Anagrelide (Xagrid®) (ANA) for myeloproliferative disorders

Indication: Patients with myeloproliferative disorders at risk of thrombosis but refractory or intolerant to hydroxycarbamide or interferon.

Paediatric/young adult population

Treatment intent: To achieve platelet count < 400 x 10^9/L

Regimen details: Anagrelide 0.5 mg orally once daily

The starting dose should be maintained for at least one week. After one week the dosage may be titrated, on an individual basis, to achieve the lowest effective dosage required to reduce and/or maintain a platelet count < 400 x 10^9/L. The dosage increment must not exceed more than 0.5mg/day in any one-week and the recommended maximum single dose should not exceed 2.5mg.

Typically, a fall in the platelet count will be observed within 14 to 21 days of starting treatment and in most patients an adequate therapeutic response will be observed and maintained at a dosage of 1-3mg/day. The maximum dose is 4.5mg/day, however in clinical development dosages of 10mg/day have been used.

Anagrelide is available as 0.5mg capsules. The daily dose should be divided.

Administration: Orally

Premedication: None required

Frequency: Continuous

Extravasation: Not applicable

Anti-emetics: Not usually required

Supportive medication: Consider the use of allopurinol especially when rapid control of blood counts is desired and in those patients with raised serum urate and/or history of gout.

Regular investigations: Chest x-ray and ECG at outset, an echocardiogram if cardiac disease is known or suspected on history or after CXR and ECG.

If the starting dose is > 1mg/day, platelet counts should be performed every 2 days during the first week of treatment and at least weekly thereafter until stable maintenance dose is reached.

FBC at every visit

LFTs and renal function every 6 months

Dose Modifications

Haematological Toxicity

Thrombocytopenia in 90% of patients; titrate against effect

Anaemia in 20-30% of patients

Renal Impairment

Anagrelide is contraindicated in severe renal impairment (creatinine clearance < 50ml/min)
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**Hepatic Impairment**

Anagrelide is contraindicated in moderate or severe hepatic impairment.

**Toxicities:**

1. **Headache:** Occurs in about 30% of patients; generally mild but can be more severe. Treat with paracetamol.
2. **Palpitations:** Occur in about 25% of patients; may require discontinuation of Anagrelide have a low threshold for investigating patients further. Avoid exercise and caffeine containing drinks immediately before or after dose.
3. **Diarrhoea:** Occurs in about 25% of patients. Supportive treatment involves adequate hydration, ingestion of low fibre foods in small amounts at frequent intervals.
4. **Fluid retention:** Occurs in about 20% of patients. Supportive treatment involves elevation of the feet and avoidance of tight clothing.
5. **Cardiac** disease. Cases of cardiomegaly and congestive heart failure have been reported. Anagrelide should be used with caution in patients of any age with known or suspected heart disease, and only if the potential benefits of therapy outweigh the potential risks.

**Drug interactions:**

Caution with concomitant use of aspirin.

Anagrelide is primarily metabolised by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine and omeprazole, and such medicinal products could theoretically adversely influence the clearance of anagrelide. Anagrelide demonstrates some limited inhibitory activity towards CYP1A2 which may present a theoretical potential for interaction with other co-administered medicinal products sharing that clearance mechanism e.g. theophylline. Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III (PDE III). The effects of medicinal products with similar properties such as the inotropes milrinone, enoximone, amrinone, olprinone and cilostazol may be exacerbated by anagrelide. Grapefruit juice has been shown to inhibit CYP1A2 and therefore could also reduce the clearance of anagrelide.

**Comments:**

Do not use during pregnancy.

For selected patients with Polycythaemia Vera (PV) anagrelide may be used in combination with hydroxyurea.

**References:**

7. Anagrelide Product Monograph.
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