DRUG NAME: BCG

SYNONYM(S): Bacillus Calmette-Guérin[1]

COMMON TRADE NAME(S): IMMUCYST®, OncoTICE®, THERACYC® (USA), 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.[1] This resultant local inflammatory response leads to destruction of tumour cells.[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 (see **Special Precautions** and **Side Effects** sections).

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 injection[5]
  - 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 preparations[5]
- evidence of active tuberculosis infection or other diseases which require the use of anti-tuberculousis agents[1]
- urinary tract infections[1,2]; postpone or interrupt BCG treatment until urine culture is negative and antibiotic and/or antiseptic therapy is completed[1]
- prior therapy-induced BCG infection[1]
- burn patients[2]
- gross hematuria[2]
- febrile illness[2]

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 infection[1]

- BCG is a live, attenuated bacteria that is potentially pathogenic[6]
  - unused BCG and all equipment, supplies, and receptacles in contact with BCG should be handled and disposed of as ***biohazardous***[6]; 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 performed[2]
  - 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 water[7]
- 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[7,8]; 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)[7]
- to protect their partner, patients are advised to either refrain from intercourse or use a condom for one week after BCG treatment[6]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: it is not known whether BCG can affect reproductive capacity[1]

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 contraindicated[1]

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.[9]

Table includes data for intravesical 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%)[1,2]
	leukopenia (≤5%)[1,2]
cardiovascular (general)	cardiac (2%, severe 1%)
coagulation	coagulopathy (≤3%)[1,2]
constitutional symptoms	***fatigue/malaise*** (7-40%, severe 0%)[1,2]
	fever (20-38%, severe ≤8%)[1-3]
	shaking chills/rigors (3%, severe 1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
dermatology/skin	*extravasation hazard: none*[10]
	rash (≤2%)[1,2]
gastrointestinal	*emetogenic potential:* rare[11]
	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]
	cystitis (6-90%, severe 2%)[1-3]; see paragraph following **Side Effects** table
	dysuria (52-60%, severe 11%)[1,2]
	genital inflammation/abscess (2%, severe 0.4%)
	hematuria (26-39%, severe 7%)[1-3]
	nocturia (5%, severe 0.6%)
	polyuria (40-42%)[2]
	renal toxicity (10%)[2]
	urethritis (1%, severe 0%)
	urgency (6-18%, severe 1%)[1,2]
	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 reference[1] 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 include[4]: 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]

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.[12]

Concern has been raised about the use of bacteriostatic urethral lubricants during catheterization for BCG instillation due to a reduction in viable mycobacteria delivered.[13] A subsequent study found no adverse effect on the clinical efficacy of intravesical BCG treatment.[14]

SUPPLY AND STORAGE:

Injection: Merck Canada Inc. supplies BCG as single use vials containing 1 to 8 x 10^8 colony forming units (CFU), which is equivalent to approximately 50 mg (wet weight), freeze-dried BCG, *TICE substrain*. Refrigerate and protect from light.[15]

Sanofi Pasteur Limited supplies vials containing 10.5+/-8.7 x 10^8 CFU, as 81 mg (dry weight) freeze-dried BCG, *Connaught substrain*. Refrigerate and protect from light. For reconstitution: 3 mL vial of diluent provided.[16]

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: The suspension must not be filtered.[1]

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	***instill and retain for 2 hours***[1,2,17,18]
Intradermal	should NOT be used[1,2]
Intralesional	***dilute and administer according to protocol***[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*:**

BC Cancer usual dose noted in ***bold, italics***

The optimal dosage regimen for adjuvant therapy with intravesical BCG has not been established.[3]
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 10^8 CFU for the *Tice substrain* or 10.5+/- 8.7 x 10^8 CFU for the *Connaught substrain*.[3]

	Cycle Length:	
Intralesional:	n/a[4]:	***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
Intravesical:	***weekly***[15,19]:	induction: ***1 vial*** (1 to 8 x 10^8 CFU) ***intravesically once weekly for 6 weeks***
	weekly[20-22]:	induction: ***one-third (1/3) vial intravesically*** (in combination ***with interferon-alfa 2b) once weekly for 6 weeks***
	weekly[23-28]:	induction: one-third (1/3) to one-half (1/2) vial intravesically once weekly for 6 weeks
	3 to 6 months[19,29]	maintenance schedule following induction: ***1 vial*** (1 to 8 x 10^8 CFU) ***intravesically once weekly for 3 consecutive weeks at 3, 6, 12, 18, 24, 30, and 36 months***
	6 months[20,22]	maintenance schedule following induction: ***one-third* (1/3) vial intravesically*** (in combination ***with interferon-alfa 2b) once weekly for 3 consecutive weeks*** beginning 3 months after the end of induction ***at 5, 11, and 17 months*** *(doses of 1/10 vial have been used for weeks 2 and 3)

BC Cancer usual dose noted in ***bold, italics***

4 weeks[15]	maintenance schedule following induction: 1 vial (1 to 8 x 10^8 CFU) intravesically at weeks 8 and 12, followed by treatments every four weeks for months 4 to 12
monthly[30]	maintenance schedule following induction: 1 vial (1 to 8 x 10^8 CFU) intravesically once monthly for 6-12 months
variable[23-28]:	maintenance schedule following induction: one-third (1/3) to one-half (1/2) vial 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

Concurrent radiation: no information found

Dosage in renal failure: no information found

Dosage in hepatic failure: no information found

Dosage in dialysis: no information found

Children: safety and effectiveness have not been established[1]

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