**Regimen Monograph**



## A - Regimen Name

# ANGR Regimen

**Anagrelide**

| | |
|---|---|
| **Disease Site** | Hematologic<br>Myeloproliferative Neoplasms (MPNs) |
| **Intent** | Palliative |
| **Regimen Category** | **Evidence-Informed :**<br>Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use. |
| **Rationale and Uses** | 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. |
| **Supplementary Public Funding** | **anagrelide**<br>ODB Limited Use (anagrelide) |

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## B - Drug Regimen

| | | | |
|---|---|---|---|
| anagrelide | 0.5 to 1 mg | PO | BID |

**OR**

| | | | |
|---|---|---|---|
| anagrelide | 0.5 mg | PO | QID |

**Titrated to lowest effective dosage**

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## C - Cycle Frequency

**CONTINUOUS TREATMENT**

Until disease progression or unacceptable toxicity

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## D - Premedication and Supportive Measures

**Antiemetic Regimen:** Not applicable

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## E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs.

- Initial dose should be 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 | |

**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 |

**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.

**Dosage in 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 - Adverse Effects

Refer to anagrelide drug monograph(s) for additional details of adverse effects.

| Common (25-49%) | Less common (10-24%) | Uncommon (< 10%), but may be severe or life-threatening |
|---|---|---|
| • Headache<br>• Diarrhea<br>• Palpitations | • Fatigue<br>• Edema<br>• Abdominal pain<br>• Nausea, vomiting<br>• Dizziness<br>• Pain<br>• Cough, dyspnea<br>• Flatulence | • ↑ LFTs<br>• Arrhythmia, QT interval prolonged<br>• Cardiotoxicity<br>• Nephritis<br>• Arterial thromboembolism<br>• Venous thromboembolism<br>• Interstitial lung disease<br>• GI bleeding |

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## G - Interactions

Refer to anagrelide drug monograph(s) for additional details.

- Avoid concurrent use with QT prolonging drugs and other PDE III inhibitors.
- Caution with CYP1A2 inhibitors and inducers. Monitor for toxicity/response and adjust anagrelide dose accordingly.
- Caution with CYP1A2 substrates, especially those with a narrow therapeutic range. Anagrelide may inhibit metabolism of these substrates.
- Caution with aspirin and monitor for bleeding closely. Use extreme caution in patients with high risk for hemorrhage and/or with platelets > 1000 x $10^9$/L before treatment.
- Caution and monitor with other drugs known to cause bleeding (e.g., anticoagulants, NSAIDs, antiplatelet agents).
- Separate administration of anagrelide and sucralfate by at least 2 hours to facilitate absorption, and monitor anagrelide response if used together.

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## H - Drug Administration and Special Precautions

Refer to anagrelide drug monograph(s) for additional details.

**Administration:**

- 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.

**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
- Not recommended for use in pregnancy. Females of child-bearing potential must not be pregnant before starting and during treatment. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose (general recommendation). Breastfeeding is not recommended.

**Pregnancy and Lactation:**

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Yes

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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

- 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; monitor closely in patients with known or suspected heart disease
- Clinical toxicity assessment for palpitations, blood pressure, headache, 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 - Administrative Information

Outpatient prescription for home administration

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## K - References

Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea Compared with Anagrelide in High-Risk Essential Thrombocythemia. N Engl J Med 2005;353:33-45.

Gisslinger H, Gotic M, Holowiecki J, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial. Blood 2013;121(10):1720-8.

**April 2024** Updated Pregnancy and Lactation section

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## M - Disclaimer

***Regimen Abstracts***

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