Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

anagrelide

COMMON TRADE NAME(S): Agrylin®

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B - Mechanism of Action and Pharmacokinetics

Anagrelide is a cyclic AMP phosphodiesterase (PDE) III inhibitor. It may decrease megakaryocyte hypermaturation, which results in dose-related reduction in platelet production. There is no clinically significant effect on red cell, white cell or coagulation parameters. It is 50 times more potent than ASA as an anticoagulant; however, platelet aggregation is inhibited at higher doses than those used to reduce platelet count.

Absorption	Longer time lag before absorption, slower absorption rate and later Tmax were observed with food administration. Food increased anagrelide exposure by 20% but did not affect the exposure of its active metabolite.	
Metabolism	Extensively metabolized by the liver, partly by CYP1A2.	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Urine	> 70%
	Half-life	1-2 hours (anagrelide); 3 hours (active metabolite)

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C - Indications and Status

Health Canada Approvals:

Treatment of patients with thrombocythemia secondary to myeloproliferative neoplasms to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms, including thrombo-hemorrhagic events

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D - Adverse Effects

The following adverse effects were observed in clinical trials, which occurred in ≥5% of patients (or life-threatening) with myelo-proliferative neoplasms of varying etiology [Essential Thrombocythemia (ET), Polycythemia Vera (PV), other myeloproliferative neoplasms (OMPN)].

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<5%)	E
	Arterial thromboembolism (rare)	E D
	Cardiotoxicity (<5%)	E D
	Palpitations (26%) ; tachycardia	E
	QT interval prolonged (rare)	E
	Venous thromboembolism (<5%)	E D
Dermatological	Rash, pruritus (8%)	E
Gastrointestinal	Abdominal pain (17%)	E
	Anorexia (8%)	E
	Diarrhea (26%)	E
	Dyspepsia (5%)	E
	Flatulence (10%)	E
	GI hemorrhage (<5%)	E
	Nausea, vomiting (17%)	I E
General	Edema (21%)	E
	Fatigue (23%)	E

	Fever (9%)	I
	Pain (15%)	E
Hepatobiliary	↑ LFTs (<5%) (may be severe - hepatitis)	E D
Nervous System	Dizziness (15%)	E
	Headache (44%)	E
	Paresthesia (6%)	E
Renal	Creatinine increased (<5%) (renal failure 1%; nephritis)	E D
Respiratory	Cough, dyspnea (12%)	E D
	Interstitial lung disease (e.g. allergic alveolitis, eosinophilic pneumonia)	E D L

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for anagrelide include headache, diarrhea, palpitations, fatigue, edema, abdominal pain, nausea/vomiting, dizziness, pain, cough/dyspnea.

Interstitial lung disease has been reported, presenting with progressive dyspnea associated with lung infiltrations. Onset ranges from 1 week to several years after starting anagrelide. Symptoms improved after anagrelide discontinuation in most cases.

Mechanistic inotropic and chronotropic effects may result in tachycardia and cardiac effects.

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E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Starting dose:

Oral: 0.5 mg QID

or

Oral: 1 mg BID

maintained for at least one week

Then, adjust to the lowest effective dose needed to reduce and maintain platelets to < 600 x 10^9/L, and ideally to the normal range.

- Do not increase more than 0.5 mg/day in any one week
- Maximum dose: 10 mg/day or 2.5 mg in a single dose
- Most patients have adequate responses at 1.5 to 3 mg/day
- Response starts within 7-14 days at the proper dosage, but may take 4-12 weeks for complete response to occur

Dosage with Toxicity:

Toxicity	Action
Interstitial lung disease	Hold when suspected; discontinue if confirmed.
CHF, MI	
Severe ↑ LFTs	
Hepatitis	

Dosage with Hepatic Impairment:

Anagrelide exposure is increased 8-fold in patients with moderate hepatic impairment. Use in mild and moderate hepatic impairment only if benefits outweigh risks. Anagrelide has not been studied in and is CONTRAINDICATED in severe hepatic impairment.

Hepatic Impairment	Starting Dose
Mild	No change; regular hepatic and cardiovascular monitoring
Moderate	0.5 mg/day for at least one week, titration with no more than a 0.5mg/day increase in any one week; regular hepatic and cardiovascular monitoring
Severe	CONTRAINDICATED

Dosage with Renal Impairment:

Serum Creatinine (micromol/L)	Dose
< 177	No dose adjustment required
≥ 177	Give only if benefits outweigh risks. Monitor closely for nephrotoxicity.

Dosage in the elderly:

No specific studies have been conducted in patients ≥ 65 years, but older patients were observed to have lower presystemic anagrelide metabolism to its active metabolite; however, no dose adjustment is needed.

Children:

Safety and efficacy of anagrelide in patients < 16 years of age have not been established. Use with caution as lower exposure has been observed in children/adolescents compared to adults (± 50% lower Cmax and AUC).

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F - Administration Guidelines

- May be given with or without food
- Grapefruit, grapefruit juice and related products should be avoided (see Drug Interactions section)
- Store at 15°C to 25°C in a light-resistant container.

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G - Special Precautions

Contraindications:

- patients with hypersensitivity to this drug or to any components in the formulation or container
- patients with severe hepatic impairment
- not recommended in women who are or may become pregnant

Other Warnings/Precautions:

- intended for chronic usage; not been evaluated for treatment of the acute life-threatening complications of thrombocytosis
- patients with mild or moderate hepatic impairment
- patients with renal impairment (Cr ≥ 177 micromol/L)
- sudden anagrelide discontinuation or interruption results in an increase in platelet count, within 4 days
- patients with known or suspected cardiac disease, due to anagrelide's positive inotropic and chronotropic effects
- patients with known risk factors for QT prolongation, such as congenital long QT syndrome, known history of acquired QTc prolongation, medications that can prolong QT, hypokalemia

Other Drug Properties:

- Carcinogenicity: Probable
  Uterine adenocarcinoma, benign and malignant pheochromocytomas were observed in animal studies.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Probable

Anagrelide is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose. (general recommendation)

- Excretion into breast milk: Yes
  Breastfeeding is not recommended.
- Fertility effects: Yes

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H - Interactions

Digoxin and warfarin do not affect pharmacokinetics (PK) of anagrelide, nor does anagrelide affect the PK of these drugs.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Other PDE3 inhibitors (e.g. milrinone, cilostazol)	↑ inotropic and chronotropic effects	Additive	Avoid
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation	Additive	Avoid
CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, grapefruit juice)	↑ anagrelide exposure	anagrelide is metabolized partly by CYP1A2	Caution; monitor for anagrelide toxicity and adjust dose accordingly
CYP1A2 inducers (e.g. omeprazole, carbamazepine)	↓ anagrelide exposure	↑ metabolism of anagrelide	Caution; monitor platelet response and titrate dose accordingly

CYP1A2 substrates (e.g. amitriptyline, haloperidol, theophylline)	↑ exposure of these substrates	anagrelide may inhibit CYP1A2	Caution, especially for substrates with narrow therapeutic range
Aspirin	↑ risk of hemorrhage; major bleeding events have been reported	Additive antiplatelet effects	Caution and monitor closely; extreme caution in patients with high risk for hemorrhage and/or with platelets > 1000 x 10^9/L before treatment
Other drugs known to cause bleeding (e.g., anticoagulants, NSAIDs, antiplatelet agents)	↑ risk of bleeding	Additive (has synergistic effect on platelet aggregation inhibition when given with heparin)	Caution; monitor closely
Sucralfate	Unknown	may interfere with anagrelide absorption	Separate sucralfate and anagrelide administration at least 2 hours apart

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, then every 2 days during the first week, and at least weekly thereafter until maintenance dosage is reached
Liver function tests	Baseline, and as clinically indicated; at least monthly in patients with hepatic impairment

Renal function tests	Baseline, and as clinically indicated; at least monthly in patients with renal impairment
Electrolytes	Baseline and regular
Cardiovascular (including ECG)	Baseline, then as indicated during treatment, closely in patients with known or suspected heart disease
Clinical toxicity assessment for headache, palpitations, blood pressure, GI, fatigue, edema, bleeding, dizziness, pulmonary effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

ODB Limited Use (ODB Formulary)

- anagrelide

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K - References

Product Monograph: Agrylin® (anagrelide). Shire Pharma Canada, March 13, 2017.

Prescribing Information: Agrylin® (anagrelide).Shire US Inc., July 2015.

Anagrelide monograph. British Columbia Cancer Agency, November 1, 2015.

April 2024 Updated Pregnancy and Lactation section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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