

DRUG NAME: BCG

SYNONYM(S): Bacillus Calmette-Guérin¹

COMMON TRADE NAME(S): OncoTICE®, VERITY-BCG®, TICE® (USA)

CLASSIFICATION: biological response modifier

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 and the resultant local inflammatory response leads to destruction of tumour cells.^{1,2} Evidence of a systemic immune response is also commonly seen, but its relationship to clinical efficacy is not established.² The development of an antitumour immune response includes T-lymphocyte activation and cytokine release.³

PHARMACOKINETICS:

Systemic absorption of BCG microorganisms is not expected to occur but may be possible.

USES:

Primary uses:

- *Bladder cancer (intravesical)
- Melanoma^{3,4} (intralesional)

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:

- impaired immune response, including positive HIV serology and immunosuppressant therapy^{1,2}
 - 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 injection⁵
 - 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 preparations⁵
- evidence of active tuberculosis infection or other diseases which require the use of anti-tuberculosis agents¹
- urinary tract infections^{1,2}; postpone or interrupt BCG treatment until urine culture is negative and antibiotic and/or antiseptic therapy is completed¹
- prior therapy-induced BCG infection¹
- burn patients²
- gross hematuria²
- febrile illness²

Caution:

- **BCG dosing** is based on the BCG strain and differs by product brand; refer to protocol to confirm the dose in milligrams, the number of colony forming units (CFU), and the number of vials required per dose for each available brand^{6,7}
- consider performing a Mantoux (PPD) test prior to the first instillation; a positive result contraindicates proceeding only in the presence of supplemental evidence of an active tuberculosis infection¹
- BCG is a live, attenuated bacteria that is potentially pathogenic⁸
 - unused BCG and all equipment, supplies, and receptacles in contact with BCG should be handled and disposed of as **biohazardous**⁸; see also **Safe Handling Precautions for the Patient***
 - to prevent cross contamination, other parenteral medications should not be prepared in an area where BCG has been prepared unless adequate cleaning of the area has been performed²
 - to prevent disseminated BCG infection following transurethral resection (TUR), biopsy, or traumatic catheterization, 7-14 days should elapse prior to BCG treatment^{1,3}

***Safe Handling Precautions for the Patient:**

- for the 6 hours post treatment, patients should sit down when urinating and clean their hands and genital area well with soap and water⁹
- for the 6 hours post treatment, the toilet bowl may be disinfected after voiding by adding 1-2 cups of liquid household bleach to the toilet bowl and waiting for 15 minutes before flushing^{9,10}; no information has been found with regard to the effect of such a method on septic systems
- other surfaces that come into contact with urine containing BCG (e.g., toilet seat) may be cleaned with a 1:20 dilution of household bleach (approximately 1 ounce of bleach in 1 cup of warm water)⁹
- to protect their partner, patients are advised to either refrain from intercourse or use a condom for one week after BCG treatment⁸

Carcinogenicity: no information found

Mutagenicity: no information found

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

Pregnancy: FDA Pregnancy Category C.² Studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.² Women should be advised not to become pregnant while on therapy.^{1,2}

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.¹¹

Table includes data for intravesical administration. For side effects particular to the intravesical 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%)
	anemia (1-21%, severe 0.4%) ^{1,2}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
blood/bone marrow/ febrile neutropenia	leukopenia ($\leq 5\%$) ^{1,2}
cardiovascular (general)	cardiac (2%, severe 1%)
coagulation	coagulopathy ($\leq 3\%$) ^{1,2}
constitutional symptoms	<i>fatigue/malaise</i> (7-40%, severe 0%) ^{1,2}
	<i>fever</i> (20-38%, severe $\leq 8\%$) ¹⁻³
	shaking chills/rigors (3%, severe 1%)
dermatology/skin	<i>extravasation hazard: none</i> ¹²
	rash ($\leq 2\%$) ^{1,2}
gastrointestinal	<i>emetogenic potential: rare</i> ¹³
	anorexia/weight loss (2-11%, severe 0.1%) ^{1,2}
	diarrhea (1-6%, severe 0.1%) ^{1,2}
	gastrointestinal, not otherwise specified (1%, severe 0%)
	nausea/vomiting (3-16%, severe 0.3%) ^{1,2}
infection	BCG sepsis (0.4%, severe 0.4%); treat according to regular treatment protocols for tuberculosis infections
	infection, not otherwise specified (3%) ²
	pulmonary infection (3%) ²
	urinary tract infection (2-18%, severe 0.9%) ^{1,2}
musculoskeletal	arthritis/myalgia (3-7%, severe 0.4%) ^{1,2}
neurology	headache/dizziness (2%, severe 0%)
pain	abdominal pain (2-3%, severe 0.6%) ^{1,2}
	bladder cramps/pain (4-6%, severe 0.9%) ^{1,2}
	genital pain (10%) ²
pulmonary	pneumonitis (1%, severe 0.6%)
	respiratory, not otherwise specified (1.6%, severe 0.2%)
renal/genitourinary	bladder spasm (5%) ²
	<i>cystitis</i> (6-90%, severe 2%) ¹⁻³ ; see paragraph following Side Effects table
	<i>dysuria</i> (52-60%, severe 11%) ^{1,2}
	genital inflammation/abscess (2%, severe 0.4%)
	<i>hematuria</i> (26-39%, severe 7%) ¹⁻³
	nocturia (5%, severe 0.6%)
	<i>polyuria</i> (40-42%) ²
	renal toxicity (10%) ²
	urethritis (1%, severe 0%)
	urgency (6-18%, severe 1%) ^{1,2}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	urinary debris (2%, severe 0.4%)
	urinary frequency (40%, severe 7%)
	urinary incontinence (2-6%; severe 0%) ^{1,2}
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.^{1,3} Symptomatic management with phenazopyridine, propantheline or oxybutinin, and acetaminophen or NSAIDs (e.g., ibuprofen) has been used.^{1,3} 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.³ 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).³

Intralesional side effects are considered to be less extensive as compared to the intravesical route. Side effects may include⁴: mild local discomfort, erythema at site of injection, ulceration with drainage, increased LFTs, anaphylactic reaction (rare).

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
antibiotics and anti-tuberculous agents, except pyrazinamide ⁶	may decrease anti-tumor effect of BCG	sensitivity of BCG to antimicrobial action of antibiotic	avoid concurrent use; postpone intravesical instillation until end of antibiotic treatment or bacterial culture is negative

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.²

Concern has been raised about the use of bacteriostatic urethral lubricants during catheterization for BCG instillation due to a reduction in viable mycobacteria delivered.¹⁵ A subsequent study found no adverse effect on the clinical efficacy of intravesical BCG treatment.¹⁶

SUPPLY AND STORAGE:

Injection:

Merck Canada Inc. supplies BCG *Tice* strain (Onco-TICE®) as 50 mg (wet weight) preservative free vials of freeze-dried powder, containing 1 to 8 x 10⁸ colony forming units (CFU). Refrigerate. Protect from light.⁶

Verity Pharmaceuticals Inc. supplies BCG *Russian BCG-I* strain (Verity-BCG®) as 40 mg preservative free vials of freeze dried powder, containing 1 to 8 x 10⁸ colony forming units (CFU). Refrigerate. Protect from light.⁷

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information:

- do NOT filter OncoTICE® (Tice strain) suspension⁶

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in **bold, italics**

Subcutaneous	should NOT be used ^{1,2}
Intramuscular	should NOT be used ¹
Direct intravenous	should NOT be used ^{1,2}
Intermittent infusion	should NOT be used ^{1,2}
Continuous infusion	should NOT be used ^{1,2}
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> ^{1,2,17}
Intradermal	should NOT be used ^{1,2}
Intralesional	<i>dilute and administer according to protocol</i> ⁴

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

Adults:

<i>Intralesional:</i>	Cycle Length: n/a ⁴ :	BC Cancer usual dose noted in bold, italics <i>0.005 mg-1.5 mg intralesionally</i> 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
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<i>Intravesical:</i>	<p>Cycle Length: BC Cancer usual dose noted in <i>bold, italics</i></p> <p>The optimal dosage regimen for adjuvant therapy with intravesical BCG has not been established.¹⁸</p> <p>Dose is expressed in milligrams. The dose in milligrams, the number of colony forming units (CFU), and the number of vials to be used per dose differs for each available brand (according to the BCG strain or substrain).</p> <p><i>Refer to protocol by which patient is being treated.</i> The typical dose used for intravesical instillation is dictated by BCG brand:</p> <p>OncoTICE® (<i>Tice strain</i>)⁶ 1 vial = 50 mg = 1 to 8 x 10⁸ CFU;</p> <ul style="list-style-type: none"> • <i>full dose = 50 mg (1 x 50 mg vial)</i> <p>Verity-BCG® (<i>Russian BCG-I strain</i>)⁷ 1 vial = 40 mg = 1 to 8 x 10⁸ CFU;</p> <ul style="list-style-type: none"> • <i>full dose = 80 mg (2 x 40 mg vials)</i>
<i>weekly</i> ^{6,7,17:}	induction: <i>full dose</i> (as per BCG brand) <i>given intravesically once weekly for 6 weeks</i>
<i>weekly</i> ^{19-24:}	induction: one-third ($\frac{1}{3}$) to one-half ($\frac{1}{2}$) dose (as per BCG brand) given intravesically once weekly for 6 weeks
<i>3 to 6 months</i> ^{7,17,25:}	maintenance schedule following induction: <i>full dose</i> (as per BCG brand) <i>given intravesically once weekly for 3 consecutive weeks at 3, 6, and 12 months OR at 3, 6, 12, 18, 24, 30, and 36 months</i>
<i>4 weeks</i> ^{6:}	maintenance schedule following 6 week induction: full dose (as per BCG brand) given intravesically at weeks 8 and 12, and then monthly for months 4 to 12
<i>monthly</i> ^{18,26:}	maintenance schedule following induction: full dose (as per BCG brand) given intravesically once monthly for 6-12 months
<i>variable</i> ^{19-24:}	maintenance schedule following induction: one-third ($\frac{1}{3}$) to one-half ($\frac{1}{2}$) dose (as per BCG brand) given intravesically once weekly for 3 consecutive weeks at 3, 6, 12, 18, 24, 30, and 36 months OR once every two weeks for up to 6 months
<i>Concurrent radiation:</i>	no information found
<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
<u>Children:</u>	safety and effectiveness have not been established ¹

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