

**DRUG NAME: Anagrelide****SYNONYM(S):** None**COMMON TRADE NAME(S):** AGRYLIN®**CLASSIFICATION:** miscellaneous*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

The exact mechanism of action is not known. It is thought that a reduction in platelet production is the result of decreased megakaryocyte hypermaturation.<sup>1</sup> Anagrelide disrupts the postmitotic phase of megakaryocyte development, resulting in a reduction in the size of these cells.<sup>2,3</sup> Anagrelide is also thought to inhibit adenosine diphosphate (ADP) and collagen induced platelet aggregation.<sup>4</sup>

**PHARMACOKINETICS:**

Interpatient variability		
Oral Absorption	> 70% absorbed, food decreases the extent and rate of absorption, but this is not considered to be clinically significant <sup>5</sup>	
	time to peak plasma concentration	1-8 hours <sup>2,4,6</sup>
Distribution	cross blood brain barrier?	no information found
	volume of distribution	12 ± 3 L/kg <sup>4</sup>
	plasma protein binding	no information found
Metabolism	extensively metabolized, <1% eliminated unchanged 4-5 metabolites have been identified, activity of these is not known <sup>4</sup>	
	active metabolite(s)	2-amino-5,6-dichloro-3,4-dihydroquinazoline <sup>7</sup>
	inactive metabolite(s)	
Excretion	primarily renally eliminated	
	urine	>70% eliminated via this route
	feces	10-30% eliminated via this route <sup>2</sup>
	terminal half life	2-3 days <sup>2</sup>
	clearance	no information found
Gender	no information found	
Elderly	no information found	
Children	no information found	
Ethnicity	no information found	

Adapted from reference 4 unless specified otherwise.

**USES:****Primary uses:**

\*Thrombocythemia secondary to myeloproliferative disorders<sup>8</sup>

**Other uses:**

none

\*Health Canada Therapeutic Products Programme approved indication

No pediatric indications are available.

**SPECIAL PRECAUTIONS:**

**Contraindicated** in patients who have a history of hypersensitivity reaction to anagrelide.<sup>2</sup>

**Heart disease:** caution in patients with known or suspected heart disease, as anagrelide may cause cardiovascular effects (see table below).<sup>2</sup>

**Renal insufficiency:** caution in patients with renal insufficiency due to increased risk of renal toxicity.<sup>2</sup>

**Hepatic dysfunction:** caution in patients with hepatic dysfunction due to increased risk of hepatic toxicity.<sup>2</sup>

**Carcinogenicity:** no information found.<sup>2</sup>

**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.<sup>2</sup>

**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.<sup>2</sup>

**Pregnancy:** FDA Pregnancy Category C. 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).<sup>2</sup>

**Breastfeeding** is not recommended due to the potential secretion into breast milk.<sup>2</sup>

**SIDE EFFECTS:**

ORGAN SITE	SIDE EFFECT	ONSET		
dose-limiting side effects are in <b>bold, italics</b> I= immediate (onset in hours to days); E = early (days to weeks) D= delayed (weeks to months); L= late (months to years)				
auditory/hearing	ear disorder (1-5%) <sup>8</sup>		E	D
	tinnitus (1-5%) <sup>8</sup>		E	D
blood/bone marrow	anemia (1-5%) <sup>8</sup>			D
	hemorrhage (1-5%) <sup>8</sup>		E	
	<b>thrombocytopenia (9%)<sup>5</sup></b>		<b>E</b>	
cardiovascular (arrhythmia)	arrhythmia (1-5%) <sup>8</sup>			D
cardiovascular (general)	angina (1-5%) <sup>8</sup>			D
	cardiomegaly			L
	cardiomyopathy (rare) <sup>9</sup>			L
	complete heart block			L

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	heart failure (1-5%) <sup>8</sup>				L
	edema/fluid retention (20%)		E		
	hypertension (1-5%) <sup>8</sup>		E	D	
	hypotension (1-5%) <sup>8</sup>		E	D	
	myocardial infarction			D	
	palpitations (27%)				L
	pericarditis				L
	postural hypotension (1-5%) <sup>8</sup>	I			
	syncope (1-5%) <sup>8</sup>		E		
	tachycardia (7%)		E		
	vasodilatation (1-5%)		E		
constitutional symptoms	chills (1-5%) <sup>8</sup>	I			
	fever (9%) <sup>8</sup>		E		
	flu-like symptoms (1-5%) <sup>8</sup>	I			
	malaise (6%)		E		
	sweating (1-5%) <sup>8</sup>		E		
dermatology/skin	alopecia (1-5%) <sup>8</sup>		E	D	
	cellulitis (1-5%) <sup>8</sup>		E		
	ecchymosis (1-5%) <sup>8</sup>		E		
	photosensitivity (1-5%) <sup>8</sup>		E		
	pruritus (6%) <sup>8</sup>	I			
	rash (8%)	I			
	skin discolouration (1-5%) <sup>8</sup>				D
	skin ulcer (1-5%) <sup>8</sup>				D
gastrointestinal	<i>emetogenic potential: low</i>				
	anorexia (6%)	I			
	belching (1-5%) <sup>8</sup>		E		
	constipation (1-5%) <sup>8</sup>		E		
	diarrhea (24%)		E		
	dysphagia (1-5%) <sup>8</sup>		E		
	dyspepsia (6%)	I			
	flatulence (11%)		E		
	gastritis (1-5%) <sup>8</sup>		E		
	gastrointestinal distress (1-5%) <sup>8</sup>		E		
	gastrointestinal hemorrhage (1-5%) <sup>8</sup>				D
	melena (1-5%)		E		
	nausea (15%)	I			
	pancreatitis				D
	pharyngitis (7%)				D
vomiting (7%)	I				

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	weight loss/weight gain (1-5%) <sup>8</sup>			D	
hepatic	elevated liver function tests (rare) <sup>2</sup>			D	
infection	infection (1-5%) <sup>8</sup>			D	
	urinary tract infection (1-5%) <sup>8</sup>		E	D	
lymphatics	lymphadenoma (1-5%) <sup>8</sup>		E	D	
musculoskeletal	arthralgia (1-5%) <sup>8</sup>			D	
	arthritis (1-5%) <sup>8</sup>			D	
	leg cramps (1-5%) <sup>8</sup>			D	
	myalgia (1-5%) <sup>8</sup>			D	
neurology	amnesia (1-5%) <sup>8</sup>			D	
	cerebrovascular accident			D	
	confusion (1-5%) <sup>8</sup>		I		
	depression (1-5%) <sup>8</sup>			D	
	dizziness (15%)		I		
	insomnia (1-5%) <sup>8</sup>		E		
	migraine (1-5%) <sup>8</sup>				
	nervousness (1-5%) <sup>8</sup>		E		
	paresthesia (7%)			D	
	seizures			D	
	somnolence (1-5%) <sup>8</sup>		E		
ocular/visual	abnormal vision (1-5%) <sup>8</sup>			D	
	amblyopia (1-5%) <sup>8</sup>			D	
	blurred vision			D	
	conjunctivitis (1-5%) <sup>8</sup>			D	
	eye disorder (1-5%) <sup>8</sup>			D	
	visual field abnormality (1-5%) <sup>8</sup>			D	
pain	abdominal pain (17%)		I		
	back pain (6%) <sup>8</sup>		E	D	
	bone pain (1-5%) <sup>8</sup>		E	D	
	chest pain (8%)		E	D	
	headache (45%)		I		
	neck pain (1-5%) <sup>8</sup>		E	D	
	pain (15%)		E	D	
pulmonary	bronchitis (1-5%) <sup>8</sup>			D	
	cough (6%) <sup>8</sup>		E	D	
	dyspnea (11%)			D	
	epistaxis (1-5%) <sup>8</sup>		E	D	
	pneumonia (1-5%) <sup>8</sup>		E	D	
	pneumonitis (rare) <sup>10</sup>			D	
	pulmonary fibrosis			D	

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	pulmonary hypertension			D
	rhinitis (1-5%) <sup>8</sup>		E	D
	sinusitis (1-5%) <sup>8</sup>		E	D
renal/genitourinary	dysuria (2%) <sup>5</sup>			D
	erectile dysfunction (rare) <sup>11</sup>			D
	hematuria (2%) <sup>5</sup>		E	D
	incontinence (1-5%) <sup>8</sup>		E	D
	nocturia (1-5%) <sup>8</sup>		E	D
	renal failure (1-5%) <sup>8</sup>			D
	urinary frequency (1-5%) <sup>8</sup>		E	D
	urinary tract disorder (1-5%) <sup>8</sup>		E	D

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#### INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
sucralfate <sup>3</sup>	unknown	case report suggesting the sucralfate may interfere with absorption of anagrelide	space administration of anagrelide and sucralfate by 2 hours

#### SUPPLY AND STORAGE:

**Oral:** Sandoz Canada Inc. supplies anagrelide as a 0.5 mg capsule. Select non-medicinal ingredients: lactose. Store at room temperature in a light-resistant container.<sup>12</sup>

#### 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<sup>2</sup>

*maintenance: 1-4 mg PO daily in 2-4 divided doses* or 1.5-3 mg daily<sup>2</sup>

- Adjust dose according to the platelet count
- 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.<sup>8</sup>
- Do not increase dose by more than 0.5 mg/day in any one week.
- Maximum dose: 10 mg/day or 2.5 mg in a single dose.

*Dosage in renal failure:* no information found

*Dosage in hepatic failure:* no information found

*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.<sup>5,13-15</sup> However, safety and efficacy have not been established.

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