

Respiratory Syncytial Virus Prophylaxis for High-Risk Infants Program Reference Manual

Drug Programs Delivery Branch
Drugs and Devices Division
Ministry of Health
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Introduction

Through the Respiratory Syncytial Virus Prophylaxis for High-Risk Infants Program (RSV program), the Ministry of Health (MOH) covers the full cost of the drug palivizumab to prevent a serious lower respiratory tract infection caused by the Respiratory Syncytial Virus (RSV) in infants who are less than two years of age at the start of the RSV season and who are at high risk for RSV disease.

Palivizumab – immunization practices and product management

Palivizumab is a monoclonal antibody that provides passive immunization against the respiratory syncytial virus and is not expected to interfere with routine vaccinations. However, like other vaccinations, palivizumab has the potential to induce an adverse event including but not limited to fevers. For proper monitoring of adverse events, palivizumab can be administered 24 hours before or after a routine vaccination.

Immunization practices that are described in the [Canadian Immunization Guide](#) should be followed. Part I of the Guide titled “Key Immunization Information” identifies these practices in the section “National Guidelines for Immunization Practices”. In addition, it is important to document the respective lot numbers of doses of palivizumab that are administered to patients.

The ministry requests that all health care providers be mindful of the costs such that drug wastage is minimized. The September 2003 Statement on the Recommended Use of Monoclonal Anti-RSV Antibody (Palivizumab) from the National Advisory Committee on Immunization (NACI) recommended that “If an entire vial (500 mg, 1 g) is not required for a patient’s monthly injection, prescribers should arrange for more than one patient to receive palivizumab within six hours in order to minimize product wastage”. It is noted that vial sharing is practiced in many jurisdictions and there is literature evidence to demonstrate cost savings associated with this practice.

The ministry is aware that the total number of vials requested for any given clinic date may be less than the calculated number of vials based on total body weight of the infants due to sharing of vials. **The dose of palivizumab is 15 mg per kg of body weight.**

Clinics should not accumulate any extra vials at the end of the season to minimize the possibility of drug spoilage during the off-season (summer months) due to unforeseen circumstances.

Section 1 Active Season for the RSV Program

The drug palivizumab is only provided during the active season to infants who meet the ministry's eligibility criteria for funding. The active season is generally from November to April, with variations in various regions of Ontario.

1.1 Season Start and End

Start

Due to the seasonality of the RSV virus, palivizumab should only be administered during the active RSV season which for eastern, central and southern Ontario generally begins in mid-November. Ontario's RSV Advisory Group recommends that the first dose be administered to eligible infants on or around the third week of November. Please see the [Important Dates for the Season](#) section for further information.

For **northern** Ontario (e.g. Sudbury and further north), the RSV season generally starts later in the year (e.g. December or January).

The RSV season may begin earlier in certain communities. Prescribers can request an earlier start of the RSV season for that region if they believe RSV activity has commenced by providing supporting evidence.

End

For most of Ontario, the prophylaxis season will finish at the end of March. For **northern** Ontario (e.g. Sudbury and further north), the end of the season is generally in April or May.

However, if continued prophylaxis is required on or after the end of the season OR if regional RSV activity persists, the requesting prescriber must confirm the RSV activity level in the infant's area of residence. The status of the regional activity must be stated on the request as per the definition below.

Regional activity can be confirmed by contacting the local or regional hospital's pediatric infectious disease department to inquire on the status of the season. The RSV season is considered on-going when there are TWO or more LOCAL RSV related hospitalizations per week for two consecutive weeks (Law et al. 2004).

The ministry will communicate to the community the official start date and a declaration to the end to the RSV season.

1.2 Dosing Schedule

Ontario's RSV Advisory Group recommends palivizumab be administered according to the following general dosing schedule for **central and southern** Ontario:

- Dose number one (week number 0) to be given starting usually in the third week of November. Please see the [Important Dates for the Season](#) section for more information.
- Dose number two (week number three) to be given in the month of December
- Dose number three (week number seven) to be given in the month of January
- Dose number four (week number 11) to be given in the month of February
- Dose number five (week number 15) to be given in the month of March

The season and prophylaxis start date for **northern** Ontario is generally delayed in comparison to southern Ontario and consequently, the suggested dosing schedule should be adjusted accordingly.

In general, the interval between the 1st and 2nd dose should be 21-28 days. The intervals between the 2nd, 3rd, 4th, and 5th doses should be 28-35 days.

Based on human pharmacokinetic modeling, the 5th dose of palivizumab will provide sufficient antibody levels to protect for at least six weeks. **As such, the 5th dose will provide the child protection through the end of April or into the month of May if the usual dosing schedule is followed.**

The RSV program covers the cost of up to five doses of palivizumab administered during the active RSV season to infants at high-risk for RSV infection. A sixth dose will NOT be covered by the RSV program except in isolated circumstances which will require approval by the ministry. These requests should be submitted to AbbVie as per the usual process and will be adjudicated by the ministry.

1.3 Important Dates for the Season

Please observe the following dates for the 2019/20 season:

- **Start of Season/First Dose:** November 18, 2019.
Ontario's RSV Advisory Group recommends that the first dose be administered to eligible infants on or after the week of November 18th, 2019. For logistical reasons, some clinics may have to commence prophylaxis the week prior to November 18th. It is important to note that under such circumstances the total number of doses permissible for the season should remain the same.
- **End of Season:** April 1st, 2019
- **First shipment of palivizumab by the manufacturer:** On or after November 4th, 2019.

1.4 Changes from the Previous Season

Criteria Revisions

Comparison of 2018 versus 2019 criteria.

2018 Criteria	2019 Criteria
<ul style="list-style-type: none"> Infants 33 – 35 completed weeks gestation and aged ≤ 6 months at the start of, or during the local RSV season, and who LIVE IN isolated communities where paediatric hospital care is not readily accessible and ambulance transportation for hospital admission is required 	<ul style="list-style-type: none"> Same as 2018 criteria, however the definition for “remote” has been updated. <ul style="list-style-type: none"> Infants 33 – 35 completed weeks gestation and aged ≤ 6 months at the start of, or during the local RSV season, and who LIVE IN remote communities defined by lack of immediate access to medical care (< 30 min) (i.e., Level I hospital) AND/OR inability to access pediatric services in a timely manner (<90 minutes)
<ul style="list-style-type: none"> Children < 12 months of age with hemodynamically significant (HS) cyanotic or acyanotic congenital heart disease (CHD): requiring corrective surgery or are on cardiac medication for hemodynamic significant disease. Children 12 – 24 months of age with ongoing HS CHD will be considered on a case-by-case basis. 	<ul style="list-style-type: none"> Same as 2018, however cardiac medication has been further defined to include indications that would be considered. <ul style="list-style-type: none"> Children < 12 months of age with hemodynamically significant (HS) cyanotic or acyanotic congenital heart disease (CHD): requiring corrective surgery or are on cardiac medication for congestive heart failure or diagnosed with moderate to severe pulmonary hypertension. Children 12 – 24 months of age with ongoing HS CHD will be

	considered on a case-by-case basis.
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RSV Form Changes

Enrolment Form

- Section 3 of the form has been updated to reflect new criteria wording for children who live in remote communities (see above).
- Section 5 of the form has been updated to:
 - Reflect new criteria wording for children with congenital heart disease.
 - A note has been added to the Section 5 heading that requests a cardiac consultation note to be provided in support of RSV prophylaxis.
 - Under the criteria for BPD/CLD, a YES/NO question has been added to indicate if the child has moderate to severe pulmonary hypertension

Frequently Asked Questions (FAQs) Changes

The following questions were added to the FAQs:

- Does RSV prophylaxis with palivizumab need to continue after cardiac surgery?
- What is the definition of an isolated or remote community?
- What supporting documentation is required to confirm a diagnosis of pulmonary hypertension?
- What is the definition of bronchopulmonary dysplasia/chronic lung disease (BPD/CLD)?

Please see the FAQs section for further information.

Section 2 Criteria for Coverage

The ministry covers the full cost of palivizumab for infants who meet the following criteria:

- Are residents of Ontario
- Have a valid Ontario Health Number
- Are less than two years of age at the start of the RSV season
- Are at high risk for RSV disease
- Meet at least one of the clinical criteria.

The clinical criteria for funding of palivizumab are:

- Infants born prematurely at ≤ 32 completed weeks gestation and aged ≤ 6 months at the start of, or during, the local RSV season; or
- Infants 33 – 35 completed weeks gestation and aged ≤ 6 months at the start of, or during the local RSV season, who DO NOT live in remote communities AND have a Risk Assessment Tool Score of 49 to 100; or
- Infants 33 – 35 completed weeks gestation and aged ≤ 6 months at the start of, or during the local RSV season, and who LIVE IN remote communities defined by lack of immediate access to medical care (< 30 min) (i.e., Level I hospital) AND/OR inability to access pediatric services in a timely manner (< 90 minutes); or
- Children < 24 months of age with Down Syndrome / Trisomy 21; or
- Children < 24 months of age with bronchopulmonary dysplasia/chronic lung disease (BPD/CLD) and who required oxygen and/or medical therapy specifically for chronic lung disease within the 6 months preceding the RSV season; or
- Children < 12 months of age with hemodynamically significant (HS) cyanotic or acyanotic congenital heart disease (CHD): requiring corrective surgery or are on cardiac medication for congestive heart failure or diagnosed with moderate to severe pulmonary hypertension. Children 12 – 24 months of age with ongoing HS CHD will be considered on a case-by-case basis.

Infants and children with other specific medical illnesses that place them at high risk of hospitalizations and complications from a RSV infection may also be considered for prophylaxis, if they meet necessary requirements. The enrolment forms for these infants and children will be reviewed on a case-by-case basis by the ministry's medical consultant(s) with expertise in RSV prophylaxis. Please see the [Special Clinical Circumstances](#) section for further information.

Multiple Birth Sets

If a high-risk infant of a multiple birth set is approved for the season, the siblings in the same set are also eligible for funding for prophylaxis. Enrolments for the siblings in the same multiple birth set should be submitted on a separate form at the same time as the

high-risk infant - irrespective of the discharge date(s) of the individual infants. Under Section 1 of the form, please specify the set (e.g. twins, triplets) and provide the multiple number (e.g. child 1, 2, 3) in the box titled, "Multiple Birth Infant Number". Although there is no specific space available on the form, you may also wish to indicate the Reference Number of the approved infant of the multiple birth set, if available.

Section 3 Patient Enrolment into the RSV Program

3.1 Enrolment Process

All enrolments will initially be processed by the Synagis Coordinator at AbbVie Canada. All enrolment forms and Medical Justification Forms (if applicable) should be faxed to the Synagis Coordinator at 1-888-703-6967.

To protect personal health information, NO personal health identifiers (e.g. name, address, Ontario Health Number, parent names) are to be provided on the forms or any supporting documents.

The RSV season reference number will be provided by the Synagis Coordinator if the enrolment request is approved. The ministry's RSV program coordinator will review enrolment requests for the BPD/CLD and CHD criteria and have requests submitted under Special Clinical Circumstances reviewed by external medical experts in RSV prophylaxis. The ministry's medical experts may directly contact the enrolling prescriber for additional information if necessary.

The turn-around time is one business day for most requests. For requests submitted under the BPD/CLD or CHD criteria and the Consideration of Special Clinical Circumstances category, the average turn-around time is three business days.

3.2 Enrolment Form

To protect personal health information, **NO** personal health identifiers (e.g. name, address, Ontario Health Number, parent names) are to be provided on the enrolment form. Fields for the infant's full name, Ontario Health Number, and other personal identifiers have been removed.

Please see Section 7 of this document for links to the enrolment form.

Section 4 How to Apply for Special Clinical Circumstances

The Special Clinical Circumstance Medical Justification Form (Medical Justification Form) has been developed to facilitate submission of enrolment requests for high-risk infants who do not satisfy the enrolment criteria for approval. This form must be completed and must accompany enrolment requests submitted for Consideration of Special Clinical Circumstances.

Infants who are over 2 years of age at the start of the active RSV season will not be approved for funding. However, enrolment requests for high-risk infants who do not satisfy the above clinical criteria will be considered by the ministry's medical experts in RSV prophylaxis. A completed Medical Justification Form must accompany the enrolment request.

The Medical Justification Form must state the infant's specific medical illness, provide sufficient clinical details regarding the risk for severe RSV disease and specify whether an infectious disease specialist, neonatologist or a respirologist has been consulted. If specialist support cannot be obtained because of limited accessibility, this should be clearly stated on the Medical Justification Form. The request will then be considered by the ministry's expert clinicians in RSV who may contact the requesting physician for additional information. When providing clinical findings/status of the infant, please be as thorough as possible to avoid delays in the review process. It is important **that no personal health identifiers** (e.g. infant's name, address, health card number, and parents' names) be provided on the Medical Justification Form.

To assist the ministry's expert clinicians in contacting the requesting physician if required, please include **a direct phone line (back-office number)** on the enrolment form, if available.

Please see Section 7 of this document for the link to the Medical Justification Form.

Section 5 How to Order a Drug Product

All shipment orders for palivizumab will be directed to the Synagis Coordinator (fax: 1-888-703-6967). The Synagis® Order Form can be found in Section 7 of this document or by calling the Synagis Coordinator at 1-888-704-8270.

The first dose can be ordered in Section 7 of the Enrolment form and will be shipped upon approval of enrolment. All subsequent shipments should be ordered on the Synagis® Order Form.

The first dose and all subsequent doses can be ordered on the Synagis® Order Form if a shipment of the first dose is not required at time of enrolment request.

If there are any vials left over from last season, please use those vials prior to ordering another shipment of palivizumab. During mid-season (mid-January), the ministry asks that you take note of the number of vials of palivizumab in your inventory and take this into account when ordering another shipment of palivizumab for the remainder of the season. The intent is to reduce inventory to zero by season end.

Except for orders placed on Fridays, weekends and statutory holidays, shipments generally occur within 24 hours. However, it is recommended that an order be placed five business days prior to the infant's date of injection to avoid any unforeseen circumstances.

Please note that the first shipment of palivizumab vials from the manufacturer will be available around the first week of November. Please see the Important Dates section for more information.

Caution: To maintain cold chain, palivizumab must be stored in refrigerated conditions between 2 and 8°C in its original container. Please ensure that the drug is stored properly upon receipt.

Section 6 Frequently Asked Questions

Who is eligible for RSV prophylaxis with palivizumab?

To be eligible for the program, the infant must be a resident of Ontario, insured under the Ontario Health Insurance Plan (OHIP) and meet the program's listed clinical criteria. Prior to the start of each prophylaxis season, the ministry updates the program's eligibility requirements and RSV Reference Manual.

When is the start date for RSV prophylaxis in Ontario?

The RSV prophylaxis start date is determined by the ministry and usually begins in the third week of November for southern, central and eastern Ontario. Northern Ontario's prophylaxis season traditionally starts later by a month or more. Prior to the start of each prophylaxis season, the ministry will communicate the start date through the RSV Reference Manual. The RSV season is influenced by local RSV activity and seasonal factors. The ministry uses this information in consultation with the Ontario RSV Advisory Group to determine the start date. However, the RSV season in any given regional area may be delayed as it relates to the actual local RSV activity. Ministry funding of palivizumab is provided between the start and end date of the RSV prophylaxis season.

When is the end date for RSV prophylaxis in Ontario? Can palivizumab be given after season end?

The end date to the RSV prophylaxis season is normally around April 1st and is communicated through the RSV Season End communiqué. For some areas of Northern Ontario, the RSV season typically ends near the end of April to early May. However, the date may change based on RSV activity trend in various regions of Ontario and tracking through the Public Health Agency of Canada (PHAC) Respiratory Virus Detection Surveillance System reports.

Doses of palivizumab should not be given after the RSV season has ended as declared by the ministry. If doses are required after the season end, the RSV program may consider those requests on a case-by-case basis but only where the local RSV season is definitely active and ongoing. The RSV season is considered ongoing when there are TWO or more local RSV related HOSPITALIZATIONS per week for TWO consecutive weeks. The requesting prescriber must state on the submitted request the current status of the LOCAL RSV season. It is important to confirm the status of your RSV season by contacting your local or regional hospital's pediatric infectious disease department. Please fax your case-by-case requests to the fax number listed on the enrolment or order form.

Can palivizumab be administered out of season and will the ministry provide appropriate funding?

Palivizumab should not be administered to high risk infants beyond the Ontario RSV season and funding for such infants will not be provided by the ministry. Similarly, prophylaxis cannot be started before the season has officially commenced without approval by the ministry, even if the child is deemed by the prescriber to be at extremely high risk based on risk factors.

How should palivizumab be administered?

Palivizumab solution for injection should not be mixed with any medications or diluents. The solution should be withdrawn based on the product monograph. Since the single-use vial does not contain a preservative, palivizumab solution for injection should be administered immediately after drawing the dose into the syringe.

A maximum volume of 1mL of solution for injection product should be drawn up in a 1mL syringe and injected intramuscularly into a single site, using a 25-gauge needle. Volumes over 1mL should be given as a divided dose into two separate sites, unless local hospital nursing guidelines dictate otherwise. It is important to note that reduced muscle mass at the selected injection site may further limit the volume of injectable product into a single site.

How are out-of-province patients treated?

Each province and territory (PT) in Canada individually administers and funds their own RSV prophylaxis program. Out-of-province patients must be enrolled with his/her home provincial RSV prophylaxis program and assigned an enrolment number. The eligibility criteria for a specific PT may differ from that of Ontario's and completion of the home provincial enrolment form is required to request enrolment in their program. This process ensures that palivizumab doses are funded appropriately through the home province, even if the doses are administered in Ontario. Conversely, an Ontario infant travelling to another PT during the season can be treated by enrolling the patient through Ontario's program. The enrolment number assigned to a patient can be used at any health facility across Canada that delivers the program.

Once an out-of-province patient has been approved by his/her home PT, the enrolment number can be used to order doses of palivizumab which will be delivered to the treating hospital/clinic in Ontario. For further information and listing of provincial contacts to clarify a province's RSV prophylaxis funding policy and procedures, please visit the [Canadian Association of Neonatal Nurses RSV internet site on RSV](#).

Are doses provided for Ontario infants travelling outside of Canada?

Funding of palivizumab is only provided to Ontario infants while they are residing within Canada. Palivizumab is available in other countries but alternative funding, such as private payment, is required and will not be reimbursed by the ministry.

What if an infant is ineligible for Ontario's RSV Prophylaxis Program?

The eligibility criteria are supported by evidence-based medicine which identifies infants at high-risk of hospitalization due to RSV. If an infant is ineligible for the RSV program but parents or guardians wish to proceed with RSV prophylaxis, palivizumab can be purchased privately. For Ontario, a prescription must be submitted to McKesson Specialty Pharmacy and arrangements made for delivery of drug product while maintaining the cold chain process such that the viability of the product is safely sustained. Parents or guardians can contact McKesson Specialty Prescription Services at 1-888-377-9353 for further information on the process to privately access palivizumab.

Is palivizumab covered for patients under the Interim Federal Health (IFH) Program?

Palivizumab is not a listed standard benefit under the IFH program but may be considered on an exceptional basis in limited circumstances. Please contact IFH directly and refer to the following link for more information regarding coverage under the IFH program including medication coverage:

[Interim Federal Health Program: Summary of Coverage](#)

Can a child get the 'flu' shot?

Yes, the flu shot prevents influenza which is a different virus. Palivizumab does not offer any protection against influenza. Unless there are medical reasons not to vaccinate against influenza, every individual six months of age and older should receive a flu shot (please refer to PIDAC guidelines and NACI). Flu shots are usually available in the late fall each year. Talk to your child's pediatrician or family doctor for more information.

Can a child have vaccines or drugs on the same day or in the same week that they receive palivizumab?

Palivizumab is not a vaccine and therefore it does not interact with other vaccines (including live attenuated vaccines i.e., MMR and Varicella) and can be safely administered concomitantly with routine childhood vaccines if the child is well and not febrile. Preferably, palivizumab should be administered 24 hours before or after a routine vaccination.

Formal studies have not been conducted to evaluate potential interactions between palivizumab and other drugs but there is no apparent increase in adverse effects when used simultaneously. Please refer to the drug product monograph for full prescribing information.

Does RSV prophylaxis with palivizumab need to continue after cardiac surgery?

It is recommended that, if the child is hemodynamically stable and does not need further surgery or medications to control congestive heart failure post cardiac surgery, RSV prophylaxis can be safely discontinued after the post dose has been received. Otherwise, RSV prophylaxis should continue.

What is the definition of an isolated or remote community?

An isolated or remote community is defined by lack of immediate access to medical care (< 30 min) and/or the inability to access pediatric care in a timely manner (<90 minutes).

What supporting documentation is required to confirm a diagnosis of pulmonary hypertension?

To support the diagnosis of pulmonary hypertension, recent echocardiogram results and/or a recent consultation from a cardiologist must be submitted at the time of application. Only moderate and severe pulmonary hypertension will be approved for RSV prophylaxis.

What is the definition of bronchopulmonary dysplasia/chronic lung disease (BPD/CLD)?

The following table provides the definition of CLD for preterm infant < 32 completed weeks gestational age:

Treatment with the following mode of respiratory support and FiO₂ at 36 weeks postmenstrual age or discharge home, if earlier:

BPD Severity	Breathing in room air	NC < 1 L/min	NC 1 to 3L/min	NC > 3L/min, nCPAP, or NIPPV	Invasive PPV
No BPD	21%	21%	21%	-	-
Grade 1	-	22-70%	22-29%	21%	-
Grade 2	-	71-100%	30-100%	22-29%	21%
Grade 3	-	-	-	30-100%	22-100%

Abbreviations: BPD, bronchopulmonary dysplasia; FiO₂, fraction of inspired oxygen; NC, nasal cannula; nCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PPV, positive pressure ventilation

For infants > 32 completed weeks gestation age with CLD the same criteria as above can be adopted with the proviso that the assessment occurs at > 28 days of age but < 56 days or at time of discharge.

Where can I get further information on the Ontario RSV Prophylaxis Program?

For questions on enrolment status, RSV season reference number, order requests, and drug-related issues (ordering, shipment, storage, reconstitution, stability,

administration), please contact the Synagis Coordinator at AbbVie Canada: 1-888-704-8270.

For further information, questions or clarifications on the Program policies and processes, please contact the ministry at RSVProphylaxisProgram@ontario.ca or at 416-327-8109 or 1-866-811-9893.

Please refer to the following links for information on RSV prophylaxis:

[National Advisory Committee on Immunization \(NACI\)](#)

[Canadian Paediatric Society](#)

[Canadian Association of Neonatal Nurses](#)

[Public Health Agency of Canada – Respiratory Virus Detections in Canada](#)

Section 7 Forms

Please find the links to the RSV Prophylaxis Program forms below:

- Enrolment Form: [English](#) / [French](#)
- Synagis® Order Form for Single or Multiple Infants: [English](#) / [French](#)
- Special Clinical Circumstance Medical Justification Form: [English](#) / [French](#)