DRUG NAME: Interferon alfa-2b

SYNONYM(S): IFN, alpha interferon

COMMON TRADE NAME(S): INTRON-A®

CLASSIFICATION: biological response modifier[1]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Interferons bind to receptors on the cell surface and initiate a cascade of intracellular events, including induction of certain enzymes. This leads to various cellular responses, including inhibition of virus replication, suppression of cell proliferation, enhancement of macrophage activity, and augmentation of the specific cytotoxicity of lymphocytes.[1] Interferon does not appear to be cell-cycle specific.

PHARMACOKINETICS:

Interpatient variability	substantial variability has been observed[2]	
Absorption	IM: 83%; SC: 90% intralesional: not specifically defined, but approximately 1/3 that of IM/SC[2]	
	time to peak plasma concentration	IM,SC: 3-12 h intralesional[2]: 6 h
Distribution	widely distributed, but not concentrated in any particular organ[2]	
	cross blood brain barrier?	no
	volume of distribution	31 L (may be 370-720 L with continuous infusion)
	plasma protein binding	no information found
Metabolism	mainly renal[2,3]; hepatic metabolism minor[3]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	mainly catabolism, renal secretion[3]; biliary excretion minor[2]	
	urine	trace amounts excreted in urine
	feces	no information found
	terminal half life	IV,IM: 2 h; SC: 3 h (may be up to 29 hours in patients with disseminated cancer)[2]
	clearance[4]	231 mL/h/kg
Gender	no information found	
Elderly	no information found	
Children	no information found	
Ethnicity	no information found	

Adapted from standard reference[5] unless specified otherwise.

USES:

Primary uses:
* Basal cell cancer
  Bladder cancer
* Kaposi's sarcoma, AIDS-related
* Leukemia, chronic myelogenous (CML)
* Leukemia, hairy cell
* Lymphoma, non-Hodgkin's
* Melanoma
* Multiple myeloma
  Renal cell cancer
* Thrombocytosis associated with CML

*Health Canada approved indication

Other uses:
Carcinoid tumour[2]
Cervical cancer[2,5]
Essential thrombocythemia[6]
Lymphoma, cutaneous T-cell[2]
Ovarian cancer[2]
Polycythemia vera[5]
Squamous cell cancer[2,5]
Thyroid cancer[5]

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to any interferon.[1]

Caution:
Caution in patients with[1]:
- creatinine clearance < 50 mL/min
- a psychiatric condition or history of severe psychiatric disorder
- autoimmune disease
- myelosuppression
- decompensated liver disease
- organ transplant (preliminary data indicates increased rate of graft rejection)
- hypertriglyceridemia
- psoriatic disease and sarcoidosis
- coagulation disorders
- severe pre-existing heart disease
- debilitating medical conditions (e.g., cardiovascular disease, pulmonary disease, diabetes) because of fever and other "flu-like" symptoms
- seizure disorders, brain metastases, or compromised CNS function[5]

Special populations:
Kaposi's sarcoma, AIDS-related: Do not use in patients with rapidly progressive visceral disease.[1] These patients require rapid cytoreduction, while the response to interferon is slow and poor.[2]

Carcinogenicity: studies have not been performed[1]

Mutagenicity: not mutagenic[1]

Fertility: Decreased serum estradiol and progesterone levels have been reported in women.[1] Menstrual cycle abnormalities and abortions have been reported in animals.

Pregnancy: FDA Pregnancy Category C.[5] Animal studies have shown fetal risks and there are no controlled studies in women. Interferon should be given only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk.[5]

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]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***acute hypersensitivity reactions*** (<5%);[5] urticaria, angioedema, bronchoconstriction, anaphylaxis
	antibody production to interferon (0-30%); highly variable, questionable clinical significance[2]
	vasculitis (<5%)[5]
auditory/hearing	hearing disorder (rare)
blood/bone marrow/ febrile neutropenia	anemia (15-65%) usually only during first six months of therapy
	hemolytic anemia (up to 10%)[5]
	leucopenia onset may be within hours, nadir may be 22-38 d
	myelosuppression[2,5]: onset 7-10 d, nadir 14 d, recovery 21 d
	neutropenia (30-70%);
	thrombocytopenia (5-70%)
cardiovascular (arrhythmia)	arrhythmia (<5%)[5]
cardiovascular (general)	angina pectoris, myocardial infarction (<5%)[5]
	hypertension (9%)[5]
	hypotension, related to fluid depletion (up to 9%)[2]
	peripheral edema (up to 9%)[2]
coagulation	thrombocytopenic purpura (<5%)[5]
constitutional symptoms	***chills*** (40-65%),[2] ***rigors*** (2-42%)[5]
	diaphoresis (2-21%)[5]
	fatigue/malaise (50-95%),[2] ***asthenia*** (less common)
	fever (40-98%)[2]
	malignant hyperpyrexia (very rare)
	weight loss (up to 25%),[2] ***cachexia*** (<1%)[2]
dermatology/skin	*extravasation hazard:* none
	alopecia (8-38%)[5]
	dry skin (1-10%)[5]
	erythema multiforme (rare)
	injection site reaction (1-20%)[5]; injection site necrosis (very rare)
	pruritis (3-11%)[5]
	rash (1-25%)[5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	Stevens-Johnson syndrome, toxic epidermal necrolysis (<5%)[5]
endocrine	adrenal hypercorticism (very rare)
	diabetes mellitus, aggravated diabetes mellitus (very rare)
	hot flashes (very rare)
	hyperthyroidism or hypothyroidism (rare), not always reversible[2]
	virilism (<1%)[2]
gastrointestinal	*emetogenic potential:* low to low-moderate
	anorexia (1-69%)[5]
	constipation (1-14%)[5]
	diarrhea (2-45%, may be severe)[5]
	dyspepsia (2-8%)[5]
	gingivitis (2-14%)[5]
	nausea (19-66%)[5]
	pancreatitis (<5%)[5]
	stomatitis (up to 6%)[2]
	taste alteration (2-24%)[5]
	vomiting (6-50%)[2]
	xerostomia (1-28%)[5]
hemorrhage	epistaxis (rare)
	gastrointestinal hemorrhage (<5%)[5]
	hemoptysis (<5%)[5]
	retinal hemorrhage (rare)
	uterine/vaginal hemorrhage (very rare)
hepatic	***fatal hepatotoxicity*** (rare)
	hepatic encephalopathy (very rare)
infection	herpes simplex (rare)
	viral infection (rare)
	fungal infection, moniliasis, sepsis (very rare)
metabolic/laboratory	***elevated alkaline phosphatase*** (48%), ***transaminases*** (up to 63% for AST)[5]
	hyperglycemia (33-39%)[5]
	hypertriglyceridemia (rare, but sometimes severe)
	hyperuricemia (15%)[2]
	hypocalcemia (10-51%)[5]
	increased creatinine, BUN (up to 10%)[2]
	proteinuria (15-20%),[2] nephrotic syndrome (<5%)[5]
musculoskeletal	myositis, rhabdomyolysis (rare)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	weakness (5-63%)[5]
neurology	***alteration of mental status*** (1-17%); encephalopathy, coma (<1%)[2]
	amnesia (1-14%)[5]
	anxiety (1-9%)[5]
	ataxia (<5%)[5]
	stroke (<5%)[5]
	confusion (1-12%)[5]
	depression (4-40%)[5]
	dizziness (7-40%),[2,5] vertigo (8%),[5] syncope (<5%)[5]
	emotional lability (<5%)[2]
	extrapyramidal symptoms (<5%)[5]
	impaired concentration (1-14%)[5]
	irritability (1-22%)[5]
	mania (<5%)[5]
	nervousness (1-3%)[5]
	paresthesia (1-21%)[5]
	psychosis, including hallucinations (<5%)[5]
	seizures (<5%)[5]
	sleep disturbance: insomnia (1-12%)[5] or somnolence (1-33%)[5]
	speech disorder (aphasia >5%[5])
	suicidal ideation, suicide attempts, suicide (<5%)[5]
ocular/visual	ocular changes (rare); see discussion following table
pain	abdominal pain (2-23%)[5]
	arthralgia (5-24%)[2]
	back pain (1-19%)[5]
	chest pain (2-28%)[5]
	headache (20-70%)[2]
	musculoskeletal pain (1-21%)[5]
	myalgia (30-75%)[2]
	other body pains (3-15%)[5]
pulmonary/upper respiratory	bronchospasm (<5%)[5]
	cough (1-31%)[5]
	dyspnea (1-34%)[5]
	pharyngitis (1-31%)[5]
	nasal congestion (1-10%)[5]
	pulmonary embolism (<5%)[5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pulmonary fibrosis (<5%)[5]
renal/genitourinary	renal failure (<5%)[5]
sexual/reproductive function	decreased libido (1-5%)[5]
	impotence (up to 6%, transient) [2]
	gynecomastia (<5%)[2]
	menstrual disorders (generally rare, up to 12% in lymphoma[5])
syndromes	***flu-like syndrome*** (98%)[2]
	lupus erythematosus (<5%)[5]
vascular	thrombosis (<5%)[5]

Adapted from standard reference[1] unless specified otherwise.

In general, almost all patients experience at least one side effect during interferon therapy.[1,2] Most are mild to moderate in severity, diminish with continued use, and may be decreased by administering interferon at bedtime.[2] However, discontinuation of therapy due to side effects may be required in 3-24% of patients.[1,2]

Side effects from ***intralesional administration*** of interferon are similar to those observed with systemic use, and can include leucopenia, thrombocytopenia, and elevated liver enzymes.[1] However, these side effects are generally transient, rapidly reversible, and mild to moderate in severity.

Side effects from ***intravesical administration*** of interferon (into the bladder), either alone or in combination with BCG, are mild to moderate in severity, and limited to flu-like symptoms (8-17%), urinary frequency, and dysuria.[8-10]

Cardiotoxicity, particularly arrhythmia, seems to be correlated with preexisting cardiovascular disease and prior cardiotoxic therapy.[1] Rarely, cardiomyopathy has been reported in patients without prior cardiac disease; this may be reversible upon discontinuation of interferon.

"Flu-like" symptoms are the most commonly reported side effects of interferon, and usually include fever, fatigue, headache, and myalgia.[1] Other symptoms may include chills, arthalgia, rigors, tachycardia, anorexia, dry mouth, taste alteration, back pain, sweating, dizziness, abdominal cramps, and diarrhea. While the symptoms develop in almost all patients, the severity of symptoms seems to be dose-related.[2]

Fever may be due to a drug-related release of hypothalamic prostaglandin (PGE_2), rather than an increase in interleukin-1. Fever may reach 40°C within 6 hours, and may last 2-12 hours if untreated.[2] Pretreatment with acetaminophen is recommended: 500-1000 mg 30 minutes before interferon (maximum 4 g daily).[1] To properly assess the source of fever, adjunctive acetaminophen should be limited to 5 consecutive days unless otherwise specified by the prescriber.

Fatigue might be distinct from the flu-like syndrome.[2] In some cases, a persistent and pervasive fatigue continues throughout treatment. This type of fatigue has been postulated to result from a neurotoxic effect of interferon. It may be accompanied by lassitude, lack of motivation, or psychomotor retardation, and may necessitate a dose reduction or discontinuation of therapy.

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[11] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[12]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h

- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[13] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[14]

Hypotension due to fluid depletion may occur.[2] Patients should be counselled to maintain adequate hydration throughout therapy. Hypotension may be treated with fluid replacement, although hypotension that develops gradually during therapy may not respond to this maneover. Severe hypotension that occurs during administration or within 2 days of interferon treatment may require dose reduction or discontinuation of therapy, in addition to supportive therapy.

Ocular changes such as retinopathy, retinal hemorrhage, cotton wool spots, retinal artery or vein obstruction, loss of visual acuity or visual field, optic neuritis, and papilledema may rarely occur.[1] A baseline eye examination is recommended for patients with diabetes mellitus or hypertension.[2] Any patient complaining of ocular symptoms, including loss of visual acuity or visual field, must have a prompt and complete eye examination.[1] Discontinuation of interferon should be considered.

Neurologic side effects are numerous. Fatigue, headache, dizziness, and malaise have been described above as part of a "flu-like syndrome." Depression, paresthesias, pain, altered mental status, sleep disturbances, anxiety, and emotional lability may also occur.[2] Risk factors may include older age, high doses, and underlying CNS impairment. Patients and their families should be aware that many of these side effects develop insidiously, and may present as problems at work or trouble with interpersonal relationships. Various EEG abnormalities have been reported, but the mechanism of CNS dysfunction has not yet been elucidated; neurotransmitters may be involved to some extent, since metoclopramide and methylphenidate have occasionally been effective. In most cases, counselling and reassurance is the treatment of choice. Pharmacologic treatment (e.g., antidepressants, anxiolytics) may be given symptomatically. Dose reduction or discontinuation of therapy may be required for severe or refractory cases.

Pulmonary changes such as pulmonary infiltrates, pneumonitis, and pneumonia may rarely occur.[1] These changes are reported more often in patients with chronic hepatitis C, but have been observed in oncologic diseases as well. The problem is more frequent when interferon is used concurrently with Shosaikoto or Xiao Chai Hu Tang (see Drug Interactions). Any patient with new onset of fever, cough, dyspnea, or other respiratory symptoms must have a chest X-ray. If the chest X-ray shows pulmonary infiltrates, monitor the patient and discontinue interferon if appropriate. Prompt discontinuation of interferon and supportive treatment including corticosteroids are associated with resolution.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
angiotensin-converting enzyme (ACE) inhibitors[15]	increased risk of granulocytopenia	unknown; observed in patients treated for cryoglobulinemia, so may involve autoimmunity	monitor
BCG[16]	potential for decreased effect of BCG with interferon ready-to-use solution	antimicrobial preservative m-cresol may decrease viability of BCG	use only the lyophilized powder formulation of interferon when given in combination with BCG
barbiturates[2]	increased levels of barbiturate and barbiturate toxicity	unknown; may be due to inhibition of CYP P450	consider decreasing dose of barbiturate

AGENT	EFFECT	MECHANISM	MANAGEMENT
erythropoietin[5,17]	possible decreased effectiveness of erythropoietin	unknown; may blunt erythroid response to erythropoietin	monitor
melphalan[5]	possible decreased effectiveness of melphalan	unknown; decreased serum levels of melphalan	monitor
prednisone[5]	possible decreased effectiveness of interferon	unknown	monitor
Sho-saiko-to (Japanese name for Xiao Chai Hu Tang)[1,18]	increased risk of pulmonary side effects	unknown	avoid concurrent use
theophylline[19]	increased levels of theophylline; more pronounced in smokers; clinical relevance unknown	inhibition of CYP 1A2 by interferon decreases metabolism of theophylline	consider decreasing dose of theophylline
warfarin[19]	possible increased effectiveness and toxicity of warfarin	unknown	monitor INR and adjust warfarin dose as needed
Xiao Chai Hu Tang; Chinese herbal remedy containing Bupleurum root, Pinellia tuber, Scutellaria root, ginseng, jujube, licorice, and ginger[1,18]	increased risk of pulmonary side effects	unknown	avoid concurrent use
zidovudine[2]	increased risk of hematologic and hepatic side effects	unknown; may be additive or synergistic	monitor

SUPPLY AND STORAGE:

Formulations[2]: Various pegylated and non-pegylated formulations of recombinant and naturally-occurring interferons are available. This information is specific to recombinant interferon alfa-2b (INTRON-A®). Dose, route of administration, and adverse effects may vary among different types of interferon, as well as different formulations of the same type. Patients should be advised not to change preparations during a course of treatment.

***Injection*:**
Merck Canada Inc. supplies interferon alfa-2b (INTRON-A®) as:
- ***lyophilized powder*** in vials containing 10 million units/vial. Each vial is packaged with one vial of diluent containing 1 mL of sterile water. Refrigerate.[20]
- ***ready-to-use solution (albumin [human] free)*** in vials containing 10 million units/1 mL, 18 million units/3 mL, and 25 million units/2.5 mL. Refrigerate. [20] Solution contains m-cresol as a preservative.[21]

Additional information:
- For the purposes of transport,
  - ❖ non-reconstituted vials of ***lyophilized powder*** may be stored at room temperature for up to four weeks before use. If not reconstituted during this 4 week period, the vial cannot be returned to the refrigerator for a new storage period and must be discarded.[20]
  - ❖ vials of ***ready-to-use solution*** may be stored at room temperature for up to 7 days before use and can be returned to the refrigerator at any time during this 7 day period. If the vial is not used during this 7 day period, the vial cannot be returned to the refrigerator for a new storage period and must be discarded.[20]
- Vials of ***ready-to-use solution*** contain overfill designed to account for loss of solution in the needle and needle hub, thereby allowing the prescribed dose to be withdrawn from the vial.[20]

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.

Compatibility: consult detailed reference

Additional information:

- The ***lyophilized powder*** may be reconstituted with the supplied diluent (sterile water for injection) OR if preferred and the patient is not allergic to benzyl alcohol, bacteriostatic water for injection may be used.[20]
- An isotonic solution is recommended for ***intralesional administration.*** Only the 10 million unit vials of lyophilized powder (following reconstitution with the supplied diluent) will provide an isotonic solution appropriate for intralesional administration. Reconstitution of other vial sizes for this use will result in a hypertonic solution.[20]
- ***Interferon eye drops:***
  Interferon eye drops 1 MU/mL can be prepared with bacteriostatic water.[22]
  - Transfer 1 mL from a 10 MU (10 MU/mL) vial of INTRON-A® Ready-To-Use solution to a sterile 15 mL eye dropper bottle.
  - Add 9 mL of bacteriostatic water to give a concentration of 1 MU/mL.

  The final product is stable for 14 days refrigerated.[23-25]

PARENTERAL ADMINISTRATION:

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

Subcutaneous	***preferred for self-administration;*** rotate sites of injection[5]
Intramuscular	may be used for self-administration[1]; rotate sites of injection avoid if patient is at risk for bleeding or is thrombocytopenic; use SC instead[2]
Direct intravenous	no information found
Intermittent infusion	in ***50 mL NS: over 20 minutes;*** in ***500 mL NS: over 60 minutes***
Continuous infusion	has been used[5]
Intraperitoneal	has been used[2]
Intrapleural	no information found
Intrathecal	has been used[2]
Intra-arterial	no information found
Intravesical	in ***50 mL preservative-free NS: dwell time 2 h***
Intralesional	Clean lesion with sterile alcohol pad. Using a fine (30) gauge needle and a 1 mL syringe, inject into the base and substance of the lesion. Avoid SC injection. An isotonic solution for injection is recommended (see Solution Preparation and Compatibility).[1]

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:

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

	Cycle Length:	
Subcutaneous/intramuscular:	***daily:***	CML, thrombocytosis[26] ***5 MU/m²*** (range 0.5-10 MU/m², to control white blood cell or platelet count) ***SC***/IM ***daily*** When controlled, dosage may be administered three times weekly.[1]
	weekly:	AIDS-related Kaposi's sarcoma[1,2] 30 MU/m² SC/IM three times weekly
	weekly:	hairy cell leukemia[2,5] 2 MU/m² SC/IM three times weekly
	weekly:	lymphoma, myeloma[1,27] ***3 MU (range 2-5 MU) SC/IM three times weekly***
	weekly:	renal cell cancer[28] ***5 MU SC three times weekly*** x 2 doses, ***then 10 MU SC three times weekly*** (range 5-20 MU SC/IM daily or ***three times weekly***) for 12 weeks or until disease progression (whichever comes first)
Intravenous:	***weekly:***	melanoma[29] ***induction: 20 MU/m² IV once daily*** for 5 consecutive days, for 4 weeks, followed by ***10 MU/m² SC three times weekly*** for 48 weeks
Intralesional:	weekly:	basal cell cancer[1] 0.5 MU/cm² of lesion's initial size (minimum 1.5 MU, maximum 5 MU) three times weekly for 3 weeks Up to three lesions < 2 cm² each may be treated concurrently. Only one lesion 2-10 cm² may be treated at a time.
Intravesical:	***weekly:***	bladder cancer[30] ***induction: 50 MU*** (with 1/3 vial BCG) ***weekly*** for 6 weeks ***maintenance: 50 MU*** (with 1/3 vial BCG) ***weekly*** for 3 consecutive weeks every 6 months
Concurrent radiation[2]:	combination therapy must be given with care; interferons may be either radioprotective or radiosensitizing; life-threatening toxicities have occurred	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure[1]:	risk of adverse reactions may be greater in patients with impaired renal function; adjustment may be necessary	

Dosage in hepatic failure: modify according to protocol by which patient is being treated; if no guidelines available, the manufacturer suggests[1]:

Indication	ALT/AST	Action
melanoma	> 5 x ULN	temporarily discontinue; restart at 50% once symptoms abate
melanoma	> 10 x ULN	discontinue
lymphoma	> 5 x ULN	discontinue

Dosage in dialysis: no specific guidelines found; in patients with hepatitis C undergoing chronic hemodialysis, interferon AUC was approximately double and clearance was approximately half that of patients with normal renal function[31]; interferon does not appear to be removed by hemodialysis[2]

Children:

Intravenous: safety and effectiveness in pediatric patients have not been studied[1]

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