DRUG NAME: Anagrelide

SYNONYM(S):

COMMON TRADE NAME(S): AGRYLIN®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Anagrelide is a highly selective platelet-lowering agent. Its effects are fully reversible.[1] The exact mechanism of action is not known. It is thought that a reduction in platelet production is the result of decreased megakaryocyte hypermaturation.[2] Anagrelide disrupts the postmitotic phase of megakaryocyte development, resulting in a reduction in the size of these cells.[3,4] Anagrelide is also thought to inhibit adenosine diphosphate (ADP) and collagen induced platelet aggregation.[5]

PHARMACOKINETICS:

Oral Absorption	> 70% absorbed, food decreases the extent and rate of absorption, but this is not considered to be clinically significant[6]	
	time to peak plasma concentration	1-8 hours[3,5,7]
Distribution	cross blood brain barrier?	no information found
	volume of distribution	12 $\pm$ 3 L/kg[5]
	plasma protein binding	no information found
Metabolism	extensively metabolized; two major metabolites (one active and one inactive)[1]	
	active metabolite(s)	3-hydroxy-anagrelide (BCH24426)[1]
	inactive metabolite(s)	5,6-dichloro-3,4-dihydroquinazolin-2-ylamine (RL603)[1]
Excretion	primarily renally eliminated	
	urine	>70% (<1% eliminated unchanged)[1]
	feces	10-30%[3]
	terminal half life	1-2 h (anagrelide); 3 h (3-hydroxy-anagrelide)[1]
	clearance	no information found
Elderly	higher C_{max} and AUC of anagrelide, but lower C_{max} and AUC of active metabolite compared to adults (likely secondary to lower presystemic metabolism to active metabolite)[1]	
Children	lower C_{max} and AUC compared to adults[1]	

Adapted from reference[4] unless specified otherwise.

USES:

Primary uses:
*Thrombocythemia secondary to myeloproliferative disorders

Other uses:

*Health Canada Therapeutic Products Programme approved indication

No pediatric indications are available.

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to anagrelide.[3]

Caution:
- Anagrelide has ***positive inotropic and chronotropic*** effects and cardiovascular side effects; associated increases in heart rate may also result in an apparent increase in ***QTc interval.*** Use caution in patients with known or suspected heart disease and those with known risk factors for QT prolongation. Pretreatment ECG is recommended for all patients.[1] See paragraph after **Side Effect** table.
- ***Hepatic impairment*** may increase drug exposure; monitor liver function prior to and during treatment.[1] See paragraph after **Side Effect** table.

Special populations:

Carcinogenicity: In rats, a higher incidence of uterine adenosarcoma was observed in females (at dose levels 174 times human AUC exposure). Also, increased benign and malignant pheochromocytomas were observed in both sexes (at all dose levels for males and at dose levels at least 10 times human AUC exposure in females).[1]

Mutagenicity: Not shown to be mutagenic in Ames test and in mammalian *in vitro* mutation test. Not shown to be clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[3]

Fertility: Studies in male rats have shown no effect on fertility and reproduction. Studies in female rats have shown a higher rate of disruption of implantation if given early in pregnancy and retarded parturition if given late in pregnancy.[3]

Pregnancy: FDA Pregnancy Category C.[3] The benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Studies in female rats have shown reduced live litter sizes, reduced pup weight, increased resorptions, and increased pup mortality after birth. Reduced fetal body weight and significant delays in fetal ossification were reported in embryo-fetal studies in rats.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk.[3]

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.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (1-5%)
	thrombocytopenia (1-5%)
cardiac (see paragraph following **Side Effects** table)	angina (1-5%)
	arrythmia, including atrial fibrillation, AV block (1-5%)
	congestive heart failure (1-5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	cardiomegaly, cardiomyopathy
	myocardial infarction
	palpitations (26%)
	tachycardia (8%)
	torsade de pointes
	ventricular tachcardia
ear and labyrinth	tinnitus, ear disorder (1-5%)
eye	amblyopia, diplopia (1-5%)
	conjunctivitis (1-5%)
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain (17%)
	constipation (1-5%)
	diarrhea (26%)
	dyspepsia (5%)
	flatulence (10%)
	gastric/duodenal ulceration
	GI hemorrhage (1-5%)
	melena (1-5%)
	nausea (17%)
	pancreatitis
	vomiting (10%)
general disorders and administration site conditions	asthenia (23%)
	edema (21%)
	fever (9%)
	malaise (6%)
	pain (15%)
	peripheral edema (9%)
	weight gain/weight loss (1-5%)
hepatobiliary	hepatitis; see paragraph following **Side Effects** table
infections and infestations	urinary tract infection (1-5%)
investigations	liver function test elevation (1-5%)
metabolism and nutrition	anorexia (8%)
musculoskeletal and connective tissue	arthralgia, myalgia (1-5%)
	back pain (6%)
	bone pain (1-5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	leg cramps (1-5%)
nervous system	amnesia (1-5%)
	dizziness (16%)
	headache (44%)
	seizure
	syncope (1-5%)
psychiatric	confusion (1-5%)
	depression (1-5%)
	insomnia/somnolence (1-5%)
renal and urinary	dysuria (1-5%)
	frequency (1-5%)
	hematuria (1-5%)
	incontinence (1-5%)
	nocturia (1-5%)
	renal failure; see paragraph following **Side Effects** table
	tubulointerstitial nephritis
respiratory, thoracic and mediastinal (see paragraph following **Side Effects** table)	allergic alveolitis
	cough (6%)
	dyspnea (12%)
	epistaxis (1-5%)
	pharyngitis (7%)
	pleural effusion
	pulmonary infiltrates/fibrosis; see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia (1-5%)
	ecchymosis (1-5%)
	pruritus (6%)
	rash, including urticaria (8%)
	skin discoloration, ulcer (1-5%)
vascular	cerebrovascular accident
	hypertension (1-5%)
	hypotension, orthostatic (1-5%)
	thrombosis (1-5%)

Adapted from standard reference[1] unless specified otherwise.

Most adverse events are dose-related, mild in intensity, decrease in frequency with continued therapy, and do not require treatment; however, serious adverse events have been reported.[1]

Cardiovascular effects such as vasodilation, tachycardia, palpitations, and congestive heart failure have been reported with therapeutic doses of anagrelide. The increase in heart rate associated with anagrelide may also result in an apparent increase in QTc interval. This effect does not appear to be a direct effect on repolarization. Cases of torsade de pointes and ventricular tachycardia have been reported. Use caution in patients with known risk factors for QT prolongation and in patients who may experience a higher maximum plasma concentration than expected (e.g., hepatic failure, concurrent therapy with interacting drug, etc.).

Hepatic metabolism represents the major route of clearance for anagrelide. Exposure is increased 8-fold in patients with moderate hepatic impairment and the AUC of the active metabolite, 3-hydroxy anagrelide, is approximately doubled. Cases of hepatitis have been reported. Monitor liver function prior to treatment and at regular intervals during treatment as indicated. A reduced starting dose is recommended for moderate hepatic impairment. Avoid use in severe impairment. Watch for cardiovascular effects and hepatic toxicity which may develop during treatment.[1] See **Dosing in hepatic failure**.

Interstitial lung diseases such as allergic alveolitis, eosinophilic pneumonia, and interstitial pneumonitis have been reported. Most cases present with progressive dyspnea associated with lung infiltrations. Time of onset ranges from 1 week to several years after initiation of treatment. Discontinue anagrelide in patients with acute pulmonary symptoms. In most patients, symptoms improve after anagrelide is discontinued.[1]

Platelet counts should be performed regularly to monitor the effect of anagrelide and prevent thrombocytopenia. Typically, platelet counts begin to respond within 7 to 14 days at the proper dosage. Time to complete response ranges from 4 to 12 weeks. Most patients will achieve an adequate response at a dose of 1.5 to 3 mg daily. ***Sudden discontinuation*** or interruption of treatment with anagrelide is followed by an increase in platelet count, usually observed within four days of discontinuation.[1]

Renal abnormalities, including renal failure, have been reported with anagrelide use and may be associated with pre-existing renal impairment. No dose adjustment is required for renal insufficiency.[1]

INTERACTIONS:

AGENT	*EFFECT*	*MECHANISM*	*MANAGEMENT*
sucralfate[4]	unknown	case report suggesting sucralfate may interfere with absorption of anagrelide	space administration of anagrelide and sucralfate by 2 hours

As an inhibitor of cyclic AMP phosphodiesterase III, anagrelide may exacerbate the effects of other products with similar properties (such as the inotrope milrinone). The active metabolite is almost forty times more potent as a phosphodiesterase inhibitor than the parent drug.[1]

Anagrelide is a substrate of CYP 1A2; coadministration with CYP 1A2 inhibitors may reduce the clearance of anagrelide and its active metabolite. Grapefruit juice has been shown to inhibit CYP 1A2 and this may reduce the clearance of anagrelide; clinical significance is unknown. Anagrelide also exhibits limited inhibitory activity toward CYP 1A2; clinical significance is unknown.[1]

SUPPLY AND STORAGE:

Oral*:* Shire Canada Inc. supplies anagrelide as a 0.5 mg capsule. Capsules contain lactose. Store at room temperature in a light-resistant container.[1]

DOSAGE GUIDELINES:

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

Oral:

initial dosing: ***0.5 mg PO four times daily*** or 1 mg PO twice daily[1,9]
maintenance: **1-4 mg PO daily in 2-4 divided doses** or 1.5-3 mg daily[1,9]

- Administer with food or on an empty stomach.[10]
- Adjust dose according to the platelet count.[1]
- Platelet counts ***every 1-2 weeks during dosage titration and every 1-3 months during maintenance*** or every 2 days during the first week of treatment and at least weekly until the maintenance dose is reached[1,9]
- Dosage increments: do not increase dose by more than 0.5 mg/day in any one week.[1]
- Maximum dose: 10 mg/day or 2.5 mg in a single dose.[1]

Dosage in renal failure:

no dosage adjustment required; monitor for renal toxicity[11]

Dosage in hepatic failure:

- mild impairment: monitor for cardiovascular effects and hepatic toxicity.[1]
- moderate impairment: starting dose of 0.5 mg/day; maintain for minimum of one week; monitor for cardiovascular effects and hepatic toxicity.[1]
  - dosage increments: do not increase dose by more than 0.5 mg/day in any one week.[1]
- severe impairment: not studied; avoid use[1]

Dosage in dialysis:

no information found

Children:

Initial dosing of 0.5 mg PO twice daily and maintenance dosing of 0.5-4 mg/day in 3 divided doses have been used.[6,12-14] However, safety and efficacy have not been established.

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