

Palivizumab
for prevention of serious
lower respiratory tract disease
caused by Respiratory
Syncytial Virus (RSV) in infants
at high risk of RSV disease

South Australian Medicines Evaluation Panel

October 2015

Summary of SAMEP review

Receipt of High Cost Medicine (HCM) formulary application:	21 st August 2015
Date of SAMEP meeting:	9 th September 2015

Name of medicine Palivizumab (Tradename: Synagis®)

Dosage form Powder for solution for intramuscular injection

**Requested
Statewide High
Cost Medicine
Formulary Listing**

Prevention of serious lower respiratory tract disease caused by RSV in infants at high risk of RSV disease:

- Children aged <2 years requiring treatment for chronic lung disease (CLD) requiring chronic corticosteroid therapy, diuretic therapy and/or supplemental oxygen within the last 6 months
- Children aged <1 year with haemodynamically significant congenital heart disease (CHD) (acyanotic heart disease on medication for congestive heart failure and requiring heart surgery, moderate to severe pulmonary hypertension, cyanotic heart disease, in consultation with paediatric cardiologist)
- Children with Severe Combined Immunodeficiency (SCID) until immune reconstituted
- All long-term ventilated children aged <12 months at the start of the RSV season and Long-term ventilated (LTV) children aged <2 years with additional co-pathology (heart disease/intrinsic lung disease as reflected by O2 dependency)

Cost per vial: \$ 1,456 per 100mg injection; \$ 795 per 50mg injection

The proposed dose is 15mg/kg monthly for 5 doses.

The cost per patient per treatment course is therefore:

Cost

Body weight	Cost per dose	Cost for 5 dose course
< 3.3kg	\$795	\$3,975
3.3 - 6.7kg	\$1,456	\$7,280
6.7 – 10kg	\$2,251	\$11,255
10 – 13.3kg	\$2,912	\$14,560

The weights below are average (50th percentile) for Australian male infants:

	Average weight (boys) (50th percentile)	Cost for 5 dose course*
28 week gestation (birth weight)	1.2kg	\$3,975
35 week gestation (birth weight)	2.5kg	\$3,975
Full term birth weight	3.5kg	\$7,280
Full term infants at 4 months	6.5kg	\$7,280
Full term infants at 11 months	10kg	\$11,255
Full term infants at 2 years	12.6kg	\$14,560

*Infants are likely to move into higher weight ranges during the treatment course. The average cost for a full term male infant < 1 year, based on the 50th percentile for weight, is likely to be approximately \$9,323 (drug cost only, excluding outpatient clinic costs), and \$14,560 for a patient between 1-2 years. For a patient on the 3%, the average estimated cost is \$8,385 < 1 year, and \$11,806 between 1-2 years.

Measurement of outcomes (as proposed in the formulary application)

Desired outcomes of proposed treatment with palivizumab:

"Reduction in hospitalisation and death due to severe RSV lower respiratory tract disease in infants in the proposed risk groups".

Practical methods to measure / monitor treatment with palivizumab:

"Follow the progress of each patient given palivizumab to determine whether RSV infection occurs and if so, whether this results in hospital admission and other complications".

SAMEP recommendations

Following the review of the current available evidence (appendix 1) in the proposed patient populations, evaluations by other jurisdictions (appendix 2), analysis of the cost-effectiveness in the proposed populations (appendix 3) and a summary of RSV-associated hospitalisations in South Australia, SAMEP recommend rejecting the application to list palivizumab on the Statewide High Cost Medicines formulary for the prevention of serious lower respiratory tract disease caused by RSV in infants at high risk of RSV disease. The recommendation is based on the following:

- The only benefit shown from the best available evidence is a reduction in absolute risk of hospitalisation from 10% to 5% in patients with chronic lung disease (CLD) & congenital heart disease (CHD), and a reduction in the admission rate to ICU. Palivizumab has not been shown to reduce the length of stay in ICU, nor has any benefit been shown in long-term ventilated patients or patients with severe combined immune deficiency (SCID). It is unclear whether palivizumab prevents RSV infection in exposed children.
- There is no evidence that palivizumab reduces mortality from RSV in any subgroup. Mortality associated with RSV is low even in very high risk populations. There were no deaths recorded in SA public hospitals among patients aged 0-4 years admitted with RSV infection in the 2013-2014 financial year.
- Prophylaxis with palivizumab does not represent good value for money given that to prevent one hospitalisation in patients with CLD, 17 patients would need to be treated (NNT). The NNT for patients with haemodynamically significant CHD is 23. The cost to treat 17 patients ranges on average from \$201,892 to 247,520 based on full term birth weights. If it is assumed that all were premature, and below the 3rd percentile in birthweight, the estimated cost is approximately 15% less, at around \$170,000. Therefore the estimated cost of palivizumab would be between approximately \$170,000 to \$247,000 to prevent one hospitalisation of 2-3 days duration. The NNT to prevent one ICU admission is 56.
- The opportunity cost is significant: Implementation of a vaccination program with palivizumab would require significant resources (including a specialist immunisation nurse, costs of drug acquisition and preparation, and program co-ordination)..
- For patients who are currently hospitalised, there is no evidence of benefit with prophylactic palivizumab.
- The cost-effectiveness is increased in very premature infants purely on the basis of the weight-based dosing and therefore the cost. However, there is no evidence of superior efficacy in these patients.

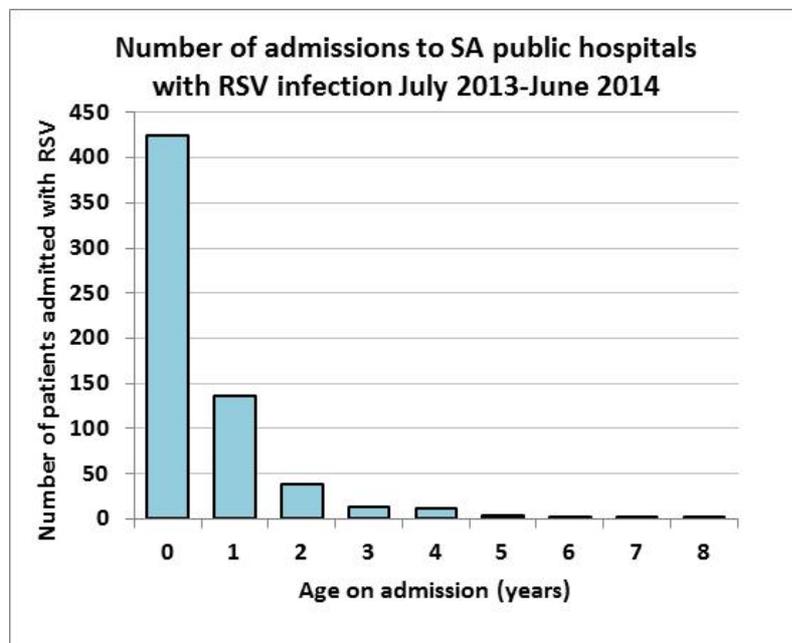
OVERVIEW OF RSV INFECTION

The Respiratory Syncytial Virus (RSV) is an enveloped, single-stranded, and negative-sense RNA virus which can cause severe lower respiratory tract disease requiring hospitalization. Two major subtypes (A and B) of RSV have been identified based on structural variations a viral surface glycoprotein (the G protein). RSV is a seasonal infectious disease with the prevalence highest in the winter months. The RSV “season” in Australia is considered to be May to October each year. The predominance of each subtype changes over successive seasons and is not associated with disease severity [1].

Epidemiology

RSV is not a notifiable disease in Australia, and therefore there is no single data source actively measuring RSV incidence across Australia. RSV is the principle cause of bronchiolitis in infants and young children worldwide, with incidence peaking between 2 and 5 months of age [2]. Using published reports from the Laboratory Virology and Serology Reporting Scheme (LabVISE), a passive surveillance system involving a network of 17-20 laboratories across Australia, and from the National Hospital Morbidity Database, the estimated annual incidence in Australia ranges from 110 -227 per 1000 in children less than 5 years of age, with the incidence among infants estimated to be 435 – 869 per 1000 [2].

The number of hospital admissions for children ≤ 8 years of age with RSV infection in South Australia for the 2013/2014 financial year are shown below [3]. For all RSV-related admissions in 2013/2014, the age at admission ranged from 0 to 99 years of age, however 88% of cases were ≤ 4 years of age, with 79% of all cases being ≤ 1 year of age.



Age on Admission	Average length of stay (days)
0	3.4
1	2.5
2	3.5
3	2.4
4	2.4

There were no deaths recorded in SA public hospitals among patients aged 0-4 years admitted with RSV infection in the 2013-2014 financial year

In 2013, the population of children aged 0-4 years of age in South Australia was estimated to be 100,171 [4]. The number of admitted cases of RSV infection for the 2013 - 2014 financial for the

0-4 year age group was 627, therefore the approximate annual hospitalisation rate in this age group in South Australia is estimated to be 6.3 per 1000.

Clinical manifestations & diagnosis

Symptoms include rhinitis (runny nose, sneezing, nasal congestion), cough, shortness of breath, lethargy, fever, shortness of breath and decreased appetite. Symptoms can progress to otitis media, bronchiolitis and acute lower respiratory tract infection, and presentation may be very similar to influenza infection [2].

Because clinical symptoms mirror influenza symptoms, definitive diagnosis is by laboratory confirmation. A number of testing methods are available with varying sensitivity and specificity including direct immunofluorescence assay, enzyme immunoassay or a positive viral culture for RSV from nasopharyngeal secretions [5].

Pathophysiology, treatment and prognosis

RSV is highly communicable, with the virus spreading through close contact with infected persons via respiratory droplets or contact with contaminated surfaces. The incubation varies from two to eight days. RSV infection is usually self-limiting, with disease severity and duration primarily being a function the patient's age, immune function and co-morbidities. Severe cases require hospitalisation for respiratory support, fluid & nutrition management. There is no recommended pharmacological treatment for RSV disease [6].

Mechanism of action of palivizumab

Palivizumab is a humanised monoclonal antibody (comprised of 95% human & 5% murine amino acid sequences) which exhibits neutralising and fusion-inhibitory activity against RSV [7]. Palivizumab reduces the ability of RSV to replicate and infect cells by binding to the antigenic A site of the F protein, a glycoprotein found on the surface of RSV. The F protein mediates the fusion between viral and cell membranes, as well as between infected cell membranes. The precise mechanism of action of palivizumab is not known, however it is likely that it inhibits a step in RSV replication after virus attachment and before virus transcription [8].

Because palivizumab only conveys passive immunity, protection against RSV is dependent upon maintaining palivizumab serum concentrations for the duration of exposure. The half-life for palivizumab is between 18 and 21 days, therefore the manufacturer recommends it is administered intramuscularly at a dose of 15 mg/kg once every 30 days during the RSV season [7].

Palivizumab-resistant strains of RSV have been reported in patients treated with palivizumab however the incidence of resistance in patients treated with palivizumab is unclear [9]. Of 254 clinical isolates from patients who have not received palivizumab, 2 (0.79%) were resistant to palivizumab [10].

SUMMARY OF EVIDENCE FOR THE USE OF PALIVIZUMAB FOR THE PREVENTION OF LOWER RESPIRATORY TRACT DISEASE CAUSED BY RSV IN INFANTS AT HIGH RISK OF RSV DISEASE

Health Technology Assessment

Citation	Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. <i>Health Technol Assess.</i> 2011;15(5)
Conflicts of interest declared?	Nil declared
Funding of study	HTA program of the National Institute of Health Research (UK)
Focused question? (population, intervention, outcomes)	Yes
Inclusion criteria of studies predefined, clearly defined, appropriate	Systematic reviews & primary studies (prognosis and hospitalisation studies)
Minimum of two independent data extractors and a consensus procedure for disagreements?	Yes. Data abstraction by one reviewer and checked by the modeller
Search method provided (databases searched, search terms used)	Databases provided, methods of study identification provided dates provided, no language restrictions, search terms all provided (Appendix 1)
Characteristics of included studies provided (assessment of bias of individual studies)	Quality assessment of included studies provided (Appendix 3)
Were the methods used to combine the findings of studies appropriate? Studies tested for heterogeneity? Clinical appropriateness of combining studies?	Yes. Studies, when combined, were tested for heterogeneity, and random effects model used when heterogeneity identified.
Odds Ratio (OR) for risk of hospitalisation: Chronic Lung Disease Congenital Heart Disease	3.44 (95% CI: 1.71 to 6.88) - based on 2 included studies 1.46 (95% CI: 1.04 to 2.05) - based on 3 included studies

Comment on the review: The above HTA is methodologically of high quality, with a concise description of search, appraisal and synthesis methods. 13 studies were included in the analysis (8 prospective studies, 2 retrospective studies and 3 studies where it was unclear whether prospective or retrospective), however over 16,000 subgroups were analysed by the authors. Because such a large number of subgroups were analysed, the number of patients in many of the subgroups would have been very small and therefore the confidence intervals for the point estimates of cost-effectiveness would be very wide.

The authors acknowledged the limitations of the results due to the quality of the included studies (8 cohort, 4 case-control and 1 prospective registry), many of which were small and under powered. Several of the meta-analyses had a high degree of heterogeneity, therefore the

accuracy of the cost-effectiveness estimates in these groups is uncertain. Different methods were used between the studies to diagnose RSV, further adding uncertainty to the results. The Quality of Life (QoL) estimates are uncertain as they were derived subjectively from parents/carers [5].

In addition to acyanotic or cyanotic CHD, any form of significant CLD, the following risk factors were analysed: gestational age, male gender, siblings at school, multiple births. exposure to passive smoke, overcrowding in the home, parental education, age < 6 weeks at start of RSV season, lack of (or minimal) breast feeding, family history of atopy.

Despite the limitations of the included studies, the authors concluded, given a willingness to pay threshold of £30,000/QALY, the cost-effectiveness of palivizumab may be increased in some subgroups depending upon age, prematurity and other risk factors.

Systematic reviews & meta-analyses

Citation	Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Vrca VB, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Evidence-Based Child Health: A Cochrane Review Journal. 2013;8(6):2243-376.
Conflicts of interest declared?	Nil applicable
Focused question? (population, intervention, outcomes)	Yes → Infants/children at high risk of LRTI caused by RSV, ie. CLD, CHD, immunodeficiency, chronic neuromuscular disease, congenital abnormalities, premature infants. Intervention: palivizumab 15mg/kg, any setting or regiment Comparator: placebo, no prophylaxis, another type of prophylaxis Outcomes: hospitalisation for RSV, all-cause mortality
Inclusion criteria of studies predefined, clearly defined, appropriate	Yes: Randomised trials, no language or publication restrictions; Economic evaluation studies.
Minimum of two independent data extractors and a consensus procedure for disagreements?	Yes
Search method provided (databases searched, search terms used)	Yes
Characteristics of included studies provided (assessment of bias of individual studies)	Yes
Were the methods used to combine the findings of studies appropriate? Studies tested for heterogeneity? Clinical appropriateness of combining studies?	Fixed effect meta-analysis where no heterogeneity ($I^2 < 40\%$); Random effects method used where $I^2 > 40\%$. Economic data combined in tabular way. Yes, heterogeneity tested using both χ^2 & I^2 statistics Yes, combined as per subgroup. However no subgroup analysis performed as there were not at least 3 studies per subgroup.
Assessment of publication bias?	Yes

Comment on the review: 7 RCTs were included in the review (3 comparing palivizumab to placebo, and 4 comparing palivizumab to motavizumab). 34 economic evaluation studies were included in the review. Of the 7 RCTs investigating the efficacy, all were sponsored by and included authors from, the manufacturers of palivizumab. 5 of the 7 trials were adequately blinded, with no details provided for the other 2. Attrition rates were reported in 6 of the 7, however in 1 trial no details were provided for patients lost to follow up, and the risk of attrition bias was high. In 3 of the 7 trials, total RSV-hospital days, days in ICU, days of mechanical ventilation and days of supplementary oxygen, were all incompletely reported, and standard deviations not provided.

A total of 2831 patients were included in the 3 trials comparing palivizumab to placebo. Palivizumab patients had a statistically significant relative risk reduction in RSV-hospitalisations compared with placebo (RR=0.49, 95% CI: 0.37 - 0.64), and a statistically significant relative risk reduction in admissions to ICU (RR=0.50, 95% CI: 0.30 - 0.81). The number requiring mechanical ventilation was similar in both groups. The number of days in ICU varied between trials and palivizumab was not shown to reduce the length of stay in ICU. Reduction in all-cause mortality was not statistically significant.

Randomised controlled trials

There have been no new published placebo-controlled trials investigating palivizumab for RSV prophylaxis since the publication of the HTA by Wang et al.

Overview of Evidence

Summary of effectiveness

The Cochrane review by Andabaka et al, 2013, is the most recent systematic review investigating the efficacy of palivizumab in reducing the risk of RSV infection in children. Based on a meta-analysis of the 3 RCTs identified comparing palivizumab to placebo, the review concluded that palivizumab prophylaxis was associated with a statistically significant reduction in RSV hospitalisations compared to placebo (RR=0.49, 95% CI: 0.37 - 0.64) [11]. The patient population in two of the included three trials were either born prematurely and were less than six months old, or less than 2 years of age with bronchopulmonary dysplasia (BPD) [12, 13]. The third study included children less than two with haemodynamically significant congenital heart disease[14]. The combined total number of bed days in the palivizumab group was 82 (number of patients in palivizumab group was 1663). The total number of bed days in the placebo group was 118 (number of patients in the placebo arm was 1168). The absolute risk of hospitalisation in the placebo group is 10.1% compared to 4.9% in the palivizumab group. The number needed to treat (NNT) to prevent one hospitalisation is therefore 20 children. For the patients in the two trials with patients CLD, the NNT is 17 and for the patients with CHD, the NNT is 23.

Admissions to ICU were fewer in the palivizumab group compared to placebo. The number of bed days in ICU in the palivizumab group was 26 in a total of 1641 children (1.6%), compared to 39 days in the placebo group of 1148 children (3.4%). 56 children would need to be treated with palivizumab to prevent one ICU admission. There was no statistically significant difference in the length of ICU stay between the palivizumab and placebo groups[11].

There is no evidence that palivizumab prophylaxis reduces the RSV-related hospitalisation rate in children with immunodeficiency.

There is no published evidence of efficacy in stem cell transplant recipients. A retrospective review of all (n=40) allogeneic stem cell transplant recipients in a single institution over a 7 year period who developed symptomatic RSV infection, concluded that palivizumab did not prevent progression to lower respiratory infection and had no impact on the overall survival rate. [15]

Summary of safety data

In the combined paediatric prophylaxis studies which studied premature infants with or without BPD, the proportions of subjects in the placebo and palivizumab groups who experienced any adverse event or any serious adverse event were similar [7].

When initially marketed, there had been no cases of anaphylaxis due to palivizumab however in 2002 following 2 cases reported to the FDA, the PI was changed to include a warning of very rare cases of anaphylaxis (<1 case per 100,000 patients). In addition, rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to palivizumab [16]

Pharmaceutical Benefits Advisory Committee (PBAC)	<p>The PBAC has rejected 3 submissions for palivizumab (however public summary documents are not available):</p> <ul style="list-style-type: none"> ○ Two submissions were prior to 2005, and documentation is not publically available; ○ March 2005: 3rd submission "for children with haemodynamically significant congenital heart disease and who are ≤ 2 years of age at the time of first inoculation; Children with a history of prematurity (gestational age ≤ 35 weeks at birth) who are less than 3 months of age at the time of first inoculation". <p>→rejected - extent of clinical benefit demonstrated for palivizumab was insufficient to justify the overall costs and cost off-sets associated with its use in the requested restriction and thus uncertain but unfavourable cost-effectiveness. PBAC noted that the Impact trial provides evidence of the drug's effectiveness in reducing hospital admissions due to RSV. However, the data from the Impact trial may be outdated and may be less valid, given improvements in neonatal management in the last seven years.[17]</p>
Canadian Agency for Drugs and Technologies in Health (CADTH) / Canadian Expert Drug Advisory Committee (CEDAC)	<p>CADTH has evaluated palivizumab for the prophylaxis of RSV:</p> <ul style="list-style-type: none"> ○ March 2007 → recommended for children at highest risk, such as children with bronchopulmonary dysplasia and children born ≤ 32 weeks gestation. (Children born between 32-35 weeks gestation may not be at high risk for RSV hospitalisation & should be assessed for other risk factors) [18]
Scottish Medicines Consortium (SMC)	<p>The SMC has not evaluated palivizumab for the prophylaxis of RSV</p>
National Institute for Health and Clinical Excellence (NICE)	<p>NICE have not evaluated palivizumab for the prophylaxis of RSV</p>
National Institute for Health Research (NIHR) Health Technology Assessment Programme	<p>Wang, D., S. Bayliss, et al. (2011). "Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses." Health Technology Assessment 15(5): iii-iv, 1-124.</p>

Western Australia Drug Evaluation Panel (WADEP)	<p>August 2012: Listed on formulary “for prophylaxis in infants at high risk of infection with respiratory syncytial virus (RSV) and its consequences, according to the following criteria,</p> <ol style="list-style-type: none"> 1. For use in infants up to 12 months of age at commencement of RSV season with cardiac lesions and haemodynamically significant left-right shunt, and/or patients with cyanotic congenital heart disease, pulmonary hypertension, or cardiomyopathy; 2. For use in infants up to 12 months of age at commencement of RSV season returning home, requiring oxygen therapy for respiratory disease.” <p>Special requirements: Palivizumab should only to be used during the recognized RSV season and for no more than 6 continuous months (no more than 5 or 6 doses per patient). NB.Hospital use of palivizumab for neonatal inpatient prophylaxis will continue to require individual patient approval (IPA) via the hospital DTC because of uncertainties about the seasonally variable number of eligible patients and associated costs [19].</p>
Pharmacology & Therapeutics Advisory Committee (PTAC) (Advisory Committee to Pharmac, NZ)	<ul style="list-style-type: none"> · February 2000 –declined · Nov 2000 – declined · Aug 2001 – moderate priority · 2005 – declined, endorsed by PHARMAC, following unsuccessful negotiations with supplier · Feb 2009: Proposed for children < 2 years, with severe CLD & supplemental home oxygen requirements. → declined

Published Clinical Guidelines

The **American Academy of Pediatrics guidelines**, 2014 [20] recommend palivizumab prophylaxis (15mg/kg/dose for maximum of 5 doses):

- In the first year of life in infants born before 29 weeks gestation (It is not recommended for otherwise healthy infants born at or after 29 weeks gestation);
- In the first year of life, for preterm infants with CLD of prematurity, defined as birth at <32 weeks gestation and a requirement for >21% oxygen for at least 28 days after birth;
- In the first year of life to certain infants with hemodynamically significant heart disease;
- in the second year of life for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy).

The American guidelines suggest that prophylaxis may be considered for:

- In the first year of life, children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways;
- In children ≤ 24 months who will be profoundly immunocompromised during the RSV season;
- Cystic fibrosis or Down syndrome - Insufficient data to recommend palivizumab prophylaxis;
- Alaska Native populations and possibly in selected other American Indian populations -burden of RSV disease and costs associated with transport from remote locations may result in a broader use of palivizumab for RSV prophylaxis;
- Palivizumab prophylaxis is not recommended for prevention of healthcare-associated RSV;
- Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.

The **Canadian Paediatric Society** position statement, 2011 [21]:

- Children with CLD of prematurity requiring ongoing medical therapy, children with haemodynamically significant congenital heart disease < 24 months at the start of the RSV season and infants born before 32 weeks gestation who are < 6 months old at the start of the RSV season → recommended to receive 5 doses of palivizumab
- Children with immunodeficiencies → Not routinely recommended. However for children < 24 months who are on home oxygen, have had a prolonged hospitalisation for severe pulmonary disease, or are severely immunocompromised, palivizumab may be considered.

Comparative costs:

Palivizumab acquisition costs¹:

- \$ 1,456 per 100mg injection; \$ 795 per 50mg injection
- The proposed dose is weight-based at 15mg/kg monthly for 5 doses.
- The cost per patient per dose based on patient weight are provided on page 1 of this document.
- The average acquisition cost of a course of 5 doses for a child (full term) who was under the age of 1 at the start of the RSV season is \$9,323. The average acquisition cost of a course of 5 doses for a child aged between 12-23 months at the start of the RSV season is \$14,560. (Costs calculated on a modelled estimation of weight of a full-term male infant on the 50th percentile for weight).

Additional costs and resources required:

- Outpatient clinic costs – 5 visits required for treatment course
- Costs of immunisation co-ordinator – accurate record keeping & follow-up of patients to ensure compliance (treatment failure more likely if the dose is not administered on time, or doses are missed)

Comparative effectiveness:

For the requested patient populations:

- Children aged < 2 years requiring treatment for CLD (chronic corticosteroid therapy, diuretic therapy or supplementary oxygen) within the last 6 months:
 - In patients born prematurely and are less than six months old, or less than 2 years of age with bronchopulmonary dysplasia, palivizumab reduces the absolute risk of hospitalisation by 5.9%, from a risk of 10.6% in the placebo group to 4.7% in the palivizumab group[11]. The number needed to treat (NNT) to prevent one hospitalisation is therefore 17 children.
- Children < 1 year with haemodynamically significant CHD (acyanotic heart disease on medication for congestive heart failure and requiring heart surgery, moderate to severe pulmonary hypertension, cyanotic heart disease):
 - In patients < 24 months old with haemodynamically significant CHD, palivizumab reduces the absolute risk of hospitalisation by 4.4 %, from a risk of

¹ The patent on palivizumab expires in the European Union in August 2015, and in the United States in October 2015 (22. WHO. *Bulletin of the World Health Organisation: Hubs to spread technology and save lives (webpage)*. <http://www.who.int/bulletin/volumes/93/5/15-020515/en/> Accessed 27 Aug 2015.) Biosimilar products entering the market following the expiry of the patents may reduce the cost.

9.7% in the placebo group to 5.3% in the palivizumab group[11]. The number needed to treat (NNT) to prevent one hospitalisation is therefore 23 children.

- Children with SCID until immune reconstituted:
 - There is no evidence that palivizumab is significantly superior to placebo in preventing RSV-hospitalisations in children with SCID.
- All long-term ventilated children < 12 months at the start of the RSV season and long term ventilated children aged < 2 years with additional co-pathology (heart disease/intrinsic lung disease as reflected by O₂ dependency):
 - There are no randomised trials specifically in ventilated patients, except for those in the first two groups with CLD & CHD above.

Number needed to treat to prevent one hospitalisation:

- Children aged < 2 years requiring treatment for CLD (chronic corticosteroid therapy, diuretic therapy or supplementary oxygen) within the last 6 months:

The NNT to prevent one hospitalisation is 17 patients:

The cost to treat 17 patients ranges on average from \$201,892 to 247,520 based on full term birth weights. If it is assumed that all were premature, and below the 3rd percentile in birthweight, the estimated cost is approximately 15% less, at around \$170,000.

The cost of 5 outpatient visits for 17 patients is \$12,708

- Children < 1 year with haemodynamically significant CHD (acyanotic heart disease on medication for congestive heart failure and requiring heart surgery, moderate to severe pulmonary hypertension, cyanotic heart disease):

The NNT, *for children < 2*, to prevent 1 hospitalisation is 23 patients. For children under 1 year, the NNT is not clear from the data available.

Estimated acquisition cost per annum in SA based on proposed patient populations

There is uncertainty regarding the estimated number of potential patients who would fit into the patient populations for which palivizumab has been requested, due to missing data, for example, the number of CLD patients on ongoing therapy is not known. It is likely that there is overlap between the group < 2 years requiring treatment for chronic lung disease, and the group requiring long term ventilation. The estimated number of cardiac patients eligible for palivizumab, based on the incidence in the published literature, the average number of births in South Australia, and the number of babies born with congenital heart defects in SA may be approximately 32 per annum [23].

The range of estimated costs are provided below:

Estimated patient number	Average cost for children < 1 year of age on 3 rd percentile for weight	Average cost for children < 2 years of age on 3 rd percentile for weight	Average cost for children < 1 year of age on 50 th percentile for weight
10 (proposed by applicant)	\$83,850	\$100,960	\$93,230
47 (best estimate)	\$394,095	\$474,512	\$438,181
73 (estimated max)	\$612,105	\$737,008	\$680,579

Medline Search strategy

Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946 to Present

- Search strategy:
1. palivizumab.mp.
 2. limit 1 to yr="2009 -Current"
 3. clinical trial.mp.
 4. clinical trial.pt.
 5. random\$.mp.
 6. tu.xs.
 7. 3 or 4 or 5 or 6
 8. randomised clinical trial.mp.
 9. randomized.ab.
 10. placebo.ab.
 11. 7 or 8 or 9 or 10
 12. 2 and 11
 13. limit 12 to randomized controlled trial

Search conducted 27 August 2015, returned 11 citations

References

1. Black, C.P., *Systematic review of the biology and medical management of respiratory syncytial virus infection*. Respiratory Care, 2003. **48**(3): p. 209-31; .
2. Ranmuthugala, G., L. Brown, and B.A. Lidbury, *Respiratory syncytial virus--the unrecognised cause of health and economic burden among young children in Australia*. Communicable Diseases Intelligence Quarterly Report, 2011. **35**(2): p. 177-84.
3. SA Health, *Admitted Patient Activity data*. 2013-2014.
4. Australian Bureau of Statistics, *Population by Age and Sex, Regions of Australia (ASGS 2011)*. 2014.
5. Wang, D., S. Bayliss, and C. Meads, *Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses*. Health Technology Assessment, 2011. **15**(5): p. iii-iv, 1-124.
6. Piedimonte, G. and M.K. Perez, *Respiratory syncytial virus infection and bronchiolitis*. [Erratum appears in *Pediatr Rev*. 2015 Feb;36(2):85;]. Pediatrics in Review, 2014. **35**(12): p. 519-30.
7. Abbvie Pty Ltd, *Product Information: Synagis (palivizumab 50mg and 100mg) powder for solution for injection*. 2014: Sydney, NSW.
8. Huang, K., et al., *Respiratory syncytial virus-neutralizing monoclonal antibodies motavizumab and palivizumab inhibit fusion*. Journal of Virology, 2010. **84**(16): p. 8132-40.
9. Adams, O., et al., *Palivizumab-resistant human respiratory syncytial virus infection in infancy*. Clinical Infectious Diseases, 2010. **51**(2): p. 185-8.
10. FDA, *Synagis (palivizumab) Prescribing Information (US) 2014*.
11. Andabaka, T., et al., *Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children*. Cochrane Database of Systematic Reviews, 2013. **4**: p. CD006602.
12. The IMpact-RSV Study Group, *Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants*. Pediatrics, 1998. **102**(3 Pt 1): p. 531-7.
13. Subramanian, K.N., et al., *Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia*. MED1-493 Study Group. Pediatric Infectious Disease Journal, 1998. **17**(2): p. 110-5.
14. Feltes, T.F., et al., *Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease*. Journal of Pediatrics, 2003. **143**(4): p. 532-40.
15. The IMpact-RSV Study Group, *Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants*. . Pediatrics, 1998. **102**(3): p. 531-7.
16. FDA. *Safety alerts for Human Medical Products*. Synagis (palivizumab). 2002 accessed 31 Aug 2015]; Available from: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm155089.htm>.
17. PBAC, *PBAC Outcomes - Subsequent decisions not to recommend 2005* Available at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2005-03/subsequent-decisions/>)
18. CADTH, *Palivizumab prophylaxis against Respiratory Syncytial Virus*., Canadian Agency for Drugs and Technologies in Health, Editor. 2007: Ottawa.
19. WADEP, *WATAG Advisory Note: Formulary status of palivizumab (Synagis) for prophylaxis against respiratory syncytial virus in infants*. , Western Australian Therapeutics Advisory Group, Editor. 2012: Perth.
20. American Academy of Pediatrics Committee on Infectious, D. and C. American Academy of Pediatrics Bronchiolitis Guidelines, *Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection*. Pediatrics, 2014. **134**(2): p. 415-20.
21. Robinson, J., *Preventing respiratory syncytial virus infections*. Paediatrics & Child Health, 2011. **16**(8): p. 487-90.
22. WHO. *Bulletin of the World Health Organisation: Hubs to spread technology and save lives (webpage)*. <http://www.who.int/bulletin/volumes/93/5/15-020515/en/> Accessed 27 Aug 2015.
23. Bergman, G., et al., *Children with hemodynamically significant congenital heart disease can be identified through population-based registers*. Clinical Epidemiology, 2015. **7**: p. 119-27.

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