SHARED CARE GUIDELINES FOR PRESCRIBING ANAGRELIDE FOR USE IN CONTROL OF THROMBOCYTOSIS IN ESSENTIAL THROMBOCYTHAEMIA.

INDICATION

This shared care guideline has been developed to support the transfer of responsibility for prescribing anagrelide from secondary to primary care. It is used locally for the second line treatment of essential thrombocythaemia. Platelet counts should be maintained at $<500x10^9$/L. Regular full blood count monitoring is required in order to adjust dosage and to detect progression to myelofibrosis and/or AML.

Anagrelide is very effective in lowering raised platelet counts. It is not a cytotoxic drug and produces its effect by interfering with megakaryocyte development. Hydroxycarbamide (Hydrea) remains the first-line treatment. However, Anagrelide has a role in patients who are refractory to Hydroxycarbamide (rare) or in whom Hydroxycarbamide causes unacceptable depression of haemoglobin and /or WBC.

It is licensed for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

An at risk patient

An at risk essential thrombocythaemia patient is defined by <u>one or more</u> of the following features:

• > 60 years of age or

• a platelet count > 1000 x 10^9/l or

• a history of thrombo-haemorrhagic events.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of anagrelide can be shared between the specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the responsibility for prescribing remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient.

- Patients will only be referred to the GP once the GP has agreed in each individual case and the patient's treatment has been stabilized.

Specialist Responsibilities	
1	To diagnose essential thrombocythaemia and to decide on treatment.
2.	Where patients is unable to receive hydroxycarbamide to initiate treatment with anagrelide and to titrate dose until platelet count is stable
3.	To advise patients of possible adverse effects
4.	To monitor full blood counts and review patient (normally every 2-6 months). Very stable patients may receive telephone appointments.

General Practitioner Responsibilities	
1.	To prescribe anagrelide once the patient has been stabilised
2.	To refer back to the consultant in the event of adverse events or a platelet count >500x10^9/L or <100x10^9/L (discovered incidentally outside of planned monitoring).

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment or is unable to comply with treatment.
2	Attend appropriate consultant and GP appointments
3	Share any concerns in relation to treatment with anagrelide
4	Use written and other information on the medication.
5	Seek help if it is suspected that anagrelide is causing side effects, or if the patient is otherwise unwell.

SUPPORTING INFORMATION

Dosage and Administration

Dose

Anagrelide is available as 0.5mg capsules. The daily dose is dictated by the platelet count and varies between one capsule (0.5mg) and ten capsules (5mg) daily. The average daily dose is four capsules (2mg) daily.

Contraindications

Contraindications included in the current Summary of Product Characteristics include:

- Hypersensitivity to anagrelide or to any of the excipients.
- Patients with moderate or severe hepatic impairment.
- Patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).
- Anagrelide should not be given during pregnancy or lactation.
- Anagrelide is contraindicated in patients with severe cardiovascular disease (vasodilator and positive inotropic effects).

Special Warnings

- The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced. It is not recommended in patients with elevated transaminases (> 5 times the upper limit of normal). Dosing in mild hepatic impairment should be reduced.

- The potential risks and benefits of anagrelide therapy in a patient with mild impairment of renal function should be assessed before treatment is commenced, as there are no specific pharmacokinetic data in this patient population.
- Therapy requires close clinical supervision of the patient which will include a full blood count (haemoglobin and white blood cell and platelet counts), and assessment of liver function (ALT and AST) and renal function (serum creatinine and urea) tests.
- The platelet count will increase within 4 days of stopping treatment with anagrelide capsules and will return to pre-treatment levels within 10 to 14 days.
- 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. Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic effects, a pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation.
- Anagrelide contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Side Effects

Patients are advised not to drive or operate machinery while taking anagrelide if dizziness is experienced. In general, anagrelide is well tolerated. The commonest adverse events leading to treatment discontinuation are headache, diarrhoea, oedema, palpitations and abdominal pain.

For full details see Manufacturer's SPC at;
http://www.medicines.org.uk/EMC/medicine/15737/SPC/Xagrid+0.5mg+hard+capsule/

Drug Interactions

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III (PDE III). Concomitant use of anagrelide with other PDE III inhibitors such as milrinone, amrinone, enoximone, olprinone and cilostazol is not recommended.

• 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.
• In vivo interaction studies in humans have demonstrated that digoxin and warfarin do not affect the pharmacokinetic properties 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.
• In vivo interaction studies in humans have demonstrated that anagrelide does not affect the pharmacokinetic properties of digoxin or warfarin.
• At the doses recommended for use in the treatment of essential thrombocythaemia, anagrelide may potentiate the effects of other medicinal products that inhibit or modify platelet function e.g. acetylsalicylic acid.
• A clinical interaction study performed in healthy subjects showed that co-administration of repeat-dose anagrelide 1 mg once daily and acetylsalicylic acid 75 mg once daily may enhance the anti-platelet aggregation effects of each drug compared with administration of acetylsalicylic acid alone. In some ET patients concomitantly treated by acetylsalicylic acid and anagrelide, major haemorrhages occurred. Therefore, the potential risks of the concomitant use of anagrelide with acetylsalicylic acid should be assessed, particularly in patients with a high risk profile for haemorrhage before treatment is initiated.

• Anagrelide may cause intestinal disturbance in some patients and compromise the absorption of hormonal oral contraceptives.

Prices (March 2012 BNF):
100 capsules 500 micrograms= £337.14

COMMUNICATION AND SUPPORT

PHT Hospital Switchboard Tel: 01202 665511	**RBCH** Hospital Switchboard Tel: 01202 303626	**DCH** Hospital Switchboard: Tel: 01305 251150
Haematologists		
Dr F Jack Dr R Maddams	Dr S Killick Dr R Walewska Dr J Chacko Dr R Hall Dr H McCarthy	Dr D Hofer Dr A Moosa
Specialist support/resources available to GP including patient information: Summary of Product Characteristics for Anagrelide accessible via www.medicines.org.uk Medicines Information: RBCH Tel 01202 704098 / PHT Tel 01202 442127/ DCH Tel 01305 255171		

References

1. Summary of product characteristics (SPC) of Anagrelide (Xagrid®)
2. BNF (March 2012)

The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Written By	**DCN lead pharmacist/ medicines management team NHS Dorset**	**March 2012**
Approved By	**Bournemouth, Dorset and Poole Health Technologies Forum**	**May 2012**

Review Date	**September 2013 or before in the light of new evidence and/or recommendations**