>14</sup> Bucher H.C., Guyatt G.H., et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology*. 1997;50(6):683-691.

[https://doi.org/10.1016/S0895-4356\(97\)00049-8](https://doi.org/10.1016/S0895-4356(97)00049-8)

**Evidence for RSVpreF + nirsevimab versus RSVpreF in Population B - infants where the mother received RSVpreF but where the immune response to the vaccine (in terms of prevention of RSV disease in the infant) may be impaired**

- 6.27 A pragmatic search of the literature performed during the evaluation did not locate any specific studies demonstrating the effectiveness of nirsevimab in an infant population where the mother received RSVpreF but where the immune response to the vaccine (in terms of prevention of RSV disease in the infant) may be impaired.
- 6.28 The resubmission (in Table 1.1.9) reported that the economic analyses presented in the resubmission did not incorporate the use of nirsevimab in this population given the likely small size of the population and lack of data for the use of nirsevimab in these circumstances.
- 6.29 The PBAC previously considered that “additional benefits of maternal vaccination plus nirsevimab would be difficult to assess due to limited data; however, it considered that there may be a small number of instances where it may be clinically appropriate for an infant to receive nirsevimab after the mother had been vaccinated” and listed the examples given for Population B. The PBAC further considered that “if clinically justified, these infants should not be precluded from accessing nirsevimab, as outlined in the ATAGI’s advice to the PBAC” (paragraph 7.10, nirsevimab July 2024 PSD).

**Evidence for nirsevimab versus no immunisation in Populations C(a) and C(b) - infants with a risk condition entering their first RSV season where infants’ mothers had not, and had, received RSVpreF, respectively**

- 6.30 The PBAC previously requested that data for the high-risk subgroup be presented separately (paragraph 7.23, nirsevimab PSD, July 2024). In presenting clinical evidence for children with risk conditions, the resubmission did not differentiate results for infants with risk conditions born during or entering their first RSV season from infants without risk conditions. However, the clinical section of the resubmission discussed the use of nirsevimab in children with risk conditions entering their second season separately.
- 6.31 The only evidence from a randomised controlled trial that specifically investigated the use of nirsevimab in children with risk conditions entering their first RSV season is the MEDLEY trial, which recruited two cohorts of children: (i) preterm infants in their first year of life born with a gestational age  $\leq 35$  weeks, excluding those with chronic lung disease (CLD) of prematurity, and eligible to receive palivizumab according to national or local guidelines; and (ii) children with CLD of prematurity or haemodynamically significant congenital heart disease (CHD). Subjects in the MEDLEY trial were randomised to either nirsevimab or palivizumab.
- 6.32 The Phase 2b trial included a subgroup of infants that would be considered to have risk conditions. Specifically, as detailed in Table 4, the subgroup of infants with gestational age  $> 29$  weeks to  $\geq 32$  weeks (34% of infants in the Phase 2b trial) would be considered to have a risk condition. Results for this subgroup were not presented

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in the resubmission but the clinical study report stated that the effectiveness of nirsevimab in terms of the MA RSV LRTI at 150 days endpoint in this subgroup was 74.7% (95% CI: 44.9%, 88.4%; 2.8% incidence of MA RSV LRTI in the nirsevimab arm vs 10.9% in the placebo arm) and 70.4% (95% CI: 44.7%, 84.2%; 2.5% incidence of MA RSV LRTI in the nirsevimab arm vs 8.4% in the placebo arm). The effectiveness of nirsevimab in these infants with a risk condition born during or entering their first RSV season is similar to the effectiveness observed in the MELODY trial. As might be expected, the risk of MA RSV LRTI in the premature subgroup of the placebo arm of Phase 2b trial was higher than observed for healthy infants in the placebo arm of the MELODY trial.

- 6.33 Of the observational studies presented in the resubmission that examined outcomes for infants experiencing their first RSV season, only the NSW RSV vulnerable babies’ program specifically involved the administration of nirsevimab to infants with risk conditions. The other observational studies, including the Western Australia (WA) and Queensland state programs, presented in the resubmission involved administration to all infants experiencing their first RSV season and did not specifically report outcomes in infants with risk conditions entering their first RSV season.
- 6.34 The NSW RSV Vulnerable Babies Program provided nirsevimab to infants who were at greatest risk of serious illness in the 2024 RSV season (March 2024 to September 2024). This included all Aboriginal and Torres Strait Islander infants and all premature infants (< 37 weeks gestational age at birth) born after 31 October 2023 and other eligible infants including those with CLD aged < 12 months, those with haemodynamically significant CHD aged < 24 months, those with combined immunodeficiency who had not received curative treatment aged < 24 months, those with Trisomy 21 aged < 12 months, those with complex conditions that significantly impair respiratory function aged < 12 months and those within 28 days of scheduled haematopoietic stem cell transplant (HSCT) or prior to engraftment after HSCT aged < 24 months. Results reporting the rate of RSV notification by age group in 2023 and 2024, as presented in the resubmission, are provided in Table 17. The submission reported that in 2023, prior to the implementation of the program, the rate of RSV notifications of all infants <6 months (6,745 per 100,000) was similar to that for infants aged 12 to <18 months (6,893 per 100,000). After the implementation of the program, the notification was 25% lower in the immunised group (7,359 vs 9,783 per 100,000).

**Table 17: Rate of RSV notifications in infants by age group in NSW, 2023 vs 2024**

Year	Age group (months)	Notifications	Population	Rate per 100,000 (95% CI)	Rate ratio (95% CI)
2023	0 – <6	3,241	48,051	6,745 (6,522, 6,973)	
	6 – <12	3,493	48,051	7,269 (7,039, 7,505)	0.93 (0.89, 0.97)
	12 – <18	3,161	45,856	6,893 (6,663, 7,129)	0.98 (0.93, 1.03)
2024	0 – <6	3,607	49,012	7,359 (7,130, 7,594)	
	6 – <12	4,976	49,012	10,153 (9,887, 10,423)	0.72 (0.69, 0.75)
	12 – <18	4,695	47,993	9,783 (9,518, 10,052)	0.75 (0.72, 0.78)

Source: Table 2.5.14 on p 92 of the resubmission

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6.35 As shown in Table 9, an ITC comparing nirsevimab and no immunisation using palivizumab as the common reference was possible for the hospitalisation endpoint but was not provided in the resubmission. Such an ITC was conducted during the evaluation based on evidence from the MEDLEY and trials reported by the IMpact Study Group 1998 and Feltes 2003 that each compared palivizumab and placebo (for no immunisation) in infants with risk conditions. Results of this ITC are presented in Table 18. There is a substantial difference in the incidence of hospitalisation in the palivizumab arm of the MEDLEY and the palivizumab arms of the trials reported by the IMpact Study Group 1998 and Feltes 2003. The difference potentially indicates that infants included in the palivizumab placebo-controlled trials were at higher risk of hospitalisation at baseline than infants included in the MEDLEY trial and thus an assumption of transitivity of the populations across the trials could potentially be violated. The IMpact trial recruited: (i) preterm infants up to 6 months of age born with a gestational age  $\leq$  35 weeks; and (ii) children up to 24 months of age with a clinical diagnosis of bronchopulmonary dysplasia (BPD). The trial reported by Feltes 2003 recruited infants up to 24 months of age with haemodynamically significant CHD. However, as noted in the MEDLEY clinical study report, COVID-19 pandemic-related measures may have reduced RSV circulation during the conduct of the trial (recruitment for infants entering their first RSV season began in mid-2019 and all patients had been followed up for 150 days by mid 2021) and resulted in lower than usual event rates. As can be seen from the last row of Table 18, the point estimate of the efficacy outcome from the ITC comparing nirsevimab with placebo (for no immunisation) is in favour of nirsevimab and is approximately consistent with the outcomes observed in healthy children however the confidence interval is very wide and the difference vs placebo does not reach statistical significance. This is likely due to the wide confidence interval around the difference in effectiveness between nirsevimab and palivizumab in the MEDLEY trial, which was not designed to establish non-inferiority of nirsevimab compared to palivizumab from an effectiveness point of view.

**Table 18: Results of an indirect treatment comparison comparing nirsevimab and no immunisation using palivizumab as the common reference**

Trial & endpoint	Nirsevimab n/N (%)	Palivizumab n/N (%)	Placebo n/N (%)	Relative risk (95% CI)
<b>Hospitalisation for RSV-related LRTI through to Day 150 after initial dose (Season 1)</b>				
MEDLEY	2/616 (0.3%)	2/309 (0.6%)	N/A	0.50 (0.07, 3.54)
IMpact Study Group 1998	N/A	48/1002 (4.8%)	53/500 (10.6%)	<b>0.45 (0.28, 0.62)</b>
Feltes 2003	N/A	34/639 (5.3%)	63/648 (9.7%)	<b>0.55 (0.33, 0.77)</b>
<b>Meta-analysis of palivizumab vs placebo trials</b>				<b>0.49 (0.37, 0.66)</b>
<b>ITC nirsevimab vs placebo</b>				0.25 (0.03, 1.78)
<b>Efficacy of immunisation [RRR] with nirsevimab vs placebo</b>				75% (-78%, 97%)

Sources: Table 27, MEDLEY CSR, Table 2 Impact Study Group 1998, Table II Feltes 2003

Note: **Bold text** indicates a statistical difference between arms.

6.36 Based on the evidence from the Phase 2b trial, which included infants who were born at  $<$  32 weeks gestation and the evidence from the indirect comparison of nirsevimab and no immunisation, using palivizumab as the common reference, the claim of

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superiority of nirsevimab versus no immunisation can be considered reasonable though there is uncertainty around the magnitude of benefit. Given the similarity of outcomes in healthy infants and infants with risk conditions, it may be reasonable to hypothesise that risk conditions are a prognostic factor rather than a modifier of treatment effect of nirsevimab.

- 6.37 No data are presented in the resubmission to inform a comparison of nirsevimab + RSVpreF vs RSVpreF alone in infants with risk conditions (where the mother had received RSVpreF– Population C(b)). A pragmatic (not systematic) search of the literature conducted during the evaluation did not identify any relevant studies investigating use of nirsevimab in infants following administration of RSVpreF that might inform such a comparison.
- 6.38 There is thus no evidence indicating that nirsevimab in addition to RSVpreF maternal vaccination confers greater protection against RSV-related illness compared to either maternal RSVpreF vaccination or nirsevimab alone for infants with risk conditions. The AIH endorses the use of nirsevimab in high-risk infants entering their first RSV season regardless of maternal vaccination RSVpreF (see Table 4).

**Evidence for nirsevimab versus no immunisation in Population D (infants with a risk condition entering their second RSV season)**

- 6.39 The only trial evidence available for nirsevimab for children with risk conditions entering their second RSV season is for children with CLD/CHD in the MEDLEY trial versus palivizumab. As discussed in paragraph 6.31, the MEDLEY trial was not designed to establish non-inferiority of nirsevimab versus palivizumab from an efficacy perspective. The MEDLEY trial gave either palivizumab or nirsevimab to participants entering their second RSV season. Participants who were randomised to nirsevimab in the first season received a single dose of 2 x 100 mg/mL nirsevimab followed by 4 once monthly doses of placebo to maintain blinding. Participants who had been randomised to palivizumab for season 1 were re-randomised 1:1 to either nirsevimab or palivizumab. Subjects who were re-randomised to the nirsevimab group received one dose of 2 x 100 mg/mL nirsevimab followed by 4 once monthly doses of placebo, while participants re-randomised to the palivizumab arm received 5 once monthly 15 mg/kg doses of palivizumab.
- 6.40 Results, as presented in the nirsevimab July 2024 PSD, are provided in Table 19.

**Table 19: Incidence of MA RSV LRTI in Season 2**

	NIRS/NIRS (N = 180) n (%)	PALI/PALI (N = 42) n (%)	PALI/NIRS (N = 40) n (%)
Through 150 days post first dose	0	0	0
From 151 to 360 days post first dose <sup>a</sup>	0	1/40 (2.5)	1/40 (2.5)
Through 360 days post first dose	0	1 (2.4)	1 (2.5)

Source: Table 30, p123 of the MEDLEY CSR

CSR = clinical study report; MA RSV LRTI = medically attended respiratory syncytial virus associated lower respiratory tract infection; NIRS = nirsevimab; PALI = palivizumab.

<sup>a</sup> The incidence rate was calculated using the number of ITT subjects followed for at least 151 days post first dose as a denominator.

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- 6.41 The potential to conduct an indirect comparison to placebo (for no immunisation), using palivizumab as the common reference, was not investigated in the resubmission. However, a pragmatic search of the literature during the evaluation did not identify any trials comparing palivizumab and placebo (for no immunisation) in children with risk conditions entering their second RSV season.
- 6.42 The primary source of evidence presented in the resubmission to support use of nirsevimab in children with risk conditions experiencing their second season of RSV was preliminary data from state nirsevimab programs in Western Australia (WA) and New South Wales (NSW). The results from the NSW program are discussed in paragraphs 6.33 and 6.34.
- 6.43 As noted in Table 8, the REVIVE study is an observational test-negative case-control cohort study of hospitalised children. The study classified hospitalisations according to whether the child had RSV-associated illness or not and whether the child had received nirsevimab or not and compared rates of RSV-associated hospitalisation in those immunised versus those not immunised. The study thus examined the effectiveness of the Western Australian nirsevimab immunisation program that offered nirsevimab to all infants aged < 12 months entering their first RSV season and to children aged < 24 months with risk conditions (including Aboriginal and Torres Strait Islander children) entering their second RSV season. The key results from the REVIVE study conducted in Western Australia are summarised in Table 20. Results are shown separately for infants entering their first RSV season and those entering their second RSV season. The results for the infants entering their first RSV season are consistent with the final results from the MELODY trial. The point estimate for the effectiveness of nirsevimab in children entering their second RSV season trended toward being lower than observed in the cohort of children experiencing their first RSV season and did not reach statistical significance.
- 6.44 The evidence supporting a claim that nirsevimab is superior to no immunisation in preventing RSV-related hospitalisations in Population D is, overall, weak. There is also a high degree of uncertainty regarding the incidence of RSV-related illness in children with risk conditions entering their second RSV season.

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Table 20: Number of children hospitalised in WA by nirsevimab immunisation status and RSV status, with associated estimates of nirsevimab effectiveness

Cohort	RSV negative		RSV positive		OR (95% CI)	Adjusted OR <sup>a</sup> (95% CI)	Nirsevimab effectiveness <sup>a</sup> (95%CI)
	Nirsevimab immunised	Not immunised	Nirsevimab immunised	Not immunised			
Y1	39	25	30	87	<b>0.221</b> (0.115, 0.424)	<b>0.161</b> (0.076, 0.339)	<b>83.9%</b> (66.1, 92.4)
Y2	3	5	3	29	0.172 (0.027, 1.108)	0.312 (0.011, 8.47)	68.9% (<0, 98.9%)

Source: Table 2.5.8 on p84 of the resubmission

<sup>a</sup> Adjusted by age group, sex, Aboriginality, comorbidity, preterm birth, grouped by month.

aOR = adjusted odd ratio; CI = confidence interval; RSV = respiratory syncytial virus, OR = odds ratio; Y1 = all infants <1 year entering their first season, Y2 = infants <2 years entering their second season who remain at risk of severe RSV disease, including Aboriginal and Torres Strait Islander children

Note: **Bold text** indicates a statistical difference between arms.

Note that the results presented in Table 20 are derived from ad-hoc analyses conducted by the authors of Wadia et al. (2025) for the applicant specifically for the purposes of informing the PBAC consideration. These analyses are not the final data from the authors of Wadia et al. (2025) study. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose. Wadia et al. (2025) has since been published in the Journal of Infection, incorporating the complete cohort and updated, validated data at <https://doi.org/10.1016/j.jinf.2025.106466>.

6.45 The PSCR noted data from the WA state immunisation program (REVIVE) have now been published by Wadia et al.<sup>15</sup> The investigators report a high VE of 98.7% (95% CI: 60.1% to 99.9%) for children entering their second RSV season. The results should be interpreted with caution due to the very small sample size (only 8 immunised children in the Y2 cohort as reported in Wadia et al. (2025), noting that data for 6 immunised children was reported in Table 20)<sup>16</sup>.

### Comparative harms

6.46 The resubmission presented the same analyses of safety data from the MELODY, Phase 2b and MEDLEY trials as presented in the first submission. The analyses are provided in Table 22, Table 23 and Table 24. The incidence of AEs in the final analysis of MELODY was approximately consistent with the incidence reported in Table 24.

<sup>15</sup> Wadia U, Moore HC, Richmond PC, Levy A, Bell L, Pienaar C, Harvey J, Finucane C, van der Helder E, Bloomfield L, Cheng A, Effler P, Blyth CC. Effectiveness of nirsevimab in preventing RSV-hospitalisation among young children in Western Australia 2024. J Infect. 2025 Apr;90(4):106466. doi: 10.1016/j.jinf.2025.106466. Epub 2025 Mar 10. PMID: 40074179.

<sup>16</sup> Note that the results presented in Table 20 are derived from ad-hoc analyses conducted by the authors of Wadia et al. (2025) for the applicant specifically for the purposes of informing the PBAC consideration. These analyses are not the final data from the authors of Wadia et al. (2025) study. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose. Wadia et al. (2025) has since been published in the Journal of Infection, incorporating the complete cohort and updated, validated data at <https://doi.org/10.1016/j.jinf.2025.106466>.

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Table 21: Incidence of key adverse events in the MELODY trial through 360 days post-injection

Adverse event	Nirsevimab (N=987) n (%)	Placebo (N=491) n (%)	Total (N=1,478) n (%)
≥1 AE	863 (87.4)	426 (86.8)	1,289 (87.2)
≤1-day post-dose	18 (1.8)	3 (0.6)	21 (1.4)
≤3 days post-dose	56 (5.7)	23 (4.7)	79 (5.3)
≤7 days post-dose	132 (13.4)	63 (12.8)	195 (13.2)
≤14 days post-dose	279 (28.3)	119 (24.2)	398 (26.9)
≥1 AE considered related to IP	10 (1.0)	7 (1.4)	17 (1.2)
≥1 skin reaction related to IP	4 (0.4)	2 (0.4)	6 (0.4)
≥1 AE of ≥Grade 3 severity	36 (3.6)	21 (4.3)	57 (3.9)
≥1 SAE <sup>c</sup>	67 (6.8)	36 (7.3)	103 (7.0)
Considered related to trial drug	0	0	0
Any AE with outcome death <sup>a</sup> (Grade 5 severity)	3 (0.3)	0	3 (0.2)
≥1 AE of special interest <sup>b</sup>	1 (0.1)	0	1 (0.1)
≥1 AE related to COVID-19	7 (0.7)	7 (1.4)	14 (0.9)
Confirmed COVID-19 case	6 (0.6)	6 (1.2)	12 (0.8)
Suspected to be related to COVID-19	1 (0.1)	1 (0.2)	2 (0.1)

Source: Table 2.5.15, p93 of the resubmission

Blue shading is indicative of information previously considered by the PBAC.

AE = adverse event; COVID-19 = coronavirus disease 2019; SAE = serious adverse event; IP = investigational product.

<sup>a</sup> No deaths were considered related to the trial drug by blinded investigators.

<sup>b</sup> AEs of special interest included hypersensitivity, immune complex disease and thrombocytopenia.

<sup>c</sup> SAEs were defined as death, events that were life-threatening or required inpatient hospitalisation, events that prolonged hospitalisation, events that were persistent or that were associated with clinically significant disability or incapacity or events that were considered to be of medical significance.

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Table 22: Incidence of adverse events in the Phase 2b Study

Adverse event <sup>a</sup>	Nirsevimab (N=969) n (%)	Placebo (N=479) n (%)
≥1 AE	834 (86.2%)	416 (86.8%)
≤1-day post-dose	24 (2.5%)	12 (2.5%)
≤7 days post-dose	121 (12.5%)	73 (15.2%)
≥1 AE considered related to IP	22 (2.3%)	10 (2.1%)
≥1 AE of ≥Grade 3 severity <sup>b</sup>	77 (8.0%)	60 (12.5%)
Death <sup>c</sup> (grade 5 severity <sup>b</sup> )	2 (0.2%)	3 (0.6%)
≥1 SAE <sup>d</sup>	108 (11.2%)	81 (16.9%)
≥1 SAE <sup>d</sup> or ≥Grade 3 severity <sup>b</sup>	124 (12.8%)	92 (19.2%)
≥1 SAE <sup>d</sup> related to trial drug	0	0
≥1 AE of special interest <sup>b</sup>	5 (0.5%)	3 (0.6%)
≥1 AESI related to IP	5 (0.5%)	3 (0.6%)
≥1 skin reaction	318 (32.9%)	148 (30.9%)
≥1 IP related skin reaction	9 (0.9%)	4 (0.8%)
≥1 skin hypersensitivity reaction	5 (0.5%)	3 (0.6%)
≥1 IP related skin hypersensitivity reaction	5 (0.5%)	3 (0.6%)
≥1 NOCD	4 (0.4%)	4 (0.8%)
≥1 IP related NOCD	0	0

Source: Table 2.5.16, p94 of the resubmission.

Blue shading is indicative of information previously considered by the PBAC.

AE = adverse event; AESI = adverse event of special interest; IP = investigational product; NOCD = new onset chronic disease; SAE = serious adverse event.

Note: Events that occurred after 360 days post dose were excluded.

<sup>a</sup> Subjects were counted once for each category regardless of the number of events.

<sup>b</sup> Grade 3: severe, Grade 4: life-threatening, Grade 5: fatal.

<sup>c</sup> One additional death occurred in the placebo group after 360 days post dose.

<sup>d</sup> Serious adverse event criteria: death, life-threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the patient).

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Table 23: Summary of AEs observed in the MEDLEY trial in the 360 days post-dose in Season 1

Adverse events	Preterm (N=612)		CHD/CLD (N=306)	
	Nirsevimab (N=406) n (%)	Palivizumab (N=206) n (%)	Nirsevimab (N=208) n (%)	Palivizumab (N=98) n (%)
≥1 AE	268 (66.0)	134 (65.0)	148 (71.2)	72 (73.5)
≥1 TRAE	6 (1.5)	4 (1.9)	4 (1.9)	2 (2.0)
≥1 AE of Grade ≥3 severity <sup>a</sup>	14 (3.4)	7 (3.4)	30 (14.4)	13 (13.3)
≥1 TRAE of Grade ≥3 severity <sup>a</sup>	0	0	0	0
Any AE with outcome of death (Grade 5 severity) <sup>a</sup>	2 (0.5)	0	3 (1.4)	1 (1.0)
≥1 SAE <sup>b</sup>	28 (6.9)	11 (5.3)	40 (19.2)	20 (20.4)
≥1 SAE, Grade ≥3 adverse event, or both <sup>a</sup>	28 (6.9)	11 (5.3)	45 (21.6)	21 (21.4)
≥1 treatment-related SAE	0	0	0	0
≥1 AESI <sup>c</sup>	1 (0.2)	0	1 (0.5)	0
≥1 COVID-19–related adverse event	8 (2.0)	1 (0.5)	2 (1.0)	1 (1.0)

Source: Table 2.5.17, p95 of the resubmission.

Blue shading is indicative of information previously considered by the PBAC.

AE = adverse event; AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; COVID-19 = coronavirus disease 2019; SAE = serious adverse event; TRAE = treatment-related adverse event.

<sup>a</sup> An AE of Grade 3 denotes a severe event, an adverse event of Grade 4 a life-threatening event, and an AE of Grade 5 a fatal event.

<sup>b</sup> SAEs were defined as death, events that were life-threatening or required inpatient hospitalisation, events that prolonged hospitalisation, events that were persistent or that were associated with clinically significant disability or incapacity, or events considered to be of medical significance.

<sup>c</sup> AESI included hypersensitivity, immune complex disease, and thrombocytopenia and was determined based on blinded investigator assessment.

6.47 The resubmission also presented data from MEDLEY reporting adverse event (AE) rates for children receiving either nirsevimab or palivizumab in Season 2. Results are summarised in Table 24. As acknowledged by the resubmission, rates of AEs were nominally higher in the cohorts of children who received nirsevimab in Season 2.

Table 24: Summary of adverse events observed in the MEDLEY trial in the 360 days post-dose in Season 2

Subjects with <sup>a</sup>	Number (%) of subjects		
	PALI/PALI (n=42)	PALI/NIRS (n=40)	NIRS/NIRS (n=180)
≥1 AE	29 (69.0)	31 (77.5)	130 (72.2)
≥1 TRAE	0	0	0
≥1 AE of Grade ≥3 severity <sup>b</sup>	2 (4.8)	4 (10.0)	19 (10.6)
≥1 TRAE of Grade ≥3 severity <sup>b</sup>	0	0	0
Any AE with outcome of death (Grade 5 severity) <sup>b</sup>	0	0	0
≥1 Serious AE <sup>c</sup>	2 (4.8)	4 (10.0)	23 (12.8)
≥1 Serious AE, Grade ≥3 AE, or both	3 (7.1)	4 (10.0)	25 (13.9)
≥1 treatment-related serious AE	0	0	0
≥1 AESI	0	0	1 (0.6)
≥1 COVID 19–related AE <sup>d</sup>	7 (16.7)	4 (10.0)	23 (12.8)

Source: Table 2.5.18 on p97 of the resubmission

AE: adverse event, AESI: adverse event of special interest, CHD: congenital heart disease, CLD: chronic lung disease, COVID 19: coronavirus disease 2019, TRAE: treatment related adverse event

<sup>a</sup> Subjects with multiple events in the same category were counted once in that category. Subjects with events in >1 category were counted once in each of those categories

<sup>b</sup> Grade 3: severe; Grade 4: life threatening; Grade 5: fatal

<sup>c</sup> Serious AE criteria: death, life threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject)

<sup>d</sup> COVID 19 confirmed events include COVID 19 positive asymptomatic and symptomatic events

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6.48 The PBAC, in its consideration of the first submission in July 2024, considered that nirsevimab was associated with an acceptable safety profile.

**Clinical claim**

6.49 The resubmission claimed that:

- For infants born during or entering their first RSV season:
  - Nirsevimab is superior in terms of effectiveness and non-inferior in terms of safety compared with no immunisation;
  - Nirsevimab is superior in terms of effectiveness and non-inferior in terms of safety compared with RSVpreF.
- For children up to 24 months who remain vulnerable to severe RSV disease through their second RSV season:
  - Nirsevimab is superior in terms of effectiveness and non-inferior in terms of safety compared with no immunisation.

6.50 A summary of the evidence for each population described in Figure 1 is provided in the following paragraphs.

6.51 Population A – nirsevimab vs no immunisation: Regarding infants experiencing their first RSV season where the mother did not receive RSVpreF and where the infant does not have a risk condition, the resubmission claims superiority of nirsevimab versus no immunisation. The evidence from the final results of the MELODY trial, reported in Table 11, supports this claim through to 150 days after dosing with nirsevimab, and the PBAC has previously accepted that nirsevimab is superior in terms of effectiveness compared to no immunisation in this population, with an acceptable safety profile in the first RSV season (paragraph 7.1, nirsevimab PSD, July 2024). The PBAC noted that nirsevimab provides protection for at least 5 months via passive immunisation (paragraph 7.4, nirsevimab PSD, July 2024), and the approved nirsevimab PI describes the duration of protection as at least 5 months based on clinical and pharmacokinetic data. The updated published evidence from the MELODY trial (not reported in the resubmission), presented in Table 12, indicates no statistically significant difference in the effectiveness of nirsevimab beyond 150 days [5 months] following dosing. The PBAC considered that the conclusion of superior efficacy for nirsevimab versus no immunisation in infants entering their first RSV season where maternal RSVpreF had not been administered was reasonable. The PBAC considered that the results from the analysis of outcomes from the MELODY trial constituted the most relevant and robust evidence upon which estimates of immunisation efficacy of nirsevimab in Season 1 for application in the economic evaluation.

6.52 Population A – nirsevimab vs RSVpreF: Regarding the population of healthy infants experiencing their first RSV season (where the mother did not receive RSVpreF), the resubmission relied on an ITC of nirsevimab and RSVpreF based on MELODY (nirsevimab vs placebo) and MATISSE (RSVpreF vs placebo) and claimed superiority

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over RSVpreF in this population. There is uncertainty regarding the ITC due to violation of the transitivity assumption underpinning the analysis and differences across the trials in definitions of the MA RSV LRTI endpoint. The ESC considered the available evidence insufficient to support a claim that nirsevimab is superior to RSVpreF vaccination due to transitivity issues that arise due to the indirect nature of the comparison. ATAGI advice supported this view, noting “the comparison of nirsevimab and RSVpreF presented in the submission was unreliable, and a conclusion of superior effectiveness is not supported by the data” (ATAGI pre-submission advice, page 11). The PBAC considered the available evidence insufficient to support a claim that nirsevimab is superior to RSVpreF vaccination due to transitivity issues between the nirsevimab trials and the RSVpreF trial (MATISSE). The PBAC noted the lack of direct evidence comparing nirsevimab with RSVpreF, however advised that nirsevimab could be considered non-inferior to RSVpreF on the basis of the data presented for Season 1.

- 6.53 Population B: Regarding the population of infants experiencing their first RSV season where the mother received RSVpreF but where the immune response to the vaccine (in terms of prevention of RSV disease in the infant) may be impaired, the resubmission claimed superiority of nirsevimab after RSVpreF maternal vaccination versus RSVpreF maternal vaccination alone (noting that a clinical claim was not made in the submission for this specific population, but it is implicitly part of the nirsevimab vs RSVpreF claim). No evidence to support this claim was presented in the resubmission. The PBAC, in its consideration of the first submission, acknowledged that the additional benefits of nirsevimab given in addition to the maternal RSVpreF vaccine in this population would be difficult to assess due to limited data and considered that there may be a small number of instances where it may be clinically appropriate for an infant to receive nirsevimab after the mother had been vaccinated. The PBAC further considered that, if clinically justified, these infants should not be precluded from accessing nirsevimab (paragraph 7.10, nirsevimab PSD, July 2024). The PBAC considered the magnitude of clinical benefit was uncertain when nirsevimab is used after maternal RSVpreF vaccination, however consistent with its previous advice considered that use of nirsevimab was appropriate in this populations consistent with the AIH recommendations. The PBAC considered it was reasonable to conclude that nirsevimab would provide a meaningful benefit in these infants with suboptimal RSV antibodies despite the mother having received RSVpreF.
- 6.54 Population C(a): Regarding infants with risk conditions experiencing their first RSV season where the mother did not receive the maternal RSVpreF vaccine, the resubmission claimed superiority of nirsevimab over no immunisation. The MEDLEY randomised controlled trial in children with risk conditions entering their first RSV season compared nirsevimab and palivizumab, although the trial was not designed or powered to determine whether nirsevimab was superior or non-inferior to palivizumab. The results of an ITC conducted during the evaluation comparing nirsevimab and no immunisation, using palivizumab as the common reference were consistent in healthy children (paragraph 6.35), although the confidence interval

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around the efficacy estimate was wide and the difference vs placebo was not statistically significant.

- 6.55 The Phase 2b trial included a subgroup of infants with gestational age > 29 weeks to  $\geq 32$  weeks (34% of infants in the Phase 2b trial) and would be considered to have a risk condition. The effectiveness of nirsevimab in these infants was similar to the effectiveness observed in the MELODY trial.
- 6.56 The evaluation considered that based on the evidence from the Phase 2b trial, and the evidence from the ITC of nirsevimab and no immunisation using palivizumab as the common reference, the claim of superiority of nirsevimab versus no immunisation in Population C(a) can be considered reasonable though there is uncertainty around the magnitude of benefit (noting that a clinical claim was not made in the submission for this specific population, but it is implicitly part of the nirsevimab vs no immunisation claim). Given the similarity of outcomes in healthy infants and infants with risk conditions, it may be reasonable to hypothesise that risk conditions are a prognostic factor rather than a modifier of treatment effect of nirsevimab. The PBAC considered it was reasonable to consider efficacy and safety in Population C(a) to be consistent with Population A, as proposed by the sponsor and accepted by the ESC.
- 6.57 Population C(b): Regarding infants with risk conditions experiencing their first RSV season where the mother had received the maternal RSVpreF vaccine, the resubmission claimed superiority for the use of both the maternal RSVpreF vaccine and nirsevimab versus use of the maternal RSVpreF vaccine alone (noting that a clinical claim was not made in the submission for this specific population, but it is implicitly part of the nirsevimab vs RSVpreF claim). No evidence to support this claim was presented in the resubmission and a pragmatic search of the literature conducted during the evaluation did not identify any potentially relevant studies. The ESC agreed with the evaluation that limited data are available to support that the addition of nirsevimab to RSVpreF is superior to maternal RSVpreF alone. The ESC considered that from a clinical perspective, it would be appropriate for infants at high risk of severe RSV to receive nirsevimab as specified in the AIH, including in cases where their mother had received RSVpreF, and noted that ATAGI estimated this to be a small population based on the list of conditions known to result in high rates of hospitalisation following RSV as documented in the AIH. The PBAC agreed with the ATAGI advice that noted the magnitude of the effectiveness of nirsevimab following maternal vaccination vs maternal vaccination alone was difficult to predict, and will change depending on the timing of the birth with respect to the first RSV season, however, it was plausible that nirsevimab will reduce the risk of RSV hospitalisations in infants who are at the highest risk of hospitalisation from RSV (Population C(b)).
- 6.58 Population D: Regarding infants with risk conditions experiencing their second RSV season, the resubmission claimed superiority over no immunisation. The MEDLEY trial versus palivizumab included children with CLD/CHD entering their second RSV season. As discussed in paragraph 6.43, the primary source of evidence presented in the resubmission for this population was data from a state program in WA. The point

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estimate for the effectiveness of nirsevimab did not reach statistical significance and was lower than observed in the cohort of children experiencing their first RSV season. The PBAC noted the evidence to support efficacy of nirsevimab in Season 2 was limited.

- 6.59 The resubmission described nirsevimab as non-inferior to no immunisation in terms of safety. Consistent with the PBAC's finding in July 2024, ESC considered that nirsevimab was associated with an acceptable safety profile. Based on the evidence presented in Table 22, Table 23, Table 24, and Table 24, this conclusion remains appropriate. The PBAC considered the clinical safety claim was reasonable.
- 6.60 The resubmission described nirsevimab as non-inferior to RSVpreF in terms of safety. The PBAC considered the clinical safety claim was reasonable.

***Economic analysis***

- 6.61 Consistent with the first submission, the resubmission presented a cost-utility analysis (CUA) based on quality-adjusted life-years (QALYs) gained and cost-effectiveness analysis based on life-years (LYs) gained. In July 2024, the PBAC considered the incremental cost-effectiveness ratio for nirsevimab for the first RSV season to be substantially underestimated and highly uncertain.
- 6.62 The model presented in the resubmission was used to calculate the cost-effectiveness of nirsevimab relative to placebo (representing no immunisation). In addition, the resubmission provided a comparison versus RSVpreF. The submission's CUA comparing nirsevimab with RSVpreF is not discussed further in these minutes, as the PBAC considered the available evidence did not support a claim that nirsevimab is superior to RSVpreF vaccination (see paragraph 6.52).
- 6.63 The model was a static state-transition cohort model (or Markov) model with a 1-month cycle. The structure of the model is shown in Figure 3. The structure is the same as used to conduct the economic evaluation presented in the first submission except that, as requested by the PBAC (paragraphs 6.84, 6.87 and 7.18, nirsevimab PSD, July 2024), a mechanical ventilation health state was removed from the model, primarily to avoid double-counting. Twelve cohorts (one for each birth month) of infants enter the model at birth (rather than at the time of administration of nirsevimab or the comparator) and the model progressed infants through 12 monthly cycles in the case of healthy infants or 24 monthly cycles in the case of infants with risk conditions. All infants surviving at this point were then applied a LY or QALY payoff such that the model considered a lifetime time horizon.
- 6.64 As described in paragraphs 7.19 to 7.21 of the PSD, several limitations of the model structure were noted by the PBAC in July 2024. These remain unaddressed by the resubmission, such as the use of a single endpoint to drive the model rather than a range of endpoints collected in the trial and other issues related to the estimation of cost-effectiveness in the proposed circumstances of use such as annual variations in RSV incidence and severity. Seasonal changes from year to year may impact the

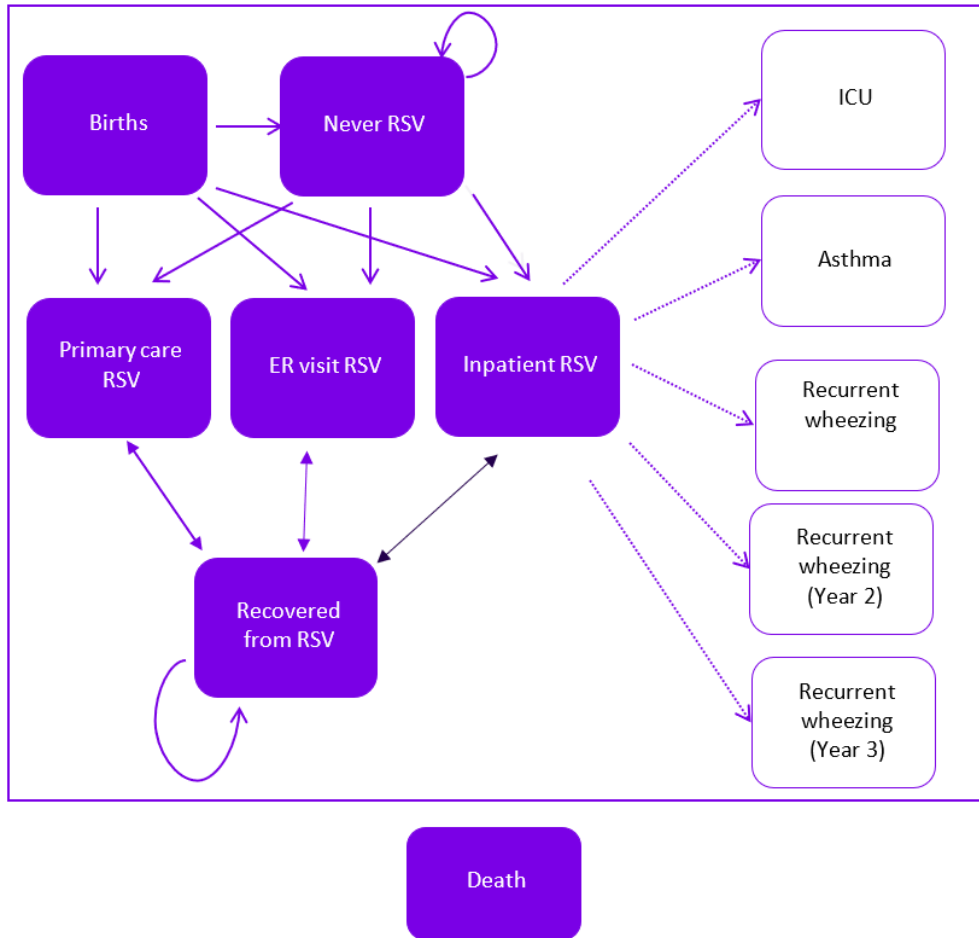
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optimal timing of administration of nirsevimab and reduce cost-effectiveness, especially in the event of a prolonged RSV season given the limited duration of protection for nirsevimab (5 months).

- 6.65 A Markov-based economic model with monthly cycles where infants enter the model at birth may not be the most suitable approach for estimating the cost-effectiveness of nirsevimab. With the Markov model, infants can cycle between the hospitalised health state and the recovered health state multiple times and could result in an infant being hospitalised multiple times due to RSV infection. This is not appropriate given the development of natural immunity in infants that are infected with RSV. In addition, the structure of the model with monthly cycles introduces complexities as a consequence of the start time in the model not being the time of administration of nirsevimab, such as needing to consider seasonality and timing of administration of nirsevimab or the comparator relative to the start of the RSV season. As noted during the PBAC's July 2024 consideration, these complexities result in uncertainty around the estimates of cost-effectiveness of nirsevimab generated by the model. Alternatively, these complexities could have been avoided by taking a straightforward decision-tree approach where infants enter the model at the time of administration of nirsevimab. Modelling using a monthly-cycle Markov model creates unnecessary challenges.
- 6.66 With regard to the requested listing (Table 3), which had changed substantially from the first submission, the resubmission did not adequately consider the possible scenarios in which nirsevimab may be used. The resubmission did not separately consider the cost-effectiveness of several of the populations identified in Figure 1.

With regard to high-risk infants, the PBAC considered in July 2024, that nirsevimab may provide higher clinical value for high-risk infants in the first RSV season, however this had not been assessed in the first submission (paragraph 7.21, nirsevimab PSD, July 2024). This was not addressed by the resubmission, although a model was provided that assumed utilisation of nirsevimab in high-risk infants for two RSV seasons (with assumption that all individuals were treated twice).

Figure 3: Structure of the Markov model used to conduct the economic evaluations presented in the resubmission



Source: Figure 3.2.1 on p125 of the resubmission  
 ER = emergency room; ICU = intensive care unit; RSV= respiratory syncytial virus

6.67 The Markov model presented in the resubmission was used to calculate the cost-effectiveness of nirsevimab in two populations:

- (i) a healthy infant population (with an implicit assumption that the mother did not receive RSVpreF) and
- (ii) a population of infants with risk conditions who receive nirsevimab twice (i.e., in two RSV seasons), again with an implicit assumption that the mother did not receive RSVpreF. By considering benefits of nirsevimab over two seasons, the resubmission provided only an overall estimate of cost-effectiveness of nirsevimab over both seasons. Given that the baseline risk of hospitalisation for RSV LRTI is likely to be reduced in Season 2 compared with Season 1, and that there are potential differences in the effectiveness of nirsevimab in Season 2 versus Season 1 (as discussed in paragraph 6.43), it is necessary for ICERs to be generated separately for infants with risk conditions treated with nirsevimab Season 1 and for those treated in Season 2. The structure of the model presented in the resubmission did not permit examination of the cost

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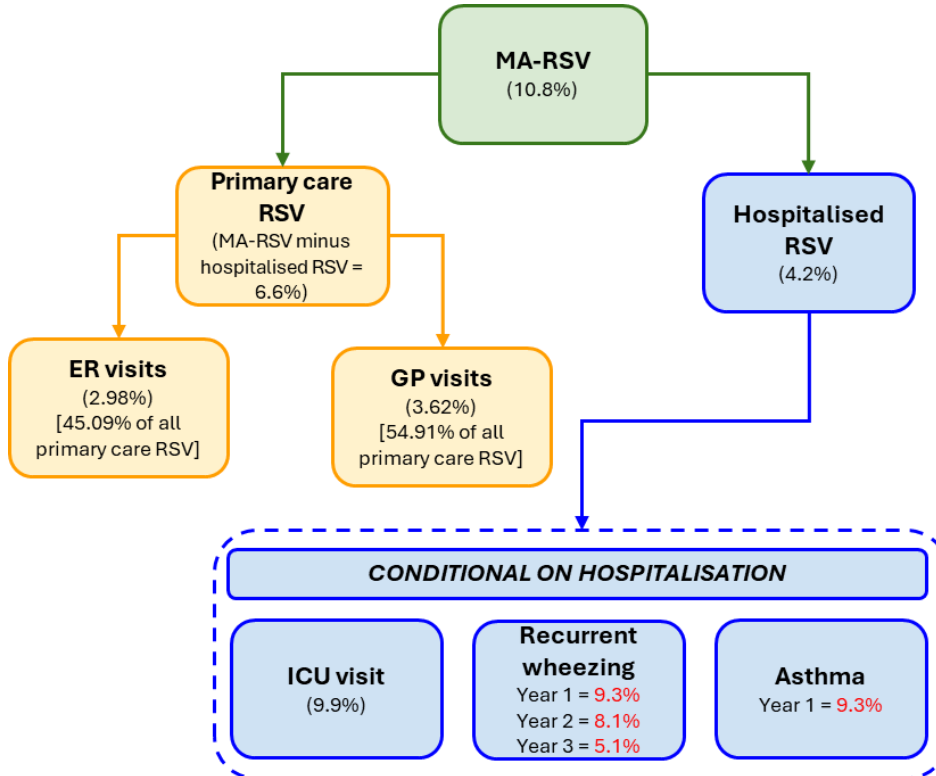
effectiveness of nirsevimab in Season 1 and Season 2 separately. A revised model was provided with the PSCR (see paragraph 6.76).

6.68 The key inputs to the resubmission's model were:

- Incidence of MA RSV LRTI in the absence of nirsevimab (i.e., the background rate of MA RSV LRTI)
- Proportion of infants with MA RSV LRTI who require hospitalisation
- Proportion of infants hospitalised for RSV LRTI who require admission to an intensive care unit (ICU)
- Mortality of infants hospitalised for RSV LRTI
- Proportion of hospitalised infants developing asthma and wheezing subsequent to hospitalisation for RSV LRTI
- Effectiveness of nirsevimab in reducing the incidence of MA RSV LRTI
- Drug costs for nirsevimab
- Costs for medical attendance for RSV LRTI
- Costs of hospitalisation for RSV LRTI
- Costs of care in ICU for RSV LRTI

Figure 4 summarises the incidence of key events assumed in the control arm of the model assessing cost-effectiveness of nirsevimab vs no immunisation in Season 1.

Figure 4: Cumulative incidence of events in the model presented for healthy infants in the resubmission



Source: Updated version (with changes in red font) of Figure 3 presented in the nirsevimab July 2024 minutes, which was generated during the evaluation of the first submission  
 Figures for recurrent wheezing in the first submission were 31%, 27%, and 17% in Year 1, Year 2, and Year 3, respectively. The figure for asthma in Year 1 in the first submission was 31%.  
 Note mechanical ventilation has been removed as a 'conditional on hospitalisation' health state as recommended by the PBAC at its July 2024 consideration.

6.69 The key matters of concern regarding the economic analyses presented in the first submission and the resubmission’s changes to the model are summarised in Table 25. Several of the PBAC recommendations were not implemented in the revised model presented in the resubmission. Of note, the inputs related to 1) effectiveness of nirsevimab; 2) baseline hospitalisation rate; 3) costs of hospitalisations; and 4) consideration of timing of nirsevimab administration, were not revised, and the base case economic evaluation continued to be informed by:

- 79.5% nirsevimab effectiveness;
  - an assumption that nirsevimab would be administered at the optimal timepoint;
  - a baseline 4.2% hospitalisation rate;
- aggregated cost of all hospitalisations over 6 months.

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**Table 25: Summary of key concerns from the PBAC’s consideration of the economic evaluation presented in the first submission in July 2024 and changes made to the economic evaluation presented in the resubmission**

Parameter	Key concern from July 2024 submission	PBAC comments and how they were addressed in the March 2025 resubmission
Effectiveness of nirsevimab	Nirsevimab was estimated to avoid 79.5% of MA RSV LRTI during the period of protection (5 months).	Not addressed ‘The PBAC considered that the result from the MELODY trial (74.5%) should be used...’ (para 6.51 of the nirsevimab July 2024 PSD) The resubmission continued to apply the pooled nirsevimab effectiveness result of 79.5% as per the previous submission. The ESC advised that the immunisation efficacy as determined from the MA RSV LRTI endpoint in the final analysis of MELODY constituted the most relevant and robust estimate for application in the economic analysis (76.4%).
Hospitalisation rate	The previous submission assumed an overall annual hospitalisation rate of 4.2% in the control arm of the model	Not addressed ‘...the PBAC considered that the hospitalisation rate in the submission was overestimated, and that a rate of 2.33% would be appropriate, based on a publication by Gebremedhin 2022...’ (para 6.55 of the nirsevimab July 2024 PSD) The base case hospitalisation rate of 4.2% remains unchanged from the previous submission. The ESC considered that a hospitalisation rate of 3.67% should be tested in sensitivity analyses as proposed in the PSCR.
Costs of hospitalisations	The previous submission applied the same initial cost for hospitalisation to subsequent hospitalisations (\$10,895), which reflected the costs of the hospitalisation for RSV LRTI and readmissions for any reason over the next months in every instance when a patient was hospitalised.	Not addressed ‘The ESC advised... reducing the costs of subsequent hospitalisations rather than applying a cost (as per the submission) that represented an aggregation of all hospitalisations over 6 months.’ (para 6.87 of the nirsevimab July 2024 PSD) The ESC maintained that the costs of hospitalisation were overestimated and advised that applying costs for the index hospitalisation and re-admissions within a month of the index hospitalisation would be appropriate.
Optimal timing of nirsevimab	Nirsevimab was administered at near optimal timing in the economic evaluation; such as given shortly after birth for infants born just before or during the RSV season.	‘The PBAC considered that the optimal administration assumed by the model did not reflect the likely use of nirsevimab in clinical practice, and noted the sensitivity analysis which showed that delaying the administration by one month in the model... resulted in an increase in the ICER of ██████%.’ (para 6.81 of the nirsevimab July 2024 PSD) The timing of nirsevimab administration remains unchanged from the previous submission. The ESC considered that the assumption that nirsevimab would be administered at the optimal time biased the analysis in favour of nirsevimab.

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Parameter	Key concern from July 2024 submission	PBAC comments and how they were addressed in the March 2025 resubmission
Mechanical ventilation	<p>2.5% of infants hospitalised with RSV received mechanical ventilation.</p> <p>The cost of mechanical ventilation was derived from AR-DRG E41A and was estimated to be \$44,682.02.</p>	<p>Addressed</p> <p>‘The PBAC agreed with the ESC that the cost of mechanical ventilation should be removed from the model as the submission’s approach double-counted these costs’ (para 6.73 of the nirsevimab July 2024 PSD)</p> <p>The resubmission, appropriately, removed costs and disutilities associated with mechanical ventilation from the base case economic evaluation.</p>
Disutilities applied to health states	<p>Disutilities applied to health states in the model for a full cycle (one month):</p> <ul style="list-style-type: none"> <li>• Primary care visits -0.16</li> <li>• ED visits -0.20</li> <li>• Hospitalisation -0.41</li> <li>• ICU admissions -0.20 plus one cycle in hospitalisation (total -0.61)</li> <li>• Mechanical ventilation -0.20 plus once cycle in hospitalisation (total -0.61)</li> </ul>	<p>Addressed</p> <p>‘The PBAC agreed with the ESC that the submission’s approach had overestimated the disutilities for RSV health events, and that the disutilities should be adjusted as proposed by the evaluation.’ (para 6.64 of the nirsevimab July 2024 PSD)</p> <p>Disutilities applied to health states were adjusted in accordance with the advice in paragraph 6.65 of the nirsevimab July 2024 minutes. The disutilities assumed to be appropriate for application in the nirsevimab model, given its structure, were as follows:</p> <ul style="list-style-type: none"> <li>• Primary care visits -0.032410</li> <li>• ED visits -0.040513</li> <li>• Hospitalisation -0.08630 (including the disutility for medical attendance)</li> <li>• ICU admissions -0.25074</li> <li>• Mechanical ventilation was removed from the base case economic evaluation</li> </ul>
Asthma and recurrent wheezing	<p>Hospitalised infants experienced:</p> <ul style="list-style-type: none"> <li>• Asthma (31%)</li> <li>• Recurrent wheezing (31%, first year after RSV LRTI hospitalisation)</li> <li>• Recurrent wheezing (27%, second year after RSV LRTI hospitalisation)</li> <li>• Recurrent wheezing (17%, third year after RSV LRTI hospitalisation)</li> </ul>	<p>Not addressed</p> <p>‘...the PBAC noted the discussion in the pre-PBAC response, however agreed with the ESC that the estimates of asthma and recurrent wheezing were uncertain and should be removed from the economic model as the estimates were not robust.’ (para 6.61 of the nirsevimab July 2024 PSD)</p> <p>The base case economic evaluation did not remove these parameters from the model but reduced the incidence of asthma and recurrent wheezing in hospitalised infants by 70% (with no reason for this extent of reduction):</p> <ul style="list-style-type: none"> <li>• Asthma (9.3%%)</li> <li>• Recurrent wheezing (9.3%, first year after RSV LRTI hospitalisation)</li> <li>• Recurrent wheezing (8.1%, second year after RSV LRTI hospitalisation)</li> <li>• Recurrent wheezing (5.1%, third year after MA RSV LRTI hospitalisation)</li> </ul>

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Parameter	Key concern from July 2024 submission	PBAC comments and how they were addressed in the March 2025 resubmission
		<p>As acknowledged by the resubmission, no causal link has been established between RSV infection and asthma or recurrent wheezing. Although an association has been observed between early childhood RSV infection and asthma and/or recurrent wheezing, the possibility that the association is due to some confounder (e.g., a genetic predisposition to respiratory conditions or exposure to an environmental factor like parental smoking) has not been excluded.</p> <p>The ESC agreed with the ATAGI advice that the inclusion of benefits relating to asthma and wheezing was inappropriate and advised such benefits should be removed from the economic analysis.</p>
Case fatality ratio	<p>Infants hospitalised with RSV experienced an RSV-specific mortality rate of 0.003%</p> <p>The PBAC considered a case fatality rate of 0.002 was appropriate for the model, based on the study by Saravanos et al (2022).</p>	<p>Addressed</p> <p>Infants hospitalised with RSV in the model experience an RSV-specific mortality rate of 0.2% (case fatality rate of 0.002), consistent with the PBAC's July 2024 recommendation and the rate reported by Saravanos 2022.</p>
Administration costs	Excluded	<p>The ESC advised that the exclusion of costs for administration of nirsevimab was not appropriate and that the economic analysis should include costs of administration for a proportion of infants who would not be immunised at the time of birth.</p> <p>If it was assumed that 50% of infants would receive nirsevimab at birth (no administration fee would apply), and the remainder would receive it at GP visits (Level A), then the average child would incur an administration cost of <math>\\$19.60 \times 0.5 = \\$9.80</math> for season 1.</p>
Hospitalisation data for high-risk population	Not modelled separately	<p>Partially addressed</p> <p>The model in the resubmission included high-risk-specific hospitalisation rates based on rates observed in an Aboriginal and Torres Strait Islander population (as a proxy for infants with risk conditions) in the REVIVE study, which assessed the effectiveness of the WA Nirsevimab Prevention Program. The program offered nirsevimab to all infants aged &lt;12 months entering their first RSV season and to children aged &lt; 24 months with risk conditions (including Aboriginal and Torres Strait Islander children) entering their second RSV season. The rates applied in the economic evaluation for infants with risk conditions were 14.32% in Season 1 and 3.54% in Season 2. The resubmission provided a presentation detailing early insights following the implementation of the WA Nirsevimab Prevention Program. However, hospitalisation rates, as applied</p>

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Parameter	Key concern from July 2024 submission	PBAC comments and how they were addressed in the March 2025 resubmission
		in the model, are not included in that presentation. It was, therefore, not possible to verify these hospitalisation rates during the evaluation. The PSCR applied a rate of 3.54% for infants with risk conditions in Season 2.

Source: Generated during the evaluation based on Table 3.1 on pp 109-111 of the resubmission.

AR-DRG = Australian refined diagnosis-related groups; ED = emergency department; ESC = Economics Sub Committee; GP = general practitioner; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LRTI = lower respiratory tract infection; MA = medically attended; NIP = National Immunisation Program; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RSV = respiratory syncytial virus

**Results for nirsevimab versus no immunisation**

6.70 Results of the economic evaluations for nirsevimab versus no immunisation, as presented in the resubmission, are summarised in Table 26 (temperate regions), Table 27 (tropical regions) and Table 28 (aggregated population). The resubmission estimated 21% use in tropical regions in season 1, which was similar to the July 2024 submission estimate (22%), based on the estimated number of infants receiving nirsevimab in the financial estimates. The ICERs that were presented in the resubmission for listing on the NIP are lower than the base case estimated in the first submission for listing on the PBS. The key driver of the reduction is the removal of markups and fees that are not applicable in the NIP setting. The ESC noted that, as shown in Table 28, cost offsets from reduced incidence of hospitalisation was a key driver of the ICER generated by the model. The ESC reiterated that baseline incidence and costs of hospitalisation were overestimated and substantially biased the results of the economic analysis in favour of nirsevimab.

**Table 26: Base case results from the economic evaluation presented in the resubmission comparing nirsevimab to no immunisation in the temperate region**

Component	Nirsevimab	No immunisation	Increment
Total costs	\$█	\$138,244,293	-\$█
MA RSV LRTI cases	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>4</sup>
LYs	4,728,541	4,728,292	249.45
QALYs	4,711,215	4,710,657	557.78
<b>Incremental cost per additional QALY gained</b>			<b>DOMINANT</b>
<b>Previous consideration</b>			
Total costs	\$█	\$155,198,766	\$█
QALYs	4,711,086	4,710,317	768
<b>Incremental cost per additional QALY gained</b>			<b>\$█<sup>1</sup></b>

Source: Table 3.8.2 on p143 of the resubmission and Table 21 of the nirsevimab July 2024 PSD

Blue shading is indicative of information previously considered by the PBAC.

LY = life-year; QALY = quality-adjusted life year; RSV = respiratory syncytial virus.

The redacted values correspond to the following ranges:

<sup>1</sup> \$5,000 to < \$15,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> 10,000 to < 20,000

<sup>4</sup> 20,000 to < 30,000

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**Table 27: Base case results from the economic evaluation presented in the resubmission comparing nirsevimab to no immunisation in the tropical region**

Component	Nirsevimab	No immunisation	Increment
Total costs	\$█	\$37,754,000	\$█
MA RSV LRTI cases	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>2</sup>
LYs	1,278,882	1,278,828	53.98
QALYs	1,274,178	1,274,057	120.97
<b>Incremental cost per additional QALY gained</b>			<b>\$█<sup>1</sup></b>
<b>Previous consideration</b>			
Total costs	\$█	\$42,384,538	\$█
QALYs	1,274,132	1,273,964	167
<b>Incremental cost per additional QALY gained</b>			<b>\$█<sup>1</sup></b>

Source: Table 3.8.2 on p143 of the resubmission and Table 21 of the nirsevimab July 2024 PSD

Blue shading is indicative of information previously considered by the PBAC.

LY = life-year; QALY = quality-adjusted life year; RSV = respiratory syncytial virus.

The redacted values correspond to the following ranges:

<sup>1</sup> \$35,000 to < \$45,000

<sup>2</sup> 500 to < 5,000

<sup>3</sup> 5,000 to < 10,000

**Table 28: Base case results from the economic evaluation presented in the resubmission comparing nirsevimab to no immunisation (aggregated population)**

Component	Nirsevimab	No immunisation	Increment
Drug costs	\$█	\$0	\$█
Hospitalisation, ICU, ED, primary care costs	\$70,529,782	\$173,203,825	-\$102,674,043
Asthma/wheezing costs	\$997,586	\$2,794,468	-\$1,796,882
Total costs	\$█	\$175,998,293	\$█
QALYs	5,985,393	5,984,715	678.75
<b>Incremental cost per additional QALY gained</b>			<b>\$█<sup>1</sup></b>
<b>Previous consideration</b>			
Total costs	\$█	\$197,583,304	\$█
QALYs	5,985,217	5,984,282	936
<b>Incremental cost per additional QALY gained</b>			<b>\$█<sup>2</sup></b>

Source: Table 3.8.7 on p147 of the resubmission and Table 21 of the nirsevimab July 2024 PSD

Blue shading is indicative of information previously considered by the PBAC.

QALY = quality-adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$5,000

<sup>2</sup> \$5,000 to < \$15,000

6.71 Results of sensitivity analyses performed during the evaluation by varying key inputs to the revised economic analysis presented in the resubmission are presented in Table 29. The results of the economic analysis are very sensitive to assumptions regarding effectiveness of nirsevimab in reducing the incidence of MA RSV LRTI, the assumed baseline incidence of MA RSV LRTI, the baseline incidence of hospitalisation for RSV LRTI, cost of nirsevimab, and costs of hospitalisation for MA LRTI. Results are moderately sensitive to the discount rate assumed and to the inclusion of an assumption of benefits for rates of asthma and wheezing. A multivariate analysis performed during the evaluation that considered the uncertainties based on ESC's previous advice as described in paragraph 6.87 of the July 2024 PSD, increased the ICER from \$0 to < \$5,000 to \$155,000 to < \$255,000 per additional QALY gained (increasing to \$155,000 to < \$255,000/QALY gained based on advice from the ESC). As

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discussed above, this is not a comprehensive list of uncertainties identified in the July 2024 PBAC consideration (see paragraph 6.69).

- 6.72 In regard to the submission's CUA, the ESC agreed with the evaluation that the resubmission did not adequately consider the previous PBAC advice. The ESC added a number of multivariate sensitivity analyses to Table 29 and noted that these were likely optimistic estimates of cost-effectiveness of nirsevimab as they did not address all issues that ESC had previously raised e.g., issues regarding assumptions of optimal timing of the dose of nirsevimab. The ESC also advised that the economic analysis should include costs of administration for a proportion of infants who would not be immunised at the time of birth (see Table 25).

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Table 29: Results of sensitivity analyses of the economic model including PBAC recommended analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change
<b>Comparing nirsevimab to no immunisation in Season 1 (aggregated population)</b>				
<b>Base case</b>	\$█	678.75	\$█ <sup>1</sup>	-
Discount rate (base case 5%) <ul style="list-style-type: none"> <li>0%</li> <li>3.5%</li> </ul>	\$█ \$█	1,673.66 792.89	\$█ <sup>1</sup> \$█ <sup>1</sup>	-█% -█%
Nirsevimab efficacy based on MELODY updated results from Muller 2023 (base case = 79.5%) <ul style="list-style-type: none"> <li>76.4%; point estimate</li> <li>62.3%; lower limit</li> <li>85.2%; upper limit</li> </ul>	\$█ \$█ -\$█	651.91 530.24 728.17	\$█ <sup>2</sup> \$█ <sup>3</sup> Dominant	+█% +█% -█%
MA RSV LRTI rate (base case 10.8%) <ul style="list-style-type: none"> <li>5.4% (MELODY update)</li> <li>6.4% (MELODY update excluding southern hemisphere)</li> </ul>	\$█ \$█	640.29 647.19	\$█ <sup>4</sup> \$█ <sup>4</sup>	+█% +█%
Varying health state costs (not varying recurrent wheezing and asthma costs) <ul style="list-style-type: none"> <li>Decrease by 20%</li> <li>Increase by 20%</li> <li>Brusco 2018 only index and up to 30 days of readmissions</li> </ul>	\$█ -\$█ \$█	678.75 678.75 678.75	\$█ <sup>5</sup> Dominant \$█ <sup>5</sup>	+█% -█% +█%
Hospitalisation rate (base case = 4.2%) <ul style="list-style-type: none"> <li>2.33%; per PBAC advice</li> <li>3.67%; per PSCR</li> </ul>	\$█ \$█	410.24 603.50	\$█ <sup>6</sup> \$█ <sup>4</sup>	+█% +█%
Removal of recurrent wheezing and asthma	\$█	592.49	\$█ <sup>2</sup>	+█%
Baseline quality of life (base case = 1) <ul style="list-style-type: none"> <li>0.86; as per Redwood 2024</li> </ul>	\$█	637.40	\$█ <sup>2</sup>	+█%
<b>Multivariate sensitivity analyses<sup>a</sup></b>				
As per July 2024 PBAC advice, noting this is not a comprehensive list of uncertainties identified in the July 2024 PBAC consideration (see paragraph 6.64). <ul style="list-style-type: none"> <li>Removal of asthma and recurrent wheezing</li> <li>Hospitalisation rate of 2.33%</li> <li>Effectiveness of nirsevimab 74.5%</li> <li>Hospitalisation costs reduced to index admission and 1-month of readmission costs from Brusco 2018</li> </ul>	\$█	338.40	\$█ <sup>7</sup>	+█%
<b>Additional analysis proposed by ESC</b> <ul style="list-style-type: none"> <li>Removal of asthma and recurrent wheezing</li> <li>Hospitalisation rate of 3.67%</li> <li>Effectiveness of nirsevimab 76.4%</li> <li>Hospitalisation costs reduced to index admission and 1-month of readmission costs from Brusco 2018</li> <li>Administration cost of \$9.80</li> </ul>	\$█	506.89	\$█ <sup>8</sup>	+█%

ICER = incremental cost-effectiveness ratio; LRTI = lower respiratory tract infection; MA = medically attended; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Scheme; QALY = quality-adjusted life year; RSV = respiratory syncytial virus.

<sup>a</sup> The multivariate sensitivity analyses were prepared by changing the following inputs:

- Treatment inputs E13 as shown in table above (efficacy rate);
- Treatment inputs Q40 as shown in table above (admin cost);
- Health events E160, G160, J160, M160 0% (recurrent wheeze and asthma);
- Health events AC25 as shown in table above (hospitalisation rate);
- Health event costs E13 \$8,419.06 (hospitalisations alone);
- Health event costs E14 \$6,488.71 (ICU);
- Health event costs E16 \$1,498.49 (ER visits).

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$5,000

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- <sup>2</sup> \$5,000 to < \$15,000
- <sup>3</sup> \$45,000 to < \$55,000
- <sup>4</sup> \$15,000 to < \$25,000
- <sup>5</sup> \$35,000 to < \$45,000
- <sup>6</sup> \$95,000 to < \$115,000
- <sup>7</sup> \$155,000 to < \$255,000
- <sup>8</sup> \$75,000 to < \$95,000

6.73 The ESC noted that if nirsevimab is considered non-inferior to RSVpreF when used in Season 1, inclusion of nirsevimab on the NIP for use in Season 1 would be appropriate on a cost-minimisation basis versus maternal RSVpreF. No cost-minimisation analysis comparing nirsevimab with RSVpreF was presented in the resubmission, however a comparison of nirsevimab and RSVpreF costs is presented in Table 30. The comparison of nirsevimab vs RSVpreF is based on an equi-effective dose of 1 nirsevimab dose (administered to the infant) to 1 RSVpreF dose (administered to the mother). The cost of RSVpreF in Table 30 is the price assumed by the submission, reflecting the private prescription price of Abrysvo (\$331.99).

**Table 30: Comparison of nirsevimab and RSVpreF costs**

Component	Nirsevimab	RSVpreF
Intervention	<ul style="list-style-type: none"> <li>• Nirsevimab, 50 mg/0.5 mL, for Season 1 &lt; 5 kg</li> <li>• Nirsevimab, 100 mg/1 mL, for Season 1 ≥ 5 kg</li> </ul>	<ul style="list-style-type: none"> <li>• RSVpreF maternal vaccination</li> </ul>
Number of doses	1	1
Cost per dose	\$ [REDACTED] (price requested by resubmission)	\$331.99 (price assumed by resubmission)
<b>Total cost</b>	<b>\$ [REDACTED]</b>	<b>\$331.99<sup>a</sup></b>

a. Price assumed by resubmission, reflecting the private prescription price of Abrysvo.  
 Source: Prepared by Secretariat.

- 6.74 The ESC did not agree with the PSCR that all infants receiving nirsevimab in Season 1 should be considered a single population. The ESC considered the populations eligible to receive nirsevimab following administration of RSVpreF as detailed in the AIH (Population B and Population C(b) in Figure 1) should be distinguished and considered separately. The relevant comparison in these populations would be nirsevimab + RSVpreF vs RSVpreF alone.
- 6.75 Given that the resubmission did not provide an economic evaluation for Population B and Population C(b) in Figure 1, the cost-effectiveness of nirsevimab in these scenarios is unknown. The PSCR acknowledged that “Cost effectiveness may be compromised in scenarios where infants receive both therapies” and proposed that “nirsevimab should be given preferentially”. The PSCR also proposed that any “reduction in overall cost effectiveness caused by a failed RSVpreF vaccination followed by immunisation with nirsevimab should not be borne by nirsevimab”. The PSCR considered that “An infant in this scenario is identical to an unvaccinated infant and, therefore, should be considered within that cost effectiveness framework.”

**Season 2 summary**

6.76 The resubmission presented overall results of the economic evaluation for nirsevimab in infants with risk conditions versus no immunisation for two RSV seasons (results not shown). The evaluation noted that baseline risk of hospitalisation for RSV LRTI is likely

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to be reduced in Season 2 compared with Season 1, and there are potential differences in the effectiveness of nirsevimab in Season 2 versus Season 1 (paragraph 6.43). The ESC considered the evidence to support efficacy of nirsevimab in Season 2 was limited and noted uncertainty regarding the baseline rate of hospitalisation due to RSV in children with risk conditions entering their second RSV season. The PSCR and pre-PBAC response presented the results for Season 2 separately. The Season 2 model was not evaluated, however the ESC noted that the PSCR model inappropriately included benefits for asthma and wheezing, inappropriately assumed immunisation efficacy of 79.5%, and inappropriately applied costs of hospitalisation that included costs for any re-admissions over the following six months. Due to a lack of data on the percentage of high-risk patients from tropical or temperate climates, an assumption of 50% of each was made for the Season 2 population. The ESC noted that the resubmission applied a cost in Season 2 of \$[REDACTED] rather than \$[REDACTED], due to an error (as clarified by the sponsor in the pre-PBAC response). Additional errors were subsequently identified including underestimation of nirsevimab treatment costs<sup>17</sup>, and therefore the PBAC considered that the Season 2 model was not reliable for decision-making.

***Drug cost/patient/course***

- 6.77 The ex-manufacturer price proposed for nirsevimab was unchanged from the first submission: \$[REDACTED]/infant entering their first RSV season and \$[REDACTED]/child entering their second RSV season.

***Estimated PBS usage & financial implications***

- 6.78 This resubmission was not considered by DUSC, however the first submission for the July 2024 PBAC consideration had previously been considered by DUSC.
- 6.79 As with the first submission, the resubmission, took an epidemiological approach in the estimation of the number of infants and children that would receive nirsevimab should it be added to the NIP.
- 6.80 The estimates provided in the resubmission did not account for potential use of the RSVpreF vaccine in the mother (in terms of both nirsevimab administration in the infant replacing prior vaccination with RSVpreF in the mother, or of a healthy infant not being eligible for nirsevimab after the mother received the RSVpreF vaccine), nor the potential use of RSVpreF together with use of nirsevimab in the infant.
- 6.81 The key inputs to the estimation of extent of use of nirsevimab in the resubmission are summarised in Table 31. The approach taken in the resubmission was largely unchanged from the approach taken in the first submission on the grounds that,

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<sup>17</sup> Errors identified in calculation of nirsevimab treatment costs: The model should have summed treatment costs for nirsevimab administered to infants during each month of the year, but the cost for 4 of the 12 months was erroneously omitted (Row 60 in 'Nirsevimab patient model costs' worksheet), therefore the nirsevimab treatment costs were significantly underestimated by the PSCR and pre-PBAC response models.

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overall, the approach taken was considered reasonable by the DUSC. Key changes to the approach include:

- Uptake rate for infants entering their first RSV season was increased from █████% to █████% to reflect uptake rates observed in state-based programs and in international settings. For the July 2024 consideration, DUSC considered an uptake rate of █████% to be reasonable. However, the ESC considered that the uptake rate should be adjusted, taking into consideration that RSVpreF is now available via the NIP. Since RSVpreF is now included on the NIP, this estimate is now likely to be a substantial overestimate assuming infants born to mothers who have received RSVpreF won't, for the most part, be eligible to receive nirsevimab. The ATAGI advice stated that programmatically, the goal will be to encourage strong RSVpreF vaccine uptake, and to offer nirsevimab to infants whose mothers do not receive the vaccine (or who meet other eligibility criteria). ATAGI considered it is currently unclear whether a pattern of provider or parental choice will emerge, and the relative uptake of nirsevimab vs maternal RSVpreF is therefore uncertain, noting that for the majority of infants only one approach will be used.
- The estimate of children entering their second RSV season in any year was updated to reflect the number of live births in the prior year as estimated by the AIHW 2022 (which is consistent with prior DUSC advice and consistent with the approach taken to estimate the number of infants entering their first RSV season).
- The estimated proportion of infants and children with risk conditions was increased from 4.34% (based on the proportion of births with gestational age < 36 weeks) to 8.18% (based on the estimated proportion of births with gestational age <32 weeks [1.08%], the prevalence of congenital heart disease in infants [0.9%] and the estimated proportion of Aboriginal and Torres Strait Islander people [6.2%]). These changes were made in response to prior advice from the DUSC that infants with congenital heart disease and Indigenous children were not accounted for in the financial estimates. The pre-PBAC response provided revised estimates in which this population was reduced to 2.0% of infants due to removing the criterion for Aboriginal and Torres Strait Islander people (see paragraph 6.82).
- Wholesaler and pharmacy mark-ups and dispensing fees were appropriately excluded from costs of nirsevimab.
- MBS fees for administration of nirsevimab by GPs were inappropriately excluded from the financial analyses. The resubmission estimated reduce primary care visits due to the introduction of nirsevimab. The ESC advised that MBS fees for administration of nirsevimab should be considered in the financial estimates. Some infants will not be immunised at birth and all children with risk conditions entering their second RSV season are likely to be immunised in the community.

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Table 31: Key inputs for financial estimates

Data	Value	Source	Comment
<b>Eligible populations</b>			
<b>Populations 1 and 2: infants entering first RSV season in temperate and tropical regions, respectively</b>			
Incident population	Yr 1: [REDACTED] 1 Yr 2: [REDACTED] 1 Yr 3: [REDACTED] 1 Yr 4: [REDACTED] 1 Yr 5: [REDACTED] 1 Yr 6: [REDACTED] 1	Table 1.1, ABS 3301.0, Births, summary, by state	The prior DUSC advice from the July 2024 PBAC meeting considered this was reasonable.
Uptake rate	[REDACTED]%	Assumption	The prior DUSC advice considered that a [REDACTED]% uptake rate was reasonable considering the introduction of state-based programs offering RSV immunisation for infants and considered that the increased awareness of RSV would lead to a high uptake of nirsevimab. Since RSVpreF is being included on the NIP, this estimate is now likely to be a substantial overestimate assuming infants born to mothers who have received RSVpreF won't, for the most part, be eligible to receive nirsevimab.
Number immunised	Yr 1: [REDACTED] 1 Yr 2: [REDACTED] 1 Yr 3: [REDACTED] 1 Yr 4: [REDACTED] 1 Yr 5: [REDACTED] 1 Yr 6: [REDACTED] 1	Estimated by multiplying the number of incident individuals and the uptake rate	Likely to be substantially overestimated given that uptake rate, as discussed in the previous row, is likely to be an overestimate.
<b>Population 3: infants aged 1-2 years who remain vulnerable receiving a second administration of nirsevimab (200 mg) when entering their second RSV season</b>			
Incident individuals	Yr 1: [REDACTED] 1 Yr 2: [REDACTED] 1 Yr 3: [REDACTED] 1 Yr 4: [REDACTED] 1 Yr 5: [REDACTED] 1 Yr 6: [REDACTED] 1	ABS 3222.0, Projected population (released in 2013).	Updated since the first submission to reflect the source recommended by the prior DUSC advice.
Eligible individuals	8.04%		Updated since the first submission to capture infants with congenital heart disease and Aboriginal and Torres Strait Islander children. The estimate now includes <ul style="list-style-type: none"> <li>▶ Births with gestational age &lt;32 weeks (1.08%)</li> <li>▶ CHD prevalence rate in infants (0.9%)</li> <li>▶ Aboriginal and Torres Strait Islander people (6.2%) but adjusted to prevent double-counting of preterm births and CHD</li> </ul> <p>This was revised in the pre-PBAC response, utilisation for Aboriginal and Torres Strait Islander people was removed.</p>
Uptake rate	[REDACTED]%	Assumption	The prior DUSC advice considered the uptake rate to be reasonable.

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Data	Value	Source	Comment
Number immunised	Yr 1: [redacted] <sup>2</sup>	Estimated by multiplying the number of incident individuals with the percentage of births with a gestational age of less than 36 weeks and the uptake rate	The prior DUSC advice considered that this was an underestimate of the proposed population, given that it did not explicitly account for infants with congenital heart disease and Indigenous children.
	Yr 2: [redacted] <sup>2</sup>		
	Yr 3: [redacted] <sup>2</sup>		
	Yr 4: [redacted] <sup>2</sup>		
	Yr 5: [redacted] <sup>2</sup>		
	Yr 6: [redacted] <sup>2</sup>		
<b>Costs</b>			
Nirsevimab 50 mg 100 mg 200 mg	\$ [redacted] \$ [redacted] \$ [redacted]	Proposed ex-manufacturer price	Wholesaler and pharmacy mark-ups and dispensing fees are not included in the base case analyses.

Source: tabulated from Table 4.2.3, page 208 of the submission.

ABS = Australian Bureau of Statistics; DPMQ = dispensed price for maximum quantity; GP = general practitioner; MBS = Medicare Benefits Schedule; NIP = national immunisation program; NP = nurse practitioner; PBS = pharmaceutical benefits schedule.

The redacted values correspond to the following ranges:

<sup>1</sup> 200,000 to < 300,000

<sup>2</sup> 20,000 to < 30,000

6.82 Table 32 summarises the resubmission’s estimates of extent of use of nirsevimab and the associated financial implications. The resubmission’s estimates of infants using nirsevimab in Season 1 is likely overestimated given that the uptake rate assumed ([redacted]%) doesn’t factor that many infants will not be eligible for nirsevimab if the infant’s mother received RSVpreF. The PSCR provided revised estimates as shown in Table 32 assuming revised uptake rates ([redacted]% in first RSV season compared with [redacted]% in resubmission; [redacted]% in second RSV season which was unchanged). The ESC noted that the uptake of nirsevimab was based on uptake in State programs when only nirsevimab was available. With the inclusion of RSVpreF on the NIP, uptake rates should be adjusted to adequately reflect the extent of use of RSVpreF following its inclusion on the NIP. The pre-PBAC response stated that the uptake rates presented in the PSCR accounted for the inclusion of RSVpreF on the NIP, and it was assumed [redacted]% of infants are expected to be immunised with nirsevimab and [redacted]% of mothers are expected to receive RSVpreF vaccination, resulting in an overall uptake of [redacted]% for the combined RSV program. The pre-PBAC response also provided revised estimates which were reduced for season 2 due to removal of Aboriginal and Torres Strait Islander children as a separate criterion for season 2 (consistent with ATAGI advice that eligibility for this group should be based on medical risk factors only and it did not support additional criteria specifically for Aboriginal and Torres Strait Islander infants and children based on current evidence, paragraph 3.5). The revised estimates in the pre-PBAC response indicated that 2.0% of the age cohort would be classified as high risk infants and be eligible for nirsevimab in season 2.

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Table 32: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use and financial implications – Season 1</b>						
Infants treated in temperate regions	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Infants treated in tropical and subtropical regions	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Total infants treated in Season 1	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost per patient	\$█					
Financial implications for NIP	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>
<b>Estimated extent of use and financial implications – Season 2</b>						
Number of children treated in Season 2	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Cost per patient	\$█					
Financial implications for NIP	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>
Total infants and children treated	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Total financial implications for NIP	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>	\$█ <sup>7</sup>
<b>Revised estimates in PSCR</b>						
Total infants and children treated	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Total financial implications for NIP	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>
<b>Revised estimates in pre-PBAC response</b>						
Treated in Season 1	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Treated in Season 2	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
Total treated	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Total financial implications for NIP	\$█ <sup>9</sup>	\$█ <sup>9</sup>	\$█ <sup>9</sup>	\$█ <sup>9</sup>	\$█ <sup>9</sup>	\$█ <sup>9</sup>
<b>Previous submission (July 2024)</b>						
Number of patients treated in Season 1	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Number of patients treated in Season 1	█ <sup>10</sup>	█ <sup>10</sup>	█ <sup>10</sup>	█ <sup>10</sup>	█ <sup>10</sup>	█ <sup>10</sup>
Net cost to PBS	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>11</sup>

Source: Table 25 and Table 26, Nirsevimab July 2024 PSD and Table 4.3.2 and Table 4.3.4, pp167-168 of the resubmission. Blue shading is indicative of information previously considered by the PBAC.

The redacted values correspond to the following ranges:

- <sup>1</sup> 100,000 to < 200,000
- <sup>2</sup> 50,000 to < 60,000
- <sup>3</sup> 200,000 to < 300,000
- <sup>4</sup> \$80 million to < \$90 million
- <sup>5</sup> 20,000 to < 30,000
- <sup>6</sup> \$10 million to < \$20 million
- <sup>7</sup> \$90 million to < \$100 million
- <sup>8</sup> 500 to < 5,000
- <sup>9</sup> \$70 million to < \$80 million
- <sup>10</sup> 10,000 to < 20,000
- <sup>11</sup> \$100 million to < \$200 million

6.83 The resubmission estimated the total cost to the NIP was estimated to be \$90 million to < \$100 million in Year 6, and a total of \$500 million to < \$600 million in the first 6 years of listing. Despite an increase in the projected number of infants and

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children to be treated with nirsevimab, the estimated financial implications are reduced in the resubmission compared with the first submission, due to the reduction in financial estimates is the removal of wholesaler and pharmacy mark-ups and dispensing fees. The PSCR and pre-PBAC response provided revised estimates as shown in Table 32. Based on the estimates in the pre-PBAC response, the total cost to NIP was estimated to be \$400 million to < \$500 million in the first 6 years of listing.

**Quality Use of Medicines**

- 6.84 The resubmission noted that nirsevimab doses are dependent on the weight of infants, and highlighted the importance of ensuring dosing is based on weight at time of immunisation, and not allowing a time delay between the decision to immunise with nirsevimab and the immunisation itself.
- 6.85 In its consideration of the first submission, the DUSC considered that given that nirsevimab is a new health technology (prophylactic antibody treatment against RSV), there would be an opportunity to educate and improve the health literacy of consumers. The DUSC also noted the complexities of optimising the timing of doses given the variation in the onset of the RSV season.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

**7 PBAC Outcome**

- 7.1 The PBAC deferred making a recommendation for nirsevimab, for the prevention of lower respiratory tract illness (LTRI) caused by respiratory syncytial virus (RSV) in neonates and infants born during or entering their first RSV season, and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The PBAC noted advice received from the Department, that the current legislative framework underpinning the National Immunisation Program (NIP) does not support the inclusion of passive immunisation strategies such as nirsevimab at this time. The PBAC noted that nirsevimab reduced medically-attended RSV LRTI, and had an acceptable safety profile. The PBAC noted that RSVpreF maternal vaccination (Abrysvo<sup>®</sup>) was added to the NIP in February 2025, and considered this was the main comparator for nirsevimab for infants in their first RSV season, since both products protect infants against RSV. The PBAC considered that nirsevimab was not clinically superior to RSVpreF maternal vaccine based on the comparison presented in the resubmission. The PBAC noted in some infants, the use of nirsevimab would provide additional protection that could not be addressed by RSVpreF maternal vaccine, for example for infants whose mother received the RSVpreF vaccine but were born within two weeks from vaccination, which would result in impaired protection from the vaccine. The PBAC also acknowledged that nirsevimab would have additional value for infants at increased risk of severe disease from RSV during their first RSV season, and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The PBAC considered that no immunisation was the appropriate comparator for the second season. The PBAC advised that the

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- cost-effective price would need to reflect the value of nirsevimab in each group, and noted that the cost-effective price would be lower than the price requested by the sponsor. The PBAC noted the high cost to Government predicted by the resubmission. The PBAC advised that further information was required to support consideration of the proposed NIP listing of nirsevimab, including further input from the sponsor, and the Department.
- 7.2 The PBAC noted that a pathway for the listing of passive immunisation strategies on the NIP would need to be established before the PBAC could recommend nirsevimab. The PBAC accepted that use of nirsevimab as an immunisation against disease, would be consistent with the goals of the NIP.
- 7.3 The PBAC noted that a number of RSV vaccines and monoclonal antibodies are in development globally for prevention of RSV disease, and the clinical algorithm is changing following TGA registration and market launch of the first wave of these products in Australia, including RSVpreF for maternal vaccination which became available on the NIP in February 2025. The PBAC noted that arrangements are in place for provision of nirsevimab free of charge, through state and territory arrangements, although precise eligibility criteria vary by jurisdiction. The PBAC considered that the proposed NIP listing, which would provide funding under a national program, would be preferable to different arrangements across the states and territories.
- 7.4 The PBAC noted that nirsevimab is a recombinant human IgG1 kappa monoclonal antibody that binds to the prefusion conformation of the RSV F protein to block viral entry into the host cell. Nirsevimab provides protection for 5 months via passive immunisation of the infant or young child.
- 7.5 The PBAC noted that some infants are at an increased risk of severe RSV complications, including First Nations infants, infants with weakened immune systems, premature babies, and those with chronic lung or heart conditions. While some high-risk pregnancies and high-risk infants can be identified before birth, the majority of risk factors for RSV-related disease cannot be identified until after birth.
- 7.6 The PBAC noted that the timing of RSV outbreaks varies with the climate across different regions of Australia and that to maximise the effectiveness of nirsevimab, the timing of administration should be targeted to cover the majority of the RSV season in temperate regions, or the period of greatest risk in tropical regions noting that the risk of RSV can persist year-round in the tropical and subtropical regions. In temperate regions, nirsevimab should be administered at birth for infants born in the RSV season, and prior to the beginning of the RSV season for infants born before the start of the season. Given the relatively short duration of protection of nirsevimab (5 months), the use of nirsevimab provides greater protection in temperate regions, in terms of the proportion of RSV cases prevented, compared with its use in tropical regions where the risk of RSV can persist year-round. The nirsevimab economic model contained two populations based on their climate, either tropical or temperate, to permit the simulation of different timing and duration of the RSV season. The

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resubmission assumed that the use of nirsevimab at the beginning of the season in temperate climates would protect against almost 90% of the yearly cases of RSV. In tropical climates, where the RSV season is more dispersed, it was assumed that nirsevimab administered at the beginning of the season provided protection against almost 80% of all yearly cases of RSV. However, this would require the provision of accurate advice about the optimal timing of nirsevimab administration for different jurisdictions, and for this advice to be precisely followed. In comparison, RSVpreF maternal vaccine is accessible via the NIP as a year-round program and may be administered during routine antenatal care (between 28 to 36 weeks gestation).

- 7.7 In July 2024, the PBAC considered there was a high clinical need for vaccines, or other interventions such as nirsevimab, to reduce the risk of RSV, noting that RSV is a common respiratory infection and although symptoms are usually mild, some children develop severe disease which poses a significant risk, especially in infants aged up to six months. At the May 2025 meeting, the PBAC considered this need has been largely addressed by the implementation of a maternal RSVpreF vaccination program through the NIP, however the PBAC considered that in some infants, the use of nirsevimab would provide additional protection that could not be addressed by RSVpreF. The PBAC noted the proposed listing for nirsevimab was supported by the consumer comments received for this resubmission.
- 7.8 The PBAC noted and welcomed the advice from the ATAGI to assist with PBAC consideration of this submission.
- 7.9 The PBAC accepted the proposed clinical place for nirsevimab 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 RSV disease through their second RSV season. The PBAC considered that the uptake rates remained uncertain but that high uptake of either maternal RSVpreF or nirsevimab in the first 8 months of life should be the goal for a national program, in order to maximise clinical benefits for infants. The PBAC noted ATAGI's advice that uptake of nirsevimab in states that have implemented programs has been high, although estimates have not yet been published. The ATAGI advice stated that the goal will be to encourage strong RSVpreF vaccine uptake, and to offer nirsevimab to infants whose mothers do not receive the vaccine (or who meet other eligibility criteria). The PBAC considered it is currently unclear whether a pattern of provider or parental choice will emerge, and the relative uptake of nirsevimab vs maternal RSVpreF is therefore uncertain, noting that for the majority of infants only one approach will be used.
- 7.10 The PBAC provided the following advice in regard to the proposed NIP listing:
- It was of a mind to support NIP listing for nirsevimab with eligibility criteria that are aligned with the AIH, including populations where ATAGI has recognised an important clinical need but there is limited evidence of comparative effectiveness, noting these populations would constitute a small proportion of nirsevimab use.

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- The resubmission's request for infants being exposed to their first RSV season was not limited by the infant's age in the proposed listing. Although this is consistent with the approved PI, the AIH recommends use of nirsevimab up to a maximum of 8 months of age (unless the infant has a risk condition). The PBAC advised that it would be appropriate to add the 8-month age limit to the proposed NIP listing for infants born during or entering their first RSV season, and update the financial estimates accordingly.
  - The resubmission did not request catch-up doses for the proposed NIP schedule. The PBAC considered this may be appropriate, although may require further consideration depending on timing of implementation on the NIP. Catch-up doses are available in some jurisdictions under current arrangements. The sponsor would need to make a request for catch-up doses if this is considered necessary in the future.
- 7.11 The PBAC noted that RSVpreF maternal vaccination (Abrysvo<sup>®</sup>) was added to the NIP in February 2025, and considered this was the main comparator for nirsevimab for infants in their first RSV season, since both products protect infants against RSV. The PBAC noted in some infants, the use of nirsevimab would provide additional protection that could not be addressed by RSVpreF maternal vaccine, for example for infants whose mother received the RSVpreF vaccine but were born within two weeks from vaccination, which would result in impaired protection from the vaccine. The PBAC considered that for populations in which the infant's mother received RSVpreF, the appropriate comparison would be nirsevimab + RSVpreF versus RSVpreF alone. The PBAC considered that no immunisation was the appropriate comparator for the second season.
- 7.12 In regard to Season 1, the PBAC previously considered that a claim of superior comparative effectiveness was reasonable for nirsevimab versus no immunisation, as supported by the relative risk reduction in MA RSV LRTI in the MELODY and Phase IIb studies. The PBAC noted that updated evidence from the MELODY trial indicated that the difference in the effectiveness of nirsevimab versus placebo beyond 150 days (5 months) is no longer significant (Table 12). The resubmission, appropriately, made no claim of effectiveness of nirsevimab beyond 150 days. The PBAC was again satisfied that the claim of non-inferior safety was reasonable based on the similar rates of AEs observed in the nirsevimab and placebo arms of both studies. The PBAC noted that the resubmission again relied on a meta-analysis of the MELODY trial (which included infants with a gestational age  $\geq 35$  weeks) and the Phase 2b trial (which included infants with a gestational age between 29 and  $< 35$  weeks). Consistent with its previous advice, the PBAC considered that the MELODY trial provided the most relevant and robust estimates of efficacy of nirsevimab compared with placebo in Season 1; updated data from the MELODY final analysis supported an efficacy estimate of 76.4% compared with 74.5% that was supported by the PBAC in July 2024. The PBAC considered it was reasonable to consider efficacy and safety in Population C(a) in

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Figure 1 to be consistent with Population A in Figure 1), as proposed by the sponsor and accepted by the ESC.

- 7.13 The resubmission maintained that nirsevimab is superior to RSVpreF in scenarios where the mother has not previously been vaccinated, which was previously not accepted by the PBAC in July 2024. The ATAGI considered “the comparison of nirsevimab and RSVpreF presented in the submission was unreliable, and a conclusion of superior effectiveness is not supported by the data” (paragraph 6.52). The PBAC agreed with ATAGI and again concluded that the indirect treatment comparison was insufficient to support a claim that nirsevimab is superior to maternal RSVpreF vaccination due to transitivity issues. The PBAC advised that nirsevimab could be considered non-inferior to RSVpreF.
- 7.14 The resubmission did not provide clinical evaluations for nirsevimab in some of the requested populations. The PBAC noted the absence of evidence to support that nirsevimab after maternal RSVpreF vaccination is superior to maternal RSVpreF vaccination alone. The PBAC agreed with the ATAGI advice that noted the magnitude of the effectiveness of nirsevimab following maternal vaccination vs maternal vaccination alone is difficult to predict, and will change depending on the timing of the birth with respect to the first RSV season, however, it was reasonable to conclude that nirsevimab would provide a meaningful benefit in 1) infants who are at the highest risk of hospitalisation from RSV (Population C(b) in Figure 1), and 2) infants with suboptimal RSV antibodies despite the mother having received the RSVpreF vaccine e.g. birth occurred within 2 weeks of the mother’s vaccination with RSVpreF (Population B in Figure 1). For season 2, the PBAC noted that the clinical trial evidence to support the superiority of nirsevimab over no immunisation in terms of effectiveness was limited but considered that this claim was reasonable. The PBAC noted the population in which nirsevimab is proposed to be used in the second RSV season is aligned with the AIH, i.e. in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season (Population D in Figure 1). The PBAC considered this population has a high clinical need for protection from RSV.
- 7.15 For the economic evaluation, the resubmission again presented a CUA based on a meta-analysis of the MELODY trial and a subgroup of the Phase 2b trial for Season 1. Consistent with the July 2024 model, the tropical and temperate populations were aggregated to generate an overall population ICER. The PBAC noted that nirsevimab was associated with lower ICERs in temperate regions (Table 26; assumed for 79% of use), compared with tropical regions (Table 27; assumed for 21% of use).
- 7.16 For the first RSV season, the PBAC considered that nirsevimab should be cost-minimised to RSVpreF for the majority of the population (corresponding to Population A in in Figure 1), based on an equi-effective dose of 1 nirsevimab dose (either 50 mg or 100 mg; administered to the infant) to 1 RSVpreF dose (one vial of Abrysvo vaccine, administered to the mother). In addition, the PBAC recognised there were additional considerations for populations B, C(a), and C(b) in Figure 1. The PBAC

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noted that the sponsor did not adequately address these populations in their resubmission. For these populations, the PBAC advised that a cost utility analysis versus no immunisation was a reasonable approach to assess the cost-effectiveness of nirsevimab in the context of the relatively small size of this combined population. The PBAC noted the sensitivity analyses explored by the ESC and agreed with ESC's advice that (i) the impact of nirsevimab on asthma and recurrent wheezing should be removed; (ii) the hospitalisation costs should be reduced to better reflect expected readmissions (apply costs for readmission within one month from Brusco 2018, rather than the total aggregated costs of hospitalisations over six months); (iii) an administration cost of \$9.80 should be included; (iv) effectiveness of nirsevimab should be based on the MA RSV LRTI endpoint in the final analysis of MELODY (76.4%); (v) a RSV hospitalisation rate of 3.67% should be used. The PBAC noted the hospitalisation rate was higher than the estimate it had previously supported in July 2024 (2.33%), however considered reasonable in the context of at least some of the population for this analysis being at high risk of severe RSV. The PBAC noted the aggregated ICER (including temperate and tropical regions) corresponding to this analysis was \$75,000 to < \$95,000/QALY (Table 29). Further it was noted this assumed optimal timing of administration of nirsevimab to maximise its activity against RSV infection. The PBAC considered that the aggregated ICER that would define acceptable cost-effectiveness should be no greater than \$15,000 to <\$25,000/QALY.

- 7.17 For the second season, the PBAC noted there was limited evidence to inform a cost-effectiveness evaluation. The PBAC considered that the Season 2 model provided by the sponsor was not reliable for decision-making (paragraph 6.76). However, in recognition of the small population size and the clinical need in this population, the PBAC considered that the same cost per dose arising from the CUA described in paragraph 7.16 could be considered acceptable for nirsevimab doses for high risk children in Season 2 (i.e. the cost for nirsevimab per child should be equal in Season 1 and Season 2). The PBAC noted that the recommended dose of nirsevimab for the second RSV season is 200 mg (2 x 100 mg), and the dose of nirsevimab in Season 1 is either 50 mg or 100 mg.
- 7.18 The PBAC provided the following advice in relation to generation of the overall price for nirsevimab:
- For the proportion of use in population B, C(a) and C(b), apply the price corresponding to the Season 1 CUA as described in paragraph 7.16. The PBAC noted the high risk population (C(a) + C(b)) was estimated in the pre-PBAC response to be 2% of births. The PBAC noted that the submission did not provide an estimate of the size of population B, however the PBAC expected that it would be small;
  - For the proportion of use in population D, apply the same cost per dose arising from the CUA described above as discussed in paragraph 7.17. The PBAC noted

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the high risk population (D) was estimated in the pre-PBAC response to be 2% of births;

- For the remaining proportion of nirsevimab use, apply the price corresponding to Season 1 CMA (Population A). The PBAC advice for the CMA is provided in paragraph 7.16. The PBAC noted that a confidential price applies to RSVpreF under the NIP, which is not available to the sponsor, however this does not prevent the sponsor from providing a written proposal for nirsevimab using an assumed price for RSVpreF (see paragraph 7.20).

7.19 In regard to the financial estimates, the PBAC noted the high uptake rate and the high cost to Government predicted by the resubmission. The pre-PBAC response stated that nirsevimab would provide parents a choice between infant immunisation and maternal vaccination, and the sponsor estimated that █████% of infants would be protected by nirsevimab while only █████% would be protected by maternal RSVpreF. This contrasted with ATAGI advice, which anticipated strong uptake of maternal RSVpreF, noting that maternal pertussis vaccine coverage was approaching 90% in recent years. It was also noted that for maternal influenza vaccination, uptake between 32% and 75% has been reported in Australian jurisdictions, with rates increasing in recent years. The PBAC considered it was uncertain to what extent the use of nirsevimab would replace the use of RSVpreF in clinical practice, however the PBAC considered that nirsevimab uptake would be lower than estimated in the resubmission. As discussed above, the PBAC advised that it would be appropriate to add the 8-month age limit to the proposed NIP listing for infants born during or entering their first RSV season (consistent with the AIH), and the financial estimates should be updated accordingly (paragraph 7.10).

7.20 The PBAC considered that nirsevimab could be recommended for NIP listing if the following criteria were met:

- Notification from the Department that a pathway for the listing of passive immunisation strategies on the NIP has been established, thereby allowing monoclonal antibodies such as nirsevimab to be made available on the NIP;
- Written proposal from the sponsor including:
  - Calculation of a weighted price for nirsevimab as described in paragraph 7.18;
  - Recalculation of the financial implications using the revised nirsevimab price, noting this would also allow the sponsor an opportunity to revise or confirm its estimates for uptake in each of the populations for nirsevimab that are used for generation of a weighted price. The revised estimates should address advice provided in paragraph 7.19.

7.21 The PBAC noted that the sponsor may reinitiate the process of PBAC consideration for nirsevimab by providing a written proposal after notification from the Department that NIP eligibility concerns have been resolved, consistent with paragraph 7.20.

**Outcome:**

Deferred

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

**9 Sponsor's Comment**

Sanofi-Aventis believes that the primary objective of an RSV immunisation program is to achieve broad coverage that ensures protection for all infants. Sanofi believes that nirsevimab plays an important role in avoiding the significant burden associated with RSV in infants. Sanofi is of the opinion that the success of nirsevimab immunisation has been demonstrated in state-based programs across Australia, in terms of vaccine effectiveness and cost effectiveness, and similar best practice programs continue to be rolled out overseas.

Sanofi recognise the legislative complexities involved in listing nirsevimab on the National Immunisation Program. Sanofi believes that, with planning already underway for next year's RSV season, timely legislative amendments are critical to ensure comprehensive national protection. While these discussions are ongoing, Sanofi remains committed to ensuring infants remain protected through established state- and territory-funded nirsevimab programs.