# DRUG NAME: Peginterferon alfa-2a

**SYNONYM(S):**

**COMMON TRADE NAME(S):** PEGASYS®

**CLASSIFICATION:** biological response modifier

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

## MECHANISM OF ACTION:

Peginterferon alfa-2a is a covalent conjugate of a polyethylene glycol chain and a human leukocyte alfa-2a interferon gene inserted and expressed in *E. coli*. It binds to specific receptors on the cell surface to initiate a complex signaling pathway that activates cellular gene transcription. Interferon-stimulated genes inhibit cell proliferation and cause immunomodulation.[1] Pegylated forms of interferon-alfa have superior pharmacokinetic and toxicity profiles as well as a more convenient dosing schedule compared with non-pegylated interferon-alfa.[2]

## PHARMACOKINETICS:

| | | |
|---|---|---|
| Absorption | sustained absorption; peak serum concentration 72-96 h after dosing; steady state serum levels within 5-8 weeks of once-weekly dosing (no accumulation after steady state) | |
| Distribution | found mainly in bloodstream and extracellular fluid | |
| | cross blood brain barrier? | no information found |
| | volume of distribution | 6-14 L |
| | plasma protein binding | no information found |
| Metabolism | mechanism not fully characterized | |
| | active metabolite(s) | no information found |
| | inactive metabolite(s) | no information found |
| Excretion | terminal half-life after subcutaneous dosing likely reflects sustained absorption, not elimination | |
| | urine | <10% as unchanged drug |
| | feces | no information found |
| | terminal half life | subcutaneous: 160 h (84-353 h)<br>IV: 60 h |
| | clearance | 100 mL/h |

Adapted from standard reference[1] unless specified otherwise.

## USES:

***Primary uses:***
Myeloproliferative neoplasms[3]

***Other uses:***

*Health Canada approved indication

## SPECIAL PRECAUTIONS:

***Contraindications:***
- history of hypersensitivity reaction to alpha interferon (pegylated or non-peglyated) or *E. coli*-derived products[1,4]
- autoimmune hepatitis or decompensated cirrhosis[4]

***Caution:***
- Peginterferon alfa-2a is ***NOT interchangeable*** with other pegylated interferons or other alpha-interferon products.[1]
- Fatal or life-threatening ***neuropsychiatric, autoimmune, infectious,*** and ***ischemic*** disorders may be caused or aggravated by peginterferon[1]; see paragraphs after **Side Effects** table.
- ***Cardiovascular events*** are associated with peginterferon alfa-2a. Consider baseline ECG in patients with pre-existing cardiac disease; avoid in patients with pre-existing severe, unstable, or uncontrolled cardiac disease.[5] See paragraph after **Side Effects** table.
- Avoid peginterferon alfa-2a in patients with uncontrolled pre-existing ***hypo/hyperthyroidism, hypo/hyperglycemia,*** or ***diabetes mellitus***.[1]
- ***Retinopathy*** has been reported. All patients should receive a baseline eye exam; patients with pre-existing eye disease should receive periodic eye exams throughout treatment.[5] See paragraph after **Side Effects** table.
- ***Liver*** and ***renal graft rejections*** have been reported; safety in transplantations has not been established.[1]

***Special populations:*** Avoid use in ***neonates and infants.*** Peginterferon alfa-2a contains benzyl alcohol; excessive exposure to benzyl alcohol has been associated with deaths in neonates and infants.[1]

***Carcinogenicity:*** no information found

***Mutagenicity:*** Not mutagenic in Ames test or clastogenic in mammalian *in vitro* chromosome mutation test.[1]

***Fertility:*** Peginterferon alfa-2a impairs fertility in female monkeys by prolonging the menstrual cycle and decreasing or delaying peak levels of 17ß-estradiol and progesterone. Normal menstruation resumed post treatment in study animals. In male monkeys, fertility was unaffected following treatment for 5 months at doses up to 25 X $10^6$ IU/kg/day.[1]

***Pregnancy:*** No information on peginterferon in pregnancy is available. However, abortifacient activity was significantly increased in monkeys treated with interferon alfa-2a, although no teratogenic effects were seen in the offspring delivered at term. Effective contraception is recommended during therapy with peginterferon alfa-2a.[1]

***Breastfeeding*** is not recommended due to the potential secretion into breast milk.[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.[6]

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia (see paragraph following **Side Effects** table) | anemia (2-6%)[2,4] |
| | ***neutropenia*** (21%, severe 7%)[4,7] |
| | leukopenia (6%)[2] |
| | thrombocytopenia (5-8%)[2,4] |
| cardiac | cardiovascular (8%)[8]; see paragraph following **Side Effects** table |

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| endocrine (see paragraph following **Side Effects** table) | hypothyroidism (3-4%) |
| | hyperthyroidism (<1%) |
| eye | blurred vision (4%) |
| | retinopathy (<1%); see paragraph following **Side Effects** table |
| gastrointestinal | *emetogenic potential: rare*[9] |
| | abdominal pain (4-15%)[1,4] |
| | colitis (<1%); see paragraph following **Side Effects** table |
| | diarrhea (6-16%, severe 4%)[1,4,7] |
| | dry mouth (6%) |
| | nausea (<4%)[2,6] |
| | pancreatitis (<1%); if diagnosed, discontinue peginterferon-alfa 2a |
| | stomatitis (2%)[2] |
| | vomiting (<1%)[6] |
| general disorders and administration site conditions (see paragraph following **Side Effects** table) | *extravasation hazard: none*[10] |
| | ***fatigue*** (20-56%)[2,4] |
| | injection site reaction (7-22%)[1,4] |
| | ***pyrexia*** (35-52%)[1] |
| | ***rigors*** (6-35%)[1,4] |
| immune system | autoimmune disorders (<1%); see paragraph following **Side Effects** table |
| | hypersensitivity reactions (<1%); see paragraph following **Side Effects** table |
| | thyroiditis (<1%)[2] |
| infections and infestations | infection (3-5%) |
| investigations | ***liver function test elevation*** (6%, severe 4%)[2,7]; may require dose reduction or discontinuation for persistent increases |
| | weight loss (4%) |
| metabolism and nutrition | appetite decrease (13-17%)[1,4] |
| | hyperglycemia (<1%) |
| | hypoglycemia (<1%) |
| musculoskeletal and connective tissue | asthenia (7-11%)[1] |
| | ***arthralgia*** (10-28%)[1,4] |
| | back pain (2-9%)[1,4] |
| | ***myalgia*** (3-37%)[1,2,4] |
| nervous system | concentration impairment (2-9%)[1] |
| | dizziness (6-16%)[1,4] |
| | ***headache*** (3-54%)[2,4] |
| | cerebral hemorrhage (<1%); see paragraph following **Side Effects** table |
| | memory impairment (5%) |
| psychiatric | ***anxiety*** (19%) |
| | ***depression*** (4-15%)[1,4]; see paragraph following **Side Effects** table |
| | insomnia (6-20%)[1,4] |
| | irritability (3-19%)[1,4] |
| | mood disorder (4%)[2] |

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| respiratory, thoracic and mediastinal | cough (4%) |
| | dyspnea (4%) |
| | pneumonitis, pulmonary hypertension (<1%); see paragraph following **Side Effects** table |
| skin and subcutaneous tissue | alopecia (3-23%)[2,4] |
| | diaphoresis (6%) |
| | dry skin (4%) |
| | skin rash (5-10%)[2,11] |
| | pruritis (6-13%)[1] |

Adapted from standard reference[4] unless specified otherwise.

"***Flu-like" symptoms*** (e.g., tiredness, pyrexia, chills, muscle aches, joint pain, and headache) are the most common side effects associated with peginterferon alfa-2a. Symptoms are usually mild to moderate and decrease after the first few weeks of treatment. Consider pre-medicating with acetaminophen or ibuprofen to decrease these symptoms. ***Persistent fever*** should be investigated, particularly in patients with neutropenia, as serious infections (bacterial, viral, and fungal) have been reported.[1]

***Autoimmune diseases*** may be caused or aggravated by peginterferon alfa-2a, although most cases are reversible following discontinuation. Reported autoimmune diseases have included: thyroiditis, thrombotic or immune thrombocytopenic purpura, rheumatoid arthritis, interstitial nephritis, systemic lupus erythematosus, myositis, hepatitis, sarcoidosis, and psoriasis.[1,4]

Peginterfon alfa-2a may suppress ***bone marrow function*** causing severe cytopenias, including pancytopenia and aplastic anemia. Use cautiously in patients with baseline ANC less than 1.5 X $10^9$/L, platelets less than 90 X $10^9$/L, or hemoglobin less than 100 g/L. White blood cell and neutrophil counts usually decrease within the first two weeks of starting treatment. Low counts can be reversed by dose reduction or treatment discontinuation and return to pretreatment levels within 4-8 weeks of permanently stopping treatment. Peginterferon alfa-2a has also been associated with small gradual decreases in hemoglobin and hematocrit.[1]

***Cardiovascular events*** such as hypertension, supraventricular arrhythmias, congestive heart failure, chest pain, and myocardial infarction have been associated with peginterferon alfa-2a. Use cautiously in patients with pre-existing cardiac disease and hold or discontinue peginterferon alfa-2a if there is any deterioration in cardiovascular status.[1]

Ischemic and hemorrhagic ***cerebrovascular*** events have been observed with peginterferon alfa-2a, even in patients with few or no reported risk factors. Accurate estimates of frequency cannot be made.[1]

Hemorrhagic/ischemic ***colitis*** (e.g., abdominal pain, bloody diarrhea, and fever) has been reported within 12 weeks of starting alpha interferon treatment. Discontinue peginterferon alfa-2a immediately for colitis symptoms. Colitis usually resolves within 1-3 weeks following discontinuation.[1]

***Endocrine disorders*** such as ***hypoglycemia***, ***hyperglycemia,*** and ***diabetes mellitus*** may develop during treatment with peginterferon alfa-2a. In addition, pre-existing ***hypo-*** and ***hyperthyroidism*** may be aggravated by treatment. Peginterferon should not be started in patients with uncontrolled endocrine disorders. Similarly, patients who develop endocrine disorders during treatment should only continue peginterferon alfa-2a if the disorder can be controlled with medication.[1]

Serious, acute ***hypersensitivity reactions*** (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) and cutaneous eruptions (e.g., Stevens Johnson syndrome, toxic epidermal necrolysis) are very rarely reported. Discontinue treatment and initiate appropriated medical therapy immediately if a reaction develops. Transient rashes do not necessitate interruption of treatment.[1]

***Ocular changes*** such as retinopathy, retinal hemorrhages, cotton wool spots, papilledema, retinal artery or vein obstruction, and retinal detachment may rarely occur. In addition, decreased vision, loss of vision, macular edema, and optic neuritis may be induced or aggravated. Baseline eye exams are recommended for all patients and patients with preexisting ophthalmologic disorders should receive periodic exams during treatment. Patients with complaints of decreased vision or vision loss require prompt assessment. Discontinue peginterferon alfa-2a in patients with new or worsening ophthalmologic disorders.[1]

***Pulmonary*** symptoms such as dyspnea, pulmonary infiltrates, pneumonia, pneumonitis, and pulmonary hypertension have been reported and are sometimes fatal. Consider a chest x-ray for any patient developing fever and cough, dyspnea, or other respiratory symptoms. Discontinue treatment for pulmonary function impairment or unexplained pulmonary infiltrates.[1]

Severe ***psychiatric reactions***, including depression, suicidal ideation, and suicide attempts may occur in patients with or without previous psychiatric illness. Other neurological effects such as aggressive behavior, confusion, anxiety, nervousness, and alterations in mental status have also been observed. For moderate depression, an initial dose reduction to 90 to 135 mcg may be needed. Discontinue treatment in patients with persistent severe symptoms. Patients with substance use disorders (e.g., alcohol, cannabis) are at increased risk of developing psychiatric disorders. Advise patients to report signs and symptoms promptly as psychiatric intervention may be required.[1]

## INTERACTIONS:

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| aldesleukin[4,12] | enhanced myocardial and renal toxicity of aldesleukin | unknown | use with caution |
| methadone[1] | 10-15% increase in serum concentration of methadone | unknown | monitor for signs and symptoms of methadone toxicity |
| telbivudine[4] | possible increased risk of peripheral neuropathy | unknown | avoid combination if possible; monitor for peripheral neuropathy |
| theophylline[11] | 25% increase in theophylline AUC | weak inhibition of CYP 1A2 by peginterferon alfa-2a | monitor theophylline serum levels; adjust dose as needed |
| Sho-saiko-to (Xiao-Chai-Hu)[1] | increased risk of pulmonary side effects | unknown | avoid concurrent use |

## SUPPLY AND STORAGE:

***Injection***: Hoffmann-La Roche Limited supplies peginterferon alfa-2a (PEGASYS®) as a ready-to-use solution for subcutaneous injection. Vials contain benzyl alcohol. Refrigerate. Protect from light. Do not shake.

- pre-filled syringe contains 180 mcg in 0.5 mL
- ProClick Autoinjector® contains 180 mcg in 0.5 mL
- single use vial contains 180 mcg in 1 mL

***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:

***For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.***

***Additional information:*** Allow peginterferon alfa-2a to come to room temperature prior to administration.
- vial: warm vial by gently rolling it in the hand for one minute
- prefilled syringe or autoinjector: allow to come to room temperature by laying on a clean flat surface
- do not use any product kept at room temperature for more than 24 hours[5,11]

***Compatibility:*** consult detailed reference

## PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

| ***Subcutaneous*** | ***into the thigh or abdomen***; rotate sites of injection[1,13] |
|---|---|
| Intramuscular | no information found |
| Direct intravenous | no information found |
| Intermittent infusion | no information found |
| Continuous infusion | no information found |
| Intraperitoneal | no information found |
| Intrapleural | no information found |
| Intrathecal | no information found |
| Intra-arterial | no information found |
| Intravesical | no information found |

## 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***

| | Cycle Length: | |
|---|---|---|
| *Subcutaneous:* | **1 week**:[2,6,7,13-15] | ***90 mcg*** (range 22.5-180 mcg) ***SC for one dose on day 1;*** adjust for toxicity and hematologic response to a dose of 180 mcg per week (range 15-300 mcg).<br><br>Doses are started low and titrated every 2 weeks.<br>Patients with complete response for more than 6 months can be adjusted to lower weekly doses or longer dosing intervals (e.g., 10-14 days). |
| *Concurrent radiation:* | no information found | |
| *Dosage in myelosuppression:* | modify according to protocol by which patient is being treated | |

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

| | |
|---|---|
| *Dosage in renal failure:*[1,6] | Cycle Length:<br>• risk of adverse reactions may be greater in patients with impaired renal function<br>• doses are started low and adjusted for toxicity and hematologic response |
| *Dosage in hepatic failure:*[1] | • mild impairment (Child Pugh A): no dose adjustment<br>• moderate or severe impairment (Child Pugh B/C): no information found |
| *Dosage in dialysis:*[5,6] | • significant drug removal by peritoneal or hemodialysis is unlikely[16]<br>• has been used; doses are started low and adjusted based on response and toxicity |
| ***Children:*** | safety and effectiveness has not been established[1] |

## REFERENCES:


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