

DRUG NAME: BCG**SYNONYM(S):** Bacillus Calmette-Guérin¹**COMMON TRADE NAME(S):** IMMUCYST®, OncoTICE®, THERACYC® (USA), TICE® (USA)**CLASSIFICATION:** biological response modifier, cytotoxic²*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

BCG is a live, attenuated, bacteria, *Mycobacterium bovis*, which exerts a variety of antitumour actions.¹ These actions include induction of a local granulomatous reaction, activation of histiocytes, and other direct and indirect stimulation of both specific and non-specific immune responses.¹ This resultant local inflammatory response leads to destruction of tumour cells.³ Evidence of a systemic immune response is also commonly seen, but its relationship to clinical efficacy is not established.³ The development of an antitumour immune response includes T-lymphocyte activation and cytokine release.⁴

PHARMACOKINETICS:

Systemic absorption of BCG microorganisms is expected not to occur but may be possible (see **Special Precautions** and **Side Effects** sections).

USES:**Primary uses:**

*Bladder cancer (intravesical)

Melanoma^{4,5} (intralesional)

*Health Canada approved indication

Other uses:**SPECIAL PRECAUTIONS:****Contraindications:**

- impaired immune response, including positive HIV serology and immunosuppressant therapy^{1,3}
 - steroid therapy does not contraindicate administration if: <2 weeks; <20 mg dose of prednisone or equivalent per day; alternate-day regimens of low-dose short-acting preparations; at physiologic doses for maintenance; topical; inhaled; or intra-articular, bursal or tendon injection⁶
 - 1 month should elapse before using in patients who have discontinued a >2 week regimen of high-dose systemic steroids, due to concern about the safety and possible reduced efficacy of live-organism preparations⁶
- evidence of active tuberculosis infection or other diseases which require the use of anti-tuberculous agents¹
- urinary tract infections^{1,3}; postpone or interrupt BCG treatment until urine culture is negative and antibiotic and/or antiseptic therapy is completed¹
- prior therapy-induced BCG infection¹
- burn patients³
- gross hematuria³
- febrile illness³

Caution:

- a Mantoux (PPD) test should be performed prior to the first instillation; a positive result contraindicates proceeding only in the presence of supplemental evidence of an active tuberculosis infection¹
- following transurethral resection (TUR), biopsy, or traumatic catheterization, 7-14 days should elapse before BCG treatment^{1,4}

- reconstitution, preparation, and administration should be performed under aseptic conditions and with due regard for the pathogenic potential of BCG; unused BCG and all equipment, supplies, and receptacles in contact with BCG should be handled and disposed of as biohazardous¹
- do not prepare parenteral medications in an area where BCG has been prepared³ unless adequate decontamination has been performed

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: it is not known whether BCG can affect reproductive capacity¹

Pregnancy: FDA Pregnancy Category C.³ Studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.³ Women should be advised not to become pregnant while on therapy.^{1,3}

Breastfeeding: it is not known whether BCG is excreted in human milk, therefore breastfeeding is contraindicated¹

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.⁷

Table includes data for intravesicular administration. For side effects particular to the intralesional route, see the paragraph following the table.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	allergy (2%, severe 0.4%)
blood/bone marrow/ febrile neutropenia	anemia (1-21%, severe 0.4%) ^{1,3}
	leukopenia (\leq 5%) ^{1,3}
cardiovascular (general)	cardiac (2%, severe 1%)
coagulation	coagulopathy (\leq 3%) ^{1,3}
constitutional symptoms	<i>fatigue/malaise</i> (7-40%, severe 0%) ^{1,3}
	<i>fever</i> (20-38%, severe \leq 8%) ^{1,3,4}
	shaking chills/rigors (3%, severe 1%)
dermatology/skin	<i>extravasation hazard: none</i> ⁸
	rash (\leq 2%) ^{1,3}
gastrointestinal	<i>emetogenic potential: rare</i> ⁹
	anorexia/weight loss (2-11%, severe 0.1%) ^{1,3}
	diarrhea (1-6%, severe 0.1%) ^{1,3}
	gastrointestinal, not otherwise specified (1%, severe 0%)
	nausea/vomiting (3-16%, severe 0.3%) ^{1,3}
infection	BCG sepsis (0.4%, severe 0.4%); treat according to regular treatment protocols for tuberculosis infections
	infection, not otherwise specified (3%) ³

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	pulmonary infection (3%) ³
	urinary tract infection (2-18%, severe 0.9%) ^{1,3}
musculoskeletal	arthritis/myalgia (3-7%, severe 0.4%) ^{1,3}
neurology	headache/dizziness (2%, severe 0%)
pain	abdominal pain (2-3%, severe 0.6%) ^{1,3}
	bladder cramps/pain (4-6%, severe 0.9%) ^{1,3}
	genital pain (10%) ³
pulmonary	pneumonitis (1%, severe 0.6%)
	respiratory, not otherwise specified (1.6%, severe 0.2%)
renal/genitourinary	bladder spasm (5%) ³
	cystitis (6-90%, severe 2%) ^{1,3,4} ; see paragraph following Side Effects table
	dysuria (52-60%, severe 11%) ^{1,3}
	genital inflammation/abscess (2%, severe 0.4%)
	hematuria (26-39%, severe 7%) ^{1,3,4}
	nocturia (5%, severe 0.6%)
	polyuria (40-42%) ³
	renal toxicity (10%) ³
	urethritis (1%, severe 0%)
	urgency (6-18%, severe 1%) ^{1,3}
	urinary debris (2%, severe 0.4%)
	urinary frequency (40%, severe 7%)
	urinary incontinence (2-6%; severe 0%) ^{1,3}
syndromes	flu-like syndrome (33%, severe 9%); typically lasts for 24-48 hours

Adapted from standard reference¹ unless specified otherwise.

Cystitis with or without hematuria occurs in up to 90% of cases, beginning 3-4 hours after instillation and lasting from 24-72 hours.¹ These effects are usually seen after the third treatment and tend to increase in severity after each administration.^{1,4} Symptomatic management with [phenazopyridine](#), [propantheline](#) or oxybutinin, and acetaminophen or NSAIDs (e.g., ibuprofen) has been used.^{1,4} Long-term urinary complications do not generally occur.¹ If hematuria persists for more than 48 hours, initiate treatment with isoniazid 300 mg once daily and continued until symptoms resolve.⁴ Isoniazid should then be re-initiated on the day before subsequent treatments (i.e., day minus 1), and continued for three additional days (i.e., days 1, 2, and 3).⁴

Intralesional side effects are considered to be less extensive as compared to the intravesicular route. Side effects may include⁵: mild local discomfort, erythema at site of injection, ulceration with drainage, increased LFTs, anaphylactic reaction (rare).

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anti-tuberculous agents, except pyrazinamide ^{1,3}	BCG is sensitive to these agents; they may interfere with the effectiveness of BCG	antimicrobial action	avoid concurrent use

Prior or concomitant use of any immune modulator may interfere with the action of BCG.¹

Immune globulins may decrease the therapeutic effect of BCG.³

When using BCG in combination with interferon alfa-2b, the powder form of interferon is preferable due to the potential for preservatives in the ready-to-use solution to be harmful to the viability of BCG.¹⁰

Concern has been raised about the use of bacteriostatic urethral lubricants during catheterization for BCG instillation due to a reduction in viable mycobacteria delivered.¹¹ A subsequent study found no adverse effect on the clinical efficacy of intravesical BCG treatment.¹²

SUPPLY AND STORAGE:

Injection: Hospira supplies Organon-manufactured vials containing 1 to 8 x 10⁸ colony forming units (CFU), which is equivalent to approximately 50 mg (wet weight), freeze-dried BCG, *TICE substrain*.¹ Refrigerate and protect from light.¹

Sanofi Pasteur Limited supplies vials containing 10.5+/-8.7 x 10⁸ CFU, as 81 mg (dry weight) freeze-dried BCG, *Connaught substrain*.¹³ Refrigerate and protect from light.¹³ 3 mL vial of diluent for reconstitution provided.

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart in Appendix](#).

SOLUTION PREPARATION AND COMPATIBILITY:

When prepared outside of a dedicated biological safety cabinet, the use of a closed-system reconstitution device is recommended.

Handling precautions:

- because of the potential risk for transmission, BCG should be prepared, handled, and disposed of as a biological agent
- unused BCG and all equipment, supplies, and receptacles in contact with BCG should be handled and disposed of as biohazardous waste¹
- during the 6 hours after treatment, patients should sit down when urinating and clean their hands and genital area well with soap and water¹⁴
- urine voided for up to 6 hours after instillation may be disinfected with 1-2 cups of liquid household bleach added to the toilet bowl and allowed to stand for 15 minutes before flushing^{14,15}; no information was found in regard to the effect of such a method on septic systems
- surfaces that have come into contact with urine containing BCG (e.g., toilet seat), may be cleaned with a 1:20 dilution (approximately 1 ounce of bleach in 1 cup of warm water) of household bleach¹⁴

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart in Appendix](#).

Additional information: The suspension must not be filtered.¹

PARENTERAL ADMINISTRATION:BCCA administration guideline noted in ***bold, italics***

Subcutaneous	should NOT be used ^{1,3}
Intramuscular	should NOT be used ¹
Direct intravenous	should NOT be used ^{1,3}
Intermittent infusion	should NOT be used ^{1,3}
Continuous infusion	should NOT be used ^{1,3}
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	<i>instill and retain for 2 hours</i> ^{1,3,16,17}
Intradermal	should NOT be used ^{1,3}
Intralesional	<i>dilute and administer according to protocol</i> ⁵

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:BCCA usual dose noted in ***bold, italics***

The optimal dosage regimen for adjuvant therapy with intravesical BCG has not been established.⁴

The dose amount expressed in milligrams varies according to the BCG substrain; the typical dose of BCG used for intravesical instillation is 1-8 x 10⁸ CFU for the *Tice substrain* or 10.5+/- 8.7 x 10⁸ CFU for the *Connaught substrain*.⁴

<i>Intralesional:</i>	Cycle Length: n/a ⁵ :	<i>0.005 mg-1.5 mg intralesionally according to dose escalation scheme described in protocol; weekly escalation until reaction observed, then at that dose level every other week for 2 doses, then every month</i>
<i>Intravesical:</i>	n/a ¹ :	1 vial (1 to 8 x 10 ⁸ CFU) intravesically once weekly for 6 weeks followed by treatments at weeks 8 and 12 and then at monthly intervals from month 4 to 12
	n/a ¹ :	1 vial (1 to 8 x 10 ⁸ CFU) intravesically once weekly for at least 6 weeks followed by treatments once monthly for up to 12 months
	weekly ^{1,4,17} :	<i>1 vial (1 to 8 x 10⁸ CFU) intravesically once weekly for 6 weeks</i>
	weekly ¹⁶ :	<i>1/3 vial intravesically (in combination with interferon-alfa 2b) once weekly for 6 weeks</i>
	n/a ³ :	1 vial intravesically once weekly for 6 weeks followed by 1 vial at 3, 6, 12, 18, and 24 months after initial treatment

	BCCA usual dose noted in <i>bold, italics</i>
n/a ³ :	1 vial intravesically once weekly for 6 weeks followed by 1 vial once monthly for 6-12 months
weekly ⁴ :	1 vial intravesically once weekly for 6 weeks followed by 6 weeks of rest and then once weekly treatment for 3 additional weeks
<i>Concurrent radiation:</i>	no information found
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"
<i>Dosage in renal failure:</i>	no information found
<i>Dosage in hepatic failure:</i>	no information found
<i>Dosage in dialysis:</i>	no information found

Children:

safety and effectiveness have not been established¹

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